Report on the Deliberation Results

May 16, 2016
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Kyprolis for Intravenous Injection 10 mg Kyprolis for Intravenous Injection 40 mg
Non-proprietary Name	Carfilzomib (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 26, 2015

Results of Deliberation

In its meeting held on April 25, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as poisonous drugs.

Conditions of approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited number of subjects in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use results survey covering all patients treated with the product until data from a specified number of patients are collected, in order to understand the characteristics of patients and to promptly collect safety and efficacy data of the product. Based on the collected data, necessary measures should be taken to ensure correct use of the product.

**Japanese Accepted Name (modified INN)*

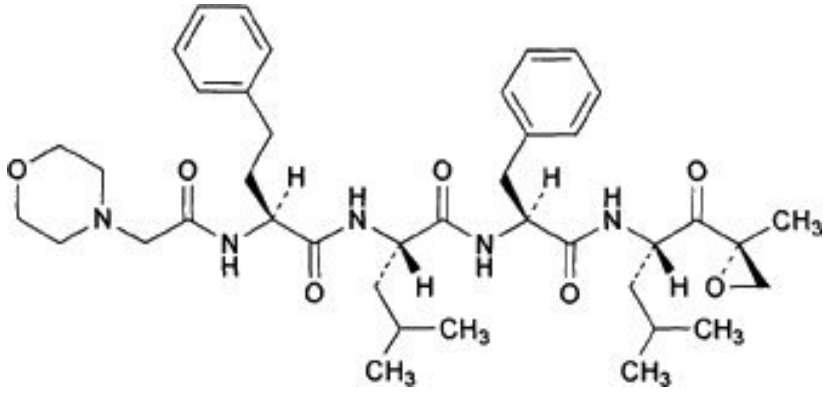
Review Report

April 13, 2016
Pharmaceuticals and Medical Devices Agency

The following are results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Kyprolis for Intravenous Injection 10 mg Kyprolis for Intravenous Injection 40 mg
Non-proprietary Name	Carfilzomib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 26, 2015
Dosage Form/Strength	Powder for reconstitution for injection, each vial contains 10.7 mg or 42.6 mg of carfilzomib
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{40}H_{57}N_5O_7$
Molecular weight: 719.91
Chemical name:
N-{(2*S*)-2-[(Morpholin-4-ylacetyl)amino]-4-phenylbutanoyl}-L-leucyl-L-phenylalanin-*N*-{(2*S*)-4-methyl-1-[(2*R*)-2-methyloxiran-2-yl]-1-oxopentan-2-yl}amide

Items Warranting Special Mention	Orphan drug (Designation No.: [*27 yaku*] No. 363, dated August 20, 2015, issued by the Evaluation and Licensing Division, PFSB/ELD Notification No. 0820-1)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of relapsed or refractory multiple myeloma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Further investigation is necessary through post-marketing surveillance for the following events: cardiac disorder, interstitial lung disease, pulmonary hypertension, haematotoxicity, infection, liver disorder, renal disorder, haemorrhage, infusion-related reaction, tumour lysis syndrome, hypertension including hypertensive crisis, venous thromboembolism, reversible posterior leukoencephalopathy syndrome and leukoencephalopathy, thrombotic microangiopathy, gastrointestinal perforation, pericarditis, and pericardial effusion.

Indication	Relapsed or refractory multiple myeloma
Dosage and Administration	In combination with lenalidomide plus dexamethasone, carfilzomib is usually administered to adult patients once daily by intravenous infusion on Days 1, 2, 8, 9, 15, and 16 followed by a 12-day rest period. This 28-day cycle is repeated until Cycle 12. From Cycle 13 onward, carfilzomib is administered once daily by intravenous infusion on Days 1, 2, 15, and 16 followed by a 12-day rest period. The dose of carfilzomib is 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1 and 27 mg/m^2 (body surface area) thereafter, and is administered as an intravenous infusion over 10 minutes. The dose may be reduced according to the patient's condition.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited number of subjects in the Japanese clinical studies, the applicant is required to conduct a post-marketing drug use results survey covering all patients treated with the product until data from a specified number of patients are collected, in order to understand the characteristics of patients and to promptly collect safety and efficacy data of the product. Based on the collected data, necessary measures should be taken to ensure correct use of the product.

Attachment

Review Report (1)

February 23, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Kyprolis for Intravenous Injection 10 mg Kyprolis for Intravenous Injection 40 mg
Non-proprietary Name	Carfilzomib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 26, 2015
Dosage Form/Strength	Powder for reconstitution for injection, each vial containing 10.7 mg or 42.6 mg of carfilzomib
Proposed indication	Relapsed or refractory multiple myeloma
Proposed Dosage and Administration	Carfilzomib is usually administered to adult patients once daily on Days 1, 2, 8, 9, 15, and 16, followed by a 12-day rest period. This 28-day cycle is repeated. The dose of carfilzomib is 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1, and 27 mg/m^2 (body surface area) thereafter, and is administered intravenously over 10 minutes.

Table of Contents

List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Application marketing approval	Application for marketing approval
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BAX	Bcl-2-associated X protein
BCRP	Breast cancer resistance protein
Boc-group	*tert*-Butoxycarbonyl group
BSC	Best supportive care
Carfilzomib	Carfilzomib

Carfilzomib/DEX	Co-administration of carfilzomib and dexamethasone
CI	Confidence interval
CLd regimen	A combined regimen of carfilzomib with lenalidomide hydrate plus dexamethasone
CL_{int}	Intrinsic clearance
CrCL	Creatinine clearance
CR	Complete response
CYP	Cytochrome P450
DEX	Dexamethasone
DLT	Dose limiting toxicity
EBMT criteria	Evaluation criteria created by European Group for Blood and Marrow Transplantation (EBMT)
FDA	Food and Drug Administration
FOB	Functional observation battery
GC	Gas chromatography
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
Hb	Hemoglobin
HCT	Hematocrit
hERG	Human ether-a-go-go-related gene
HLT	High level term
HPLC	High performance liquid chromatography
HPBCD	Hydroxypropyl-beta-cyclodextrin
IDMC	Independent data monitoring committee
ILD	Interstitial lung disease
Immunodeficient mouse	Nude mouse NIH-Lyst^{bg} Foxn1^{nu} Btk^{xid}
IMWG	International Myeloma Working Group
IMWG criteria	Evaluation criteria created by the International Myeloma Working Group (IMWG)
IR	Infrared spectroscopy
IRC	Independent review committee
IRR	Infusion-related reaction
ITT	intent-to-treat
LD regimen	A combined regimen of lenalidomide hydrate and high-dose dexamethasone
Ld regimen	A combined regimen of lenalidomide hydrate and dexamethasone
Lenalidomide	Lenalidomide hydrate

MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	Multiple Myeloma
MR	Minimal response
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PDQ	National Cancer Institute Physician Data Query Multiple Myeloma and Other Plasma Cell Neoplasms
NE	Not Evaluable
NK	Neurokinin
OS	Overall survival
$P_{app\ A \rightarrow B}$	Apparent permeability in apical to basolateral direction
$P_{app\ B \rightarrow A}$	Apparent permeability in basolateral to apical direction
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PPK	Population pharmacokinetics
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
QTcF	QT interval corrected according to Fridericia's formula
SBECD	Sulfobutylether-beta-cyclodextrin sodium
sCR	Stringent complete response
SD	Stable disease
Site 2	Sodium channel site 2
SMQ	Standard MedDRA query
SOC	System organ class

Study 009	Study PX-171-009
Study 011	Study PX-171-011
Study 01	Study ONO-7057-01
Study 05	Study ONO-7057-05
The product	Kyprolis for Intravenous Injection
TLS	Tumor lysis syndrome
TMA	Thrombotic microangiopathy
VGPR	Very good partial response
V1	Central volume of distribution
V2	Peripheral volume of distribution
[^{3}H]-labeled carfilzomib	[^{3}H]-labeled carfilzomib

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Summary of product submitted for registration

Carfilzomib is a proteasome inhibitor developed by Proteolix, Inc. (currently Onyx Therapeutics, Inc.) in the US. Carfilzomib is expected to bind to the chymotrypsin-like active sites of the 20S proteasome in the ubiquitin-proteasome system, inhibiting 20S proteasome activity to induce apoptosis of the tumor cells and thereby suppressing tumor growth.

1.2 Development history

Onyx Therapeutics, Inc., in the US started Study PX-171-002 (phase I study) in patients with progressive haematopoietic malignancy outside Japan from September 2005. Then, Onyx Pharmaceuticals, Inc., in the US conducted additional studies in patients with relapsed or refractory multiple myeloma (MM), namely, Study PX-171-003, a phase II study of carfilzomib monotherapy from [redacted] 20[redacted], Study 009, a phase III study of carfilzomib combination therapy with lenalidomide hydrate plus dexamethasone (DEX) (CLd regimen) from July 2010; and Study 2011-003, a phase III study of carfilzomib/ DEX from June 2012.

In the US, the application for marketing approval was filed in September 2011 for carfilzomib monotherapy based on the results from the pivotal Study PX-171-003. The application was approved through expedited procedures in July 2012. At that time, the indication was described as follows: "KYPROLIS is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified." In January 2015, an application for marketing approval was filed for the CLd regimen both in the US and EU, based on the results from the pivotal Study 009. In the US, the CLd regimen was approved in July 2015 with the indication described as "Kyprolis in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy," In the EU, the CLd regimen was approved in November 2015 with the indication described as "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." Further, in the US, another application was filed in July 2015 based on the results from the pivotal Study 2011-003. In January 2016, the indications for monotherapy and combination therapy were modified as follows: for monotherapy, "KYPROLIS is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy"; for combination therapy, "KYPROLIS is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy."

As of January 2016, carfilzomib has been approved in 41 countries and regions for the indication of MM.

In Japan, the applicant started a phase I/II study (Study 01) of carfilzomib monotherapy in [redacted] 20[redacted], and a phase I study (Study 05) of the CLd regimen in [redacted] 20[redacted], both in patients with relapsed or refractory MM.

Based on the results of pivotal studies (Studies 05 and 009), an application for marketing approval of carfilzomib was submitted recently.

In August 2015, carfilzomib was designated as an orphan drug (Designation No.: [*27 yaku*] No. 363) with the proposed indication of "Relapsed or refractory multiple myeloma."

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to grayish white solid. Its description, solubility, hygroscopicity, melting point, optical rotation, dissociation constant, partition coefficient, and specific surface area were determined.

The chemical structure of the drug substance was elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectroscopy (UV/Vis), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), and single crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is a compound from starting materials of [redacted],[1] [redacted],[2] and [redacted]. There are 2 manufacturing methods. The major difference between the 2 methods is [redacted]. Equivalence in quality characteristics between the drug substances manufactured by Methods 1 and 2 was confirmed by a batch analysis and stability study.

The [redacted] processes of [redacted][3] and [redacted],[4] and the drug substance purification process were defined as the critical steps. In [redacted],[5] [redacted],[6] [redacted], and the drug substance purification process, process control items and process control values were specified.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and high performance liquid chromatography [HPLC]), purity (clarity and color of solution, [redacted] [inductively coupled plasma atomic emission spectrophotometry], related substances [HPLC], residual solvents [gas chromatography; GC], [redacted] [HPLC], and [redacted] [GC]), water content, residue on ignition, bacterial endotoxins, microbial limit testing, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows the stability of the drug substance. The results of the photostability studies showed that the drug substance is unstable when exposed to light.

Table 1. Stability studies of the drug substance

Study	Manufac-turing method	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	1	3 production batches	5 ± 3°C	–	Double-layered low density polyethylene bag + light-shielding, high density polyethylene drum	36 months
	2	3 pilot scale batches				
		3 production batches				24 months
Accelerated	1	3 production batches	25 ± 2°C	60 ± 5%RH		6 months
	2					

1 [redacted]
2 [redacted]
3 [redacted]
4 [redacted]
5 [redacted]
6 [redacted]

Based on the above, a retest period of 36 months was proposed for the drug substance when placed in a double-layered polyethylene bag, stored protected from light in a high-density polyethylene drum at 2°C to 8°C.

2.2 Drug product

2.2.1 Description and composition of the drug product, and formulation design

The drug product is a lyophilized powder for injection provided in vials, each containing 10.7 or 42.6 mg of the drug substance. The drug product contains sulfobutyl-ether-beta-cyclodextrin (SBECD), anhydrous citric acid, and sodium hydroxide as excipients. SBECD has been registered in the drug master files for drug substances by the US-based [redacted] (MF registration No. [redacted]). The vial is overfilled with the drug substance to ensure that the content of the drug substance is 10 mg in 5-mL injectable solution and 40 mg in 20-mL injectable solution as per label indication, after reconstituted in 5 and 20 mL of water for injection, respectively.

2.2.2 Manufacturing process

The drug product is produced through the manufacturing process comprising [redacted], [redacted], [redacted], [redacted], inspection, packaging/labeling, and testing/storage.

[redacted], [redacted], and [redacted] were the critical steps. Process control items and process control values were specified for [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (HPLC), osmotic pressure, pH, purity (related substances [HPLC]), water content, bacterial endotoxins, uniformity of dosage units (mass variation test), foreign insoluble matter, insoluble particulate matter, sterility, dissolution time, and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows the summary of the stability studies for the drug product. The results of the photostability study showed that the drug product is unstable when exposed to light.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot scale batches	5 ± 3°C	–	Glass vial + rubber stopper + paper carton	24 months
Accelerated	3 pilot scale batches	25 ± 2°C	60 ± 5%RH		6 months

Based on the above, a shelf life of 24 months was proposed for the drug product when packaged in glass vials sealed with a rubber stopper ([redacted]), stored protected from light in a paper carton at 2°C to 8°C. The long-term stability study will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.R.1 New excipient

The drug product contains SBECD, which is regarded as a new excipient with no use experience. Based on the following discussions, PMDA accepted the use of SBECD in the drug product in view of the seriousness of the indicated illness. In this regard, however, the use of SBECD in this drug product is exceptional and should not be a precedent for standard use.

2.R.1.1 Specifications, testing methods, and stability
Based on the data submitted, PMDA concluded that there are no problems with the specifications, testing methods, and stability of SBECD.

2.R.1.2 Safety
According to the review of the application for the marketing approval of Vfend 200 mg for intravenous infusion, exceptional use of SBECD as an excipient was allowed for this particular drug and should not be regarded as a precedent for standard use, because of the potential risks for (a) SBECD-associated anaphylactoid reactions, which occurred in clinical studies and (b) renal toxicity due to the accumulation of SBECD (See the "Review Report of Vfend 200 mg for intravenous infusion" dated February 16, 2005).
Results of 32 studies including the following were submitted as SBECD toxicity data: single-dose intravenous administration studies using mice or rats, 14-day to 6-month intravenous administration studies using rats or dogs, reproductive and developmental toxicity studies and genotoxicity studies using rats or rabbits. The approximate lethal dose of SBECD was determined to be >2000 mg/kg based on the single-dose toxicity studies. In repeat-dose toxicity studies, changes including vacuolization of tubular epithelial cells were observed at ≥160 mg/kg in rats and at ≥60 mg/kg in dogs. The no-observed-adverse-effect level (NOAEL) for the reproductive and developmental toxicity studies was determined to be 600 mg/kg. Genotoxicity was not observed.

PMDA's view on the stability of SBECD:
The use of SBECD in the drug product is acceptable given the seriousness of the indicated illness. However, PMDA considers that the use of SBECD in carfilzomib should not regarded as a precedent for standard use and should remain as an exceptional case on the basis of the following concern: as compared with the maximum daily dose of SBECD contained in this drug, 49.5 mg/kg, the safety margin appears insufficient over the dose at which findings including vacuolization of tubular epithelial cells were observed in toxicity studies of SBECD in rats and dogs, and it is therefore possible that renal toxicity develops during the use of this drug in clinical practice.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Proteasome inhibitory activity (CTD 4.2.1.1-1, 4.2.1.1-2 [reference data], 4.2.1.1-3 [reference data], and 4.2.1.1-4 [reference data])

The inhibitory effect of carfilzomib on the chymotrypsin-like activity of purified human 20S proteasome was studied by measuring the fluorescence intensity of fluorogenic substrates specific to chymotrypsin-like activity. The IC_{50} was 2.08 ± 0.0478 nmol/L (mean ± standard error, n = 3).

The inhibitory effect of carfilzomib on the chymotrypsin-like activity, caspase-like activity, and trypsin-like activity of purified human 20S proteasome was studied by measuring the fluorescence intensity of fluorogenic substrates specific to each activity. The IC_{50} of carfilzomib for the chymotrypsin-like activity, caspase-like activity, and trypsin-like activity was 4.4, 1650, and 2400 nmol/L, respectively. The inhibitory effect of bortezomib was studied in a similar manner and resulted in IC_{50} of 3.9, 75, and 2840 nmol/L, respectively.

The inhibitory effect of carfilzomib on the chymotrypsin-like activity, caspase-like activity, and trypsin-like activity of 20S proteasome was studied in human MM ANBL-6 cell lysate by measuring the fluorescence intensity of fluorogenic substrates specific to each activity. The results showed that ≥80% inhibitory effect of carfilzomib on the chymotrypsin-like activity was observed at concentrations of ≥10 nmol/L. In contrast, the inhibitory effect of carfilzomib on the caspase-like activity and trypsin-like activity was weaker than that on the chymotrypsin-like activity.

Binding characteristics of carfilzomib to proteasome subunits in ANBL-6 cell lines (chymotrypsin-like site [β5], caspase-like site [β1], and trypsin-like site [β2]) were studied with enzyme-linked immunosorbent assay (ELISA) using cell lysates treated with carfilzomib. Carfilzomib bound more readily to the chymotrypsin-like site (β5) than to other subunits.

The reversibility of chymotrypsin-like activity in 20S proteasomes in carfilzomib-treated human colorectal carcinoma HT-29 cell lines and human MM RPMI-8226 cell lines was studied by measuring the fluorescence intensity using fluorogenic substrates specific to chymotrypsin-like activity. The chymotrypsin-like activity in cells treated with carfilzomib recovered over time.

3.1.2 Apoptosis inducing activity (CTD 4.2.1.1-4 and 4.2.1.1-5 [both are reference data])

The effects of carfilzomib on the accumulation of polyubiquitinated proteins and Bcl-2-associated X protein (BAX), and activation of caspase 3 were studied by Western blot using HT-29, RPMI-8226, and human acute lymphocytic leukemia MOLT-4 cell lines. Carfilzomib treatment caused the accumulation of polyubiquitinated proteins in all cell lines studied, the accumulation of BAX in RPMI-8226 cell lines, and the activation of caspase 3 in MOLT-4 cell lines.

The apoptosis-inducing activity of carfilzomib in HT-29, RPMI-8226, and MOLT-4 cell lines was studied by flow cytometry using annexin V and propidium iodide staining as an indicator. Apoptosis induction occurred in all cell lines studied after the treatment with carfilzomib.

3.1.3 Inhibition of proteasome activity in blood or in tissue (CTD 4.2.1.1-17 and 4.2.1.1-22 [reference data])

Rats received 1, 2, or 4 mg/kg of carfilzomib intravenously, once daily on Days 1, 2, 8, 9, 15, and 16 of every 28-day cycle. The inhibitory activity of carfilzomib against chymotrypsin-like activity of the proteasome in blood on Day 1 of Cycles 1, 3, and 6 was studied by measuring the fluorescence intensity using fluorogenic substrates specific to chymotrypsin-like activity. At 1 hour pose-dose, chymotrypsin-like activity was inhibited by >85%, >90%, and >90%, respectively, on Day 1 of Cycles 1, 3, and 6 as compared to baseline. In addition, prior to the administration of carfilzomib on Day 1 of Cycles 3 and 6, chymotrypsin-like activity had recovered slightly (12.7% to 30.2%) in spite of the irreversible binding of carfilzomib to proteasome. The applicant considers that the recovery of chymotrypsin-like activity is attributable to proteasome in newly produced erythrocytes.

Cynomolgus monkeys received a single intravenous dose of carfilzomib (2 mg/kg), and inhibition of the chymotrypsin-like activity of proteasome by carfilzomib in tissues 2 hours post-dose was studied using fluorogenic substrates specific to chymotrypsin-like activity in whole blood, bone marrow, the adrenal gland, brain, heart, liver, lung, and inguinal lymph node by measuring the fluorescence intensity as an indicator. As compared to the vehicle (10-mmol/L citric acid solution containing 10 w/v% SBECD, pH 3.5), carfilzomib inhibited the chymotrypsin-like activity statistically significantly in whole blood, bone marrow, the adrenal gland, heart, and lung ($P < 0.05$ for whole blood, bone marrow, and the adrenal gland; $P < 0.01$ for the lung; and $P < 0.001$ for the heart; one-way ANOVA).

3.1.4 Antiproliferative activities against malignant tumor cells

3.1.4.1 *In vitro*

3.1.4.1.1 Antiproliferative activities against multiple myeloma cell lines (CTD 4.2.1.1-6 and 4.2.1.1-3 [reference data])

The antiproliferative effect of carfilzomib against human MM cell line MM.1S was studied using redox dye. IC_{50} after 1-hour and 24-hour continuous treatment with carfilzomib was 35.7 and 5.9 nmol/L, respectively.

The antiproliferative effect of carfilzomib against RPMI-8226 cell lines was studied by adenosine triphosphate (ATP) assay using luminescence from luciferase as an indicator. IC_{50} values after 1-hour and 72-hour continuous treatment with carfilzomib were 71 and 10 nmol/L, respectively. The antiproliferative effect of bortezomib was also studied in a similar manner.IC_{50} values after 1-hour and 72-hour continuous treatment with bortezomib were 303 and 4.5 nmol/L, respectively.

3.1.4.1.2 Antiproliferative effects against non-multiple myeloma cell lines (CTD 4.2.1.1-3 [reference data])

The antiproliferative effects of carfilzomib and bortezomib against the following cell lines were studied by intracellular ATP assay: human haematopoietic tumor cell lines (Burkitt lymphoma cell line HS-Sultan, MOLT4, and non- Hodgkin's lymphoma cell line RL), human solid tumor cell lines (HT-29, pancreatic cancer cell line MiaPaCa-2, and non-small-cell lung cancer cell line A549), and human normal tissue cell lines (normal human dermal fibroblast [NHDF] cell line, and human umbilical vein endothelial cell [HUVEC] cell line). The IC_{50} values of carfilzomib against these cell lines are shown in Table 3.

Table 3. Antiproliferative activities of carfilzomib and bortezomib against various cell lines

	Cell line	IC_{50} value (nmol/L)			
		1-hour treatment		72-hour treatment	
		Carfilzomib	Bortezomib	Carfilzomib	Bortezomib
Haematopoietic tumor cell lines	HS-Sultan	135 ± 30	454 ± 60	5.2 ± 2.3	5.4 ± 2.0
	MOLT4	31 ± 17	126 ± 52	3.1 ± 1.6	6.2 ± 2.7
	RL	164 ± 92	814 ± 476	2.4 ± 0.4	3.4 ± 2.0
Solid tumor cell lines	HT-29	350 ± 84	2190 ± 390	6.2 ± 3.9	5.0 ± 2.6
	MiaPaCa-2	1110 ± 240	>6500	8.9 ± 6.5	8.3 ± 2.3
	A549	1200 ± 900	4600 ± 1900	20 ± 8	13 ± 8
Normal tissue cell lines	NHDF	389 ± 128	2460 ± 1120	14 ± 4.5	6.3 ± 4.1
	HUVEC	455 ± 45	3510 ± 390	7.2 ± 1.3	3.5 ± 0.5

Mean ± standard deviation, $n \geq 3$

3.1.4.1.3 Antiproliferative effects against drug-resistant cell lines (CTD 4.2.1.1-7 and 4.2.1.1-4 [reference data])

The antiproliferative effects of carfilzomib against the following cell lines were studied using redox dye: HT-29, MM.1S, RPMI-8226, HT-29 that acquired bortezomib resistance, MM.1S that acquired DEX resistance, RPMI-8226 that acquired melphalan resistance, and RPMI-8226 that acquired doxorubicin resistance. The IC_{50} values of carfilzomib were 14.9, 29.3, 89.9, 64.4, 15.2, 83.3, and >1000 nmol/L, respectively.

3.1.4.2 *In vivo*

3.1.4.2.1 Inhibition of tumor growth in multiple myeloma cell lines (CTD 4.2.1.1-8)

Tumor growth inhibitory effect of carfilzomib was studied using immuno-deficient mice after subcutaneous implantation of MM.1S cell lines. On 16 days after transplantation, the tumor volume reached about 82.5 mm^3, and the mice started to receive carfilzomib (3 or 5 mg/kg) intravenously twice weekly (on the first and second days of each week) for 5 weeks to calculate tumor volume. Carfilzomib 5 mg/kg inhibited tumor growth statistically significantly ($P < 0.01$, Dunnett's method for multiple comparisons) as compared to the vehicle (10-mmol/L citric acid solution containing 10 w/v% SBECD, pH 3.5).

3.1.4.2.2 Inhibition of tumor growth in non-multiple myeloma malignant tumor cell lines (CTD 4.2.1.1-9 and 4.2.1.1-3 [reference data])

Tumor growth inhibitory effect of carfilzomib was studied using immuno-deficient mice after subcutaneous implantation of HT-29, RL, or HS-Sultan cell lines. Carfilzomib inhibited tumor growth in all cell lines following administration.

3.2 Secondary pharmacodynamics

3.2.1 Effects on enzymes and receptors (CTD 4.2.1.2-1, 4.2.1.2-2, and 4.2.1.2-3 [reference data])

The inhibitory effects of carfilzomib (10 μmol/L) and bortezomib (10 μmol/L) against 21 proteases except proteasome were studied using specific fluorogenic substrates with the fluorescence intensity as an indicator. Carfilzomib did not show ≥50% inhibition against any of the proteases.

The inhibitory effects of carfilzomib (10 μmol/L) against 67 receptors and 16 enzymes were studied. Carfilzomib inhibited NK_1 and NK_2 receptors and Site 2 by ≥50%.

The applicant's explanation about the possibility of adverse events attributable to the inhibitory effect of carfilzomib against ligand binding to NK_1 and NK_2 receptors and Site 2 in the clinical use of carfilzomib:

Because (1) NK_1 and NK_2 receptors and their ligands are localized in the central nervous system (*Eur J Pharmacol*. 1999;375:51-60. *Expert Opin Ther Pat*. 2012;22:57-77), and (2) Site 2 is involved in neurotransmission (*J Physiol*. 2012:590:2577-89), there is a possibility that carfilzomib affects the central nervous system through the inhibition of NK_1 and NK_2 receptors and Site 2. However, given that effects of carfilzomib on the central nervous system were not observed in the safety pharmacology studies [see Section 3.3.1], it is unlikely that the inhibitory activity of carfilzomib against ligand binding to NK_1 and NK_2 receptors and Site 2 will trigger an adverse event in the clinical use of carfilzomib.

3.2.2 Effects on neurons (CTD 4.2.1.2-3 [reference data])

Effects of carfilzomib and bortezomib on neurite outgrowth were studied by immunostaining for β III tubulin using human neuroblastoma cell line SH-SY5Y which was differentiated into neurons. The results did not indicate any effects of carfilzomib on neurite outgrowth. In contrast, a reduction in total and mean lengths of neurite was observed in cells exposed to bortezomib.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3-1, 4.2.3.2-4, 4.2.3.2-5, 4.2.3.2-7, and 4.2.3.2-8)

Cynomolgus monkeys (4 animals/group) received a single dose of 1, 2, or 3 mg/kg of carfilzomib intravenously, and their behavior was observed. Decreases in locomotor activity and alertness were noted only in 1 animal that received 3 mg/kg. The applicant explained that these changes may be attributable to circulatory failure due to the effect of carfilzomib on the myocardium [see Section 3.3.2.2].

Cynomolgus monkeys (10 animals/group) received 0.5, 1, or 2 mg/kg of carfilzomib intravenously for 1 month (2 cycles, once daily on Day 1 to Day 5 of each 14-day cycle), and their behavior was observed. Similarly, cynomolgus monkeys (8 to 12 animals/group) received 0.5, 1, or 2 mg/kg of carfilzomib intravenously for 9 months (9 cycles, once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle), and their behavior was studied. No abnormal changes related to carfilzomib were observed in these studies.

Rats (20 to 26 animals/group) received 0.5 to 6 mg/kg of carfilzomib intravenously for 1 month (2 cycles, once daily on Day 1 to Days 5 of each 14-day cycle), and effects on the central nervous system were assessed by a functional observational battery (FOB). Similarly, rats (50 animals/group) received 1 to 4 mg/kg of carfilzomib intravenously for 6 months (6 cycles, once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle), and the animal behavior was studied. No carfilzomib-treatment related effects were observed in these studies.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on human ether-a-go-go-related gene potassium current (CTD 4.2.1.3-2)

The effects of carfilzomib (0.7 to 2.2 μmol/L) on human ether-a-go-go-related gene (hERG) potassium current were studied using hERG transfected human embryonic kidney cell line HEK293. The IC_{50} for carfilzomib was 2.1 μmol/L (1500 ng/mL).[7]

3.3.2.2 Effects on blood pressure, heart rate, and electrocardiograms (CTD 4.2.1.3-1)

Cynomolgus monkeys (4 animals/group) received a single dose of carfilzomib at 1, 2, or 3 mg/kg intravenously, and the effects of carfilzomib on blood pressure, heart rate, and electrocardiograms were studied. An electrocardiogram (ECG) of 1 animal receiving the 3-mg/kg dose showed ST-segment elevation and increased T-wave amplitude along with decreased blood pressure, increased heart rate, and decreases in PR, QRS, and QT intervals. In another animal, blood pressure decreased and the frequency of premature ventricular contractions increased as compared to baseline. The applicant explained that the changes after the 3-mg/kg dose such as decreased blood pressure and ischemic ECG changes are attributable to the effects of carfilzomib on the myocardium.

The discussion on the risk of carfilzomib-induced cardiac disorder is presented with clinical study results in Section "7.R.3.3 Cardiac disorders."

3.3.3 Effects on the respiratory system (CTD 4.2.1.3-1)

Cynomolgus monkeys (4 animals/group) received a single dose of carfilzomib at 1, 2, or 3 mg/kg intravenously, and the effects of carfilzomib on respiratory rate, tidal volume and respiratory minute volume were studied. No carfilzomib-treatment related effects were observed.

3.R Outline of the review conducted by PMDA

Based on the data submitted and the following discussions, PMDA concluded that the efficacy of carfilzomib in the treatment of MM is promising.

3.R.1 Mechanism of action and efficacy of carfilzomib

The applicant's explanation about the mechanism of action:
Carfilzomib binds to 20S proteasome (*Curr Opin Drug Discov Devel*. 2008;11:616-25) and inhibits chymotrypsin-like activity of 20S proteasome, inducing apoptosis of tumor cells [see Section 3.1.2] and thereby inhibiting tumor growth.

Bortezomib inhibits 20S proteasome as with carfilzomib, and carfilzomib may be administered to patients with bortezomib-resistant MM. PMDA asked the applicant to explain the efficacy of carfilzomib in the treatment in such patients.

The applicant's response:
The mechanism to acquire resistance to bortezomib is explained by the mutation in the proteasome β5-subunit (mutation of a cysteine residue [C], the amino acid at position 63, into phenylalanine [F], [mutation C63F]) has been reported (*PLoS One*. 2011;6:e27996). The mutation facilitates dissociation of the binding of bortezomib to the proteasome β5-subunit, resulting in weakened inhibitory effect of chymotrypsin-like activity. In contrast, this mutation is not considered to affect the binding of carfilzomib to the proteasome β5-subunit (*PLoS One*. 2011;6:e27996).

In fact, carfilzomib was shown to have antiproliferative effect against bortezomib-resistant tumor cell lines [see Section 3.1.4.1.3].

Based on the above, carfilzomib is expected to show its efficacy in the treatment of patients with bortezomib-resistant MM.

---

[7] Following administration of carfilzomib at 20/27 mg/m^2 to Japanese patients with relapsed or refractory MM, C_{max} on Day 16 of Cycle 1 was 2300 ng/mL [see Section 6.2.1.1].

PMDA's view:
The applicant's explanation about the efficacy of carfilzomib in the treatment of bortezomib-resistant MM is basically acceptable. However, the molecular mechanism of action of carfilzomib in its antiproliferative activity against bortezomib-resistant MM cell lines remains unclear at this point. A full explanation about this mechanism of action is expected to be of great help in determining patients' eligibility for carfilzomib treatment. Therefore, data collection should be continued to keep healthcare professionals updated appropriately with new knowledge on the drug.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics (PK) of carfilzomib in animals was studied in mice, rats, and monkeys. Studies on plasma protein binding, drug-metabolizing enzymes, and transporters of carfilzomib were performed using human or animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

A single intravenous bolus of carfilzomib 5 mg/kg was administered to female mice to study the plasma concentration of carfilzomib (Table 4). Carfilzomib was rapidly eliminated.

Male rats received a single intravenous bolus of carfilzomib 2, 4.5, 8, or 9 mg/kg, or a single intravenous carfilzomib at 8 mg/kg by 30-minute infusion to study the plasma concentration of carfilzomib (Table 4). The AUC_{inf} of carfilzomib at the doses studied increased in a less than dose-proportional manner. The applicant has not clarified the reasons for these results.

A single intravenous bolus of carfilzomib 1, 2, or 4 mg/kg was administered to male monkeys to study the plasma concentration of carfilzomib (Table 4). The C_{max} and AUC_{inf} of carfilzomib at the doses studied show dose proportionality.

Table 4. Pharmacokinetic parameters of carfilzomib (a single intravenous dose was administered to all animal species)

Animal species	Dose (mg/kg)	Sex	N	C_{max} (ng/mL)	t_{max} (min)	AUC_{inf} (ng·min/mL)	$t_{1/2}$ (min)	CL (mL/min/kg)	V_{ss} (L/kg)
Mouse[*1]	5	F	3[*2]	7490	–	53,000	19	94	0.39
Rat[*3]	2	M	3	706 ± 321	2 ± 0	5479 ± 2449	11.8 ± 1.2	439 ± 171	1.54 ± 0.983
	4.5	M	3	1301 ± 76	2 ± 0	9573 ± 495	12.5 ± 0.6	471 ± 25	2.13 ± 0.095
	9	M	3	1824 ± 217	2 ± 0	14,060 ± 1891	23.3 ± 2.0	652 ± 86	3.70 ± 0.432
Rat[*3]	8	M	4	1120 ± 60	2 ± 0	9000 ± 580	6 ± 4	890 ± 56	4.0 ± 0.68
	8[*4]	M	3	1120 ± 270	25 ± 9	25,800 ± 5200	10 ± 6	319 ± 66	2.0 ± 0.5
Monkey	1	M	3	789 ± 421	–	5335 ± 2637	6.9 ± 0.7	234 ± 97	0.91 ± 0.62
	2	M	3	1350 ± 792	–	12,657 ± 8214	7.5 ± 0	286 ± 296	1.06 ± 1.56
	4	M	3	2235 ± 725	–	22,039 ± 4261	7.2 ± 0.3	187 ± 39	0.26 ± 0.14

Mean ± standard deviation
[*1] PK parameters were calculated based on the mean carfilzomib plasma concentration at each measuring time point; [*2] the number of animals for the measuring time point; [*3] between these groups, the quantification method and blood sampling time points for plasma carfilzomib concentration are different. [*4] a 30-minute intravenous infusion; –, not calculated.

4.1.2 Repeated dose studies

Intravenous boluses of carfilzomib were administered to male and female rats at 1, 2, or 4 mg/kg for 6 cycles, once daily on Days 1, 2, 8, 9, 15, and 16, of each 28-day cycle to study the plasma concentrations of carfilzomib and its metabolites (M15, a hydrolyzed product; M14, a hydrolyzed product of M15; and M16, a diol) (Table 5).

While C_{max} and AUC_{last} of carfilzomib at the doses studied indicated dose proportionality, the values in male rats increased in a more than dose-proportional manner on Day 57 and in a less than dose-proportional manner on Day 142. The applicant explains that the reason for the inconsistent trend in linearity on different treatment days is not known. No clear sex difference was observed in C_{max} and AUC_{last} of carfilzomib at any doses. The metabolites, i.e., M14, M15, and M16, were produced immediately after the intravenous administration of carfilzomib, and the t_{max} was 5 to 15 minutes.

Table 5. Pharmacokinetic parameters of carfilzomib (6-month repeated intravenous administration to male and female rats)

Measured date (Day)	Dose (mg/kg)	Sex	C_{max} (ng/mL)	AUC_{last} (ng·min/mL)	$t_{1/2}$ (min)	CL (mL/min/kg)	V_{ss} (L/kg)
1	1	M	146	2637	11	378	1.57
		F	128	2311	8	427	1.51
	2	M	341	6360	10	314	1.24
		F	278	5178	12	384	1.57
	4	M	809	14,728	13	270	1.12
		F	721	13,599	12	293	1.09
57	1	M	173	2980	12	333	1.82
		F	212	4211	13	236	0.84
	2	M	678	13,350	11	150	0.46
		F	471	9230	12	216	0.74
	4	M	1169	22,277	12	179	0.65
		F	981	17,041	31	230	1.4
142	1	M	258	4741	13	210	0.92
		F	204	4027	13	247	0.88
	2	M	519	10,215	12	195	0.67
		F	466	9281	12	215	0.72
	4	M	729	12,262	12	323	2.11
		F	636	11,318	13	350	1.75

Mean, N = 2 to 4 animals/measuring time point (PK parameters were calculated based on the mean plasma carfilzomib concentrations at each measuring time point.)

Intravenous boluses of carfilzomib were administered to male monkeys at 0.5, 1, or 2 mg/kg for 9 cycles, once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, to study the plasma concentrations of carfilzomib and its metabolites (M14, M15, and M16) (Table 6).

Because AUC_{last} of carfilzomib was similar on Days 1 and 225, the applicant does not consider that carfilzomib accumulates. The C_{max} and AUC_{last} of carfilzomib at the doses studied increased in a less than dose-proportional manner. The applicant explained that the reason for the results is not clear. No clear difference was observed between the sexes in C_{max} and AUC_{last} of carfilzomib at any dose. The metabolites, i.e., M14, M15, and M16, were produced immediately after the intravenous administration of carfilzomib, and the t_{max} was 5 to 19 minutes.

Table 6. Pharmacokinetic parameters of carfilzomib
(9-month repeated intravenous administration to male and female monkeys)

Measured date (Day)	Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	AUC_{last} (ng·min/mL)	$t_{1/2}$ (min)	CL (mL/min/kg)	V_{ss} (L/kg)
1	0.5	M	4	41.2 ± 5.0	785 ± 90	11 ± 1	632 ± 79	7.4 ± 0.9
		F	4	45.7 ± 5.3	890 ± 74	12 ± 2	551 ± 44	6.7 ± 1.0
	1	M	4	62.3 ± 8.4	1163 ± 134	12 ± 0	851 ± 93	9.8 ± 1.6
		F	4	51.6 ± 5.6	1047 ± 41	13 ± 1	933 ± 37	12.0 ± 0.7
	2	M	6	103 ± 37	1934 ± 555	12 ± 1	1085 ± 317	12.2 ± 4.0
		F	6	86.9 ± 24.1	1692 ± 380	14 ± 2	1181 ± 230	16.7 ± 4.9
57	0.5	M	4	41.4 ± 5.9	779 ± 89	11 ± 1	637 ± 74	7.3 ± 1.5
		F	4	48.5 ± 4.2	918 ± 69	11 ± 1	534 ± 42	6.3 ± 0.6
	1	M	4	58.9 ± 9.6	1122 ± 183	12 ± 0	889 ± 133	10.7 ± 1.8
		F	4	52.3 ± 7.8	1009 ± 123	12 ± 1	979 ± 121	12.3 ± 2.4
	2	M	6	87.1 ± 15.4	1581 ± 245	13 ± 1	1242 ± 239	14.8 ± 3.0
		F	6	107 ± 34	2015 ± 515	15 ± 3	1010 ± 234	12.9 ± 5.0
141	0.5	M	4	41.1 ± 7.3	830 ± 153	12 ± 0	603 ± 98	7.6 ± 1.2
		F	4	46.8 ± 7.2	942 ± 136	13 ± 2	522 ± 77	7.1 ± 1.1
	1	M	4	61.4 ± 8.7	1241 ± 129	13 ± 1	789 ± 85	10.2 ± 1.7
		F	4	60.9 ± 14.2	1236 ± 132	14 ± 2	786 ± 73	10.8 ± 2.8
	2	M	6	76.7 ± 22.7	1572 ± 323	15 ± 1	1268 ± 295	18.0 ± 3.8
		F	5	81.6 ± 29.3	1741 ± 376	15 ± 2	1135 ± 239	17.7 ± 4.7
225	0.5	M	4	43.1 ± 4.6	804 ± 99	11 ± 0	616 ± 70	6.9 ± 0.6
		F	4	47.5 ± 9.4	886 ± 148	11 ± 1	566 ± 96	6.5 ± 1.5
	1	M	4	66.8 ± 12.2	1237 ± 199	14 ± 1	801 ± 128	9.6 ± 2.2
		F	4	69.1 ± 8.6	1449 ± 453	12 ± 1	716 ± 181	8.7 ± 1.3
	2	M	5	85.0 ± 7.1	1624 ± 180	15 ± 1	1192 ± 131	16.2 ± 1.8
		F	5	114 ± 26	2129 ± 414	14 ± 2	935 ± 177	12.0 ± 3.4

Mean ± standard deviation

4.2 Distribution

4.2.1 Tissue distribution

A single intravenous bolus injection of ^{3}H-labeled carfilzomib 2 mg/kg was administered to male albino rats to study the tissue distribution of radioactivity by quantitative whole-body autoradiography. Radioactivity was distributed in all tissues studied[8] at higher concentrations in the tissue sites except for the brain and the spinal cord than in plasma. Radioactivity reached their maximum levels within 24 hours following administration in tissue sites. At 30 minutes after administration, radioactivity levels were high in the pancreas, bladder, and gastric mucosa and were 15.8, 12.2, and 10.7 μg Eq/g, respectively. At 24 hours after administration, radioactivity levels in the pituitary gland, bone marrow,

[8] The brain, spinal cord, eye, intraorbital lacrimal gland, exorbital lacrimal gland, Harderian gland, nasal concha, salivary gland, thyroid, thymus, myocardium, lung, diaphragm, liver, kidney, renal cortex, renal medulla, adrenal gland, spleen, pancreas, fat, muscles, bone, bone marrow, periosteum, skin, lymph node, testis, seminal vesicle, epididymis, preputial gland, prostate, bladder, oesophagus, stomach, gastric mucosa, small intestine, cecum, and colon. (Radioactivity levels at 168 hours after administration in the pineal body and intraorbital lacrimal gland were not studied.)

thyroid, and lung were as high as 7.82, 7.79, 7.40, and 7.35 µg Eq/g, respectively. At 168 hours after administration, radioactivity levels were 0.410 to 3.51 µg Eq/g in all tissue sites except cerebrospinal fluid, abdominal fat, and bone, and the radioactivity levels in these sites were lower than the lower limit of quantitation (0.351 µg Eq/g).

4.2.2 Plasma protein binding and transfer to blood cells

Carfilzomib (0.4 or 4 µmol/L) was incubated with rat, monkey, or human plasma at 37°C for 6 hours, and binding of carfilzomib with plasma proteins was studied using equilibrium dialysis. Binding rates of carfilzomib 0.4 and 4 µmol/L to plasma proteins were 97.6% and 96.6% in rats, 94.4% and 94.4% in monkeys, and 97.3% and 96.9% in humans, respectively, which were generally consistent in each animal species regardless of carfilzomib concentration. When carfilzomib (0.4 to 10 µmol/L) was incubated with human serum albumin (45 mg/mL) or human α1-acid glycoprotein (1 mg/mL) at 37°C for 6 hours, binding rates of carfilzomib to human serum albumin and human α1-acid glycoprotein were 90.64% to 94.59% and 40.42% to 48.21%, respectively. The binding ratio of carfilzomib to human plasma was similar to that to human serum albumin. The applicant explained that the results suggested albumin as the main binding component of carfilzomib in human plasma.

Carfilzomib (0.4 to 10 µmol/L) was incubated with rat, monkey, or human plasma at 37°C for 45 minutes to study transfer of carfilzomib to blood cells. The blood-to-plasma carfilzomib concentration ratios were 0.861 to 1.01 in rats, 0.622 to 0.857 in monkeys, and 0.408 to 0.621 in humans, showing overall consistency in each animal species regardless of carfilzomib concentration:.

4.2.3 Transfer through the placenta to fetus

There are no reports on carfilzomib concentrations in fetal blood following administration of carfilzomib to pregnant dams.

4.3 Metabolism

4.3.1 *In vitro*

Carfilzomib (1 µg/mL) was incubated with rat blood or tissue homogenates of rat liver, lung, or kidney at 37°C for 90 minutes, and the peak area ratio of each metabolite to the internal standard substance (PR-054591, 1 µmol/L) was calculated to examine the relative amounts of the carfilzomib metabolites (M14, M15, and M16) in each sample. The mean peak area ratios of M14, M15 and M16 at 2 to 90 minutes after administration in blood were 0.143% to 44.7%, 0.168% to 20.8%, and 0.0716% to 0.0917%, respectively, in liver homogenate, 8.83% to 98.2%, 3.19% to 15.6%, and 0.323% to 1.42%, respectively, in lung homogenate, 5.08% to 163%, 3.95% to 18.4%, and 0.0786% to 0.224%, respectively, and in kidney homogenate, 26.4% to 123%, 37.1% to 64.6%, and 0.0608% to 0.192%, respectively.

Carfilzomib (1 µmol/L) was incubated in mouse, rat, monkey, and human liver microsomes or liver cytosols at 37°C for 90 minutes to evaluate CL_{int} of carfilzomib. The analysis using liver microsomes was performed with or without nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and CL_{int} was calculated based on the elimination rate of carfilzomib observed in each animal species. The results showed that the CL_{int} values of carfilzomib in mouse, rat, monkey, and human liver microsome were 989, 499, 138, and 302 µL/min/mg, respectively, with NADPH, and 0.70, 5.6, 69, and 14 µL/min/mg, respectively, without NADPH. According to the applicant, the results suggest that the metabolism of carfilzomib in liver microsomes is primarily mediated by CYP. The CL_{int} values of carfilzomib in mouse, rat, monkey, and human liver cytosols were 0.68, 3.7, 5.3, and 4.0 µL/min/mg, respectively.

The quantity of metabolites of carfilzomib (percentage to radioactivity administered) was studied by incubating ^{3}H-carfilzomib (3 µmol/L) with rat, monkey, and human hepatocytes at 37°C for 2 hours. The metabolites detected in rat, monkey, and human hepatocytes were M16 (6.30%, 4.11%, and 35.02%,

respectively), M1 (tyrosine[9]; 6.65%, 1.52%, and 1.96%, respectively), M2 (phenylalanine[9]; 10.00%, 10.96%, and 15.73%, respectively), M3 (undetermined structure; 6.94%, 2.37%, and 4.82%, respectively), M4 (undetermined structure[9]; 23.79%, 6.79%, and 18.29%, respectively), and M6 (diol of carfilzomib with unsaturated morpholino ring; 1.12%, 0%, and 5.05%, respectively). The applicant explained that M14 and M15 were not detected in this study because ^{3}H-label could not be attached to these metabolites.

Human hepatocytes and carfilzomib (1 µmol/L) were incubated in the presence or absence of inhibitors of CYP isozymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) at 37°C for 2 hours to investigate CYP isozymes involved in the metabolism of carfilzomib. These inhibitors did not show clear effect on carfilzomib metabolism. Further, human hepatocytes and carfilzomib (10 µmol/L) were incubated at 37°C for 2 hours to study the proposed structures of carfilzomib metabolites, and M5, M7, M11, M14, M15, and M16 were detected. Because CYP isozymes made little contribution to carfilzomib metabolism and products of peptide bond hydrolysis and epoxide hydrolysis were detected as carfilzomib metabolites, the applicant considers that carfilzomib is mainly metabolized by peptidase and epoxide hydrolase.

4.3.2 *In vivo*

Male and female rats were given intravenous bolus injections of carfilzomib 1, 2, or 4 mg/kg once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, and the peak area ratio of each metabolite to carfilzomib in plasma was studied. The predominant metabolites detected in plasma up to 1 hour post-dose were M14 (7.0% to 49.7%) and M16 (<0.1% to 18.7%) at all doses.

Bile-duct cannulated male rats were given a single intravenous bolus injections of carfilzomib 2 mg/kg, and the peak area ratio of each metabolite to carfilzomib in urine and bile was studied. The predominant metabolites detected in 0 to 4 hours post-dose and 4 to 8 hours post-dose were M14 (1328.9% and 1348.3%, respectively) in urine, and M14 (1327.1% and 113.4%, respectively) and M16 (1008.7% and 8.95%, respectively) in bile.

Male and female monkeys were given intravenous bolus injections of carfilzomib at 0.5, 1, or 2 mg/kg once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, and the peak area ratio of each metabolite to carfilzomib in plasma was studied. The predominant metabolites detected in plasma up to 1 hour post-dose were M14 (22.3% to 78.9%) and M16 (2.3% to 119.1%) at all doses.

4.4 Excretion

4.4.1 Urinary, biliary, fecal, and expiratory excretion

Based on the examination results shown below, the applicant explained that metabolized carfilzomib is excreted in urine, feces, and expired air.

- Male rats received a single intravenous bolus injection of ^{3}H-labelled carfilzomib 2 mg/kg, and recovery rates of radioactivity in urine, feces, and expired air was studied. The recovery rates of radioactivity in urine, feces, and expired air (percentage to the dose administered) up to 168 hours post dose were 12.0%, 16.7%, and 4.69%, respectively, and 51.2% of the administered radioactivity remained in the carcass. According to the applicant, this was explained by the amino acid detected as a carfilzomib metabolite [see Section 4.3.1], which was ^{3}H-labeled, used for protein synthesis, and taken into tissues.

- Bile-duct cannulated male rats received a single intravenous bolus injection of carfilzomib at 2 mg/kg, and the excretion rate of carfilzomib and its metabolites (M14, M15, and M16) in bile and urine was studied. The excretion rates of carfilzomib (percentage to the dose administered) in bile up to 8 hours and in urine up to 24 hours post dose were all <1%. The excretion rates of M14, M15, and M16 in bile up to 8 hours post dose were 13.1%, 14.7%, and 2.65%, respectively, and those in

[9] The metabolites M1, M2, and M4 detected in the study with rat, monkey, and human hepatocytes were determined to be identical to M5, M7, and M11, respectively, in the study with human hepatocytes.

urine up to 24 hours post dose were 25.7%, 0.236%, and 0.164%, respectively. Therefore, the excretion rates for the total of carfilzomib and its metabolites were 30.5% in bile and 26.2% in urine.

Following intravenous administration of carfilzomib to rats, the plasma concentrations of carfilzomib and its metabolites did not show a multiple peak pattern suggestive of enterohepatic circulation. The applicant therefore considers that enterohepatic circulation has little contribution to the pharmacokinetics of carfilzomib.

4.4.2 Excretion in breast milk

Excretion of carfilzomib in breast milk was not evaluated. According to the applicant, there is a possibility that carfilzomib is transferred to breast milk, given that weakly basic lipophilic compounds are readily transferred to breast milk (*Jpn J Pediatr Med*. 1993;25:52-7), and that carfilzomib has physicochemical properties characterized by pKa and log *P* being 5.14 and 3.77, respectively.

4.5 Pharmacokinetic drug interactions

4.5.1 Inhibition of enzymes

In the presence of carfilzomib (0.01 to 10 µmol/L), substrates for CYP isozymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) were incubated with human liver microsomes to study the inhibitory effect of carfilzomib on the CYP isozymes. While carfilzomib inhibited metabolism of the substrate of CYP3A (midazolam) with a K_i of 1.7 µmol/L (IC_{50} of 1.6 µmol/L), inhibitory effects on other CYP substrates were not evident. Further, carfilzomib inhibited CYP3A in a time-dependent manner (K_i values and k_{inact} values of carfilzomib are 11 µmol/L and 0.09 min^{-1}, respectively, against testosterone; and 11 µmol/L and 0.10 min^{-1}, respectively, against midazolam). However, the inhibition against other CYP substrates was not observed in a time-dependent manner.

4.5.2 Enzyme induction

Human hepatocytes were treated with carfilzomib (0.1 to 2.5 µmol/L) for 3 days, and the enzyme activities of CYP1A2 and CYP3A were studied. Carfilzomib did not clearly induced enzyme activities of these CYP substrates.

4.5.3 Transporters

P-glycoprotein (P-gp)-mediated transport of carfilzomib (0.1 µmol/L) was studied using the human colon cancer cell line Caco-2. The apparent permeability ratios of the basolateral-to-apical direction to the apical-to-basolateral directions (apparent permeability in basolateral to apical direction [$P_{app\ B\rightarrow A}$]/apparent permeability in apical to basolateral direction [$P_{app\ A\rightarrow B}$]) in the presence of P-gp inhibitors, cyclosporin A (10 µmol/L) and ketoconazole (10 µmol/L), were 1.4 and 3.8, respectively, and those in the absence of P-gp inhibitors were 12.5 and 28.6, respectively. These results show that carfilzomib is a P-gp substrate. However, P-gp is expressed in the digestive tract and thus is less likely to affect the pharmacokinetics of carfilzomib administered intravenously. The applicant therefore considers the possibility is low that the co-administration of carfilzomib and P-gp inhibitors causes pharmacokinetic interactions.

Breast cancer resistance protein (BCRP)-mediated transport of carfilzomib (1 µmol/L) was studied using Caco-2 cells and the CPT-B1 cell line (a type of Caco-2 cell line with repressed BCRP expression). The results showed that apparent permeability ratios of carfilzomib in Caco-2 and CPT-B1 cell lines were 8.84 and 31.3, respectively. The ratio of these permeability ratios (Caco-2 to CPT-B1) was <2, indicating that carfilzomib is not a substrate of BCRP.

The inhibitory effect of carfilzomib (3 µmol/L) on P-gp-mediated transport of digoxin (10 µmol/L) was studied using the Caco-2 cell line. The inhibitory effect of carfilzomib (3 µmol/L) on BCRP-mediated transport of cladribine (10 µmol/L) was also studied using the CPT-P1 cell line (a type of Caco-2 cell line with repressed P-gp expression). According to the applicant, carfilzomib inhibited transport of digoxin and cladribine by 25% and 22.9%, respectively, and the IC_{50} was not achieved at the concentration of carfilzomib studied.

4.R Outline of the review conducted by PMDA
Based on the data submitted, PMDA concluded that the discussions of the applicant regarding the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of carfilzomib are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

In *in vivo* studies, unless otherwise specified, carfilzomib was administered using 10 w/v% SBECD in 10-mmol/L citric acid solution, pH 3.5, as a solvent.

5.1 Single-dose toxicity

5.1.1 Single intravenous dose toxicity studies in rats (reference data)

Data of 3 single intravenous dose toxicity studies in rats were submitted.

In 2 studies, male SD rats (n = 3 to 15/group) received a single intravenous bolus of carfilzomib 0 (solvent as control, 10-mmol/L citric acid solution containing 10 w/v% SBECD or 5 w/v% HPBCD solution), 0.5, 1, 1.5, 2, 3, 4.5, 7, 9, 10, 15, or 25 mg/kg. Some animals died following a dose of ≥9 mg/kg. Decreased platelet count was observed at ≥3 mg/kg; lethargy, piloerection, and increased reticulocyte count at ≥4.5 mg/kg; decreased inorganic phosphorus levels at ≥7 mg/kg; body weight decreased at ≥9 mg/kg; dyspnoea and ruffled fur at ≥10 mg/kg.

Based on the results, the approximate lethal dose was determined to be 9 mg/kg.

A study was conducted for the comparison of acute toxicity of carfilzomib between intravenous bolus injection and continuous intravenous infusion, and to evaluate the toxicity associated with continuous intravenous infusion. Male SD rats (8 to 32 animals/group) received a single intravenous dose of carfilzomib 0 or 8 mg/kg as a bolus injection or a continuous infusion over 10 or 30 minutes. Also, male SD rats (6 animals/group) received a single intravenous dose of carfilzomib 10 or 12 mg/kg over 30 minutes.

Deaths occurred in 14 of 32 animals in the bolus group and 1 of 8 animals in the 10-minute infusion group. No animals died in the 30-minute infusion group. The following changes were noted in animals receiving a bolus injection: ruffled fur; auricular pallor; dyspnoea; lethargy; decreased platelet count; increases in neutrophil count, blood urea nitrogen (BUN), creatinine, and alanine aminotransferase (ALT); enlarged stomach and impacted stomach contents; pale liver; and congestion in the adrenal gland, intestinal tract, kidney, and lung. These changes tended to be alleviated in the animals receiving 10-minute or 30-minute infusion. The C_{max} was higher in the bolus group than in the 30-minute infusion group by approximately 28-fold. In contrast, AUC_{last} values were similar between the bolus and 30-minute infusion groups. The applicant explained that C_{max} is a contributory factor of the carfilzomib-associated acute toxicity.

Deaths occurred in 1 of 6 animals at 10 mg/kg and 4 of 6 animals at 12 mg/kg.

Based on the results, the approximate lethal dose was determined to be 8 mg/kg for intravenous bolus injection, and 10 mg/kg for intravenous infusion over 30 minutes.

5.1.2 Single intravenous dose toxicity studies in monkeys (reference data)

Male cynomolgus monkeys (2 to 3 animals/group) received intravenous bolus injections of carfilzomib 0 (solvent as control, 50-mmol/L sodium citrate solution containing 5 w/v% HPBCD, pH 3.35), 1, 1.16, 2, or 4 mg/kg.

One of 3 animals receiving 4 mg/kg died. The following changes were noted in the animal that died: hunched posture; vomiting; pericardial effusion; eosinophilic degeneration in cardiomyocytes and pyknosis, which are considered to be degenerative changes in the myocardium; congestion of the liver

and kidneys; discoloration of the gastrointestinal mucosa; haemorrhage and necrosis in the gastric mucosa; and necrosis of submucosal lymphatic tissue in the colon.

Based on the results, the approximate lethal dose was determined to be 4 mg/kg.

5.2 Repeat-dose toxicity

5.2.1 One-month repeated intravenous dose toxicity study in rats

Male and female SD rats (10 to 13 animals of each sex per group) received bolus intravenous injections of carfilzomib 0 (solvent as control), 0.5, 1, 2, 4, or 6 mg/kg once daily. One treatment cycle consisted of 14 days. Animals were treated on Days 1 to 5 in each cycle, and some animals had a 2-week recovery period was provided after Cycle 2.

Deaths occurred in 1 of 20 animals at 1 mg/kg, 1 of 26 animals at 2 mg/kg, 3 of 26 animals at 4 mg/kg, and 2 of 26 animals at 6 mg/kg. The following changes were noted in the animals that died: pale discoloration of the heart; reddening of the lung; pericardial and pleural effusions; pericardial thickening; congestion, haemorrhage, necrosis, and mineralization in the epicardium and myocardium; and haemorrhage and interstitial inflammation of the lung. The causes of death were determined to be cardiomyopathy and interstitial inflammation of the lung.

The following changes were noted during treatment and after Cycle 2:
At ≥1 mg/kg
Reddening and interstitial inflammation of the lung and increased megakaryocyte count in the bone marrow

At ≥2 mg/kg
Decreased platelet count; increased total cholesterol levels; decreased alkaline phosphatase (ALP), aspartate aminotransferase (AST), and ALT levels; and decreased cell density in the splenic marginal zone

At ≥4 mg/kg
Decreases in food intake, body weight, fecal amount, and locomotor activity; soiled perineal region; increased respiration rate; decreased red blood cell count, Hb levels, hematocrit (HCT) levels, mean corpuscular hemoglobin concentration (MCHC), and eosinophil count; increased mean corpuscular volume (MCV), red cell distribution width, fibrinogen, and BUN; decreased thymus weight; increased liver weight; fibrotic change of the heart; cardiomyopathy; increased cardiac valve cell density; haemorrhage of the lung; enlargement of perilobular hepatocytes; increased number of hepatocyte division observed; increased extramedullary haematopoiesis in the spleen; thymic lymphocyte depletion; ulcer in the glandular stomach; epithelial hyperplasia in the small and large intestines; and increased apoptosis and acinar cell atrophy in the pancreas

At 6 mg/kg
Increases in monocyte count, triglyceride, and AST; decreases in albumin and globulin; reddening of the heart; reddening of the stomach; swelling of the liver and spleen; pleural effusion; atrophy and thinning of the myocardium; apoptosis of the hepatocytes; mucosal necrosis, haemorrhage, regenerative epithelial hyperplasia, inflammatory cell infiltration, and gland enlargement of the glandular stomach; and haemorrhage in the colon.

The applicant explained that the pancreatic toxicity may have been due to acinar cell atrophy, single cell necrosis, and apoptosis, which occur in rats or mice spontaneously or in a fasted or starved state (*Virchows Arch B Cell Pathol*. 1974;15:107-18), intensified by continuously decreased food consumption after the administration of carfilzomib.

After the 2-week recovery period, all changes had resolved or were resolving.

Based on the results, the NOAEL for the study was determined to be 0.5 mg/kg.

5.2.2 Six-month repeated intravenous dose toxicity study in rats

Male and female SD rats (25 animals of each sex per group) received intravenous bolus injections of carfilzomib 0 (solvent as control), 1, 2, or 4 mg/kg once daily. Each cycle consisted of 28 days. Animals were treated on Days 1, 2, 8, 9, 15, and 16 in each cycle, and some animals had an 8-week recovery period after Cycle 6.

Three of 50 animals in the 2 mg/kg group and 16 of 50 animals in the 4 mg/kg group died or were sacrificed moribund. The following were noted in the animals that died or were sacrificed moribund:

At ≥2 mg/kg
Decreases in locomotor activity and fecal amount, soiled perineal region, hunched posture, lethargy, labored breathing, swelling and pale discoloration of the kidney, glomerulonephropathy, and fibrotic change of the heart

At 4 mg/kg
Reddening of the gastrointestinal tract; jaundice of adipose tissue; congestion and haemorrhage in the heart; degeneration and necrosis of the myocardium; thrombosis in the kidney; haemorrhage, congestion, necrosis, erosion, and ulcer in the gastrointestinal tract; and acute tubular necrosis and centrilobular hepatocyte necrosis, which are considered to be secondary changes resulting from ischaemia

The causes of death were fibrotic change, congestion, and haemorrhage in the heart; degeneration and necrosis of the myocardium; tubular necrosis; glomerulonephropathy; and haemorrhage and congestion of the gastrointestinal tract.

The following changes were noted during treatment and after Cycle 6:

At ≥1 mg/kg
Decreased body weight and food intake; decreased body weight gain; increases in Hb levels, HCT levels, MCV, neutrophil count, monocyte count, total cholesterol levels, and fibrinogen levels; decreases in MCHC, platelet count, AST, and ALT levels; increased liver weight; decreased pituitary gland weight; chronic progressive nephropathy; decreased cell density in the splenic marginal zone; increased number of mast cells in lymph nodes; and increased bone marrow cell density in the femur

At ≥2 mg/kg
Hunched posture, piloerection, increased reticulocyte count, decreased albumin, increased splenic weight, degeneration and necrosis of the myocardium, and perilobular hepatocyte enlargement and vacuolation

At 4 mg/kg
Decreases in fecal amount and locomotor activity; soiled perineal region; chromodacryorrhea; emaciation; irregular gait; lethargy; decreased red blood cell count, total protein, globulin, and potassium; increased triglyceride, BUN, inorganic phosphorus, creatinine, and ALP; increases in heart weight, kidney weight, adrenal gland weight, and ovary weight; decreased uterus weight; swelling and pale discoloration of the kidney; swelling of the heart and liver; myocardial hypertrophy; glomerulonephropathy; and hemosiderin deposition in Kupffer cells

The following additional changes were noted after the 8-week recovery period: proteinuria and granular cast associated with chronic progressive nephropathy; increases in red blood cell count, total bilirubin, AST, and ALT; and decreased reticulocyte count. All the changes observed following treatment had resolved or were resolving, except increased Hb and HCT levels and perilobular hepatocyte enlargement. Based on the above, the NOAEL for the study was determined to be <1 mg/kg. The

maximum tolerated dose (MTD) was determined to be 1 mg/kg. The AUC_{last} for the 1 mg/kg group (4384 ng·min/mL) is 0.17 times that of the clinical exposure level.[10]

5.2.3 Seven-day repeated intravenous dose toxicity study in monkeys

Male cynomolgus monkeys (6 animals/group) received intravenous bolus injections of carfilzomib at 0 (solvent as control) or 2 mg/kg for 2 consecutive days. After a 5-day washout period, the animals were necropsied.

The following changes were noted:
Day 1: scratching both limbs and continuous motion
Day 2: tremor; decreased locomotor activity; decreases in platelet count, albumin, total protein, albumin-to-globulin ratio, and calcium; increases in neutrophil count, monocyte count, fibrinogen levels, C-reactive protein, BUN, and creatinine; and increased urine specific gravity
Day 3: increased troponin I and decreased inorganic phosphorus
Day 4: decreases in red blood cell count, reticulocyte count, Hb levels, and HCT levels.
By Day 7, all hematological and biochemical changes had returned to normal except increased monocyte count. Also, on Day 7, additional findings were noted: degeneration and congestion of the myocardium, and monocyte infiltration and increased mesangial matrix in the kidney.

Based on the above, the NOAEL for the study was determined to be <2 mg/kg.

5.2.4 One-month repeated intravenous dose toxicity study in monkeys

Male and female cynomolgus monkeys (5 animals of each sex per group) received intravenous bolus injections of carfilzomib 0 (solvent as control), 0.5, 1, or 2 mg/kg (mg/mL) once daily. One treatment cycle consisted of 14 days. Animals were treated on Day 1 through Day 5 of Cycles 1 and 2. A total of 3 animals of each sex per group were necropsied after the final dose in Cycle 2, and 2 animals of each sex per group after the end of Cycle 2. In the 2 mg/kg group, 6 of 10 animals died or were sacrificed moribund, and the animals in this group were treated only in Cycle 1 and necropsied on Day 29.

The following changes were noted in the animals that died or were sacrificed moribund in the 2 mg/kg group: dyspnoea; decreases in locomotor activity and fecal amount; hunched posture; red nasal discharge; decreases in red blood cell count, Hb levels, HCT levels, albumin, and globulin; increases in monocyte count and fibrinogen levels; extension of activated partial thromboplastin time; hydropericardium and thickening of pericardium; pericardial and pleural effusion; reddening of the heart and lung; frothy fluid retention in the trachea; acute inflammation, haemorrhage, necrosis, and oedema in the myocardium; and inflammatory cell infiltration, alveolar haemorrhage, necrosis, and oedema in the lung. The causes of death were haemorrhage and oedema in the lung and inflammation and haemorrhage in the heart.

The following changes were noted after the final dose in Cycle 2 in animals treated at ≥1 mg/kg: decreases in platelet count, reticulocyte count, total protein, and globulin; increased BUN and total bilirubin; increased lung weight; decreased thymic weight; whitening of the heart; enlargement of the myocardium; subepicardial inflammatory cell infiltration; inflammatory cell infiltration in the lung; alveolar haemorrhage; fibrin deposition and oedema; pleural oedema; increased megakaryocytes in the sternum bone marrow; perivascular tissue necrosis, oedema, fibrosis, and inflammatory cell infiltration in administration site, and inflammatory cell infiltration in the vein. Additional changes noted after the completion of Cycle 2 were enlargement of the myocardium and increased cell density at ≥1 mg/kg and fibrotic change of the myocardium at 2 mg/kg.

Based on the above, the NOAEL for the study was determined to be 0.5 mg/kg and the MTD 1 mg/kg.

---

[10] Following an intravenous infusion of carfilzomib 20/27 mg/m^2 over 10 minutes to Japanese patients with relapsed or refractory MM on Day 16 of Cycle 1, AUC_{last} was 26,160 ng·min/mL (Study 01).

5.2.5 Nine-month repeated intravenous dose toxicity study in monkeys

Cynomolgus monkeys (4 to 6 animals of each sex per group) received intravenous bolus injections of carfilzomib at 0 (solvent as control), 0.5, 1, or 2 mg/kg (mg/mL) once daily. One treatment cycle consisted 28 days. Animals were treated on Days 1, 2, 8, 9, 15, and 16 of each cycle, and some animals had an 8-week recovery period after the completion of Cycle 9.

A total of in 2 of 12 animals at 2 mg/kg died or were sacrificed moribund. The following changes were noted in the 2 dead animals: decreased body weight, lying on the side, pallor, subcutaneous oedema, decreased albumin, increased ALT and ALP, red spots in the lung, pale discoloration of the kidney and liver, swelling of the kidney, enlargement and degeneration of the myocardium, inflammatory cell infiltration in the heart, interstitial inflammation of the lung, alveolar oedema, interstitial inflammation and fibrotic change of the kidney, tubular atrophy or dilation, thinning of renal tubular wall, increased cell density, glomerulonephropathy, multiorgan atrophy, and diffuse glycogen degeneration of hepatocytes. The causes of death were cardiac inflammation, pulmonary inflammation and oedema, and multi-organ toxicity including renal impairment.

The following changes were noted during treatment or after the final dose in Cycle 9:

At ≥0.5 mg/kg
Decreased red blood cell count; haematuria; interstitial inflammation and fibrotic change of the kidney; erythrocyte cast; tubular atrophy or dilation; thinning of renal tubular wall; increased cell density; glomerulonephropathy; degeneration and inflammatory cell infiltration of the myocardium; and increased bone marrow cell density in the femur

At ≥1 mg/kg
Vomiting; hunched posture; decreased locomotor activity; increases in reticulocyte count; neutrophil count, monocyte count; fibrinogen levels, and potassium levels; decreases in total protein, albumin, and total cholesterol levels; proteinuria; increases in kidney weight, splenic weight, and heart weight; swelling, pale discoloration, and red lesions of the kidney; interstitial inflammation of the lung; and inflammatory cell infiltration; oedema; and perivascular tissue haemorrhage in administration site

At 2 mg/kg
Decreased food intake; emaciation; increased R-wave amplitudes of the ECG in Cycle 3 onward; decreases in Hb, HCT, inorganic phosphorus, and calcium; increases in liver weight and adrenal gland weight; enlargement of the myocardium; intramedullary granulocytes and granulopoiesis in mediastinal lymph nodes; and administration site necrosis.

After the 8-week recovery period, the above changes resolved except decreased albumin, proteinuria, haematuria, and swelling and pale discoloration of the kidney.

Based on the above, the NOAEL for the study was determined to be <0.5 mg/kg, and the MTD 1 mg/kg. The AUC_{last} in the 0.5 mg/kg group (845 ng·min/mL) is 0.03 times that of the clinical exposure level.[11]

5.2.6 Three-week repeated intravenous dose-finding study in rats (reference data, non-GLP study)

Male SD rats (4 animals/group) received intravenous bolus injection of carfilzomib 0 (solvent as control, 50-nmol/L sodium citrate solution containing 10 w/v% HPBCD), 2, 4, or 6 mg/kg once daily. One treatment cycle consisted of 7 days. Animals were treated on Days 1 to 5 in each cycle.

Changes noted:
At ≥2 mg/kg
Pancreatic acinar cell necrosis

[11] Following an intravenous infusion of carfilzomib 20/27 mg/m^2 over 10 minutes to Japanese patients with relapsed or refractory MM on Day 16 of Cycle 1, AUC_{last} was 26,160 ng·min/mL (Study 01).

At ≥4 mg/kg
Inflammation accompanied by adipocyte degeneration of mesenteric fat and fatty marrow

At 6 mg/kg
Inflammation of fatty marrow accompanied by fibrin clots within blood vessels in the bone marrow, necrotizing arteritis, and inflammation in the lamina propria mucosae of the large intestine

5.3 Genotoxicity

Genotoxicity studies included a bacterial reverse mutation assay, a chromosomal aberration assay in human peripheral blood lymphocytes, and a micronucleus assay in mouse bone marrow.

All samples were tested negative for bacterial reverse mutation and micronucleus. In the chromosomal aberration assay, the expression of structural chromosome aberration increased at concentrations ≥2.5 μg/mL in the presence of S9mix, and at concentrations ≥0.0625 μg/mL in the absence of S9mix by continuous treatment assay.

The applicant noted a risk of chromosome aberration in clinical use of carfilzomib due to its proteasome inhibitory effect for the following reasons:

- In the micronucleus assay in mice, micronucleus induction was not observed at the highest dose studied (2.5 mg/kg for males and 1.25 mg/kg for females). The estimated exposure levels in mice (AUC_{last} values were 26,060 ng·min/mL in male and 13,030 ng·min/mL in female) were lower than the clinical exposure levels.[12]

- In the chromosomal aberration assay in human peripheral blood lymphocytes, carfilzomib induced chromosomal aberrations at a concentration lower than the clinical exposure levels.

5.4 Carcinogenicity

No carcinogenicity study has been performed because carfilzomib is intended for the treatment of patients with advanced cancer.

5.5 Reproductive and developmental toxicity

The dose-finding studies in rats and rabbits in relation to embryo-fetal development, and an embryo-fetal development study in rats were conducted to evaluate reproductive and developmental toxicity.

5.5.1 Study of fertility and early embryonic development to implantation

No study of fertility and early embryonic development to implantation has been performed, because carfilzomib is intended for the treatment of patients with advanced cancer.

The repeat-dose toxicity studies revealed no effects on reproductive organs in male or female in [see Section 5.2]. Despite that, the risk of carfilzomib-induced chromosome aberration remains in clinical use [see Section 5.3]. Therefore, the applicant explains that patients of reproductive potential are required to use effective contraception during treatment and for a certain period of time after treatment, and that the healthcare professionals should be advised to this effect.

5.5.2 Embryo-fetal development toxicity study in rats receiving intravenous injections

Pregnant SD rats (22 animals/group) received intravenous bolus injections of carfilzomib 0 (solvent as control), 0.5, 1, or 2 mg/kg, once daily on Gestation Day 6 through Day 17.

Deaths occurred in 2 of the 22 dams receiving the 2-mg/kg doses. The following changes were observed in the dead dams: emaciation, pleural effusion, dilation of the colon, reddening of the jejunal serosa,

[12] Following an intravenous infusion of carfilzomib 20/27 mg/m^2 over 10 minutes to Japanese patients with relapsed or refractory MM on Day 16 of Cycle 1, AUC_{last} was 26,160 ng·min/mL (Study 01).

reduction in spleen size, and swelling of the heart. Other changes noted were piloerection, hunched posture, decreased food intake and body weight at ≥1 mg/kg; decreased locomotor activity, soiled perineal region, pallor, and labored breathing at 2 mg/kg. No carfilzomib-related changes were observed in embryos or fetuses.

Based on the above, the NOAEL for this study was determined to be 0.5 mg/kg for dams and 2 mg/kg for embryo-fetal development. The AUC_{last} at the NOAEL for embryo-fetal development (4474 ng·min/mL) was 0.17 times that of the clinical exposure levels.[13]

5.5.3 Dose-finding study in relation to embryo-fetal development in rabbits receiving intravenous bolus injections (reference data)

Pregnant NZW rabbits (n = 8/group) received intravenous bolus injections of carfilzomib 0 (solvent as control), 0.2, 0.4, or 0.8 mg/kg, once daily on Gestation Day 6 through Day19.

Effects on dams: Of 7 dams in the 0.8 mg/kg group, 1 died presenting with pericardial effusion, pleural effusion, hydropericardium, swelling of mediastinal lymph nodes, and oedema of the thymus. Other changes noted in animals in the 0.8 mg/kg group were decreases in food intake, fecal amount, and body weight, pallor, and pale green matter in the vagina.

Effects on embryos and fetuses: In the 0.8 mg/kg group; increased post-implantation embryo-fetal mortality (16.1% in the 0.8 mg/kg group and 5.8% in the control group) and decreased body weight in surviving fetuses (a decrease of 9.1% in the 0.8 mg/kg group compared to the control group). The applicant explained that increased embryo-fetal mortality is associated with maternal toxicity.

Based on the above, the maternal and embryo-fetal NOAEL for this study was determined to be 0.4 mg/kg. The human equivalent dose of the embryo-fetal NOAEL was 0.13 mg/kg, which is 0.18 times the maximum clinical dose (0.73 mg/kg).

The applicant explained that no additional embryo-fetal development studies using rabbits would be conducted because the effects of carfilzomib on embryo-fetal development have already been clarified.

5.6 Local tolerance

The 1- to 6-month repeat-dose toxicity studies in rats revealed no effects of carfilzomib at the injection site and surrounding tissues up to the maximum concentration studied (2 mg/mL) [see Sections 5.2.1 and 5.2.2]. In the 1- to 9-month repeat-dose toxicity studies in monkeys, changes in local tolerance were noted at the injection site and surrounding tissues at ≥1 mg/mL, including inflammatory cell infiltration, oedema, and necrosis [see Sections 5.2.4 and 5.2.5].

The applicant explained that the risk of carfilzomib-induced local irritation would be low, given that the carfilzomib concentration in the actual clinical dose (about 0.62 mg/mL) is lower than the minimum carfilzomib concentration at which local irritation was observed in the 1- to 9-month repeat-dose toxicity studies in monkeys (1 mg/mL).

5.7 Other toxicity studies

5.7.1 Phototoxicity

No phototoxicity study of carfilzomib has been performed. The molar extinction coefficient is 98.7 $L \cdot mol^{-1}cm^{-1}$ at the absorption maximum wavelength of carfilzomib of 295 nm. This was <1000 $L \cdot mol^{-1}cm^{-1}$, above which direct phototoxicity may be caused (see "Guideline: Photosafety Evaluation of Pharmaceuticals," PFSB/ELD Notification No. 0521-1, dated May 21, 2014).

[13] Following an intravenous infusion of carfilzomib 20/27 mg/m^2 over 10 minutes to Japanese patients with relapsed or refractory MM on Day 16 of Cycle 1, AUC_{last} was 26,160 ng·min/mL (Study 01).

5.7.2. Safety evaluation for impurities

The drug substance or drug product contains the following impurities. Impurity A (specifications of the drug product, ≤[redacted]%), Impurity B/Impurity C (specifications of the drug substance and drug product, ≤[redacted]%), Impurity D (specifications of the drug substance, ≤[redacted]%), Impurity E (specifications of the drug product, ≤[redacted]%), Impurity F (specifications of the drug product, ≤[redacted]%), and Impurity G (specifications of the drug product, ≤[redacted]%). The concentrations of these impurities exceeded the threshold requiring safety evaluation. The safety of these impurities were verified after the discussions in the following subsections.

5.7.2.1 General toxicity of impurities

The applicant's explanation about general toxicity of impurities:

Impurity A is formed as M16, one of the major metabolites of carfilzomib in rats and monkeys. Therefore, the toxicity of Impurity A has already been evaluated in repeat-dose toxicity studies [see Section 5.2]. Toxicity of Impurities B, C, D, E, F, and G were investigated in the 6-month repeated intravenous dose toxicity study in rats and the 9-month repeated intravenous dose toxicity study in monkeys. In the studies, the doses of these impurities administered to the animals were equivalent to or higher than their maximum clinical doses. The results of these studies revealed cardiac, pulmonary, renal, gastrointestinal, and hematopoietic changes that are probably attributable to the proteasome inhibitory effect of carfilzomib but no other anomalous toxicological changes [see Sections 5.2.2 and 5.2.5]. Therefore, the applicant does not consider that the impurities would pose significant safety concerns.

5.7.2.2 Genotoxicity of impurities

A bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral blood lymphocytes were conducted to study carfilzomib containing Impurities A, B, C, and D exceeding their upper specification limits. Also, a mouse micronucleus assay in mouse bone marrow was performed to study carfilzomib containing Impurities A, B, D, E, F, and G that exceeded the upper specification limit.

The results of the reverse mutation assay and micronucleus assay had no indication of mutagenicity or micronucleus induction. On the other hand, the results of the chromosomal aberration assay using a short-term treatment method showed increased expression of structural chromosome aberrations at 3 μg/mL in the presence of S9mix, and at concentrations ≥0.04 μg/mL in the absence of S9mix. However, the applicant explained that a risk of impurity-induced chromosomal aberrations is low for the following reasons:

- Given the variation in human lymphocyte sensitivity, no effects of the impurities were revealed in the comparison between the results of the chromosomal aberration assay of carfilzomib using human peripheral blood lymphocytes [see Section 5.3] and those of the same assay of carfilzomib containing impurities exceeding the upper specification limit.

- The maximum doses of impurities in the mouse micronucleus assay were compared with those in humans receiving carfilzomib containing impurities at the upper specification limit. The safety margin for the above impurities was 4.1 to 12 times in females and 2.1 to 6.2 times in males. Therefore, it is unlikely that impurity-related chromosome aberration would be induced.

Further, *in silico* analyses were performed using Deductive Estimation of Risk from Existing Knowledge (DEREK) and Leadscope Model Applier, to evaluate Impurities E, F, and G, for which the maximum daily clinical dose of <1 mg. The analytical results did not indicate that these impurities have structures likely to cause genotoxicity.

5.R Outline of the review conducted by PMDA

Based on the data submitted and the following discussions, PMDA concluded that in the non-clinical toxicity evaluation, no problems are associated with the clinical use of carfilzomib.

5.R.1 Administration of carfilzomib to women who are or may be pregnant

A visceral examination was not performed in the dose-finding study conducted in relation to embryo-fetal development in rabbits. PMDA asked the applicant to explain the possibility that carfilzomib may cause teratogenicity in rabbits.

The applicant's explanation:
The apoptosis induction by the proteasome inhibitory effect of carfilzomib in the embryo-fetal development stage may have been a mechanism contributed to the embryonic/fetal deaths in the reproductive and developmental toxicity studies (*Int Rev Cell Mol Biol.* 2008;267:59-124). Because no visceral examination was performed in the preliminary study, it is not known whether carfilzomib is teratogenic to rabbits. However, a possible risk of carfilzomib for teratogenicity cannot be ruled out in light of its pharmacological action.

The package insert (draft) submitted for the marketing approval application had a piece of advice not to administer carfilzomib to women who are or may be pregnant as a rule. PMDA asked the applicant to explain the reasons for the advice.

The applicant's explanation:
In the reproductive and developmental toxicity studies, carfilzomib caused embryonic/fetal deaths despite its lower doses than the clinical dose [see Section 5.5.3]. This means that carfilzomib may have a certain effect on embryos and fetuses in clinical use as well. Even so, treatment options for relapsed or refractory MM are limited and there may be pregnant or potentially pregnant women suffering MM and needing to receive carfilzomib. In this situation, carfilzomib should offer a therapeutic opportunity to these patients rather than being contraindicated, with a remainder of the general rule not to use carfilzomib in pregnant or potentially pregnant women. Furthermore, healthcare professionals should also be advised, via the package insert, to be aware of the need for the use of contraception for women of reproductive potential.

PMDA's view:
In principle, bortezomib, another tumor growth inhibitor with a proteasome inhibitory effect similar to carfilzomib, is not allowed to be administered to pregnant or potentially pregnant women based on the results of its embryo-fetal development studies in rats and rabbits. In the dose-finding study of carfilzomib in relation to embryo-fetal development in rabbits, the increased death date was due to maternal toxicity. The available data from reproductive and developmental toxicity studies are, however, not adequate to assess the teratogenicity of carfilzomib. Given this situation, the possibility cannot be ruled out that proteasome inhibition by carfilzomib may cause developmental toxicity including teratogenicity, and the use of carfilzomib in pregnant or potentially pregnant patients is inappropriate. Therefore, the administration of carfilzomib should be contraindicated in pregnant or potentially pregnant patients.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Data on Clinical Pharmacology Studies, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The concentrations of carfilzomib and its metabolites (M15, a hydrolyzed product; M14, a hydrolyzed product of M15; and M16, a diol) in human plasma and feces were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limits of quantitation for carfilzomib, M14, M15, and M16 in plasma were 0.1,[14] 0.5, 0.5, and 0.5 ng/mL, respectively, and those in feces were all 10 ng/g. The concentrations of carfilzomib, M14, and M15 in human urine were measured by LC-MS/MS, and their lower limits of quantitation were 4, 10, and 4 ng/mL, respectively.

[14] In Study PX-171-005, one of the studies submitted for marketing approval, the lower limit of quantitation of carfilzomib in plasma was 0.3 ng/mL.

6.2 Clinical pharmacology studies

The pharmacokinetics of carfilzomib was evaluated in its monotherapy and combination therapy with midazolam, DEX, and lenalidomide for cancer patients. The effect of carfilzomib on the PK of midazolam was also studied.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I/II study (CTD 5.3.5.2-1, Study ONO-7057-01 [ongoing since [redacted] 20[redacted], data cut-off on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in 50 patients with relapsed or refractory MM (17 of these subjects were included in the PK analysis set) to investigate the pharmacokinetics of carfilzomib. In a 28-day cycle, (a) 15 or 20 mg/m^2 of carfilzomib was administered intravenously once daily as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16; or (b) 20 mg/m^2 of carfilzomib were administered intravenously once daily as a 10-minute infusion on Days 1 and 2 and 27 mg/m^2 once daily on Days 8, 9, 15, and 16 to evaluate plasma concentrations (Table 7). The C_{max} and AUC_{last} on Day 16 exhibited dose proportionality within the dose range studied. No accumulation of carfilzomib from repeated administration was observed.

Table 7. Pharmacokinetic parameters of carfilzomib

Measured date (Day)	Dose (mg/m^2)	N	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
1	15	4	1010 ± 99.0	0.159 (0.0833, 0.167)	212 ± 40.4	0.571 ± 0.139	119 ± 33.4	13.3 ± 4.64
	20[*2]	13	1530 ± 407	0.150 (0.0833, 0.250)	306 ± 69.9	0.706 ± 0.248	110 ± 24.4	11.9 ± 4.56
16	15	4	1030 ± 453	0.159 (0.117, 0.167)	211 ± 81.8	0.484 ± 0.0794	132 ± 59.2	15.2 ± 7.55
	20	4	1570 ± 125	0.150 (0.133, 0.183)	330 ± 64.7	0.424 ± 0.169	107 ± 28.2	15.1 ± 9.65
	27	6	2300 ± 974	0.150 (0.0833, 0.167)	436 ± 133	0.659 ± 0.172	105 ± 26.7	8.50 ± 2.95

Arithmetic mean ± standard deviation; [*1] median (range); [*2] consolidated data on (a) 20 mg/m^2 of intravenous carfilzomib administered once daily on Days 1, 2, 8, 9, 15, and 16; and (b) 20 mg/m^2 of intravenous carfilzomib administered once daily on Days 1 and 2, and 27 mg/m^2 once daily on Days 8, 9, 15, and 16.

6.2.1.2 Japanese phase I clinical study (CTD 5.3.5.2-12, Study 05 [ongoing since in [redacted] 20[redacted], data cut-off on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in 26 patients with relapsed or refractory MM (11 of these subjects were included in the PK analysis set) to evaluate the pharmacokinetics of carfilzomib. In a 28-day cycle, 20 mg/m^2 of carfilzomib were administered intravenously once daily as a 10-minute infusion on Days 1 and 2, and 27 mg/m^2 on Days 8, 9, 15, and 16, in combination with 25 mg of oral lenalidomide administered once daily at on Days 1 to 21 and 40 mg of oral or intravenous DEX administered once daily on Days 1, 8, 15 and 22, and the plasma concentrations of carfilzomib were measured (Table 8).

Table 8. Pharmacokinetic parameters of carfilzomib

Measured date (Day)	Dose (mg/m^2)	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
1	20	11	1540 ± 391	0.150 (0.0833, 0.167)	326 ± 73.5	0.580 ± 0.260	102 ± 27.3	10.9 ± 4.39
16	27	9	2030 ± 282	0.150 (0.133, 0.183)	444 ± 56.0	0.740 ± 0.272	98.8 ± 16.1	11.7 ± 5.40

Arithmetic mean ± standard deviation; * median (range)

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.2-1, Study PX-171-001 [October 2005 to [redacted] 20[redacted]])

An open-label uncontrolled study was conducted in 29 patients with progressive haematopoietic malignancy (11 of these subjects were included in the PK analysis set) to evaluate the PK of carfilzomib. In a 14-day cycle, 1.2, 2.4, 4, 6, 8.4, 11, 15, or 20 mg/m^2 of carfilzomib was administered as an intravenous bolus over 1 to 2 minutes once daily on Days 1 to 5, and plasma concentrations on Day 1 were evaluated. According to the applicant, >50% of the specimens in the 1.2 and 2.4 mg/m^2 groups had values below the limit of quantitation (0.1 ng/mL) and the elimination phase could not be observed in the 4, 6, and 8.4 mg/m^2 groups owing to limited quantifiable sampling time points. Data from these groups were therefore excluded from the analysis.

Table 9 shows the pharmacokinetic parameters of carfilzomib. The C_{max} and AUC_{last} values did not show dose-dependent increases. The applicant presumably attributed this outcome to the small sample size of the 11 mg/m^2 group and large interindividual variation in C_{max} and AUC_{last} values.

Table 9. Pharmacokinetic parameters of carfilzomib

Dose (mg/m^2)	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
11	2	282, 2490	0.083, 0.13	49.3, 319	0.15, 0.383	72.7, 506	5.21, 79.2
15	5	326 ± 218	0.12 (0.083, 0.12)	49.9 ± 32.9	0.45 ± 0.483	931 ± 943	129 ± 90.1
20	4	683 ± 599	0.10 (0.083, 0.12)	91.6 ± 74.5	0.38 ± 0.167	794 ± 639	96.6 ± 95.6

Arithmetic mean ± standard deviation (individual values for 11 mg/m^2 group [N = 2]); * median (range)

6.2.2.2 Foreign phase I study (CTD 5.3.3.2-2, Study PX-171-002, Part 1 [September 2005 to [redacted] 20[redacted]] and Part 2 [[redacted] 20[redacted] to October 2009])

An open-label uncontrolled study was conducted in 48 patients with progressive haematopoietic malignancies (29 of these subjects [20 in Part 1 and 9 in Part 2] were included in the PK analysis set) to investigate the pharmacokinetics and of carfilzomib. In Part 1 of the study, 1.2, 2.4, 4, 6, 8.4, 11, 15, 20, or 27 mg/m^2 of carfilzomib was administered as an intravenous bolus over 2 minutes once daily on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Part 2 consisted of a carfilzomib monotherapy cohort and a carfilzomib plus DEX cohort. In the monotherapy cohort, 20 mg/m^2 of carfilzomib was administered as an intravenous bolus over 2 minutes once daily on Days 1 and 2, and 27 mg/m^2 once daily on Days 8, 9, 15, and 16 of a 28-day cycle. In the carfilzomib plus DEX cohort, 20 and 27 mg/m^2 of carfilzomib was administered in a 28-day cycle according to the same schedule as the monotherapy cohort, and 20 mg of DEX was administered once daily orally on Days 1, 2, 8, 9, 15, and 16 of the cycle. According to the applicant, approximately 50% of the specimens in the 1.2, 2.4, 4, 6, and 8.4 mg/m^2 groups showed values below the limit of quantitation (0.1 ng/mL), and these data were therefore excluded from the analysis set.

Table 10 shows the pharmacokinetic parameters of carfilzomib on Day 1. In Part 1 of Study PX-171-002, the C_{max} and AUC_{last} values did not show dose-dependent increases. Although not clear, the reason for this phenomenon may have been the large interindividual variation in C_{max} and AUC_{last} values. Further, in Part 2, while the C_{max} and AUC_{last} values were lower in the carfilzomib plus DEX cohort than

in the carfilzomib monotherapy cohort, the obtained values of pharmacokinetic parameters largely dispersed. The applicant explained that these results precluded a discussion on the effects of DEX on the pharmacokinetics of carfilzomib.

Table 10. Pharmacokinetic parameters of carfilzomib

Dose (mg/m^2)	N	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
Part 1							
11	3	505 ± 485	0.0833 (0.0833, 0.0833)	67.5 ± 61.6	0.215 ± 0.108	626 ± 658	68.4 ± 79.5
15	3	143 ± 97.2	0.0833 (0.0833, 0.117)	23.6 ± 15.3	0.218 ± 0.06	1821 ± 1433	199 ± 117
20	8	528 ± 406	0.1 (0.0833, 0.167)	81.9 ± 58.3	0.657 ± 0.48	659 ± 353	108 ± 71.2
27	5[*2]	406 ± 517	0.0833 (0.0833, 0.167)	56.8 ± 66.1	0.447 ± 0.0783	4475 ± 6536	1539 ± 2862
Part 2							
20	4[*3]	410 ± 521	0.242 (0.100, 0.317)	99.5 ± 127	0.517 ± 0.218	1079 ± 1045	231 ± 157
20 (with DEX)	4	371 ± 542	0.242 (0.117, 0.667)	66.1 ± 71.0	1.04 ± 0.72	1035 ± 857	709 ± 782

Arithmetic mean ± standard deviation; [*1] median (range); [*2] One subject was excluded because of no pharmacokinetic data available; [*3] One subject was excluded because of deviation from in the plasma concentration time course of uncertain cause.

6.2.2.3 Foreign phase Ib/II study (CTD 5.3.3.2-4, Study PX-171-007 [ongoing since September 2007, data cut-off on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in 79 patients with progressive solid cancer (30 of these subjects were included in the PK analysis set) to investigate the pharmacokinetics of carfilzomib. In a 28-day cycle, (a) 20 mg/m^2 of carfilzomib was administered intravenously over 2 to 10 minutes once daily on Days 1, 2, 8, 9, 15, and 16, or (b) 20 mg/m^2 of carfilzomib were administered intravenously over 2 to 10 minutes once daily on Days 1 and 2, and 27 or 36 mg/m^2 intravenously over 2 to 10 minutes once daily on Days 8, 9, 15, and 16 to evaluate plasma concentrations of carfilzomib (Table 11). At the doses studied, C_{max} and AUC_{last} increased dose-proportionally.

Table 11. Pharmacokinetic parameters of carfilzomib

Measured date (Day)	Dose (mg/m^2)	N	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
1	20[*2]	30	3060 ± 1791	0.0500 (0, 0.167)	312 ± 183	0.761 ± 0.625[*3]	263 ± 398[*3]	27.7 ± 48.6[*3]
16	20	3	3707 ± 1953	0.0333 (0.0333, 0.0500)	301 ± 180	1.08 ± 0.0696	136 ± 52.8	7.75 ± 3.77
	27	5	4564 ± 1784	0.0500 (0.0333, 0.133)	389 ± 99.0	0.470 ± 0.307[*4]	150 ± 30.9[*4]	11.1 ± 4.45[*4]
	36	13	6211 ± 2458	0.0500 (0.0333, 0.117)	677 ± 449	0.948 ± 0.361[*5]	116 ± 48.6[*5]	9.33 ± 4.80[*5]

Arithmetic mean ± standard deviation; [*1] median (range); [*2] The data from following regimens were consolidated: (a) intravenous doses of carfilzomib were administered at 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16; and (b) intravenous doses of carfilzomib were administered at 20 mg/m^2 once daily on Days 1 and 2, and at 27 or 36 mg/m^2 once daily on Days 8, 9, 15, and 16; [*3] n = 23; [*4] n = 4; and [*5] n = 10

6.2.3 Pharmacokinetic interaction with midazolam (CTD 5.3.3.4-2, Study PX-171-008 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label uncontrolled study was conducted in 18 patients with progressive solid cancer (17 of these subjects were included in the PK analysis set) to investigate the effects of carfilzomib on the pharmacokinetics of midazolam (CYP3A substrate). In Part 1, a single oral dose of midazolam 2 mg was administered. In Part 2, 27 mg/m^2 of carfilzomib was administered as an intravenous bolus over 1 to 4 minutes, once daily on Days 1, 2, 8, 9, 15, and 16, and 2 mg of oral midazolam were administered once daily on Days 1 and 16. Parts 1 and 2 were separated by a washout period of 7 days.

The geometric mean ratios of C_{max} and AUC_{inf} of midazolam in the carfilzomib and midazolam combination therapy to those in the midazolam monotherapy were 0.99 (90% confidence interval [CI], 0.83-1.18), and 0.95 (90% CI, 0.85-1.07), respectively, on Day 1; and 0.98 (90% CI, 0.80-1.20) and 1.08 (90% CI, 0.94-1.24) respectively, on Day 16. The applicant explained that the combination use of carfilzomib with a CYP3A substrate is unlikely to cause a pharmacokinetic interaction.

Further, on Day 1 of Part 2, urinary concentrations of carfilzomib, M14, and M15, and fecal concentrations of carfilzomib, M14, M15, and M16 were studied. The urinary excretion rates (percentage to the administered dose) of carfilzomib, M14, and M15 up to 24 hours post-dose were 0.3%, 25%, and 1.9%, respectively. While the fecal excretion rate of M14 was 0.8%, carfilzomib, M15, and M16 were present at less than the lower limit of quantitation (10 ng/g) in feces. The applicant explained that the results indicate the small contribution of fecal excretion to the elimination of carfilzomib.

6.2.4 Foreign phase II study in patients with renal impairment (CTD 5.3.3.2-3, Study PX-171-005 [November 2008 to November 2012])

An open-label uncontrolled study was conducted in 12 patients with relapsed or refractory MM with normal renal function (8 of these subjects were included in the PK analysis set), and 38 patients with relapsed or refractory MM suffering mild, moderate, severe, or dialysis-requiring renal impairment (27 of these were included in the PK analysis set), to investigate the effects of renal impairment on the pharmacokinetics of carfilzomib and its metabolites (M14, M15, and M16). The patients were treated 15 mg/m^2 of intravenous carfilzomib over 2 to 10 minutes, once daily on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle.

Table 12 shows the pharmacokinetic parameters of carfilzomib and its metabolites in patients with MM suffering renal impairment. On either day (Day 1 or 15), the exposure (AUC_{last}) to carfilzomib and M16 did not vary clearly by the severity of renal impairment. In contrast, the exposure (AUC_{last}) to M14 and M15 increased with increasing severity of renal impairment. Further, the urinary excretion rate (Fe) of carfilzomib was <1% regardless of the severity of renal impairment; however, the urinary excretion rates of M14 and M15 decreased with increasing severity of renal impairment. The applicant explained that these results suggest that renal excretion is the major route of elimination of M14 and M15. On the other hand, the protein binding rates of carfilzomib ranged from 97.6% to 98.3% in patients suffering mild, moderate, severe, or dialysis-requiring renal impairment, indicating no obvious difference among the patients.

Table 12. Pharmacokinetic parameters of carfilzomib and its metabolites (M14, M15, and M16) in MM patients with renal impairment

Severity of renal impairment[*1]	Measured date (Day)	N	Analyte	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	Fe (%)
Normal	1	8	Carfilzomib	2546 ± 1406	220 ± 117	0.450 ± 0.103[*2]	151 ± 79.3[*2]	0.490 ± 0.316
			M14	92.2 ± 18.9	275 ± 97.4	1.85 ± 0.777[*7]	–	33.1 ± 13.1
			M15	14.8 ± 3.48	25.2 ± 7.26	1.42 ± 0.248	–	1.93 ± 1.12
			M16	151 ± 36.4	66.9 ± 18.9	0.656 ± 0.174	–	–[*9]

Severity of renal impairment[*1]	Measured date (Day)	N	Analyte	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	Fe (%)
	15	7	Carfilzomib	2550 ± 1683	228 ± 134	0.710 ± 0.574[*3]	660 ± 1134[*3]	0.446 ± 0.357
			M14	106 ± 37.5	358 ± 160	2.88 ± 1.35	–	30.6 ± 11.6
			M15	17.0 ± 4.78	26.3 ± 7.07	1.55 ± 0.317	–	1.91 ± 1.03
			M16	179 ± 26.8	75.6 ± 12.3	0.672 ± 0.211	–	–[*9]
Mild	1	9	Carfilzomib	2227 ± 1353	220 ± 91.4	0.842 ± 0.854[*2]	113 ± 40.7[*2]	0.429 ± 0.271[*8]
			M14	96.2 ± 16.4	278 ± 108	1.79 ± 0.997[*8]	–	25.0 ± 4.81
			M15	15.5 ± 3.79	23.6 ± 5.24	1.34 ± 0.251[*7]	–	1.42 ± 0.314
			M16	139 ± 59.7	59.3 ± 17.5	0.609 ± 0.230	–	–[*9]
	15	8	Carfilzomib	2673 ± 1352	333 ± 218	0.678 ± 0.266[*3]	115 ± 34.7[*3]	0.428 ± 0.262[*2]
			M14	98.5 ± 14.1	308 ± 118	2.21 ± 1.06	–	27.0 ± 8.47[*2]
			M15	15.3 ± 2.68	24.3 ± 3.92	1.45 ± 0.278	–	1.55 ± 0.602[*2]
			M16	166 ± 49.6	67.2 ± 7.22	0.669 ± 0.245[*7]	–	–[*9]
Moderate	1	5	Carfilzomib	2234 ± 1245	241 ± 129	0.601 ± 0.0496[*4]	288 ± 264[*4]	0.160 ± 0.101[*7]
			M14	130 ± 51.4	683 ± 329	3.32 ± 1.19[*5]	–	21.7 ± 7.59[*7]
			M15	16.4 ± 2.94	35.7 ± 9.31	1.75 ± 0.263[*5]	–	0.776 ± 0.387*7
			M16	139 ± 39.4	68.5 ± 31.2	0.708 ± 0.179	–	–[*9]
	15	5	Carfilzomib	2718 ± 705	414 ± 218	0.816 ± 0.471[*4]	119 ± 16.5[*4]	0.202 ± 0.116
			M14	125 ± 48.5	728 ± 374	3.94 ± 0.708	–	22.0 ± 6.89
			M15	15.7 ± 1.38	33.6 ± 10.3	1.58 ± 0.133[*5]	–	0.856 ± 0.377
			M16	149 ± 48.8	74.2 ± 30.4	0.629 ± 0.119	–	–[*9]
Severe	1	5	Carfilzomib	1605 ± 799	153 ± 72.5	1.51 ± 1.53[*5]	170 ± 58.4[*5]	0.226 ± 0.0921
			M14	150 ± 25.7	836 ± 293	3.58 ± 0.887[*5]	–	19.2 ± 4.36
			M15	17.3 ± 8.78	41.1 ± 21.9	1.79 ± 0.207[*5]	–	0.578 ± 0.230
			M16	163 ± 108	72.9 ± 29.0	0.784 ± 0.263	–	–[*9]
	15	4	Carfilzomib	2335 ± 1311	375 ± 176	10.7[*6]	110[*6]	0.168 ± 0.0670
			M14	142 ± 30.2	1091 ± 375	5.22 ± 1.89	–	17.0 ± 4.67
			M15	18.2 ± 2.55	40.8 ± 11.1	2.10 ± 0.437[*4]	–	0.475 ± 0.249
			M16	150 ± 26.4	83.8 ± 19.8	0.864 ± 0.193	–	–[*9]
Requiring dialysis	1	8	Carfilzomib	2071 ± 1996	233 ± 166	1.65 ± 1.80[*3]	170 ± 60.2[*3]	–[*10]
			M14	165 ± 49.7	1992 ± 811	5.04 ± 1.24[*7]	–	–[*10]
			M15	17.8 ± 6.12	57.3 ± 57.6	2.24 ± 1.40[*7]	–	–[*10]
			M16	113 ± 48.8	59.3 ± 32.0	0.792 ± 0.321[*7]	–	–[*10]
	15	6	Carfilzomib	3397 ± 1212	281 ± 106	1.45 ± 1.20[*3]	114 ± 61.2[*3]	–[*10]
			M14	190 ± 63.4	1849 ± 847	4.57 ± 1.73[*3]	–	–[*10]
			M15	17.7 ± 3.20	40.0 ± 12.0	1.80 ± 0.365	–	–[*10]
			M16	143 ± 39.4	70.1 ± 23.6	0.681 ± 0.108	–	–[*10]

Arithmetic mean ± standard deviation; [*1] CrCL of >80 mL/min (normal), ≥50 and ≤80 mL/min (mild), ≥30 and <50 mL/min (moderate), and <30 mL/min (severe); [*2] N = 6; [*3] N = 5; [*4] N = 3; [*5] N = 4; [*6] N = 1; [*7] N = 7; [*8] N = 8; [*9] Urinary concentration of M16 was not measured; [*10] Urinalysis was not performed for patients on dialysis; –, not calculated

6.2.5 Relationships between the exposure and QT/QTc interval change

A relationship between plasma carfilzomib concentration and QTcF was investigated in a Japanese phase I study (Study 05) and a Japanese phase I/II study (Study 01) by linear mixed-effects modeling (N = 50; 280 measuring time points). The results showed no clear relationship between plasma carfilzomib concentration and QTcF. and the estimated QTcF change from baseline at the point when the C_{max} (arithmetic mean, 2130 ng/mL) was reached following intravenous administration of carfilzomib 27 mg/m^2 was 6.07 msec (90% CI, 2.74-9.40 msec), indicating the upper limit of 90% confidence interval of <10 msec. Also, a relationship between plasma carfilzomib concentration and QTcF was investigated by linear mixed-effects modeling (N = 154; 488 measuring time points) in a Foreign phase II study (Study PX-171-005) and a Foreign phase Ib/II study (Study PX-171-007), showing no clear relationship.

Accordingly, the applicant explained that 27 mg/m^2 of intravenous carfilzomib is unlikely to cause QT/QTc interval prolongation.

6.2.6 Population pharmacokinetic analysis

A population pharmacokinetic (PPK) analysis was performed by non-linear mixed-effects modeling (Phoenix NLME software, Version 1.2) using PK data for carfilzomib (443 subjects; 3226 measuring time points) obtained from foreign clinical studies (Studies PX-171-003-A1, PX-171-004, PX-171-005, PX-171-006, PX-171-007, and 009). The pharmacokinetics of carfilzomib was described using a 2-compartment model with first-order elimination.

In this analysis, the following potential covariates for (a) CL, (b) V_1, and (c) V_2 were assessed: (a) age, body weight, body surface area, CrCL, sex, ethnicity, and carcinoma; (b) age, body weight, body surface area, sex, ethnicity, and carcinoma; and (c) age, body weight, body surface area, sex, and ethnicity. As a result, body surface area was selected as a significant covariate of CL. CL of carfilzomib estimated by the PPK analysis, as compared with a patient with the median body surface area (1.9 m^2), was lower by 13% in a patient with the smallest body surface area (1.37 m^2) and higher by 19% in a patient with the largest body surface area (2.82 m^2). However, the applicant explained that, given that the interindividual variation for CL was 59.9%, the clinical significance of the effect of body surface area on the CL of carfilzomib is unclear.

6.2.7 Relationship between carfilzomib exposure and efficacy or safety

6.2.7.1 Relationship between carfilzomib exposure and efficacy

The C_{max} and AUC of carfilzomib were analyzed by logistic regression to evaluate their relationship to response rate, duration of response, and progression-free survival (PFS) according to the International Myeloma Working Group (IMWG) criteria (e.g., *Leukemia*. 2006;20:1467-73) using the results of Study 009, in which carfilzomib was administered as per the same dosage regimen as the proposed dosage and administration. The applicant explained that no clear relationship was noted between the C_{max} or AUC of carfilzomib and response rate, duration of response, or PFS.

6.2.7.2 Relationship between carfilzomib exposure and safety

A relationship between C_{max} or AUC of carfilzomib and incidence of adverse events of all grades or Grades 3 or 4 were analyzed by logistic regression using the results of Studies PX-171-003-A1, PX-171-004, PX-171-005, PX-171-006, PX-171-007, and 009. The applicant explained that no clear relationship was noted between the C_{max} or AUC of carfilzomib and incidence of either group of adverse events.

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetic drug interactions with lenalidomide and dexamethasone

PMDA asked the applicant to explain the pharmacokinetic drug interactions in the CLd regimen.

The applicant's explanation:
There are no clinical study data on the pharmacokinetic drug interactions in the CLd regimen. However, the following factors indicate a low possibility of pharmacokinetic drug interactions resulting from the combination regimen:

- There were no significant differences in C_{max}, AUC_{last}, and $t_{1/2}$ between the carfilzomib monotherapy in the Japanese phase I/II study (Study 01) and the CLd regimen in Japanese phase I study (Study 05) [see Sections 6.2.1.1 and 6.2.1.2].

- Because lenalidomide is not metabolized in the liver and is predominantly excreted in the urine as unchanged lenalidomide (see "Package insert of Revlimid Capsules 2.5 mg and 5 mg"), it is unlikely that carfilzomib affects the pharmacokinetics of lenalidomide. Although lenalidomide was reported to be a substrate for P-gp (*Cancer Chemother Pharmacol.* 2014;73:869-74), it is unlikely that the clinical use of lenalidomide induces a pharmacokinetic interaction with carfilzomib's P-gp inhibitory activity [see Section 4.5.3].

- DEX is a substrate for CYP3A (see "Package insert of LenaDex Tablets 4 mg"). Carfilzomib did not affect the pharmacokinetics of midazolam, which is also a CYP3A substrate, in the study on the carfilzomib-midazolam interaction [see Section 6.2.3]. Based on these facts, it is unlikely that carfilzomib affects the pharmacokinetics of DEX.

PMDA's view:
The applicant's explanation is acceptable. However, no clinical studies have been conducted on drug interactions in the CLd regimen, and, therefore, data on pharmacokinetic drug interactions in the regimen and relevant published literature should be further collected, and any new findings should be communicated to healthcare professionals in an appropriate manner.

6.R.2 Administration of carfilzomib to patients with hepatic impairment
The applicant's explanation about the administration of carfilzomib to patients with hepatic impairment:
A foreign phase I study (Study CFZ002, ongoing since October 2013, data cut-off on [redacted], 20[redacted]) was conducted in patients with solid cancer or haematopoietic malignancy having hepatic impairment to investigate the effects of hepatic impairment on the pharmacokinetics of carfilzomib. The treatment regimen of this study consisted of 2 cycles, each of which was 28 days long. In Cycle 1, 20 mg/m^2 of carfilzomib was intravenously infused over 30 minutes once daily on Days 1 and 2, and 27 mg/m^2 once daily on Days 8, 9, 15, and 16. In Cycle 2, 56 mg/m^2 of carfilzomib was intravenously infused over 30 minutes once daily on Days 1, 2, 8, 9, 15, and 16. Oral or intravenous DEX was administered at 8 mg once daily on Day 1 of each cycle.

Table 13 shows the pharmacokinetic parameters of carfilzomib in Study CFZ002. At the beginning, 4 patients having severe hepatic impairment were enrolled. However, they did not undergo blood sampling for a drug concentration analysis (1 subject each died of septic shock, multi-organ failure, and acute hepatic failure, and 1 subject discontinued treatment due to acute kidney injury. For all 4 cases, a causal relationship to carfilzomib was ruled out). The enrollment of patients with severe hepatic impairment was then stopped, considering the difficulty to continue the study with these patients.

For the following reasons, the applicant considers that the influence of hepatic impairment on the pharmacokinetics of carfilzomib is insignificant and thus precautionary advice is not necessary on the use of carfilzomib inpatients with hepatic impairment:

- As compared to patients with normal hepatic function, the AUC_{last} of carfilzomib in patients with mild and moderate hepatic impairment was higher by approximately 40% to 44% and 5.5% to 23%, respectively. However, increased AUC_{last} due to hepatic impairment was within the range of the coefficient of variation (33.1% to 100.5%). Furthermore, AUC_{last} did not increase with increasing severity of hepatic impairment.

- From the plasma clearance and blood to plasma concentration ratio [see Sections 6.2.1.1 and 4.2.2], the estimated blood clearance of carfilzomib is 160 to 250 L/h, which is higher than the reported hepatic blood flow in humans of 75 L/h (*Pharm Res.* 1993;10:1093-5). This indicates a significant involvement of extrahepatic metabolism in the elimination of carfilzomib.

Table 13. Pharmacokinetic parameters of carfilzomib in patients with solid cancer or haematopoietic malignancy patients having hepatic impairment (Study CFZ002)

Measured date (Day)	Dose (mg/m^2)	Severity of hepatic impairment*	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)
16	27	Normal	10	1090 ± 796	405 ± 164
		Mild	14	1424 ± 700	584 ± 227
		Moderate	9	1107 ± 503	500 ± 170
29	56	Normal	8	2055 ± 1029	951 ± 546
		Mild	8	3190 ± 1818	1328 ± 852
		Moderate	5	2308 ± 1102	1003 ± 470

Arithmetic mean ± standard deviation; * classification based on the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria

PMDA's view:
Patients with severe hepatic impairment enrolled in Study CFZ002 were not able to undergo blood sampling for a drug concentration analysis due to death and other reason, and the enrollment of the patients with severe hepatic impairment was cancelled. During the treatment with carfilzomib in patients in this population, patients' condition should be carefully monitored for adverse events. In addition, in Study CFZ002, exposure to carfilzomib tended to increase in patients with mild to moderate hepatic impairment as compared to those in patients with normal hepatic function. Data from Study CFZ002, including the background of the study discontinuation in patients with severe hepatic impairment, should be provided to healthcare professionals in an appropriate manner through the package insert or other written materials.

6.R.3 Differences in pharmacokinetics of carfilzomib between Japanese and non-Japanese populations

PMDA asked the applicant to explain the differences in the pharmacokinetics of carfilzomib between Japanese and non-Japanese populations.

The applicant's explanation:
From the results of the Japanese phase I/II study (Study 01), foreign phase II study (Study PX-171-005), and foreign phase Ib/II study (Study PX-171-007) [see Sections 6.2.1.1, 6.2.2.3, and 6.2.4], C_{max}, AUC_{last}, and $t_{1/2}$ on Day 1 or 15 of Cycle 1 after the intravenous infusion of 15 or 20 mg/m^2 of carfilzomib over 10 minutes are shown in Table 14. Based on the similarity in the distribution of individual values (range) between Japanese and non-Japanese populations, there are no clear differences in the pharmacokinetics of carfilzomib between Japanese and non-Japanese populations.

Table 14. Pharmacokinetic parameters of Japanese and non-Japanese populations

	Study	Dose (mg/m^2)	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
Japanese	01	15	4	1000 (911, 1120)	197 (184, 271)	0.519 (0.474, 0.772)
		20	13	1510 (927, 2560)	292 (194, 454)	0.812 (0.396, 1.10)
Non-Japanese	PX-171-005	15	4	1720 (1180, 2610)	197 (105, 332)	1.24 (0.778, 1.73)
	PX-171-007	20	1	6730*	916*	0.661*

Median (range); * individual values

According to the applicant, a new cohort of patients treated with carfilzomib over 30 minutes was added in Study PX-171-007 [see Section 7.2.2.1]. PMDA has requested pharmacokinetic data of carfilzomib, including the result of 30-minute intravenous infusion, to verify differences between Japanese and non-Japanese populations.

7. Summary of Submitted Data on Clinical Efficacy and Safety, and Outline of the Review Conducted by PMDA

Unless otherwise specified, the dosing regimens of carfilzomib used in the clinical studies explained in this section are as shown in Table 15.

Table 15. Dosing regimen of carfilzomib for the clinical studies

	Dosing regimen of carfilzomib
20/27 mg/m^2	Each cycle consisting of 28 days 20 mg/m^2 once daily on Days 1 and 2 of Cycle 1 27 mg/m^2 once daily on Days 8, 9, 15, and 16 of Cycle 1, Days 1, 2, 8, 9, 15, and 16 from Cycle 2 onward
20/36 mg/m^2	Each cycle consisting of 28 days 20 mg/m^2 once daily on Days 1 and 2 of Cycle 1, 36 mg/m^2 once daily on Days 8, 9, 15, and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15, and 16 from Cycle 2 onward

As efficacy and safety evaluation data, the results from a total of 8 studies were submitted: 1 Japanese phase I study, 1 Japanese phase I/II study, 3 foreign phase I studies, 1 foreign phase II study, and 2 foreign phase III studies (Table 16). The results from a total of 8 studies were also submitted as reference data: 2 foreign phase I studies, 1 foreign phase I/II study, 4 foreign phase II studies, and 1 foreign compassionate use study (Table 16).

Table 16. Clinical studies for efficacy and safety evaluations

Data category	Site	Study	Phase	Target patients	N	Main dosing regimen	Main objective
Evaluation	Japan	ONO-7057-01	I/II	Relapsed or refractory MM	50 (a) 17 (b) 33	(a) Phase I: Intravenous carfilzomib 15 or 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, or 20/27 mg/m^2 (b) Phase II: Carfilzomib 20/27 mg/m^2	Safety Efficacy PK
		ONO-7057-05	I	Relapsed or refractory MM	26	Carfilzomib 20/27 mg/m^2, oral lenalidomide 25 mg on Day 1 through Day 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle	Safety Efficacy PK
	Outside Japan	PX-171-002 Part 1	I	Progressive haematopoietic malignancy	37	Intravenous carfilzomib 1.2, 2.4, 4.0, 6.0, 8.4, 11, 15, 20, 27, or 36 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle	Safety PK
		PX-171-002 Part 2	I	Progressive haematopoietic malignancy	11 (a) 7 (b) 4	(a) Carfilzomib monotherapy cohort: Intravenous carfilzomib 20 mg/m^2 once daily in Cycle 1 and 27 mg/m^2 from Cycle 2 onward on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (b) Carfilzomib/DEX combination cohort: oral DEX 20 mg with carfilzomib according to the schedule in (a)	Safety PK

Data category	Site	Study	Phase	Target patients	N	Main dosing regimen	Main objective
		PX-171-003 Part 2 (A1)	II	Relapsed or refractory MM	266	Intravenous carfilzomib 20 mg/m^2 once daily in Cycle 1 and 27 mg/m^2 from Cycle 2 onward, on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle	Efficacy Safety
		PX-171-006	Ib	Relapsed or refractory MM	84 (a) 40 (b) 44	(a) Dose escalation: Intravenous carfilzomib 15 or 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16, or 20/27 mg/m^2; oral lenalidomide 10, 15, 20, or 25 mg on Day 1 through Day 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle (b) Dose expansion: Carfilzomib 20/27 mg/m^2, and oral lenalidomide 25 mg on Days 1 to 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle	Safety
		PX-171-009	III	Relapsed or refractory MM	792 (a) 396 (b) 396	(1) CLd arm: Carfilzomib 20/27 mg/m^2, oral lenalidomide 25 mg on Day 1 through Day 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22 of 28-day cycle (2) Ld arm: Oral lenalidomide 25 mg on Day 1 to 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle	Efficacy Safety
		PX-171-011	III	Relapsed or refractory MM	315 (1) 157 (2) 158	(1) Carfilzomib arm[*1]: Carfilzomib 20/27 mg/m^2 (2) BSC (best supportive care) arm: An oral or intravenous corticosteroid[*2] equivalent up to 84 mg of DEX with optional concomitant cyclophosphamide hydrate 50 mg once daily in 28-day cycles	Efficacy Safety
Reference	Outside Japan	PX-171-001	I	Progressive haematopoietic malignancy	29	Intravenous carfilzomib 1.2, 2.4, 4.0, 6.0, 8.4, 11, 15, or 20 mg/m^2 once daily on Day 1 through Day 5 of each 14-day cycle	Safety PK
		PX-171-008	Ib	Progressive solid cancer	18	Period 1: A single oral midazolam 2 mg Period 2: Intravenous carfilzomib 27 mg/m^2 on Days 1, 2, 8, 9, 15, and 16, oral midazolam 2 mg on Days 1 and 16	Safety PK
		PX-171-007	Ib/II	Progressive solid cancer or haematopoietic malignancy	79 (a) 14 (b) 65	(a) Phase Ib: Intravenous carfilzomib 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16, or 20/27 mg/m^2 or 20/36 mg/m^2 of each 28-day cycle. (b) Phase II part: Carfilzomib 20/36 mg/m^2	Safety PK
		PX-171-003 Part 1 (A0)	II	Relapsed or refractory MM	46	Intravenous carfilzomib 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle	Safety
		PX-171-004	II	Relapsed or refractory MM	164	Intravenous carfilzomib 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, or 20/27 mg/m^2	Efficacy Safety
		PX-171-005	II	Relapsed or refractory MM including patients with renal impairment	50	Intravenous carfilzomib 15 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle	Safety PK

Data category	Site	Study	Phase	Target patients	N	Main dosing regimen	Main objective
		PX-171-010	II	Patients with solid cancer or MM who completed carfilzomib clinical study	62	The same regimen of carfilzomib as that used at the last visit for the previous clinical study of carfilzomib	Safety Efficacy
		2011-002	CU	Relapsed or refractory MM	338	Carfilzomib 20/27 mg/m^2	Safety Efficacy

CU, compassionate use; [*1] Dose omission on Days 8 and 9 was allowed from Cycle 10 onward; [*2] Alternate-day administration of prednisolone 30 mg or DEX 6 mg, or an equivalent corticosteroid regimen

The following sections summarize the clinical studies.
Major adverse events observed in the studies except for deaths are described in Section "7.3 Adverse events and other findings observed in clinical studies," and study results related to pharmacokinetics in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods," and "6.2 Clinical pharmacology studies."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I/II study (CTD 5.3.5.2-1, Study ONO-7057-01 [ongoing since [redacted] 20[redacted], data cut-off on [redacted] [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 9 to 18 subjects in the phase I, and 24 subjects in the phase II) in 15 centers in Japan to investigate the tolerability, safety, pharmacokinetics, and efficacy of carfilzomib.

In the phase I, patients received 15 or 20 mg/m^2 of intravenous carfilzomib once daily on Days 1, 2, 8, 9, 15, and 16 of 28-day cycles, or 20/27 mg/m^2. In the phase II, patients received 20/27 mg/m^2 of intravenous carfilzomib.

All 17 subjects (4 in the 15 mg/m^2 group, 6 in the 20 mg/m^2 group, and 7 in the 20/27 mg/m^2 group) enrolled in the phase I part and all 33 subjects enrolled in the phase II part were included in the efficacy analysis set. These subjects were also included in the safety analysis set.

In Cycle 1 of the phase I, the predefined dose limiting toxicity (DLT) assessment period, DLT was observed in 1 of 6 subjects (Grade 4 thrombotic microangiopathy [TMA]/cardiomyopathy/liver disorder/sensorimotor disorder) in the 20 mg/m^2 group, but was not observed in the 20/27 mg/m^2 group. Therefore, it was determined that carfilzomib 20/27 mg/m^2 is tolerable.

The primary endpoint of efficacy was the response rate (percentage of sCR, CR, VGPR, or PR) according to the IMWG criteria (e.g., *Leukemia*. 2006;20:1467-73). In the phase I, the response rate during the evaluation period (30 days after the final dose of carfilzomib, or starting date of other treatment after the final dose, whichever comes first) at 15 mg/m^2 and 20 mg/m^2 was 25% (95% CI, 4.6%-69.9%) and 0% (95% CI, 0.0%-39.0%), respectively. Table 17 shows the best overall response and the response rate of 40 subjects who received carfilzomib 20/27 mg/m^2 (7 in the phase I, 33 in the phase II) in the evaluation period (30 days after the final dose of carfilzomib, or starting date of other treatment after the final dose, whichever comes first). The threshold response rate specified in advance was 5%.

Table 17. Best overall response
(determined by the investigator, at 20/27 mg/m^2, data cut-off on [redacted])

Best overall response	Number of subjects (%) 40
sCR	0
CR	0
VGPR	2 (5.0)
PR	7 (17.5)
SD	18 (45.0)
PD	9 (22.5)
NE	4 (10.0)
Response (sCR, CR, VGPR, or PR)	9
(Response rate (%), [95% CI*])	(22.5 [12.3-37.5])

* Normal approximation by WILSON's method

In both phases of the study, there were no deaths during carfilzomib treatment or within 30 days of the last dose.

7.1.1.2 Japanese phase I study CTD 5.3.5.2-12, Study ONO-7057-05 [ongoing since [redacted], data cut-off on [redacted])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 26 subjects) in 9 centers in Japan to investigate the safety, tolerability, efficacy, and pharmacokinetics of the CLd regimen.

Subjects received 20/27 mg/m^2 of intravenous carfilzomib for 12 cycles. From Cycles 13 through 18, 27 mg/m^2 of intravenous carfilzomib was administered once daily on Days 1, 2, 15, and 16. The Ld regimen consisted of 28-day cycles. In the regimen, oral lenalidomide 25 mg was administered on Days 1 through Days 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22. Treatment with these study drugs for >18 cycles were not allowed.

All 26 subjects enrolled were included in the efficacy analysis set, and they were also included in the safety analysis set. In the protocol revised on [redacted], the target sample size was changed from 6 to 26 subjects, and the threshold response rate for efficacy evaluation was set at 66.7%, based on the Ld regimen response rate (66.7%) of the control group in the foreign phase III study (Study 009).

Table 18 shows the best overall response and the response rates determined by the investigator according to the IMWG criteria in the evaluation period (30 days after the final dose of carfilzomib, or starting date of other treatment after the final dose, whichever comes first). The lower limit of the 90% confidence interval for response rate was 72.8%, which is greater than the prescribed threshold response rate of 66.7%.

Table 18. Best overall response (determined by the investigator, efficacy analysis set, data cut-off on [redacted])

Best overall response	Number of subjects (%) 26 subjects
sCR	0
CR	1 (3.8)
VGPR	5 (19.2)
PR	17 (65.4)
MR*	1 (3.8)
SD	2 (7.7)
PD	0
NE	0
Response (sCR, CR, VGPR, or PR) (Response rate (%) [90% CI])	23 (88.5 [72.8-96.8])

* Evaluation was based on the EBMT criteria (*Br J Haematol.* 1998;102:1115-23). Of the subjects categorized as SD according to the IMWG criteria, 1 patient was categorized as minimum response (MR) according to the EBMT criteria.

There were no deaths during carfilzomib treatment or within 30 days of the end of treatment.

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase I study (CTD 5.3.5.2-3, Study PX-171-002, Part 1 [September 2005 to [redacted]])

An open-label uncontrolled study was conducted in patients with progressive haematopoietic malignancies (target sample size, 50 subjects) in 3 centers outside Japan to investigate the safety, tolerability, and pharmacokinetics of carfilzomib.

Patients received intravenous carfilzomib at 1.2, 2.4, 4.0, 6.0, 8.4, 11, 15, 20, 27, or 36 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The treatment was repeated for 12 cycles.

All 37 subjects enrolled in the study (3 each in the 1.2, 2.4, 6.0, 8.4, and 15 mg/m^2 groups; 4 each in the 4.0 and 11 mg/m^2 groups; 8 in the 20 mg/m^2 group; and 6 in the 27 mg/m^2 group) were included in the safety analysis set.

In Cycle 1, the predefined DLT assessment period, DLT was observed in 1 subject each in the 1.2, 20, and 27 mg/m^2 groups (Grade 3 fatigue/AST increased, Grade 3 renal failure, and Grade 3 hypoxia, respectively). At 27 mg/m^2, although MTD was not reached, 3 of 6 the subjects (50.0%) experienced adverse events attributable to tumour lysis syndrome. Therefore, the 36-mg/m^2 dose was not studied.

The safety analysis revealed 2 deaths during the treatment or within 30 days from the last dose in the 37 subjects (5.4%). One of 3 subjects (33.3%) in the 2.4 mg/m^2 group and another was 1 of 6 subjects (16.7%) in the 27 mg/m^2 group. The cause of death of the subject receiving the 2.4-mg/m^2 dose was infection, for which a causal relationship to carfilzomib could not be ruled out. The subject receiving the 27-mg/m^2 dose died due to disease progression.

7.1.2.2 Foreign phase I study (CTD 5.3.5.2-4, Study PX-171-002, Part 2 [[redacted] to October 2009])

An open-label uncontrolled study was conducted in patients with progressive haematopoietic malignancies (target sample size, 24 subjects in the carfilzomib monotherapy cohort, and 12 subjects in the carfilzomib/DEX combination therapy cohort) in 5 centers outside Japan to investigate the safety, tolerability, and pharmacokinetics of carfilzomib.

Patients received intravenous carfilzomib once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, at 20 mg/m^2 in Cycle 1 and 27 mg/m^2 from Cycle 2 onward. The treatment was repeated for 12 cycles. In the carfilzomib/DEX cohort, 20 mg of oral DEX was administered prior to the treatment with carfilzomib. The dose titration of carfilzomib from 20 mg/m^2 to 27 mg/m^2 was initially planned at Week 2 of Cycle 1. However, 2 of 3 subjects enrolled experienced adverse events including increased blood creatinine attributable to tumor lysis. Therefore, the protocol was revised (dated [redacted], 20[redacted]) to change the dose titration period to Week 1 of Cycle 2.

A total of 11 subjects were enrolled in the study (7 in the carfilzomib monotherapy cohort, and 4 in the carfilzomib/DEX cohort) and were all included in the safety analysis set. Because tolerability during the dose titration from 20 mg/m^2 to 27 mg/m^2 was adequately evaluated in both Parts 1 and 2 of Study PX-171-002, Part 2 was terminated early after the 11th subject was enrolled.

In Cycle 1, the predefined DLT assessment period, DLT (Grade 3 ALT increased/AST increased/blood ALP increased) was observed in 1 subject in the carfilzomib/DEX cohort.

The safely analysis revealed deaths of 1 of 7 subjects (14.3%) in the carfilzomib monotherapy cohort and 1 of 4 subjects (25.0%) in the carfilzomib/DEX cohort during treatment or within 30 days from the last dose. The cause of death was disease progression for both cases, and a causal relationship to carfilzomib was ruled out.

7.1.2.3 Foreign phase II study (CTD 5.3.5.2-6, Study PX-171-003, Part 2 [A1] [[redacted] 20[redacted] to October 2012])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 250 subjects) in 31 centers outside Japan to evaluate the efficacy and safety of carfilzomib.

Patients received carfilzomib intravenously once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for 12 cycles at 20 mg/m^2 in Cycle 1 and 27 mg/m^2 from Cycle 2 onward.

All 266 subjects enrolled in the study were included in the safety analysis set. The efficacy analysis set consisted of 257 subjects who had efficacy evaluations at baseline and at least once during treatment.

The primary endpoint was the best overall response and the response rate determined by the Independent Review Committee (IRC) according to the IMWG criteria (Table 19). The prescribed threshold response rate was 10%.

Table 19. Best overall response (determined by the Independent Review Committee, efficacy analysis set, data cut-off on [redacted], 20[redacted])

Best overall response	N (%) 257
sCR	0
CR	1 (0.4)
VGPR	13 (5.1)
PR	47 (18.3)
MR*	34 (13.2)
SD	81 (31.5)
PD	69 (26.8)
NE	12 (4.7)
Response (sCR, CR, VGPR, or PR) (Response rate (%) [95% CI])	61 (23.7 [18.67-29.42])

* Evaluation was based on EBMT criteria (*Br J Haematol*. 1998;102:1115-23). Of the subjects categorized as SD according to the IMWG criteria, those categorized as MR by the EBMT criteria were excluded.

The safety analysis revealed deaths of 24 of 266 subjects (9.0%) during carfilzomib treatment or within 30 days of the last dose. Besides disease progression in 14 patients, other causes of death were cardiac arrest (3 subjects), hepatic failure (2 subjects), sepsis, dyspnoea, pneumonia, cerebral haemorrhage, and unknown cause (1 subject each). A causal relationship to carfilzomib could not be ruled out for cardiac arrest (3 subjects), hepatic failure (2 subjects), dyspnoea, pneumonia, and unknown cause (1 subject each).

7.1.2.4 Foreign phase 1b study (CTD 5.3.5.2-10, Study PX-171-006 [May 2008 to May 2013])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, approximately 40 subjects for the dose escalation part, and 30 subjects for the dose expansion part) in 11 centers outside Japan to evaluate the safety and MTD of the CLd regimen.

In the dose escalation part of the study, patients received intravenous carfilzomib 15 or 20 mg/m^2 once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle, or 20/27 mg/m^2; oral lenalidomide 10, 15, 20, or 25 mg on Day 1 through Day 21; and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22. In the dose expansion part of the study, patients received intravenous carfilzomib 20/27 mg/m^2, oral lenalidomide 25 mg on Day 1 through Day 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22. This regimen was repeated through Cycle 12. From Cycle 13 onward, the doses on Days 8 and 9 could optionally be omitted.

All 84 subjects enrolled in the study (40 for the dose escalation part, and 44 for the dose expansion part) were included in the safety analysis set. Of these, 83 subjects were included in the efficacy analysis set, and 1 subject was excluded because of not undergoing efficacy evaluation during treatment.

Cycle 1 was defined as DLT assessment period. DLT (Grade 4 neutropenia) was observed in 1 of 8 subjects in the 20/27 mg/m^2 arm of the dose escalation part.

The safety analysis revealed deaths of 3 of the 84 subjects (3.6%) during carfilzomib treatment or within 30 days of the last dose. All 3 deaths occurred in the carfilzomib 20/27 mg/m^2 arm (3 of 52 subjects, 5.8%). The cause of death for all 3 cases was disease progression, and its causal relationship to carfilzomib was ruled out.

7.1.2.5 Foreign phase III study (CTD 5.3.5.1-1, Study PX-171-009 [ongoing since in July 2010, data cut-off on June 16, 2014])

An open-label randomized study in patients with relapsed or refractory MM (target sample size, 780 subjects) in 129 centers outside Japan for the comparison of efficacy and safety between the CLd regimen and the Ld regimen.

Subjects received intravenous carfilzomib 20/27 mg/m^2 from Cycle 1 through Cycle 12. From Cycle 13 through Cycle 18, carfilzomib 27 mg/m^2 was administered intravenously once daily on Days 1, 2, 15, and 16. In the Ld regimen in 28-day cycles, subjects received oral lenalidomide 25 mg on Day 1 through Day 21, and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22. From Cycle 19 onward, subjects in the CLd arm continued treatment only with the Ld regimen, while those in the Ld arm continued with the dosing regimen used until Cycle 18.

The efficacy analysis set was the intent-to-treat (ITT) population, consisting of 792 subjects enrolled in the study and randomized (396 each in the CLd and Ld arms). A total of 4 subjects in the CLd arm and 7 subjects in the Ld arm did not receive the study drug. The remaining 781 subjects (392 in the CLd arm and 389 in the Ld arm) were included in the safety analysis set.

The primary endpoint was PFS assessed by the IRC according to the IMWG criteria. Two interim analyses were planned. The first interim analysis was to be performed approximately 15 months after the randomization of the first patient (planned enrollment period, approximately 18 months) to re-evaluate the sample size. The second interim analysis was planned to evaluate efficacy when 80% of the

targeted number of PFS events of 526 (approximately 420 events) was achieved. The O'Brien-Fleming type alpha-spending function based on Lan-DeMets method was used for the adjustment of the significance level required for the interim analyses. The first interim analysis was conducted by independent data monitoring committee (IDMC) in [redacted] 20[redacted]. Based on the total number of PFS events observed in both arms, the planned sample size was increased from 700 to 780 subjects to shorten the time to reach the targeted number of PFS events of 526. The results of the second interim analysis indicated significant prolongation of PFS in the CLd arm; therefore, the study was discontinued prematurely as recommended by IDMC.

Table 20 and Figure 1 show the results of PFS in the second interim analysis, indicating that the superiority of the CLd regimen to the Ld regimen.

Table 20. PFS in the second interim analysis (determined by the IRC, ITT population, data cut-off on June 16, 2014)

	CLd	Ld
N	396	396
Death or disease progression (%)	207 (52.3)	224 (56.6)
Median [95% CI] (months)	26.3 [23.3-30.5]	17.6 [15.0-20.6]
Hazard ratio[*1] [95% CI]	0.69 [0.57-0.83]	
P-value (one-sided)[*2]	<0.0001	

[*1] Calculated using a Cox proportional hazard model adjusted with the following stratification factors: baseline β2 microglobulin level (<2.5 mg/L vs. ≥2.5 mg/L), prior treatment with bortezomib, and prior treatment with lenalidomide; [*2] stratified log-rank test (with the same stratification factors as the Cox proportional hazard model), one-sided significance level, 0.0127.

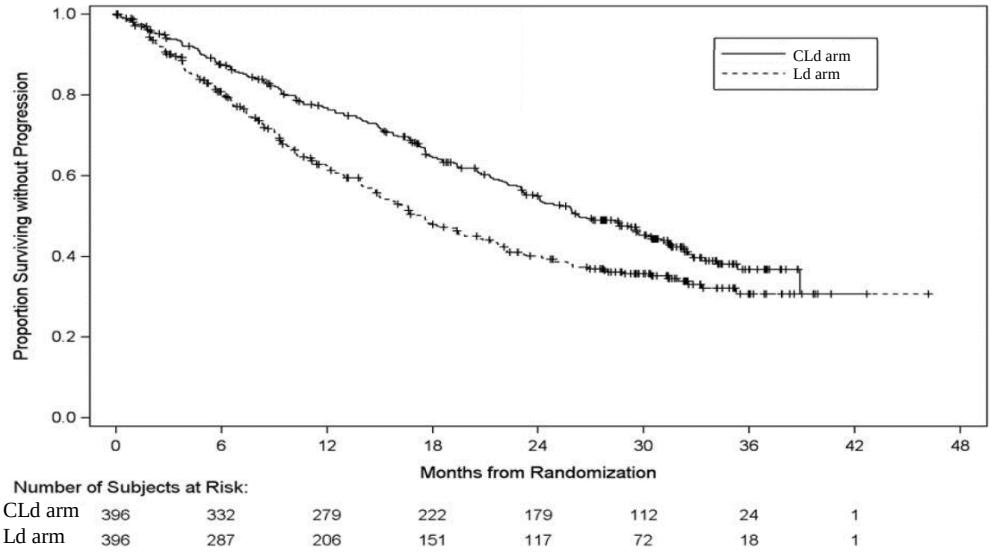


Figure 1. Kaplan-Meier plot of PFS in the second interim analysis (determined by IRC, ITT population, data cut-off on June 16, 2014)

The safety analysis revealed deaths of 30 of 396 subjects (7.7%) in the CLd arm, and 33 of 396 subjects (8.5%) in the Ld arm during carfilzomib treatment or within 30 days of the last dose. Besides disease progression (2 subjects in the CLd arm and 6 subjects in the Ld arm), the causes of deaths were myocardial infarction and sepsis (3 subjects each), cardiac arrest, bronchopneumonia, acute respiratory distress syndrome, and death (2 subjects each), cardiac failure, cardiac failure acute, circulatory collapse, left ventricular dysfunction, cardiopulmonary failure, septic shock, endocarditis, pneumonia, upper respiratory tract infection, subdural haematoma, haemorrhage intracranial, multi-organ failure, sudden death, and completed suicide (1 subject each) in the CLd arm; cardiac failure, sepsis, septic shock,

pneumonia, death, and myelodysplastic syndrome (2 subjects each), cardiac failure/lung disorder, myocardial infarction, arrhythmia, cardiopulmonary failure, acute coronary syndrome, urosepsis, pneumonia viral, bronchopneumonia, hepatic infection, acute kidney injury, multi-organ failure, sudden death, pulmonary embolism, coma, and respiratory failure (1 subject each) in the Ld arm. A causal relationship to the study drug could not be ruled out for cardiac arrest, sepsis, pneumonia, and haemorrhage intracranial (1 subject each) in the CLd arm, acute coronary syndrome, septic shock, sepsis, hepatic infection, acute kidney injury, pulmonary embolism, myelodysplastic syndrome, and respiratory failure (1 subject each) in the Ld arm.

7.1.2.6 Foreign phase III study (CTD 5.3.5.1-2, Study PX-171-011 [September 2010 to July 2014])

An open-label randomized study was conducted in patients with relapsed or refractory MM (target sample size, 302 subjects) in 77 centers outside Japan for the comparison of the efficacy and safety between carfilzomib monotherapy and best supportive care (BSC).

In the carfilzomib monotherapy arm, patients received intravenous carfilzomib 20/27 mg/m^2 from Cycle 1 through Cycle 9. From Cycle 10 onward, dose omission was allowed on Days 8 and 9. In the BSC arm, patients received oral or intravenous corticosteroids[15] equivalent to a maximum of 84 mg of DEX per 28-day cycle, with optional cyclophosphamide hydrate 50 mg once daily.

The efficacy analysis set was the ITT population, consisting of all 315 subjects enrolled in the study (157 in the carfilzomib monotherapy arm and 158 in the BSC arm). Of these, 5 subjects did not receive the study drug, and the remaining 310 subjects (157 in the carfilzomib monotherapy arm and 153 in the BSC arm) were included in the safety analysis set.

The primary endpoint was overall survival (OS). The target number of OS events was 253. An interim efficacy analysis was planned to be performed when 75% of the target number of OS events (189 events) occurred. The O'Brien-Fleming type alpha-spending function based on Lan-DeMets method was used for the adjustment of the significance level required for the interim analysis. The interim analysis was actually conducted when 197 OS events occurred. The IDMC recommended to continue the study.

Table 21 and Figure 2 show the results of final OS analysis. The results do not show the superiority of the carfilzomib monotherapy arm over the BSC arm.

Table 21. Final OS analysis (ITT population, data cut-off on July 10, 2014)

	Carfilzomib	BSC
N	157	158
Deaths (%)	129 (82.2)	125 (79.1)
Median [95% CI] (months)	10.2 [8.4-14.4]	10.0 [7.7-12.0]
Hazard ratio[*1] [95% CI]	0.975 [0.760-1.249]	
P-value (one-sided)[*2]	0.4172	

[*1] Calculated using a Cox proportional hazard model adjusted with the following stratification factors: number of previous therapies (3 vs. 4 vs. ≥5) and geographical region (Europe vs. non-Europe); [*2] stratified log-rank test (with the same stratification factors as the Cox proportional hazard model), one-sided significance level, 0.0217.

[15] Alternate-day administration of prednisolone 30 mg or DEX 6 mg, or a corticosteroid regimen equivalent to one of these.

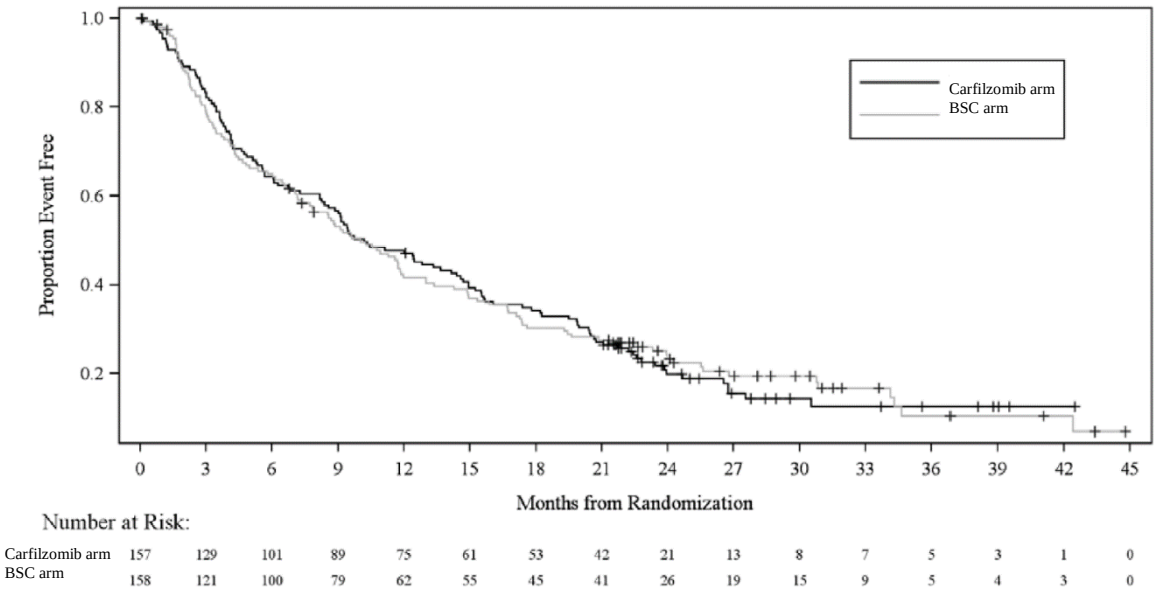


Figure 2. Kaplan-Meier plot of the final OS analysis (ITT population, data cut-off on July 10, 2014)

The safety analysis revealed deaths of 29 of the 157 subjects (18.5%) in the carfilzomib arm, and 34 of the 153 subjects (22.2%) in the BSC arm during carfilzomib treatment or within 30 days from the end of treatment. Besides disease progression (13 subjects in the carfilzomib arm and 14 subjects in the BSC arm), causes of deaths were in the carfilzomib arm were cardiac arrest, acute kidney injury, and multi-organ failure (2 subjects each), cardio-respiratory arrest, cardiac failure, cardiac failure acute, pulmonary oedema, bronchopneumonia, pneumonia, sepsis, staphylococcal sepsis, kidney infection, and upper gastrointestinal haemorrhage (1 subject each); and in the BSC arm were pneumonia (7 subjects), septic shock (2 subjects), cardiac failure, cardiac arrest, acute pulmonary oedema, bronchopneumonia, sepsis, neutropenic sepsis, pulmonary haemorrhage, acute myeloid leukaemia, bronchitis, general physical health deterioration, and death (1 subject each). A causal relationship to the study drug could not be ruled out for cardiac failure (1 subject) in the carfilzomib arm, and pneumonia (2 subjects) and septic shock (1 subject) in the BSC arm.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The results from the following studies were submitted as data from pharmacology studies [see Section 6.2.2]. There were no deaths during the study period of 2 studies summarized in Sections 7.2.1.1 and 7.2.1.2, which were conducted in patients.

7.2.1.1 Foreign phase I study (CTD 5.3.5.2-2, Study PX-171-001 [October 2005 to [redacted] 20[redacted]])

7.2.1.2 Foreign phase Ib study (CTD 5.3.3.4-1, Study PX-171-008 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.2.2 Foreign clinical studies

7.2.2.1 Foreign phase Ib/II study (CTD 5.3.5.2-11, Study PX-171-007 [ongoing since September 2007, data cut-off on [redacted] [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in patients with progressive solid cancers or haematopoietic malignancies (target sample size, 235 subjects) in 5 centers outside Japan to evaluate the safety, tolerability, and efficacy of carfilzomib.

All 79 subjects enrolled in the study (14 in the phase Ib and 65 in the phase II) were included in the safety analysis set. The phase II had 5 cohorts by cancer type (e.g., non-small cell lung cancer), and initially each cohort was planned to enroll 14 subjects and to have additional subjects until up to 16 when ≥1 subject responded to the treatment. After that, however, a new cohort was added in the phase Ib. In the new cohort, infusion time of carfilzomib was extended to 30 minutes (extended from 2- to 10-

minutes). Then, the enrollment in the phase II study, in which carfilzomib was infused for a 2- to 10-minutes, was closed when 65 subjects were enrolled.

The safety analysis revealed deaths of 4 of the 79 subjects (5.1%) during treatment or within 30 days of the last dose. The cause of deaths was disease progression for all cases, and a causal relationship to carfilzomib was ruled out.

7.2.2.2 Foreign phase II study (CTD 5.3.5.2-5, Study PX-171-003, Part 1 [A0] [August 2007 to October 2012])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 20 to 40 subjects) in 12 centers outside Japan to evaluate the efficacy and safety of carfilzomib.

All 46 subjects enrolled in the study were included in the safety analysis set.

The safety analysis revealed deaths of 4 of the 46 subjects (8.7%) during treatment or within 30 days of the last dose. The cause of death was disease progression for all cases, and a causal relationship to carfilzomib was ruled out.

7.2.2.3 Foreign phase II study (CTD 5.3.5.2-7, Study PX-171-004 [September 2007 to January 2013])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, about 155 subjects) in 19 centers outside Japan to evaluate the efficacy and safety of carfilzomib.

All 164 subjects enrolled in the study were included in the safety analysis set.

The safety analysis revealed deaths of 4 of the 164 subjects (2.4%) during carfilzomib treatment or within 30 days of the last dose. The death of 1 of the 94 subjects (1.1%) in the 20 mg/m^2 arm was due to multi-organ failure, and 3 of 70 subjects (4.3%) in the 20/27 mg/m^2 arm died from cardiac disorder, acute kidney injury, and disease progression (1 subject each). A causal relationship to carfilzomib could not be ruled out for multi-organ failure and cardiac disorder.

7.2.2.4 Foreign phase II study (CTD 5.3.5.2-9, Study PX-171-005 [November 2008 to November 2012])

An open-label uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 36 subjects) in 5 centers outside Japan to evaluate the safety and pharmacokinetics of carfilzomib.

All 50 subjects enrolled in the study were included in the safety analysis set.

The safety analysis revealed deaths of 7 of the 50 subjects (14%) during treatment or within 30 days of the last dose. The cause of death, except disease progression in 6 subjects, was pneumonia bacterial in 1 subject, for which a causal relationship to carfilzomib was ruled out.

7.2.2.5 Foreign phase II study (CTD 5.3.5.4-1, Study PX-171-010 [ongoing since [redacted] 20[redacted], data cut-off on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in 17 centers outside Japan to evaluate the safety and efficacy of carfilzomib in long-term treatment. Study participants were patients with progressive solid cancers or MM who had completed a prior clinical study on carfilzomib with maintained antitumor effect rated as stable disease (SD) or greater.

Subjects were treated as per the dosage regimen of the prior clinical study on carfilzomib[16] followed until the last follow-up visit

Of 62 subjects[16] enrolled in the study, 3 subjects did not receive carfilzomib (2 in Study PX-171-005 and 1 in Study PX-171-003 Part 2 [A1]), and the remaining 59 subjects were included in the safety analysis set.

The safety analysis revealed no deaths during treatment or within 30 days of the last dose.

7.2.2.6 Foreign compassionate use study (CTD 5.3.5.4-2, Study 2011-002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An expanded access program for carfilzomib was conducted in patients with relapsed or refractory MM.

Patients received intravenous carfilzomib 20/27 mg/m^2 from Cycle 1 through Cycle 9, and intravenous carfilzomib once daily on Days 1, 2, 15, and 16 of from Cycle 10 onward.

Of 338 subjects enrolled in the study, 10 subjects did not receive carfilzomib. The remaining 328 subjects were included in the safety analysis set.

Of the 328 subjects, 34 (10.4%) died during treatment or within 30 days of the last dose. The causes of the deaths other than disease progression in 29 subjects were cerebral haemorrhage, haemorrhage intracranial, renal failure, sepsis, and unknown (1 subject each). A causal relationship to carfilzomib was ruled out for all these events.

7.R Outline of the review conducted by PMDA

7.R.1 Review policy

PMDA considers that Study 009, a foreign phase III study conducted in patients with relapsed or refractory MM, is the pivotal study for the evaluation of the efficacy and safety of carfilzomib.

The evaluation of the efficacy and safety of carfilzomib in Japanese patients will focus on Study 05, a Japanese phase I study conducted in patients with relapsed or refractory MM to evaluate the safety and efficacy of the CLd regimen.

7.R.2 Efficacy

After the discussions in the following subsections, PMDA concluded that the efficacy of carfilzomib in the treatment of relapsed or refractory MM was demonstrated.

7.R.2.1 Control arm

The applicant's rationale for the use of the control arm in Study 009:
Study 009 was planned in 2009. At that time, outside Japan, the IMWG guidelines for the management of MM patients (*Leukemia.* 2009;23:1716-30) recommended the Ld regimen[17] for the treatment of relapsed or refractory MM, the indication of carfilzomib in Study 009, based on the results of foreign clinical studies (e.g., *New Engl J Med.* 2007;357:2123-32). In Japan, *the Guideline for the Treatment of Multiple Myeloma,* second ed. [in Japanese] (Tokyo: Bunkodo Co., Ltd.; 2008), recommended salvage therapy with lenalidomide for relapsed MM after chemotherapy based on the above-mentioned foreign clinical studies. Also, in a foreign clinical study conducted in patients with untreated MM, the Ld regimen resulted in longer PFS than the LD regimen (median PFS in the LD and Ld regimens, 19.1 and 25.3 months, respectively) (*J Clin Oncol.* 2007;25(18 suppl). Paper presented at: ASCO Annual Meeting 2007. Abstract 8025. *Lancet Oncol.* 2010;11:29-37).

---

[16] These studies were: Studies PX-171-002, PX-171-003 Part 1 (A0), PX-171-003 Part 2 (A1), PX-171-004 Part 1, PX-171-004 Part 2, PX-171-005, PX-171-006, PX-171-007, and PX-171-008. The numbers of subjects enrolled in these prior studies were 1, 1, 22, 1, 21, 6, 1, 4, and 5, respectively.

[17] In 28-day cycles, subjects received lenalidomide 25 mg on Day 1 through Day 21 and DEX 40 mg on Day 1 through Day 4, Day 9 through Day 12, and Day 17 through Day 20.

Accordingly, the Ld regimen was used as a control group in Study 009.

PMDA accepted the applicant's explanation.

7.R.2.2 Primary endpoint

The applicant's rationale for selecting PFS as the primary endpoint of Study 009:
Because of the intractable nature of the disease, treatment of relapsed or refractory MM is aimed to extend the lives of patients, and thus PFS is a recommended endpoint to show clinical study data on the treatment of the disease (*Leukemia.* 2006;20:1467-73). Therefore, PFS was selected as the primary endpoint of Study 009, which was conducted in patients with relapsed or refractory MM.

PMDA's view:
The applicant's explanation is reasonable. However, because of a lack of standard therapies established for relapsed or refractory MM, OS should also be an important endpoint to assess the efficacy of treatment for the disease. Therefore, the efficacy of carfilzomib will be evaluated based primarily on PFS, and the OS data will also be referred.

7.R.2.3 Results of efficacy evaluation

The results of PFS assessed by IRC using the IMWG criteria, the primary endpoint for Study 009, demonstrated the superiority of the CLd arm over the Ld arm [see Section 7.1.2.5]. The revised study protocol dated [redacted], 20[redacted] required an interim analysis of OS, one of the secondary endpoints if the results of the primary PFS analysis (the second interim or final analysis) indicated a significant increase in PFS in the CLd arm, as well as the final OS analysis after the deaths of 510 subjects. The O'Brien-Fleming type alpha-spending function based on Lan-DeMets method was used for the adjustment of the significance level required for the interim OS analysis.

Table 22 and Figure 3 show the results of the interim OS analysis. The protocol specified that the study be continued until the final OS analysis if OS did not meet the efficacy criteria for early termination in the interim analysis, and the results of interim OS analysis did not meet the efficacy criteria for early termination. Results of the final OS analysis will be available in the first quarter of 2018.

Table 22. The interim OS analysis (ITT population, data cut-off on June 16, 2014)

	CLd	Ld
N	396	396
Deaths (%)	143 (36.1)	162 (40.9)
Median [95% CI] (months)	– [–, –]	– [32.1, –]
Hazard ratio[*1] [95% CI]	0.787 [0.628-0.985]	
P-value (one-sided)[*2]	0.0182	

–, Unable to be estimated; [*1] Calculated using a Cox proportional hazard model adjusted with the following stratification factors: baseline β2 microglobulin level (<2.5 mg/L and ≥2.5 mg/L), prior treatment with bortezomib, and prior treatment with lenalidomide; [*2] stratified log-rank test (with the same stratification factors as the Cox proportional hazard model); one-sided significance level, 0.0051.

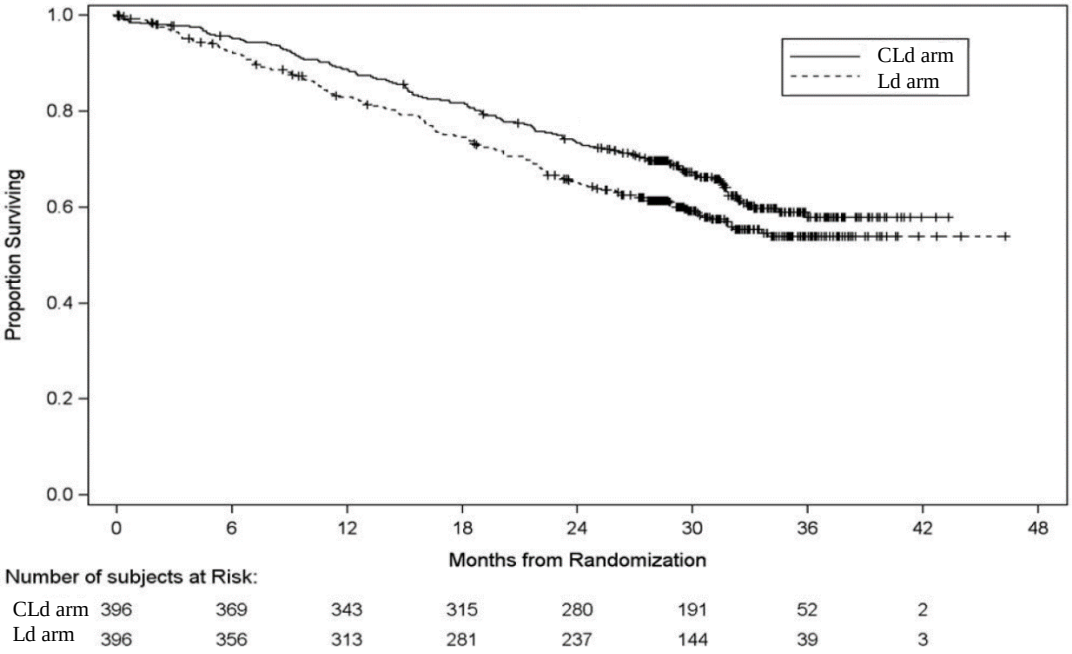


Figure 3. Kaplan-Meier plot of the interim OS analysis (ITT population, data cut-off on June 16, 2014)

PMDA's conclusion:
The efficacy of the CLd regimen in the target patients of Study 009 was demonstrated for the reasons listed below. Further, the results of the final OS analysis for Study 009 should be communicated to healthcare professionals through written materials or handled in any appropriate manner as soon as available.

- The results of IRC-assessed PFS, the primary endpoint of Study 009, demonstrated the superiority of the CLd regimen to the Ld regimen.

- The results of the interim OS analysis (data cut-off on June 16, 2014) did not show the inferiority of the CLd regimen to the Ld regimen.

7.R.2.4 Efficacy of carfilzomib in Japanese patients

The applicant's explanation about the efficacy of carfilzomib in Japanese patients:
The response rate in Study 05 based on the IMWG criteria, the efficacy endpoint, was 88.5% (90% CI, 72.8%-96.8%) (23 of 26 subjects). The lower limit of the 90% confidence interval was higher than the threshold response rate (66.7%). In Study 009, the IMWG criteria-based response rate was 87.1% (95% CI, 83.4%-90.3%) (345 of 396 subjects) in the CLd arm, and 66.7% (95% CI, 61.8%-71.3%) (264 of 396 subjects) in the Ld arm. The response rate in Study 05 was higher than that of the Ld arm in Study 009, similarly to the response rate the CLd arm in Study 009. Based on the above, carfilzomib is expected to be effective in Japanese patients with relapsed or refractory MM as in non-Japanese patients.

PMDA accepted the applicant's explanation.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events and other findings observed in clinical studies"]

PMDA's view
Based on the discussions in the following subsections, adverse events of particular concern during treatment with carfilzomib are: cardiac disorder, interstitial lung disease (ILD), pulmonary hypertension, haematotoxicity, infection, liver disorder, renal disorder, haemorrhage, infusion-related reaction (IRR), tumor lysis syndrome (TLS), hypertension including hypertensive crisis, venous thromboembolism, posterior reversible encephalopathy syndrome (PRES), encephalopathy, TMA, gastrointestinal

perforation, pericarditis, and pericardial effusion. Careful vigilance is required against these adverse events during the use of carfilzomib. However, carfilzomib is tolerable with appropriate follow-up by a physician with sufficient knowledge and experience in the treatment of haematopoietic malignancies, in particular, monitoring and control of adverse events and dose adjustment by means of dose suspension or reduction or treatment discontinuation.

7.R.3.1 Safety profile of carfilzomib

Table 23 summarizes the safety data obtained from foreign clinical studies (Studies 009 and 011) that were conducted in patients with relapsed or refractory MM.

Table 23. Summary of safety data (Studies 009 and 011)

	N (%)			
	Study 009		Study 011	
	CLd N = 392	Ld N = 389	Carfilzomib N = 157	BSC N = 153
All adverse events	380 (96.9)	380 (97.7)	154 (98.1)	143 (93.5)
Adverse events, Grade ≥3	328 (83.7)	316 (81.2)	118 (75.2)	109 (71.2)
Adverse events resulting in death	36 (9.2)	36 (9.3)	29 (18.5)	34 (22.2)
Serious adverse events	235 (59.9)	210 (54.0)	92 (58.6)	78 (51.0)
Adverse events leading to discontinuation of treatment	102 (26.0)	98 (25.2)	23 (14.6)	31 (20.3)
Adverse events leading to suspension of treatment	290 (74.0)	219 (56.3)	59 (37.6)	28 (18.3)
Adverse events leading to dose reduction	223 (56.9)	202 (51.9)	9 (5.7)	19 (12.4)

Table 24 shows adverse events that occurred at an incidence of ≥10% in any arm in Studies 009 and 011.

Table 24. Adverse events occurring at an incidence of ≥10% in any arm (Studies 009 and 011)

Preferred term (PT) (MedDRA/J ver. 15.1)	N (%)							
	Study 009				Study 011			
	CLd		Ld		Carfilzomib		BSC	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	380 (96.9	328 (83.7)	380 (97.7)	316 (81.2)	154 (98.1)	118 (75.2)	143 (93.5)	109 (71.2)
Anaemia	169 (43.1	70 (17.9)	155 (39.8)	69 (17.7)	88 (56.1)	40 (25.5)	74 (48.4)	47 (30.7)
Diarrhoea	166 (42.3	15 (3.8)	131 (33.7)	16 (4.1)	24 (15.3)	4 (2.5)	18 (11.8)	2 (1.3)
Neutropenia	148 (37.8	116 (29.6)	131 (33.7)	103 (26.5)	23 (14.6)	12 (7.6)	26 (17.0)	19 (12.4)
Fatigue	129 (32.9	30 (7.7)	120 (30.8)	25 (6.4)	29 (18.5)	2 (1.3)	28 (18.3)	2 (1.3)
Thrombocytopenia	115 (29.3	66 (16.8)	89 (22.9)	48 (12.3)	59 (37.6)	38 (24.2)	46 (30.1)	34 (22.2)
Cough	113 (28.8	1 (0.3)	69 (17.7)	0	19 (12.1)	1 (0.6)	10 (6.5)	1 (0.7)
Pyrexia	112 (28.6	7 (1.8)	81 (20.8)	2 (0.5)	44 (28.0)	5 (3.2)	30 (19.6)	0
Upper respiratory tract infection	112 (28.6	7 (1.8)	76 (19.5)	4 (1.0)	16 (10.2)	2 (1.3)	3 (2.0)	0

Preferred term (PT) (MedDRA/J ver. 15.1)	N (%)							
	Study 009				Study 011			
	CLd		Ld		Carfilzomib		BSC	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypokalaemia	108 (27.6	37 (9.4)	52 (13.4)	19 (4.9)	14 (8.9)	3 (1.9)	13 (8.5)	1 (0.7)
Muscle spasms	104 (26.5	4 (1.0)	82 (21.1)	3 (0.8)	8 (5.1)	0	7 (4.6)	0
Oedema peripheral	85 (21.7	5 (1.3)	75 (19.3)	2 (0.5)	17 (10.8)	0	12 (7.8)	0
Nasopharyngitis	84 (21.4	1 (0.3)	63 (16.2)	0	14 (8.9)	0	10 (6.5)	0
Constipation	79 (20.2	1 (0.3)	67 (17.2)	2 (0.5)	10 (6.4)	0	20 (13.1)	1 (0.7)
Nausea	78 (19.9	2 (0.5)	55 (14.1)	4 (1.0)	32 (20.4)	2 (1.3)	14 (9.2)	2 (1.3)
Insomnia	77 (19.6	11 (2.8)	64 (16.5)	11 (2.8)	4 (2.5)	0	18 (11.8)	2 (1.3)
Dyspnoea	77 (19.6	11 (2.8)	58 (14.9)	7 (1.8)	23 (14.6)	2 (1.3)	13 (8.5)	0
Bronchitis	74 (18.9	7 (1.8)	54 (13.9)	7 (1.8)	15 (9.6)	3 (1.9)	14 (9.2)	2 (1.3)
Asthenia	73 (18.6	14 (3.6)	56 (14.4)	8 (2.1)	26 (16.6)	4 (2.5)	21 (13.7)	5 (3.3)
Back pain	69 (17.6	5 (1.3)	80 (20.6)	8 (2.1)	16 (10.2)	5 (3.2)	18 (11.8)	2 (1.3)
Pneumonia	68 (17.3	49 (12.5)	56 (14.4)	41 (10.5)	12 (7.6)	10 (6.4)	20 (13.1)	19 (12.4)
Hypocalcaemia	63 (16.1	13 (3.3)	46 (11.8)	7 (1.8)	11 (7.0)	3 (1.9)	10 (6.5)	2 (1.3)
Hypertension	57 (14.5	18 (4.6)	29 (7.5)	8 (2.1)	23 (14.6)	5 (3.2)	9 (5.9)	0
Headache	53 (13.5	3 (0.8)	31 (8.0)	2 (0.5)	17 (10.8)	1 (0.6)	6 (3.9)	0
Hypophosphataemia	52 (13.3	33 (8.4)	29 (7.5)	18 (4.6)	5 (3.2)	1 (0.6)	2 (1.3)	0
Rash	52 (13.3	5 (1.3)	60 (15.4)	6 (1.5)	3 (1.9)	0	2 (1.3)	0
Hyperglycaemia	49 (12.5	20 (5.1)	38 (9.8)	18 (4.6)	7 (4.5)	4 (2.5)	9 (5.9)	2 (1.3)
Arthralgia	49 (12.5	2 (0.5)	51 (13.1)	2 (0.5)	11 (7.0)	0	7 (4.6)	1 (0.7)
Dizziness	48 (12.2	2 (0.5)	44 (11.3)	2 (0.5)	11 (7.0)	1 (0.6)	3 (2.0)	0
Vomiting	47 (12.0	0	32 (8.2)	2 (0.5)	15 (9.6)	1 (0.6)	5 (3.3)	2 (1.3)
Pain in extremity	46 (11.7	4 (1.0)	41 (10.5)	6 (1.5)	12 (7.6)	0	7 (4.6)	0
Decreased appetite	44 (11.2	0	35 (9.0)	2 (0.5)	9 (5.7)	1 (0.6)	7 (4.6)	1 (0.7)
Respiratory tract infection	43 (11.0	16 (4.1)	39 (10.0)	8 (2.1)	11 (7.0)	1 (0.6)	10 (6.5)	3 (2.0)
Bone pain	40 (10.2	2 (0.5)	36 (9.3)	5 (1.3)	19 (12.1)	3 (1.9)	18 (11.8)	5 (3.3)
Hyperuricaemia	20 (5.1)	2 (0.5)	10 (2.6)	0	19 (12.1)	4 (2.5)	11 (7.2)	3 (2.0)
Renal failure acute	15 (3.8)	8 (2.0)	11 (2.8)	5 (1.3)	16 (10.2)	12 (7.6)	6 (3.9)	5 (3.3)
Hypercalcaemia	5 (1.3)	0	13 (3.3)	7 (1.8)	17 (10.8)	6 (3.8)	10 (6.5)	7 (4.6)
Disease progression	4 (1.0)	4 (1.0)	8 (2.1)	8 (2.1)	16 (10.2)	15 (9.6)	18 (11.8)	15 (9.8)

In Study 009, adverse events with an incidence ≥10% higher in the CLd arm than in the Ld arm were cough (113 of 392 subjects [28.8%] in the CLd arm and 69 of 389 subjects [17.7%] in the Ld arm), hypokalaemia (108 of 392 subjects [27.6%] and 52 of 389 subjects [13.4%]). There were no Grade ≥3 adverse events, serious adverse events, and adverse events leading to dose reduction or treatment discontinuation with an incidence higher in the CLd arm than in the Ld arm by ≥5%. Adverse events that led to suspension of administration of the study drug with an incidence higher in the CLd arm than in the Ld arm by ≥5% were neutropenia (76 of 392 subjects [19.4%] and 54 of 389 subjects [13.9%]), upper respiratory tract infection (44 of 392 subjects [11.2%] and 12 of 389 subjects [3.1%]), and respiratory tract infection (29 of 392 subjects [7.4%] and 8 of 389 subjects [2.1%]).

In Study 011, the adverse event with an incidence higher in the carfilzomib arm than in the BSC arm by ≥10% was nausea (32 of 157 subjects [20.4%] in the carfilzomib arm and 14 of 153 subjects [9.2%] in the BSC arm). There were no Grade ≥3 adverse events with an incidence higher in the carfilzomib arm than in the BSC arm by ≥5%. The serious adverse event with an incidence higher in the carfilzomib arm than in the BSC arm by ≥5% was renal failure acute (15 of 157 subjects [9.6%] in the carfilzomib arm and 6 of 153 subjects [3.9%] in the BSC arm). There were no adverse events that led to study drug dose reduction, suspension of administration, or treatment discontinuation with an incidence higher in the carfilzomib arm than in the BSC arm by ≥5%.

PMDA's view:
Thrombocytopenia, hypertension, etc. occurred more frequently in the carfilzomib arm than in the control arms in both Studies 009 and 011. These events require attention during treatment with carfilzomib, and this should be communicated to healthcare professionals in an appropriate manner.

7.R.3.2 Differences in the safety of carfilzomib between Japanese and non-Japanese patients
The applicant's explanation about the differences in the safety of carfilzomib between Japanese and non-Japanese patients:
Table 25 summarizes the safety data from Japanese clinical studies (data of the 20/27 mg/m^2 arms in Studies 05 and 01) and foreign clinical studies (data for the CLd and carfilzomib arms in Studies 009 and 011, respectively) in patients with relapsed or refractory MM.

Table 25. Summary of safety data (20/27 mg/m^2 arms in Studies 05 and 01, CLd arm in Study 009, and carfilzomib arm in Study 011)

	N (%)			
	Japanese		Non-Japanese	
	Study 05 N = 26	Study 01 N = 40	Study 009 N = 392	Study 011 N = 157
All adverse events	26 (100)	40 (100)	380 (96.9)	154 (98.1)
Adverse events, Grade ≥3	19 (73.1)	37 (92.5)	328 (83.7)	118 (75.2)
Adverse events resulting in death	0	0	36 (9.2)	29 (18.5)
Serious adverse events	1 (3.8)	5 (12.5)	235 (59.9)	92 (58.6)
Adverse events leading to treatment discontinuation	1 (3.8)	4 (10.0)	102 (26.0)	23 (14.6)
Adverse events leading to treatment suspension	15 (57.7)	20 (50.0)	290 (74.0)	59 (37.6)
Adverse events leading to dose reduction	7 (26.9)	1 (2.5)	223 (56.9)	9 (5.7)

Safety in the CLd regimen:
Adverse events with an incidence ≥20% higher in Study 05 than in Study 009 (CLd arm) were platelet count decreased (14 of 26 subjects [53.8%] in Study 05 and 18 of 392 subjects [4.6%] in the CLd arm of Study 009), lymphocyte count decreased (14 of 26 subjects [53.8%] and 0 subjects), hypophosphataemia (10 of 26 subjects [38.5%] and 52 of 392 subjects [13.3%]), hyperglycaemia (10 of 26 subjects [38.5%] and 49 of 392 subjects [12.5%]), white blood cell count decreased (8 of 26 subjects [30.8%] and 4 of 392 subjects [1.0%]), ALT increased (7 of 26 subjects [26.9%] and 20 of 392 subjects [5.1%]), and neutrophil count decreased (7 of 26 subjects [26.9%] and 20 of 392 subjects [5.1%]). Grade ≥3 adverse events with an incidence ≥10% higher in Study 05 than in Study 009 (CLd arm) by were lymphocyte count decreased (11 of 26 subjects [42.3%] and 0 subjects), platelet count decreased (6 of 26 subjects [23.1%] and 12 of 392 subjects [3.1%]), hypophosphataemia (5 of 26 subjects [19.2%] and 33 of 392 subjects [8.4%]), and white blood cell count decreased (3 of 26 subjects [11.5%] and 3 of 392 subjects [0.8%]). Adverse events leading to dose suspension with an incidence ≥10% higher in Study

05 than in Study 009 (CLd arm) were rash (4 of 26 subjects [15.4%] and 11 of 392 subjects [2.8%]) and upper respiratory tract inflammation (3 of 26 subjects [11.5%] and 0 subjects). There were no adverse events leading to dose reduction or treatment discontinuation with an incidence ≥10% higher in Study 05 than in Study 009 (CLd arm).

Safety in carfilzomib monotherapy:
Adverse events with an incidence ≥20% higher in Study 01 (20/27 mg/m^2 arm) than in Study 011 (carfilzomib monotherapy) were lymphocyte count decreased (33 of 40 subjects [82.5%] in Study 01 and 0 subjects in Study 011), platelet count decreased (30 of 40 subjects [75.0%] and 12 of 157 subjects [7.6%]), neutrophil count decreased (23 of 40 subjects [57.5%] and 13 of 157 subjects [8.3%]), white blood cell count decreased (21 of 40 subjects [52.5%] and 1 of 157 subjects [0.6%]), haemoglobin decreased (17 of 40 subjects [42.5%] and 0 subjects), hypophosphataemia (16 of 40 subjects [40.0%] and 5 of 157 subjects [3.2%]), blood creatinine increased (15 of 40 subjects [37.5%] and 13 of 157 subjects [8.3%]), blood lactate dehydrogenase increased (12 of 40 subjects [30.0%] and 6 of 157 subjects [3.8%]), white blood cell count increased (11 of 40 subjects [27.5%] and 0 subjects), and AST increased (9 of 40 subjects [22.5%] and 3 of 157 subjects [1.9%]). Grade ≥3 adverse events with an incidence ≥10% higher in Study 01 (20/27 mg/m^2 arm) than in Study 011 (carfilzomib monotherapy) were lymphocyte count decreased (27 of 40 subjects [67.5%] and 0 subjects), neutrophil count decreased (16 of 40 subjects [40.0%] and 5 of 157 subjects [3.2%]), platelet count decreased (12 of 40 subjects [30.0%] and 5 of 157 subjects [3.2%]), white blood cell count decreased (12 of 40 subjects [30.0%] and 1 of 157 subjects [0.6%]), and haemoglobin decreased (11 of 40 subjects [27.5%] and 0 subjects). The adverse event leading to dose suspension with an incidence ≥10% higher in Study 01 than in Study 011 (carfilzomib arm) was neutrophil count decreased (6 of 40 subjects [15.0%] in Study 01 and 2 of 157 subjects [1.3%] in Study 011). There were no adverse events leading to dose reduction or treatment discontinuation with an incidence ≥10% higher in Study 01 than in Study 011 (carfilzomib arm).

PMDA's view:
Close attention is required for adverse events that occurred more frequently in the Japanese clinical studies (Studies 05 and 01) than in the foreign clinical studies (Studies 009 and 011), including lymphocyte count decreased, platelet count decreased, hypophosphataemia, white blood cell count decreased, neutrophil count decreased, and haemoglobin decreased. The clinical study data showing differences in the safety of carfilzomib between Japanese and non-Japanese subjects should be provided to healthcare professionals in an appropriate manner. Further, due to the paucity of safety data on the use of carfilzomib in Japanese patients, post-marketing safety data should be collected, and any new knowledge should be provided to healthcare professionals promptly when available.

The following subsections are PMDA's summaries of the safety results with focuses on Studies 009, 05, 011, and 01, especially on fatal adverse events and serious adverse events with a suspected causal relationship to carfilzomib.

7.R.3.3 Cardiac disorders
The applicant's explanation about the occurrence of cardiac disorders following administration of carfilzomib as follows:

As cardiac disorder-related adverse events, preferred terms (PTs) categorized into the Standard MedDRA queries (SMQ) (MedDRA/J ver. 18.0) of "Cardiac failure," "Ischaemic heart disease," "Cardiac arrhythmias," and "Torsade de pointes/QT prolongation" were summarized (Tables 26 and 27).

Table 26. Cardiac disorders
(Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders	165 (42.1)	51 (13.0)	141 (36.2)	32 (8.2)	2 (7.7)	1 (3.8)
Oedema peripheral	71 (18.1)	3 (0.8)	61 (15.7)	2 (0.5)	1 (3.8)	0
Peripheral swelling	20 (5.1)	2 (0.5)	20 (5.1)	0	0	0
Oedema	17 (4.3)	1 (0.3)	19 (4.9)	1 (0.3)	0	0
Palpitations	14 (3.6)	1 (0.3)	9 (2.3)	0	0	0
Atrial fibrillation	13 (3.3)	5 (1.3)	18 (4.6)	7 (1.8)	0	0
Cardiac failure	10 (2.6)	3 (0.8)	7 (1.8)	4 (1.0)	0	0
Angina pectoris	9 (2.3)	3 (0.8)	8 (2.1)	2 (0.5)	0	0
Cardiac failure congestive	8 (2.0)	5 (1.3)	6 (1.5)	1 (0.3)	1 (3.8)	0
Tachycardia	8 (2.0)	1 (0.3)	7 (1.8)	0	0	0
Syncope	7 (1.8)	5 (1.3)	14 (3.6)	10 (2.6)	0	0
Myocardial infarction	7 (1.8)	6 (1.5)	2 (0.5)	2 (0.5)	0	0
Sinus bradycardia	7 (1.8)	0	2 (0.5)	1 (0.3)	0	0
Bradycardia	5 (1.3)	2 (0.5)	10 (2.6)	0	0	0
Acute myocardial infarction	4 (1.0)	4 (1.0)	1 (0.3)	1 (0.3)	0	0
Pulmonary oedema	4 (1.0)	3 (0.8)	3 (0.8)	1 (0.3)	0	0
Supraventricular extrasystoles	4 (1.0)	1 (0.3)	2 (0.5)	0	0	0
Prinzmetal angina	0	0	0	0	1 (3.8)	1 (3.8)

Table 27. Cardiac disorders
(Studies 011 and 01 [20/27 mg/m^2]; with an incidence rate of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders	44 (28.0)	17 (10.8)	29 (19.0)	7 (4.6)	6 (15.0)	0
Oedema peripheral	14 (8.9)	0	7 (4.6)	0	2 (5.0)	0
Cardiac failure	6 (3.8)	2 (1.3)	1 (0.7)	1 (0.7)	0	0
Oedema	6 (3.8)	1 (0.6)	4 (2.6)	0	0	0
Tachycardia	4 (2.5)	0	3 (2.0)	0	0	0
Atrial fibrillation	3 (1.9)	2 (1.3)	2 (1.3)	0	0	0
Peripheral swelling	3 (1.9)	0	5 (3.3)	0	0	0
Cardiac arrest	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)	0	0
Pulmonary oedema	2 (1.3)	2 (1.3)	1 (0.7)	0	0	0

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01	
	Carfilzomib N = 157		BSC N = 153		(20/27 mg/m^2) N = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac failure congestive	2 (1.3)	2 (1.3)	4 (2.6)	3 (2.0)	2 (5.0)	0
Palpitations	1 (0.6)	0	0	0	1 (2.5)	0
Troponin T increased	1 (0.6)	0	0	0	1 (2.5)	0
Atrioventricular block first degree	0	0	0	0	1 (2.5)	0

In Study 009, fatal cardiac disorders occurred in 10 of 392 subjects (2.6%) in the CLd arm and 8 of 389 subjects (2.1%) in the Ld arm. The fatal events in the CLd arm were myocardial infarction (3 subjects), cardiac arrest (2 subjects), cardiac failure, cardiac failure acute, sudden death, left ventricular dysfunction, and cardiopulmonary failure (1 subject each). A causal relationship to the study drug could not be ruled out for cardiac arrest (1 subject) in the CLd arm and acute coronary syndrome (1 subject) in the Ld arm. Serious cardiac disorders occurred in 44 of 392 subjects (11.2%) in the CLd arm and 29 of 389 subjects (7.5%) in the Ld arm. The serious events in the CLd arm were atrial fibrillation and myocardial infarction (6 subjects each), cardiac failure congestive (5 subjects), cardiac failure, acute myocardial infarction, and pulmonary oedema (4 subjects each), syncope (3 subjects), cardiac arrest, angina pectoris, and left ventricular dysfunction (2 subjects each), cardiac stress test abnormal, atrial tachycardia, ventricular tachycardia, myocardial ischaemia, coronary artery disease, atrioventricular block complete, stress cardiomyopathy, atrial flutter, tachycardia, sudden death, coronary artery occlusion, ventricular arrhythmia, cardiac failure acute, cardiopulmonary failure, and loss of consciousness (1 subject each) (a single patient may have had >1 event). A causal relationship to the study drug could not be ruled out for pulmonary oedema (3 subjects), cardiac failure congestive and atrial fibrillation (2 subjects each), angina pectoris, atrial flutter, cardiac arrest, syncope, tachycardia, ventricular arrhythmia, and cardiac stress test abnormal (1 subject each). In the CLd and Ld arms of Study 009, cardiac disorders led to dose reduction in 19 of 392 subjects (4.8%) and 15 of 389 subjects (3.9%), respectively; treatment suspension in 33 of 392 subjects (8.4%) and 17 of 389 subjects (4.4%), respectively; and treatment discontinuation in 11 of 392 subjects (2.8%) and 9 of 389 subjects (2.3%), respectively.

In Study 05, cardiac disorders led to dose suspension in 1 of 26 subjects (3.8%). However, there were no fatal or serious cardiac disorders, or those leading to dose reduction or treatment discontinuation.

In Study 011, fatal cardiac disorders occurred in 5 of 157 subjects (3.2%) in the carfilzomib arm and 3 of 153 subjects (2.0%) in the BSC arm. The fatal events were cardiac arrest (2 subjects), cardio-respiratory arrest, cardiac failure acute, and pulmonary oedema (1 subject each), and a causal relationship to carfilzomib was ruled out for all events. Serious cardiac disorders occurred in 14 of 157 subjects (8.9%) in the carfilzomib arm and 6 of 153 subjects (3.9%) in the BSC arm. The serious adverse events were cardiac failure (3 subjects), cardiac arrest, cardiac failure congestive, and pulmonary oedema (2 subjects each), acute pulmonary oedema, atrial fibrillation, atrial flutter, atrioventricular block complete, cardiac failure acute, cardio-respiratory arrest, pulmonary congestion, and acute left ventricular failure (1 subject each) (some patients had ≥1 events). A causal relationship to carfilzomib could not be ruled out for atrioventricular block complete, cardiac failure, cardiac failure congestive, and pulmonary congestion (1 subject each). In Study 011, cardiac disorders led to dose reduction in 1 of 157 subjects (0.6%) in the carfilzomib arm and 3 of 153 subjects (2.0%) in the BSC arm, dose suspension in 9 of 157 subjects (5.7%) and 3 of 153 subjects (2.0%), and treatment discontinuation in 6 of 157 subjects (3.8%) and 3 of 153 subjects (2.0%).

In Study 01, cardiac disorders led to the suspension of treatment with carfilzomib in 1 of 40 subjects (2.5%) in the 20/27 mg/m^2 arm. There were no fatal or serious cardiac disorders, or those leading to dose reduction or treatment discontinuation.

The safety pharmacology study in cynomolgus monkeys detected changes in electrocardiogram, and the safety pharmacology study using human embryonic kidney cell line identified the inhibition of hERG current [see Section 3.3.2.1]. PMDA asked the applicant to explain the effects of carfilzomib on corrected QT interval (QTc).

The applicant's explanation:
In Studies 009 and 05, 12-lead electrocardiography was performed on a regular basis, and, therefore, the effects of carfilzomib on QTc were investigated based on the data from these studies. The results showed that 12-lead electrocardiograms with a maximum QTc of >500 msec or a change in QTc from baseline of >60 msec was observed in 67 of 392 subjects (17.1%) in the CLd arm and 41 of 389 subjects (10.5%) in the Ld arm in Study 009, and in 1 of 26 subjects (3.8%) in Study 05.

PMDA's view:
Carfilzomib caused fatal cardiac disorders including cardiac failure and acute myocardial infarction, and 12-lead electrocardiograms tended to show prolonged QTc after carfilzomib dose. These facts indicate the importance of close attention to carfilzomib-induced cardiac disorders. Healthcare professionals should monitor patients regularly by electrocardiography, electrolyte testing, etc., during treatment and take appropriate actions such as treatment discontinuation in case of any abnormality. This should be advised in the package insert, etc.

7.R.3.4 ILD
The applicant's explanation about the occurrence of ILD following administration of carfilzomib:
As ILD-related adverse events, PTs classified under the SMQ (MedDRA/J ver. 18.0) of "Interstitial lung diseases" were summarized.

In Study 009, ILDs occurred in 10 of 392 subjects (2.5%) in the CLd arm and 5 of 389 subjects (1.3%) in the Ld arm. Grade ≥3 ILDs occurred in 9 of 392 subjects (2.3%) in the CLd arm and 3 of 389 subjects (0.8%) in the Ld arm. In the CLd arm of Study 009, fatal ILDs occurred in 2 of 392 subjects (0.5%), and both events were classified as acute respiratory distress syndrome. A causal relationship to the study drug was ruled out for these events. There were no fatal ILDs in the Ld arm. In Study 009, serious ILDs occurred in 8 of 392 subjects (2.0%) in the CLd arm and 3 of 389 subjects (0.8%) in the Ld arm. Serious ILDs in the CLd arm were acute respiratory distress syndrome (3 subjects), bronchiolitis, pneumonitis, alveolitis, eosinophilic pneumonia, and ILD (1 subject each). A causal relationship to the study drug could not be ruled out for bronchiolitis, pneumonitis, eosinophilic pneumonia, and ILD (1 subject each). In the CLd and Ld arms, ILDs led to dose reduction in 0 subjects and 1 of 389 subjects (0.3%), respectively; dose suspension in 4 of 392 subjects (1.0%) and 2 of 389 subjects (0.5%), respectively; and treatment discontinuation in 3 of 392 subjects (0.8%) and 1 of 389 subjects (0.3%), respectively.

No ILDs occurred in Study 05.

In Study 011, ILDs occurred in 1 of 157 subjects (0.6%) in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm. Grade ≥3 ILDs occurred in 1 of 157 subjects (0.6%) in the carfilzomib arm and none in the BSC arm. There were no fatal or serious ILDs, those leading to dose reduction or suspension or treatment discontinuation.

No ILD occurred in the 20/27 mg/m^2 arm of Study 01.

PMDA's view:
Serious pneumonitis and ILD with a suspected causal relationship to carfilzomib were reported. Therefore, treatment with carfilzomib requires attention to the development of ILDs. The occurrence of

ILDs in the clinical studies should be communicated to healthcare professionals through the package insert or other written materials in an appropriate manner.

7.R.3.5 Pulmonary hypertension

The applicant's explanation about the occurrence of pulmonary hypertension following administration of carfilzomib:

As pulmonary hypertension-related adverse events, PTs classified under the SMQ (MedDRA/J ver. 18.0) of "Pulmonary hypertension" were summarized (Tables 28 and 29).

Table 28. Pulmonary hypertension
(Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pulmonary hypertension	92 (23.5)	14 (3.6)	71 (18.3)	9 (2.3)	1 (3.8)	0
Dyspnoea	77 (19.6)	11 (2.8)	58 (14.9)	7 (1.8)	1 (3.8)	0
Dyspnoea exceptional	21 (5.4)	1 (0.3)	17 (4.4)	1 (0.3)	0	0

Table 29. Pulmonary hypertension
(Studies 011 and 01 [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pulmonary hypertension	25 (15.9)	3 (1.9)	19 (12.4)	0	1 (2.5)	0
Dyspnoea	23 (14.6)	2 (1.3)	13 (8.5)	0	1 (2.5)	0
Dyspnoea exceptional	3 (1.9)	1 (0.6)	6 (3.9)	0	0	0

In Study 009, there were no fatal pulmonary hypertension in the CLd or Ld arm, and serious pulmonary hypertension occurred in 5 of 392 subjects (1.3%) in the CLd arm and 3 of 389 subjects (0.8%) in the Ld arm. The serious pulmonary hypertension occurring in the 5 subjects in the CLd arm was dyspnoea, for 3 of which a causal relationship to the study drug could not be ruled out. In the CLd and Ld arms, pulmonary hypertension led to dose reduction in 6 of 392 subjects (1.5%) and 1 of 389 subjects (0.3%), respectively; dose suspension in 12 of 392 subjects (3.1%), and 7 of 389 subjects (1.8%), respectively; and treatment discontinuation in 0 subjects and 1 of 389 subjects (0.3%), respectively.

In Study 05, there were no fatal or serious pulmonary hypertension or pulmonary hypertension leading to dose reduction, treatment suspension or discontinuation.

In Study 011, there were no fatal pulmonary hypertension in the carfilzomib or BSC arm. Serious pulmonary hypertension occurred in 3 of 157 subjects (1.9%) in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm. The serious pulmonary hypertensive events were dyspnoea (2 subjects) and dyspnoea exceptional (1 subject), and a causal relationship to carfilzomib could not be ruled out for dyspnoea in 1 subject. In the carfilzomib and BSC arms, pulmonary hypertension led to dose suspension

in 3 of 157 subjects (1.9%) and 0 subjects, respectively; and treatment discontinuation in 0 subjects and 2 of 153 subjects (1.3%), respectively. No pulmonary hypertension led to dose reduction of carfilzomib.

In Study 01, there were no fatal or serious pulmonary hypertension or pulmonary hypertension leading to carfilzomib dose reduction, dose suspension or treatment discontinuation in the 20/27 mg/m^2 arm.

The safety of carfilzomib was evaluated based on the data including the results of Study 2011-003, a foreign phase III study conducted in patients with relapsed or refractory MM. A foreign corrective action report dated June 18, 2015 was submitted to call attention of healthcare professionals to pulmonary hypertension associated with the administration of carfilzomib. In response, PMDA asked the applicant to explain the occurrence of pulmonary hypertension following administration of carfilzomib including post-marketing experiences in foreign countries.

The applicant's explanation:
A data summary using the database of the Amgen Inc. in the US showed that pulmonary hypertension occurred in 1303 patients clinical studies and post-marketing use in and outside Japan (data cut-off on February 17, 2016). (Unless otherwise specified, the occurrence of events in clinical studies and post-marketing use in and outside Japan presented hereafter in the section of "7.R.3 Safety" refers to that based on the summary of the mentioned database. The data from Study PX-171-010, an extension study, which results were combined with the data from the prior study.) Fatal pulmonary hypertension resulted in death in 3 subjects, which was namely dyspnoea (2 subjects) and pulmonary hypertension (1 subject). A causal relationship to carfilzomib could not be ruled out for 1 each of these adverse events. Serious pulmonary hypertension occurred in 285 subjects, which was namely dyspnoea (224 subjects), pulmonary hypertension (45 subjects), dyspnoea exceptional (8 subjects), right ventricular failure (4 subjects), pulmonary arterial hypertension (3 subjects), right ventricular systolic pressure increased, dilatation ventricular, and emphysema (1 subject each) (a single patient may have had >1 event). A causal relationship to carfilzomib could not be ruled out for dyspnoea (163 subjects), pulmonary hypertension (40 subjects), dyspnoea exceptional (5 subjects), right ventricular failure (3 subjects), pulmonary arterial hypertension (2 subjects), right ventricular systolic pressure increased, dilatation ventricular, and emphysema (1 subject each).

PMDA's view:
Because of the occurrence of serious pulmonary hypertension with a suspected causal relationship to carfilzomib, treatment with carfilzomib requires close attention to the development of pulmonary hypertension. The occurrence of pulmonary hypertension in the clinical studies should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner.

7.R.3.6 Haematotoxicity
The applicant's explanation about the occurrence of haematotoxicity following administration of carfilzomib:
The PTs of haematotoxicity-related adverse events classified under the SMQs (MedDRA/J ver. 18.0) of "Haematopoietic erythropenia," "Haematopoietic leukopenia," and "Haematopoietic thrombocytopenia" were summarized (Tables 30 and 31).

Table 30. Haematotoxicity
(Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haematotoxicity	251 (64.0)	178 (45.4)	236 (60.7)	166 (42.7)	23 (88.5)	14 (53.8)
Anaemia	169 (43.1)	70 (17.9)	155 (39.8)	69 (17.7)	4 (15.4)	3 (11.5)
Haemoglobin decreased	6 (1.5)	3 (0.8)	2 (0.5)	1 (0.3)	4 (15.4)	1 (3.8)
Neutropenia	148 (37.8)	116 (29.6)	131 (33.7)	103 (26.5)	0	0
Leukopenia	31 (7.9)	12 (3.1)	22 (5.7)	16 (4.1)	0	0
Neutrophil count decreased	20 (5.1)	12 (3.1)	22 (5.7)	11 (2.8)	7 (26.9)	3 (11.5)
Febrile neutropenia	13 (3.3)	10 (2.6)	5 (1.3)	4 (1.0)	0	0
Lymphopenia	12 (3.1)	11 (2.8)	14 (3.6)	8 (2.1)	0	0
White blood cell count decreased	4 (1.0)	3 (0.8)	6 (1.3)	3 (0.8)	8 (30.8)	3 (11.5)
Lymphocyte count decreased	0	0	2 (0.5)	0	14 (53.8)	11 (42.3)
Thrombocytopenia	115 (29.3)	66 (16.8)	89 (22.9)	48 (12.3)	0	0
Platelet count decreased	18 (4.6)	12 (3.1)	13 (3.3)	9 (2.3)	14 (53.8)	6 (23.1)

Table 31. Haematotoxicity
(Studies 011 and 01, [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haematotoxicity	112 (71.3)	72 (45.9)	98 (64.1)	71 (46.4)	39 (97.5)	35 (87.5)
Anaemia	88 (56.1)	40 (25.5)	74 (48.4)	47 (30.7)	12 (30.0)	6 (15.0)
Red blood cell count decreased	1 (0.6)	0	0	0	4 (10.0)	0
Haemoglobin decreased	0	0	2 (1.3)	1 (0.7)	17 (42.5)	11 (27.5)
Haematocrit decreased	0	0	1 (0.7)	0	5 (12.5)	1 (2.5)
Neutropenia	23 (14.6)	12 (7.6)	26 (17.0)	19 (12.4)	0	0
Neutrophil count decreased	13 (8.3)	5 (3.2)	10 (6.5)	4 (2.6)	23 (57.5)	16 (40.0)
Leukopenia	10 (6.4)	5 (3.2)	15 (9.8)	11 (7.2)	0	0
Lymphopenia	5 (3.2)	5 (3.2)	3 (2.0)	1 (0.7)	1 (2.5)	1 (2.5)
Febrile neutropenia	3 (1.9)	3 (1.9)	2 (1.3)	2 (1.3)	0	0
White blood cell count decreased	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	21 (52.5)	12 (30.0)
Lymphocyte count decreased	0	0	1 (0.7)	0	33 (82.5)	27 (67.5)
Monocyte count decreased	0	0	0	0	1 (2.5)	0
Thrombocytopenia	59 (37.6)	38 (24.2)	46 (30.1)	34 (22.2)	0	0
Platelet count decreased	12 (7.6)	5 (3.2)	12 (7.8)	7 (4.6)	30 (75.0)	12 (30.0)

In Study 009, there were no fatal haematotoxicity in the CLd or Ld arm, while serious haematotoxicity occurred in 21 of 392 subjects (5.4%) in the CLd arm and 20 of 389 subjects (5.1%) in the Ld arm. The serious events in the CLd arm were febrile neutropenia and anaemia (8 subjects each), thrombocytopenia (6 subjects), neutropenia (4 subjects), leukopenia, haemoglobin decreased, and neutropenic sepsis (1 subject each) (a single patient may have had >1 event). A causal relationship to the study drug could not be ruled out for febrile neutropenia (8 subjects), anaemia (6 subjects), neutropenia and thrombocytopenia (4 subjects each), leukopenia, haemoglobin decreased, and neutropenic sepsis (1 subject each). In the CLd and Ld arms of Study 009, haematotoxicity led to dose reduction in 86 of 392 subjects (21.9%) and 56 of 389 subjects (14.4%), respectively; dose suspension in 112 of 392 subjects (28.6%) and 79 of 389 subjects (20.3%), respectively; and treatment discontinuation in 11 of 392 subjects (2.8%) and 11 of 389 subjects (2.8%), respectively.

In Study 05, there were no fatal or serious haematotoxicity. Haematotoxicity led to dose reduction in 1 of 26 subjects (3.8%) and dose suspension in 3 of 26 subjects (11.5%). There were no haematotoxicity leading to treatment discontinuation.

In Study 011, fatal haematotoxicity occurred in 1 of 153 subjects (0.7%) in the BSC arm but none in the carfilzomib arm. In the study, serious haematotoxicity occurred in 10 of 157 subjects (6.4%) in the carfilzomib arm and 17 of 153 subjects (11.1%) in the BSC arm. The serious haematotoxicity in the carfilzomib arm were anaemia (4 subjects), febrile neutropenia and thrombocytopenia (3 subjects each), and leukopenia and neutropenia (1 subject each) (a single patient may have had >1 event), and a causal relationship to carfilzomib could not be ruled out for febrile neutropenia (3 subjects), and anaemia and thrombocytopenia (1 subject each). Haematotoxicity led to carfilzomib dose reduction in 1 of 157 subjects (0.6%) in the carfilzomib arm and 5 of 153 subjects (3.3%) in the BSC arm, dose suspension in 7 of 157 subjects (4.5%) in the carfilzomib arm and 8 of 153 subjects (5.2%) in the BSC arm, and treatment discontinuation in 1 of 157 subjects (0.6%) in the carfilzomib arm and 5 of 153 subjects (3.3%) in the BSC arm.

In Study 01, there were no fatal haematotoxicity in the 20/27 mg/m^2 arm. Serious hepatotoxicity (thrombocytopenia) occurred in 1 of 40 subjects (2.5%), for which a causal relationship to carfilzomib could not be ruled out. Haematotoxicity led to dose suspension in 7 of 40 subjects (17.5%). There were no haematotoxicity that led to dose reduction or discontinuation of carfilzomib.

PMDA's view:
Serious haematotoxicity was reported, and a causal relationship to carfilzomib could not be ruled out for the event. Therefore, treatment with carfilzomib requires regular hematological testing so that appropriate actions can be taken in case of an abnormality. This should be communicated to healthcare professionals through the package insert, etc.

7.R.3.7 Infections
The applicant's explanation about the occurrence of infections following administration of carfilzomib:
Infection-related adverse events were summarized with the PTs under the MedDRA SOC (MedDRA/J ver. 18.0) of "Infections and infestations"; PTs equivalent to the MedDRA HLT (MedDRA/J ver. 18.0) of "Herpes viral infections," "Bacterial lower respiratory tract infections," "Fungal lower respiratory tract infection," "Parasitic lower respiratory tract infections," "Lower respiratory tract infections NEC," "Viral lower respiratory tract infections," "Bacterial upper respiratory tract infections," "Viral upper respiratory tract infections," and "Upper respiratory tract infections NEC"; and the PT (MedDRA/J ver. 18.0) of "urinary tract infection" (Tables 32 and 33).

Table 32. Infections (Studies 009 and 05; with an incidence of ≥2% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections	310 (79.1)	114 (29.1)	270 (69.4)	93 (23.9)	10 (38.5)	2 (7.7)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	76 (19.5)	4 (1.0)	1 (3.8)	1 (3.8)
Nasopharyngitis	80 (20.4)	1 (0.3)	62 (15.9)	0	3 (11.5)	0
Bronchitis	74 (18.9)	7 (1.8)	54 (13.9)	7 (1.8)	2 (7.7)	0
Pneumonia	68 (17.3)	49 (12.5)	56 (14.4)	41 (10.5)	3 (11.5)	2 (7.7)
Respiratory tract infection	43 (11.0)	16 (4.1)	39 (10.0)	8 (2.1)	1 (3.8)	1 (3.8)
Urinary tract infection	34 (8.7)	4 (1.0)	21 (5.4)	1 (0.3)	0	0
Influenza	26 (6.6)	2 (0.5)	12 (3.1)	2 (0.5)	0	0
Viral infection	24 (6.1)	0	10 (2.6)	0	0	0
Sinusitis	22 (5.6)	2 (0.5)	16 (4.1)	0	0	0
Rhinitis	19 (4.8)	0	8 (2.1)	0	0	0
Gastroenteritis	17 (4.3)	3 (0.8)	12 (3.1)	1 (0.3)	0	0
Bronchopneumonia	15 (3.8)	7 (1.8)	9 (2.3)	7 (1.8)	0	0
Cellulitis	14 (3.6)	1 (0.3)	11 (2.8)	1 (0.3)	0	0
Pharyngitis	13 (3.3)	0	7 (1.8)	0	2 (7.7)	0
Respiratory tract infection viral	8 (2.0)	0	7 (1.8)	0	0	0
Cystitis	8 (2.0)	0	5 (1.3)	0	0	0
Lower respiratory tract infection	7 (1.8)	2 (0.5)	8 (2.1)	3 (0.8)	0	0
Herpes zoster	6 (1.5)	0	9 (2.3)	0	0	0
Tinea pedis	1 (0.3)	0	2 (0.5)	0	1 (3.8)	0

Table 33. Infections (Studies 011 and 01, [20/27 mg/m^2]; with an incidence of ≥2% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections	85 (54.1)	34 (21.7)	71 (46.4)	34 (22.2)	19 (47.5)	2 (5.0)
Upper respiratory tract infection	16 (10.2)	2 (1.3)	3 (2.0)	0	1 (2.5)	0
Bronchitis	15 (9.6)	3 (1.9)	14 (9.2)	2 (1.3)	0	0
Nasopharyngitis	14 (8.9)	0	10 (6.5)	0	10 (25.0)	0
Pneumonia	12 (7.6)	10 (6.4)	20 (13.1)	19 (12.4)	1 (2.5)	0
Respiratory tract infection	11 (7.0)	1 (0.6)	10 (6.5)	3 (2.0)	0	0
Bronchopneumonia	8 (5.1)	6 (3.8)	5 (3.3)	5 (3.3)	1 (2.5)	1 (2.5)
Urinary tract infection	8 (5.1)	4 (2.5)	5 (3.3)	0	0	0
Influenza	8 (5.1)	0	4 (2.6)	0	1 (2.5)	0
Oral candidiasis	4 (2.5)	0	1 (0.7)	0	0	0
Infection	3 (1.9)	1 (0.6)	4 (2.6)	2 (1.3)	0	0
Gastroenteritis	2 (1.3)	0	3 (2.0)	0	0	0
Pharyngitis	1 (0.6)	0	3 (2.0)	1 (0.7)	5 (12.5)	0
Septic shock	0	0	3 (2.0)	3 (2.0)	0	0
Herpes zoster	0	0	5 (3.3)	2 (1.3)	0	0
Rhinitis	0	0	3 (2.0)	0	0	0
Pneumonia viral	0	0	0	0	1 (2.5)	1 (2.5)
Enteritis infectious	0	0	0	0	1 (2.5)	0
Lip infection	0	0	0	0	1 (2.5)	0
Gingivitis	1 (0.6)	0	1 (0.7)	0	1 (2.5)	0

In Study 009, fatal infections occurred in 10 of 392 subjects (2.6%) in the CLd arm and 10 of 389 subjects (2.6%) in the Ld arm. The fatal events in the CLd arm were sepsis (3 subjects), bronchopneumonia and pneumonia (2 subjects each), endocarditis, septic shock, and upper respiratory tract infection (1 subject each). A causal relationship to the study drug could not be ruled out for pneumonia and septic shock (1 subject each). In the study, serious infections occurred in 120 of 392 subjects (30.6%) in the CLd arm and 97 of 389 subjects (24.9%) in the Ld arm. The serious events in the CLd arm were pneumonia (56 subjects), respiratory tract infection (15 subjects), bronchitis (8 subjects), bronchopneumonia (5 subjects), gastroenteritis, sepsis, and upper respiratory tract infection (4 subjects each), clostridium difficile colitis, influenza, septic shock, sinusitis, urinary tract infection, lung infection, and device-related infection (3 subjects each), bacteraemia, lobar pneumonia, lower respiratory tract infection, tracheobronchitis, and clostridium difficile infection (2 subjects each), bronchiolitis, cellulitis, chronic hepatitis C, diverticulitis, endocarditis, Escherichia sepsis, gingivitis, infection, liver abscess, peritonitis, pneumonia influenzal, pneumonia respiratory syncytial viral, respiratory syncytial virus bronchiolitis, urosepsis, neutropenic sepsis, staphylococcal bacteraemia, streptococcal bacteraemia, postoperative abscess, Escherichia urinary tract infection, catheter site cellulitis, sepsis syndrome, salmonella sepsis, abdominal abscess, bacterial infection, laryngitis bacterial, testicular abscess, enterocolitis bacterial, incision site infection, Pneumocystis jirovecii pneumonia, and cholangitis infective (1 subject each) (a single patient may have had >1 event). A causal relationship to carfilzomib could not be ruled out for pneumonia (22 subjects), respiratory tract infection (4 subjects), sepsis, upper respiratory tract infection, clostridium difficile colitis, and septic shock (2

subjects each), bronchitis, bronchopneumonia, influenza, sinusitis, urinary tract infection, lung infection, lobar pneumonia, lower respiratory tract infection, clostridium difficile infection, bronchiolitis, pneumonia influenzal, urosepsis, neutropenic sepsis, salmonella sepsis, and Pneumocystis jirovecii pneumonia (1 subject each). In the CLd and Ld arms of Study 009, infections led to dose reduction in 27 of 392 subjects (6.9%) and 21 of 389 subjects (5.4%), respectively; dose suspension in 165 of 392 subjects (42.1%) and 90 of 389 subjects (23.1%), respectively; and treatment discontinuation in 19 of 392 subjects (4.8%) and 12 of 389 subjects (3.1%), respectively.

Study 05
There were no fatal infections. Serious pneumonia/respiratory tract infection occurred in 1 of 26 subjects [3.8%]), and a causal relationship to the study drug could not be ruled out for either events. Infections led to dose suspension in 5 of 26 subjects (19.2%). There were no infections leading to study drug dose reduction or treatment discontinuation.

Study 011
Fatal infection occurred in 5 of 157 subjects (3.2%) in the carfilzomib arm and 12 of 153 subjects (7.8%) in the BSC arm. The fatal events in the carfilzomib arm were bronchopneumonia, kidney infection, pneumonia, sepsis, and staphylococcal sepsis (1 subject each). A causal relationship to carfilzomib was ruled out for all events. Serious infections occurred in 30 of 157 subjects (19.1%) in the carfilzomib arm and 35 of 153 subjects (22.9%) in the BSC arm. The serious events in the carfilzomib arm were pneumonia (10 subjects), bronchopneumonia (6 subjects), bronchitis, sepsis, and urinary tract infection (3 subjects each), clostridium difficile colitis, infection, influenza, kidney infection, lobar pneumonia, lower respiratory tract infection, meningitis, nasopharyngitis, pneumonia pneumococcal, pneumonia streptococcal, upper respiratory tract infection, staphylococcal sepsis, respiratory tract infection, and metapneumovirus infection (1 subject each) (a single patient may have had >1 event). A causal relationship to carfilzomib could not be ruled out for pneumonia (3 subjects), bronchopneumonia, nasopharyngitis, and urinary tract infection (1 subject each). In the carfilzomib and BSC arms, infections led to carfilzomib dose reduction in 0 subjects and 1 of 153 subjects (0.7%), respectively; dose suspension in 24 of 157 subjects (15.3%) and 13 of 153 subjects (8.5%), and treatment discontinuation in 4 of 157 subjects (2.5%) and 8 of 153 subjects (5.2%), respectively.

Study 01
There were no fatal infections in the 20/27 mg/m^2 arm. Serious infections occurred in 2 of 40 subjects (5.0%), and were, namely, pneumonia and pneumonia viral (1 subject each). Infections led to dose suspension in 7 of 40 subjects (17.5%). There were no infections leading to carfilzomib dose reduction or treatment discontinuation.

As explained earlier by the applicant, bortezomib, a proteasome inhibitor like carfilzomib, is known to induce herpes zoster, and subjects of the clinical studies of carfilzomib were pretreated with an antiviral drug to prevent herpes zoster. PMDA asked the applicant to explain (a) the occurrence of herpes zoster and opportunistic infections such as reactivated tuberculosis, PML, and reactivated viral hepatitis associated with treatment with carfilzomib and (b) the actual measures taken for the prevention of infections in Studies 009 and 05.

The applicant's explanation:
In Study 009, herpes zoster occurred in 6 of 392 subjects (1.5%) in the CLd arm and 9 of 389 subjects (2.3%) in the Ld arm; herpes zoster disseminated in 0 subjects and 1 of 389 subjects (0.3%), and PML in 1 of 392 subjects (0.3%) and 0 subjects. In the CLd arm, none of these events were fatal or serious. In Study 009, there were no reactivated tuberculosis or reactivated hepatitis viral. In the carfilzomib arm of Studies 05 and 011 and the 20/27 mg/m^2 arm of Study 01, there were no herpes zoster, PML, reactivated tuberculosis, or reactivated hepatitis viral.

Because reactivated herpesvirus was detected in patients treated with bortezomib, prophylactic measures for the infection were required in Studies 009 and 05. The administration of an anti-herpesvirus agent was required during study drug treatment in all subjects in Study 009 and those with a history of herpes

virus infection in Study 05. In Cycle 1 of Studies 009 and 05, the administration of ciprofloxacin or other antibacterial agent was required. However, there were no adequate data on anti-herpesvirus and antibacterial medication to clarify whether the medication given was for prophylactic purpose or to treat subjects who had already been infected. Furthermore, the efficacy of prophylactic medication in carfilzomib-induced infections has never been investigated in clinical studies.

In Study 009, anti-herpesvirus agents were administered to 371 of 392 subjects (94.6%) in the CLd arm and 260 of 389 subjects (66.8%) in the Ld arm; and herpes virus infection[18] occurred in 13 of 392 subjects (3.3%) and 19 of 389 subjects (4.9%). In Study 05, all subjects received anti-herpesvirus agents for prophylaxis, and none of them experienced herpes virus infection. Further, in Cycle 1 of Study 009, an antibacterial agent was administered to 381 of 392 subjects (97.2%) in the CLd arm and 371 of 389 subjects (95.4%) in the Ld arm. Infections occurred in 64 of 392 subjects (16.3%) in the CLd arm and 71 of 389 subjects (18.3%) in the Ld arm. In Cycle 1 of Study 05, while an antibacterial agent was administered to all subjects, infections occurred in 5 of 29 subjects (19.2%).

PMDA's view:
Because of the reported fatal infections with a suspected relationship to carfilzomib, treatment with carfilzomib requires close attention to the development of infections. The occurrence of infections in clinical studies should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner. Further, healthcare professionals should also be informed of the prophylactic measures against infections required in the clinical studies in an appropriate manner through written materials. To understand the use or non-use of prophylactic medication, specific types of prophylactic medication used, and the occurrence of infections in clinical settings, relevant data should be collected after the market launch.

7.R.3.8 Hepatic disorders

The applicant's explanation about the occurrence of hepatic disorders following administration of carfilzomib:
Liver disorder-related adverse events were summarized using PTs equivalent to the SMQ (MedDRA/J ver. 18.0) of "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "Hepatitis, non-infectious," "Cholestasis and jaundice of hepatic origin," and "Liver related investigations, signs and symptoms,

"PTs classified under the SOC (MedDRA/J ver. 18.0) of "hepatobiliary disorders"; and PTs (MedDRA/J ver. 18.0) of "ALT abnormal," "ALT increased," "AST abnormal," "AST increased," "hepatic enzyme abnormal," "hepatic enzyme increased," "hypertransaminasaemia," "mitochondrial aspartate aminotransferase increased," "transaminases abnormal," and "transaminases increased" (Tables 34 and 35).

Table 34. Hepatic disorders (Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic disorders	77 (19.6)	27 (6.9)	54 (13.9)	11 (2.8)	14 (53.8)	3 (11.5)
ALT increased	20 (5.1)	9 (2.3)	15 (3.9)	3 (0.8)	7 (26.9)	2 (7.7)
Hyperbilirubinaemia	15 (3.8)	5 (1.3)	3 (0.8)	1 (0.3)	0	0
Blood bilirubin increased	12 (3.1)	4 (1.0)	5 (1.3)	0	4 (15.4)	0

[18] Preferred terms included in "Herpes viral infections" (MedDRA HLT)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypoalbuminaemia	10 (2.6)	2 (0.5)	11 (2.8)	1 (0.3)	0	0
AST increased	8 (2.0)	5 (1.3)	7 (1.8)	1 (0.3)	4 (15.4)	1 (3.8)
Blood ALP increased	7 (1.8)	0	5 (1.3)	1 (0.3)	2 (7.7)	0
GGT increased	6 (1.5)	2 (0.5)	10 (2.6)	2 (0.5)	2 (7.7)	0
Hepatitis toxic	4 (1.0)	1 (0.3)	1 (0.3)	0	0	0
Cholelithiasis	4 (1.0)	1 (0.3)	4 (1.0)	0	0	0
Hepatic function abnormal	0	0	0	0	2 (7.7)	1 (3.8)

Table 35. Hepatic disorders (Studies 011 and 01, [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	Number of subjects (%)					
	Study 011				Study 01 (20/27 mg/m^2) 40 subjects	
	Carfilzomib 157 subjects		BSC 153 subjects			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic disorders	20 (12.7)	11 (7.0)	15 (9.8)	2 (1.3)	17 (42.5)	2 (5.0)
Hyperbilirubinaemia	4 (2.5)	1 (0.6)	2 (1.3)	0	0	0
ALT increased	3 (1.9)	2 (1.3)	3 (2.0)	0	8 (20.0)	1 (2.5)
Hypoalbuminaemia	3 (1.9)	0	3 (2.0)	1 (0.7)	5 (12.5)	0
AST increased	3 (1.9)	2 (1.3)	3 (2.0)	0	9 (22.5)	2 (5.0)
GGT increased	2 (1.3)	1 (0.6)	6 (3.9)	0	1 (2.5)	0
Biliary colic	2 (1.3)	1 (0.6)	0	0	0	0
Cholelithiasis	2 (1.3)	1 (0.6)	0	0	0	0
Hepatomegaly	2 (1.3)	1 (0.6)	0	0	0	0
Transaminases increased	2 (1.3)	2 (1.3)	0	0	0	0
Hepatic enzyme increased	2 (1.3)	1 (0.6)	0	0	0	0
Blood bilirubin increased	2 (1.3)	1 (0.6)	0	0	1 (2.5)	0
Blood ALP increased	0	0	1 (0.7)	0	4 (10.0)	0
Hepatic steatosis	0	0	0	0	1 (2.5)	0
Urobilinogen urine increased	0	0	0	0	1 (2.5)	0

Study 009

There were no fatal hepatic disorders in the CLd or Ld arm. Serious hepatic disorders occurred in 10 of 392 subjects (2.6%) in the CLd and 6 of 389 subjects (1.5%) in the Ld arm. The serious events in the CLd arm were cholecystitis acute (3 subjects), cholangitis (2 subjects), bile duct stone, cholelithiasis, hepatitis toxic, hypoalbuminaemia, and ALT increased (1 subject each). A causal relationship to the study drug could not be ruled out for cholecystitis acute, hepatitis toxic, hypoalbuminaemia, and ALT increased (1 subject each). In the CLd and Ld arms, hepatic disorders led to dose reduction in 8 of 392 subjects (2.0%) and 3 of 389 subjects (0.8%), respectively; dose suspension in 23 of 392 subjects (5.9%)

and 8 of 389 subjects (2.1%), respectively; and treatment discontinuation in 1 of 392 subjects (0.3%) and 3 of 389 subjects (0.8%), respectively.

Study 05
Hepatic disorders led to dose suspension in 2 of 26 subjects (7.7%). There were no fatal or serious hepatic disorders or no hepatic disorders leading to dose reduction or treatment discontinuation.

Study 011
There were no fatal hepatic disorders in the carfilzomib or BSC arm. In the carfilzomib arm, serious hepatic disorders occurred in 2 of 157 subjects (1.3%), which were biliary colic and cholelithiasis (1 subject each). A causal relationship to carfilzomib was ruled out for both events. No serious hepatic disorders occurred in the BSC arm. In either arm, there were no hepatic events leading to discontinuation or dose reduction of carfilzomib. Hepatic disorders led to dose suspension in 1 of 157 subjects (0.6%) in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm.

Study 01
In the 20/27 mg/m^2 arm, there were no fatal or serious hepatic disorders or those leading to carfilzomib dose reduction or suspension or treatment discontinuation.

Study PX-171-003
In Part 2 (A1), fatal hepatic disorders occurred in 2 of 266 subjects (0.8%). Both events were hepatic failure, and a causal relationship to carfilzomib could not be ruled out for 1 of these events.

PMDA's view:
Because of the reported fatal hepatic disorders with a suspected causal relationship to carfilzomib, patients should undergo regular liver function tests before starting and during the treatment with carfilzomib it is necessary to advise caution in the package insert or relevant documents to those engaged in medical practice, because liver function tests should be performed prior to and during treatment on a regular basis to ensure that appropriate measures such as discontinuing carfilzomib treatment can be taken if any abnormalities are observed.

7.R.3.9 Renal disorders
The applicant's explanation about the occurrence of renal disorders following administration of carfilzomib:
Renal disorder-related adverse events were summarized using PTs equivalent to the SMQ (MedDRA/J ver. 18.0) of "Acute renal failure" and "Chronic kidney disease" (Tables 36 and 37).

Table 36. Renal disorders (Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorders	120 (30.6)	39 (9.9)	101 (26.0)	28 (7.2)	6 (23.1)	0
Hypocalcaemia	63 (16.1)	13 (3.3)	46 (11.8)	7 (1.8)	0	0
Blood creatinine increased	26 (6.6)	4 (1.0)	18 (4.6)	1 (0.3)	2 (7.7)	0
Acute kidney injury	15 (3.8)	8 (2.0)	11 (2.8)	5 (1.3)	0	0
Hyponatraemia	15 (3.8)	6 (1.5)	10 (2.6)	6 (1.5)	3 (11.5)	0
Creatinine renal clearance decreased	11 (2.8)	1 (0.3)	9 (2.3)	2 (0.5)	0	0
Renal failure	10 (2.6)	4 (1.0)	7 (1.8)	2 (0.5)	0	0

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypoalbuminaemia	10 (2.6)	2 (0.5)	11 (2.8)	1 (0.3)	0	0
Renal impairment	10 (2.6)	2 (0.5)	9 (2.3)	4 (1.0)	1 (3.8)	0
Hyperkalaemia	8 (2.0)	3 (0.8)	6 (1.5)	1 (0.3)	3 (11.5)	0
Chronic kidney disease	5 (1.3)	3 (0.8)	4 (1.0)	0	0	0
Hyperphosphataemia	4 (1.0)	0	0	0	1 (3.8)	0

Table 37. Renal disorders (Studies 011 and 01 [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorders	65 (41.4)	35 (22.3)	38 (24.8)	16 (10.5)	26 (65.0)	6 (15.0)
Acute kidney injury	16 (10.2)	12 (7.6)	6 (3.9)	5 (3.3)	0	0
Blood creatinine increased	13 (8.3)	3 (1.9)	10 (6.5)	1 (0.7)	15 (37.5)	1 (2.5)
Renal impairment	11 (7.0)	6 (3.8)	5 (3.3)	1 (0.7)	0	0
Hypocalcaemia	11 (7.0)	3 (1.9)	10 (6.5)	2 (1.3)	2 (5.0)	0
Renal failure	10 (6.4)	8 (5.1)	3 (2.0)	2 (1.3)	0	0
Creatinine renal clearance decreased	9 (5.7)	1 (0.6)	4 (2.6)	3 (2.0)	0	0
Hyperkalaemia	8 (5.1)	3 (1.9)	2 (1.3)	1 (0.7)	6 (15.0)	0
Hyponatraemia	5 (3.2)	2 (1.3)	4 (2.6)	2 (1.3)	6 (15.0)	4 (10.0)
Hypoalbuminaemia	3 (1.9)	0	3 (2.0)	1 (0.7)	5 (12.5)	0
Blood sodium decreased	2 (1.3)	2 (1.3)	2 (1.3)	2 (1.3)	0	0
Oliguria	2 (1.3)	1 (0.6)	0	0	0	0
Hyperphosphataemia	2 (1.3)	0	1 (0.7)	0	2 (5.0)	0
Blood bicarbonate decreased	2 (1.3)	0	0	0	0	0
Blood urea increased	1 (0.6)	0	1 (0.7)	0	8 (20.0)	0
Chronic kidney disease	0	0	2 (1.3)	0	0	0
Proteinuria	0	0	0	0	4 (10.0)	1 (2.5)
Blood phosphorus increased	0	0	0	0	2 (5.0)	0
Protein urine present	0	0	0	0	1 (2.5)	0
Blood potassium increased	0	0	0	0	1 (2.5)	0

Study 009
Fatal renal disorder (acute kidney injury) occurred in 1 of 389 subjects (0.3%) in the Ld arm, and a causal relationship to the study drug could not be ruled out for this event. There were no fatal renal disorders in the CLd arm. Serious renal disorders occurred in 11 of 392 subjects (2.8%) in the CLd arm and 11 of 389 subjects (2.8%) in the Ld arm. The serious events in the CLd arm were acute kidney injury (6 subjects), hypocalcaemia (2 subjects), renal failure, renal impairment, hypoalbuminaemia, hyponatraemia, and nephrotic syndrome (1 subject each) (a single patient may have had >1 event). A causal relationship to the study drug could not be ruled out for acute kidney injury and hypocalcaemia (2 subjects each), and hypoalbuminaemia (1 subject). Renal disorders led to dose reduction in 25 of 392 subjects (6.4%) in the CLd arm and 25 of 389 subjects (6.4%) in the Ld arm, dose suspension in 27 of 392 subjects (6.9%) and 18 of 389 subjects (4.6%), and treatment discontinuation in 8 of 392 subjects (2.0%) and 3 of 389 subjects (0.8%).

Study 05
There were no fatal or serious renal disorder. Renal disorders that led to dose reduction occurred in 1 of 26 subjects (3.8%). There were no renal disorders leading to dose suspension or treatment discontinuation.

Study 011
Fatal renal disorder (acute kidney injury) occurred in 2 of 157 subjects (1.3%) in the carfilzomib arm. A causal relationship to the study drug was ruled out for these events. In the BSC arm, there were no fatal renal disorder. Serious renal disorders occurred in 21 of 157 subjects (13.4%) in the carfilzomib arm and 6 of 153 subjects (3.9%) in the BSC arm. The serious events in the carfilzomib arm were acute kidney injury (15 subjects), renal failure (3 subjects), renal impairment (2 subjects), and hyperkalaemia and oliguria (1 subject each) (a single patient may have had >1 event). A causal relationship to carfilzomib could not be ruled out for acute kidney injury (1 subject). In the carfilzomib and BSC arms, renal disorders led to dose reduction of carfilzomib in 1 of 157 subjects (0.6%) and 0 subjects, respectively; dose suspension of carfilzomib in 8 of 157 subjects (5.1%) and 3 of 153 subjects (2.0%), respectively; and treatment discontinuation with carfilzomib in 5 of 157 subjects (3.2%) and 0 subjects, respectively.

Study 01
In the 20/27 mg/m^2 arm, there were no fatal or serious renal disorders and those leading to carfilzomib dose reduction, dose suspension, or treatment discontinuation.

PMDA's view:
Considering serious renal disorders including acute kidney injury with a suspected causal relationship to carfilzomib, close attention to renal disorders is required during treatment with carfilzomib. The occurrence of renal disorders in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.3.10 Haemorrhage
The applicant's explanation about the occurrence of haemorrhage following administration of carfilzomib:
Haemorrhage-related adverse events were summarized using PTs classified into the SMQs (MedDRA/J ver. 18.0) of "Haemorrhage laboratory terms" and "Haemorrhage terms (excluding laboratory test terms)" (Tables 38 and 39).

Table 38. Haemorrhage
(Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 392		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhage	75 (19.1)	12 (3.1)	68 (17.5)	17 (4.4)	6 (23.1)	1 (3.8)
Epistaxis	19 (4.8)	1 (0.3)	16 (4.1)	1 (0.3)	1 (3.8)	0
Contusion	12 (3.1)	0	16 (4.1)	1 (0.3)	0	0
Ecchymosis	11 (2.8)	0	0	0	0	0
Haemoglobin decreased	6 (1.5)	3 (0.8)	2 (0.5)	1 (0.3)	4 (15.4)	1 (3.8)
International normalised ratio increased	5 (1.3)	3 (0.8)	8 (2.1)	7 (1.8)	0	0
Haematoma	5 (1.3)	0	12 (3.1)	3 (0.8)	1 (3.8)	0
Rectal haemorrhage	5 (1.3)	0	1 (0.3)	0	0	0
Haematuria	4 (1.0)	0	2 (0.5)	0	0	0
Petechiae	4 (1.0)	0	2 (0.5)	0	0	0
Increased tendency to bruise	1 (0.3)	0	5 (1.3)	1 (0.3)	0	0
Gastrointestinal haemorrhage	0	0	5 (1.3)	3 (0.8)	0	0

Table 39. Haemorrhage (Studies 011 and 01 [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhage	29 (18.5)	10 (6.4)	27 (17.6)	7 (4.6)	20 (50.0)	11 (27.5)
Epistaxis	13 (8.3)	5 (3.2)	10 (6.5)	2 (1.3)	0	0
Haematoma	5 (3.2)	0	4 (2.6)	0	0	0
Conjunctival haemorrhage	2 (1.3)	0	0	0	1 (2.5)	0
Gingival bleeding	2 (1.3)	0	0	0	0	0
Haematuria	2 (1.3)	0	0	0	0	0
Petechiae	2 (1.3)	0	1 (0.7)	0	0	0
Upper gastrointestinal haemorrhage	1 (0.6)	1 (0.6)	0	0	1 (2.5)	0
Mouth haemorrhage	1 (0.6)	0	2 (1.3)	0	0	0
Rectal haemorrhage	1 (0.6)	0	2 (1.3)	0	0	0
Red blood cell count decreased	1 (0.6)	0	0	0	4 (10.0)	0
Gastrointestinal haemorrhage	0	0	2 (1.3)	1 (0.7)	0	0
Haemoglobin decreased	0	0	2 (1.3)	1 (0.7)	17 (42.5)	11 (27.5)
Vaginal haemorrhage	0	0	2 (1.3)	1 (0.7)	0	0

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01	
	Carfilzomib N = 157		BSC N = 153		(20/27 mg/m^2) N = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Ear haemorrhage	0	0	2 (1.3)	0	0	0
Ecchymosis	0	0	2 (1.3)	0	0	0
Contusion	0	0	2 (1.3)	0	2 (5.0)	0
Haemorrhoidal haemorrhage	0	0	2 (1.3)	0	0	0
Haematocrit decreased	0	0	1 (0.7)	0	5 (12.5)	1 (2.5)
Blood urine present	0	0	0	0	2 (5.0)	0
International normalised ratio increased	0	0	1 (0.7)	0	1 (2.5)	1 (2.5)
Activated partial thromboplastin time prolonged	0	0	0	0	1 (2.5)	0
Reticulocyte count increased	0	0	0	0	1 (2.5)	0

Study 009
Fatal haemorrhage occurred in 2 of 392 subjects (0.5%) in the CLd arm and 1 of 389 subjects (0.3%) in the Ld arm. The fatal events in the CLd arm were subdural haematoma and haemorrhage intracranial (1 subject each). A causal relationship to the study drug could not be ruled out for haemorrhage intracranial (1 subject). Serious haemorrhage occurred in 5 of 392 subjects (1.3%) in the CLd arm and 4 of 389 subjects (1.0%) in the Ld arm. The serious events in the CLd arm were haematuria, haemoglobin decreased, subdural haematoma, lower gastrointestinal haemorrhage, and haemorrhage intracranial (1 subject each). A causal relationship to the study drug could not be ruled out for haemoglobin decreased, lower gastrointestinal haemorrhage, and haemorrhage intracranial (1 subject each). Haemorrhage led to dose reduction in 3 of 392 subjects (0.8%) in the CLd arm and 3 of 389 subjects (0.8%) in the Ld arm; dose suspension in 7 of 392 subjects (1.8%) and 5 of 389 subjects (1.3%); and treatment discontinuation in 2 of 392 subjects (0.5%) and 1 of 389 subjects (0.3%).

Study 05
There were no fatal or serious haemorrhage and haemorrhage leading to study drug dose reduction, dose suspension, or treatment discontinuation.

Study 011
Fatal haemorrhage occurred in 1 of 157 subjects (0.6%) in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm. The fatal event in the carfilzomib arm was upper gastrointestinal haemorrhage, and a causal relationship to carfilzomib was ruled out for the event. Serious haemorrhage occurred in 5 of 157 subjects (3.2%) in the carfilzomib arm and 4 of 153 subjects (2.6%) in the BSC arm. The serious events in the carfilzomib arm were epistaxis (2 subjects), gastric haemorrhage, haematemesis, and upper gastrointestinal haemorrhage (1 subject each). A causal relationship to carfilzomib could not be ruled out for gastric haemorrhage and haematemesis (1 subject each). Haemorrhage led to dose reduction of carfilzomib in 0 subjects in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm, dose suspension of carfilzomib in 4 of 157 subjects (2.5%) and 1 of 153 subjects (0.7%), and discontinuation of carfilzomib in 1 of 157 subjects (0.6%) and 2 of 153 subjects (1.3%).

Study 01
There were no fatal or serious haemorrhage and haemorrhage leading to dose reduction or suspension or discontinuation of carfilzomib in the 20/27 mg/m^2 arm.

PMDA's view:
Considering the reported serious haemorrhage with a suspected causal relationship to carfilzomib, close attention to haemorrhage is required during treatment with carfilzomib. The occurrence of haemorrhage in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.3.11 Infusion related reactions

The applicant's explanation about the occurrence of infusion related reactions (IRRs) following administration of carfilzomib:
IRRs were summarized using the following MedDRA PTs (MedDRA/J ver. 18.0): "angina pectoris," "angina unstable," "arthralgia," "asthenia," "chills," "dyspnoea," "dyspnoea at rest," "dyspnoea exceptional," "dyspnoea paroxysmal nocturnal," "face oedema," "flushing," "hypotension," "myalgia," "orthopnoea," "orthostatic hypotension," "platypnoea," "presyncope," "Prinzmetal angina," "pyrexia," "syncope," "trepopnoea," "vomiting," "nocturnal dyspnoea," "laryngeal dyspnoea," "diastolic hypotension," and "transfusion-associated dyspnoea" (Table 40). These terms were selected as IRR-relevant events from all adverse events that occurred within 24 hours after the start of carfilzomib treatment.

Table 40. Infusion related reactions
(Studies 009, 05, 011, and 01 [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)							
	CLd regimen				Carfilzomib monotherapy			
	Study 009 N = 392		Study 05 N = 26		Study 011 N = 157		Study 01 [20/27 mg/m^2] N = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
IRR	166 (42.3)	14 (3.6)	7 (26.9)	0	67 (42.7)	8 (5.1)	10 (25.0)	1 (2.5)
Pyrexia	61 (15.6)	4 (1.0)	4 (15.4)	0	30 (19.1)	2 (1.3)	8 (20.0)	1 (2.5)
Dyspnoea	50 (12.8)	3 (0.8)	0	0	16 (10.2)	0	0	0
Asthenia	41 (10.5)	5 (1.3)	1 (3.8)	0	22 (14.0)	3 (1.9)	0	0
Arthralgia	21 (5.4)	0	0	0	9 (5.7)	0	1 (2.5)	0
Vomiting	18 (4.6)	0	1 (3.8)	0	11 (7.0)	1 (0.6)	2 (5.0)	0
Chills	17 (4.3)	0	0	0	7 (4.5)	0	1 (2.5)	0
Dyspnoea exceptional	16 (4.1)	0	0	0	2 (1.3)	0	0	0
Flushing	13 (3.3)	0	2 (7.7)	0	0	0	0	0
Hypotension	11 (2.8)	0	0	0	2 (1.3)	2 (1.3)	0	0
Myalgia	10 (2.6)	0	0	0	2 (1.3)	0	1 (2.5)	0

Study 009
There was no fatal IRR. Serious IRRs occurring in 13 of 392 subjects (3.3%) were pyrexia (9 subjects), dyspnoea (2 subjects), syncope, asthenia, and angina pectoris (1 subject each) (a single patient may have had >1 event). A causal relationship to the study drug could not be ruled out for pyrexia (4 subjects), dyspnoea, angina pectoris, and asthenia (1 subject each). IRRs led to dose reduction of the study drug in 12 of 392 subjects (3.1%), suspension of the study drug in 22 of 392 subjects (5.6%), and discontinuation of the study drug in 2 of 392 subjects (0.5%).

Study 05
There was no fatal or serious IRR. IRR led to dose reduction of the study drug in 1 of 26 subjects (3.8%). No IRR led to suspension or discontinuation of the study drug.

Study 011
There was no fatal IRR. Serious IRRs occurred in 7 of 157 subjects (4.5%) and were pyrexia (4 subjects), hypotension (2 subjects), and dyspnoea (1 subject). A causal relationship to carfilzomib could not be ruled out for pyrexia, hypotension, and dyspnoea (1 subject each). IRRs led to dose suspension of the study drug in 4 of 157 subjects (2.5%) and discontinuation of the study drug in 1 subject (0.6%). No IRR led to dose reduction of the study drug.

Study 01
In the 20/27 mg/m^2 arm, IRR led to dose reduction of carfilzomib in 1 of 40 subjects (2.5%) and suspension of carfilzomib in 1 of 40 subjects (2.5%). There was no fatal or serious IRR or that leading to discontinuation of carfilzomib.

In clinical studies of carfilzomib conducted after Part 2 of Study PX-171-002 (a foreign phase I study), including Studies 009, 05, 011, and 01, required premedication with DEX to alleviate IRRs [see Section 7.R.5.2].

Table 41 shows the occurrence of IRRs by cycle in Studies 009, 05, 011, and 01. IRR occurred regardless of the number of carfilzomib doses given.

Table 41. Infusion related reactions by cycle (pooled analysis of Studies 009, 05, 011, and 01 [20/27 mg/m^2])

Cycle	N (%)		
	N	All Grades	Grade ≥3
Cycle 1	615	113 (18.4)	9 (1.5)
Cycle 2	575	76 (13.2)	2 (0.3)
Cycle 3	541	41 (7.6)	2 (0.4)
Cycle 4	508	42 (8.3)	0
Cycle 5	470	25 (5.3)	1 (0.2)
Cycle 6	439	26 (5.9)	2 (0.5)
Cycle 7	403	19 (4.7)	1 (0.2)
Cycle 8	378	20 (5.3)	0
Cycle 9	354	17 (4.8)	1 (0.3)
Cycle 10	336	18 (5.4)	1 (0.3)
Cycle 11	318	14 (4.4)	1 (0.3)
Cycle 12	305	7 (2.3)	0
Cycle 13 onward	296	32 (10.8)	1 (0.3)

PMDA's view:
Considering serious IRRs with a suspected causal relationship to carfilzomib, close attention to IRRs is required during treatment with carfilzomib. The occurrence of IRRs in the clinical studies and the prophylactic premedication with DEX for IRRs specified in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.3.12 Tumor lysis syndrome

The applicant's explanation about the occurrence of tumor lysis syndrome (TLS) following administration of carfilzomib:
TLS-related adverse events were summarized using a MedDRA PT (MedDRA/J ver. 18.0) of "tumour lysis syndrome."

Study 009
In the CLd arm, TLS occurred in 3 of 392 subjects (0.8%). All were serious events, for which a causal relationship to the study drug could not be ruled out. The events occurred on Days 1, 2, and 24, and all resolved. There was no fatal TLS. TLS led to suspension of the study drug in 1 of 392 subjects (0.3%). There was no TLS leading to dose reduction or discontinuation of the study drug. No TLS occurred in the Ld arm.

Study 05
No TLS occurred.

Study 011
In the carfilzomib arm, TLS occurred in 3 of 157 subjects (1.9%). All were serious events, for which a causal relationship to carfilzomib could not be ruled out. The events occurred on Days 5, 7, and 10 of Cycle 1, and their outcomes were "resolved," "resolving," and "not resolved." There was no fatal TLS. TLS led to suspension and discontinuation of carfilzomib in 1 of 157 subjects (0.6%) each. There was no TLS leading to dose reduction of carfilzomib. No TLS occurred in the BSC arm.

Study 01
In the 20/27 mg/m^2 arm, TLS occurred in 1 of 40 subjects (2.5%). The event was serious, for which a causal relationship to carfilzomib could not be ruled out. The event occurred on Day 9, and resolved. There was no fatal TLS. TLS led to suspension of carfilzomib in 1 of 40 subjects (2.5%). There was no TLS leading to reduction or discontinuation of carfilzomib.

PMDA's view:
Considering serious TLS reported with a suspected causal relationship to carfilzomib, close attention to TLS is required during treatment with carfilzomib. The occurrence of TLS in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.3.13 Hypertension including hypertensive crisis

The applicant's explanation about the occurrence of hypertension including hypertensive crisis following administration of carfilzomib:
Hypertension-related adverse events were summarized using PTs classified under the SMQ (MedDRA/J ver. 18.0) of "Hypertension."

Study 009
Hypertension occurred in 62 of 392 subjects (15.8%) in the CLd arm and 33 of 389 subjects (8.5%) in the Ld arm. Grade ≥3 hypertension occurred in 22 of 392 subjects (5.6%) in the CLd arm and 9 of 389 subjects (2.3%) in the Ld arm. No fatal hypertension occurred. Serious hypertension occurred in 1 of 392 subjects (0.3%) in the CLd arm and 1 of 389 subjects (0.3%) in the Ld arm. The serious event in the CLd arm was hypertension, for which a causal relationship to the study drug was ruled out. Hypertension led to reduction of the study drug in 3 of 392 subjects (0.8%) in the CLd arm and 3 of 389 subjects (0.8%) in the Ld arm, suspension of the study drug in 4 of 392 subjects (1.0%) in the CLd arm and 2 of 389 subjects (0.5%) in the Ld arm, and discontinuation of the study drug in 1 of 392 subjects (0.3%) in the CLd arm and 1 of 389 subjects (0.3%) in the Ld arm.

Study 05
Hypertension occurred in 4 of 26 subjects (15.4%), none of which were Grade ≥3. There was no fatal or serious hypertension, hypertension leading to reduction, suspension, or discontinuation of the study drug.

Study 011
Hypertension occurred in 25 of 158 subjects (15.9%) in the carfilzomib arm and 9 of 153 subjects in the BSC arm (5.9%). Grade ≥3 hypertension occurred in 6 of 157 subjects (3.8%), all of which were in the carfilzomib arm. There was no fatal of serious hypertension. Hypertension led to dose suspension in 2 of 157 subjects (1.3%) in the carfilzomib arm and 1 of 153 subjects (0.3%) the BSC arm, and carfilzomib treatment discontinuation in 0 subjects in the carfilzomib arm and 1 of 153 subjects (0.3%) in the BSC arm. There were no hypertension leading to carfilzomib dose reduction.

Study 01
In the 20/27 mg/m^2 arm, hypertension occurred in 6 of 40 subjects (15.0%). Grade ≥3 hypertension occurred in 4 of 40 subjects (10.0%). There was no fatal or serious hypertension or hypertension leading to reduction, suspension, or discontinuation of carfilzomib.

Following the evaluation of the safety of carfilzomib based on data including the results of Study 2011-003 (a foreign phase III study in patients with relapsed or refractory MM), a foreign corrective action report (dated June 18, 2015) was issued to call attention of medical institutions overseas to hypertension including hypertensive crisis associated with the administration of carfilzomib. PMDA asked the applicant to explain the occurrence of hypertension including hypertensive crisis following administration of carfilzomib including that in post-marketing use outside Japan.

The applicant's explanation:
The data from foreign and Japanese clinical studies and post-marketing use results data (data cut-off on February 17, 2016) revealed hypertension occurring in 650 patients, including 1 fatal case. The event was classified as hypertension, for which a causal relationship to carfilzomib was ruled out. Serious hypertension occurring in 86 patients included hypertension (57 patients), hypertensive crisis (10 patients), blood pressure increased (7 patients), hypertensive emergency (4 patients), hypertensive encephalopathy (2 patients), orthostatic hypertension, blood pressure abnormal, blood pressure fluctuation, hypertensive cardiomegaly, retinopathy hypertensive, and essential hypertension (1 patient each). A causal relationship to carfilzomib could not be ruled out for hypertension (40 patients), hypertensive crisis (8 patients), blood pressure increased (7 patients), blood pressure abnormal, blood pressure fluctuation, hypertensive emergency, hypertensive cardiomegaly, hypertensive encephalopathy, and essential hypertension (1 patient each).

PMDA's view:
Considering the reported serious hypertensive crisis with a suspected causal relationship to carfilzomib, patients must be carefully monitored for hypertension including hypertensive crisis during treatment with carfilzomib by blood pressure taking at clinical examination. The occurrence of hypertension including hypertensive crisis in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.3.14 Venous thromboembolism
The applicant's explanation about the occurrence of venous thromboembolism following administration of carfilzomib:
Venous thromboembolism-related adverse events were summarized using PTs classified under the SMQ (MedDRA/J ver. 18.0) of "Embolic and thrombotic events, venous" (Tables 42 and 43).

Table 42. Venous thromboembolism
(Studies 009 and 05; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 009				Study 05	
	CLd N = 39		Ld N = 389		N = 26	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism	60 (15.3)	22 (5.6)	35 (9.0)	15 (3.9)	0	0
Deep vein thrombosis	26 (6.6)	7 (1.8)	15 (3.9)	4 (1.0)	0	0
Pulmonary embolism	14 (3.6)	12 (3.1)	9 (2.3)	9 (2.3)	0	0
Thrombophlebitis superficial	11 (2.8)	0	6 (1.5)	1 (0.3)	0	0
Thrombophlebitis	8 (2.0)	2 (0.5)	3 (0.8)	0	0	0
Venous thrombosis limb	6 (1.5)	0	0	0	0	0
Venous thrombosis	1 (0.3)	1 (0.3)	4 (1.0)	0	0	0

Table 43. Venous thromboembolism
(Studies 011 and 01 [20/27 mg/m^2]; with an incidence of ≥1% in any arm)

Event (MedDRA/J ver. 18.0)	N (%)					
	Study 011				Study 01 (20/27 mg/m^2) N = 40	
	Carfilzomib N = 157		BSC N = 153			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism	2 (1.3)	2 (1.3)	3 (2.0)	1 (0.7)	0	0
Deep vein thrombosis	0	0	2 (1.3)	1 (0.7)	0	0

Study 009
Fatal venous thromboembolism occurred in 1 of 389 subjects (0.3%) in the Ld arm. There was no fatal venous thromboembolism in the CLd arm. Serious venous thromboembolism occurred in 22 of 392 subjects (5.6%) in the CLd arm and 16 of 389 subjects (4.1%) in the Ld arm The serious events in the CLd arm were pulmonary embolism (12 subjects), deep vein thrombosis (9 subjects), and thrombophlebitis (1 subject). A causal relationship to the study drug could not be ruled out for pulmonary embolism (10 subjects), deep vein thrombosis (9 subjects), and thrombophlebitis (1 subject). Venous thromboembolism led to study drug dose reduction in 9 of 392 subjects (2.3%) in the CLd arm and 5 of 389 subjects (1.3%) in the Ld arm, dose suspension in 20 of 392 subjects (5.1%) in the CLd arm and 10 of 389 subjects (2.6%) in the Ld arm, and treatment discontinuation in 4 of 392 subjects (1.0%) in the CLd arm and 5 of 389 subjects (1.3%) in the Ld arm.

Study 05
There was no fatal or serious venous thromboembolism or thromboembolism leading to reduction, suspension, or discontinuation of the study drug.

Study 011
There was no fatal venous thromboembolism. Serious venous thromboembolism occurred in 2 of 157 subjects (1.3%) in the carfilzomib arm and 1 of 153 subjects (0.7%) in the BSC arm. The serious events in the carfilzomib arm were pulmonary embolism and venous thrombosis (1 subject each). A causal relationship to carfilzomib drug could not be ruled out for pulmonary embolism (1 subject). Venous thromboembolism led to dose suspension in 1 of 157 subjects (0.6%) in the carfilzomib arm and 0

subjects in the BSC arm. There were no venous thromboembolism leading to reduction or discontinuation of carfilzomib.

Study 01
In the 20/27 mg/m^2 arm, there was no fatal or serious venous thromboembolism. No venous thromboembolism led to reduction, suspension, or discontinuation of carfilzomib.

PMDA's view:
Considering the reported serious venous thromboembolism with a suspected causal relationship to carfilzomib, close attention to venous thromboembolism is required during treatment with carfilzomib. The occurrence of venous thromboembolism in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

On January 22, 2016, the applicant expressed their intention to revise the Company Core Data Sheet based on their latest safety data of carfilzomib, which include the results from Study 2011-003 (a foreign phase III study conducted in patients with relapsed or refractory MM), to call attention to haemorrhage associated with venous thromboembolism and thrombocytopenia. PMDA then asked the applicant to provide data on the occurrence of relevant events.

7.R.3.15 Others
The following sub-sections summarize PMDA's discussions on PRES, TMA, gastrointestinal perforation, pericarditis, and pericardial effusion. These events were highlighted in the corrective action report issued to medical institutions outside Japan as adverse events associated with the treatment with carfilzomib based on foreign post-marketing use results data.

(a) PRES and encephalopathy
The applicant's explanation about PRES associated with carfilzomib treatment:
As PRES-related adverse events, the MedDRA PT (MedDRA/J ver. 18.0) of "PRES" was used.

PRES did not occur in Study 009, 05, 011, or 01 (20/27 mg/m^2 arm).

Japanese and foreign clinical study results and foreign post-marketing data (data cut-off on February 17, 2016) revealed that a total of 12 patients had experienced PRES. There were no fatal PRES. PRES was serious and a causal relationship to carfilzomib could not be ruled out in all 12 patients.

PMDA asked the applicant to explain the occurrence of encephalopathy, taking note particularly of fatal encephalopathy in post-marketing use of carfilzomib outside Japan.

The applicant's explanation:
Encephalopathy-related adverse events were summarized using MedDRA PTs (MedDRA/J ver. 18.0) "encephalopathy," "metabolic encephalopathy," and "hepatic encephalopathy."

Encephalopathy did not occur in Study 009, 05, 011, or 01 (20/27 mg/m^2 arm).

Japanese and foreign clinical study results and post-marketing data (data cut-off on February 17, 2016) revealed a total of 15 patients experiencing encephalopathy. Of these, 2 patients died, 1 from metabolic encephalopathy and another from encephalopathy. A causal relationship to carfilzomib could not be ruled out for either event. Serious encephalopathy occurred in 13 patients. Serious events were, namely, encephalopathy (6 patients), hepatic encephalopathy (5 patients), and metabolic encephalopathy (2 patients). A causal relationship to carfilzomib could not be ruled out for encephalopathy (6 patients), hepatic encephalopathy (5 patients), and metabolic encephalopathy (1 patient).

(b) TMA
The applicant's explanation about the occurrence of TMA following administration of carfilzomib:

TMA-related adverse events were summarized using MedDRA PTs (MedDRA/J ver. 18.0) of "haemolytic uraemic syndrome (HUS)," "thrombotic thrombocytopenic purpura (TTP)," and "TMA."

TMA did not occur in Study 009, 05, 011, or 01 (20/27 mg/m^2 arm).

Data from Japanese and foreign clinical studies and post-marketing experience outside Japan (data cut-off on February 17, 2016) revealed a total of 33 patients experiencing TMA, including 1 fatal event. The fatal event was classified as TTP, for which a causal relationship to carfilzomib could not be ruled out. Serious TMA occurred in 33 patients, and they were TMA (13 patients), TTP (11 patients), and HUS (9 patients). A causal relationship to carfilzomib could not be ruled out for TMA (12 patients), TTP (11 patients), and HUS (9 patients).

(c) Gastrointestinal perforation
The applicant's explanation about the occurrence of gastrointestinal perforation following administration of carfilzomib:
Gastrointestinal perforation-related adverse events were summarized using PTs classified under the SMQ (MedDRA/J ver. 18.0) of "Gastrointestinal perforation."
In the CLd arm of Study 009, gastrointestinal perforation occurred in 5 subjects, including Grade ≥3 gastrointestinal perforation in 4 subjects. There were no fatal events. Serious gastrointestinal perforation occurring in 4 subjects were namely diverticular perforation (2 subjects), abdominal abscess, large intestine perforation, peritonitis (1 subject each) (a single patient may have had >1 event). A causal relationship to the study drug was ruled out for all events. In Studies 05, 011, and 01 (20/27 mg/m^2 arm), no gastrointestinal perforation occurred.

Japanese and foreign clinical study results and post-marketing data outside Japan (data cut-off on May 26, 2015) revealed a total of 28 patients experiencing gastrointestinal perforation, including 3 patients who had died. The fatal events were namely intestinal perforation (2 patients) and large intestine perforation (1 patient), and a causal relationship to carfilzomib could not be ruled out for intestinal perforation (1 patient). Serious gastrointestinal perforation occurred in 24 patients, and they were namely intestinal perforation (6 patients), diverticular perforation (5 patients), peritonitis (4 patients), large intestine perforation (3 patients), perirectal abscess (2 patients), abdominal abscess, anal abscess, abscess intestinal, and gastric perforation (1 patient each). A causal relationship to carfilzomib could not be ruled out for intestinal perforation (2 patients), peritonitis (2 patients), large intestine perforation, anal abscess, and diverticular perforation (1 patient each).

(d) Pericarditis
The applicant's explanation about the occurrence of pericarditis following administration of carfilzomib:
Pericarditis-related adverse events were summarized by PT equivalent to MedDRA HLT (MedDRA/J ver. 18.0) of "Infectious pericarditis" and "Noninfectious pericarditis."

Pericarditis did not occur in Studies 009, 05, 011, and 01 (20/27 mg/m^2 arm).

Japanese and foreign clinical study results and post-marketing data outside Japan (data cut-off on May 26, 2015) revealed a total of 4 patients experiencing pericarditis. There were no fatal pericarditis, while serious pericarditis occurred in 4 patients. All serious events were classified as pericarditis, and a causal relationship to carfilzomib could not be ruled out for 2 patients.

(e) Pericardial effusion
The applicant's explanation about the occurrence of pericardial effusion following administration of carfilzomib:
Pericardial effusion-related adverse events were summarized by MedDRA PT (MedDRA/J ver. 18.0), namely "pericardial effusion" and "pericardial effusion malignant."

In Study 009, pericardial effusion occurred in 1 subject in the CLd arm. The event was serious, and its causal relationship to carfilzomib was ruled out. There were no fatal pericardial effusion. No pericardial effusion-related events occurred in Studies 05, 011, and 01 (20/27 mg/m^2 arm).

Japanese and foreign clinical study results and overseas post-marketing data (data cut-off on May 26, 2015) revealed a total of 10 patients experiencing pericardial effusion. There were no fatal events. Serious pericardial effusion occurred in 8 patients, all which were classified as pericardial effusion. A causal relationship to carfilzomib could not be ruled out in 7 of the 8 patients.

PMDA's view:
Considering the reported serious PRES/encephalopathy, TMA (HUS/TTP and TMA), gastrointestinal perforation, pericarditis, and pericardial effusion with a suspected causal relationship to carfilzomib, close attention is required to these events during treatment with carfilzomib. The occurrence of these events in the clinical studies should be communicated to healthcare professionals in an appropriate manner through the package insert, etc.

7.R.4 Clinical positioning and indications

The proposed indication of carfilzomib was "relapsed or refractory multiple myeloma." The applicant also intends to highlight in the "Precautions for indication" section to the effect that carfilzomib should be indicated for the treatment of patients who have not responded to ≥1 prior standard therapy or patients with MM recurring after prior therapy.

Based on the discussions in sections of "7.R.2 Efficacy" and "7.R.3 Safety" and the following subsections, PMDA concluded that the indication of carfilzomib should be defined as "relapsed or refractory multiple myeloma" as proposed. The "Precautions for indication" section should provide the following advice:

- Carfilzomib should be administered to patients who have not responded to at least 1 prior standard therapy or patients in a recurring condition after prior therapy.

- Before selecting eligible patients, healthcare professionals should understand the efficacy and safety of carfilzomib well through a careful review of the "Clinical studies" section that elaborates prior therapies, etc. of patients enrolled in the clinical studies.

7.R.4.1 Clinical positioning of carfilzomib

PMDA confirmed the descriptions of carfilzomib used in the treatment of patients with relapsed or refractory MM in clinical practice guidelines and representative hematology and clinical oncology text books published in and outside Japan as listed below. On the other hand, there were no descriptions on carfilzomib in the following guidelines and textbooks: The Japanese Society of Hematology. *The Hematopoietic Tumor Guidelines* 2013 (in Japanese) (Tokyo: Kanehara & Co., Ltd.; 2013), Japanese Society of Medical Oncology. *New Clinical Oncology*, fourth edition. (in Japanese) (Tokyo: Nankodo Co., Ltd.; 2015), a representative textbook of clinical oncology in Japan, and *Williams Hematology*, eighth edition. (US: The McGraw-Hill Companies, Inc.; 2010), one of the representative textbooks of hematology in other countries.

Clinical practice guidelines

- NCCN Guidelines (Multiple Myeloma) (v. 2.2016): The CLd regimen (Category 1 recommendation; based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate), and carfilzomib monotherapy (Category 2A recommendation; based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) are recommended as therapeutic options for patients with previously treated MM.

- PDQ of US NCI (December 9, 2015 edition): The results of a randomized controlled study (Study 009) showed that the median PFS values were 26.3 months in the CLd arm and 17.6 months in the Ld arm, indicating that significantly increased PFS in the CLd arm.

- Japanese Society of Myeloma. *Guideline for the treatment of multiple myeloma*, third edition. (in Japanese) (Tokyo: Bunkodo Co., Ltd.; 2012): In the US, carfilzomib monotherapy was approved in July 2012, based on the results of Part 2 (A1) of phase II Study PX-171-003. In Japan, a phase I/II study (Study 01) is underway.

Textbooks

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 10th ed. (Lippincott Williams & Wilkins, 2014, USA): The efficacy results of Study PX-171-006, a phase Ib/II study conducted in patients with relapsed or refractory MM, showed that the response rate of the CLd regimen was 77% with the median response duration of 22 months. Study 009 is underway. Based on the efficacy data from Part 2 (A1) of Study PX-171-003, a phase II study in patients with relapsed or refractory MM (response rate, 24%; median response duration, 8 months), FDA granted an accelerated approval in 2012 for the indication of "patients with relapsed or refractory MM who received prior therapy with bortezomib or an immunomodulatory agent."

- *Wintrobe's Clinical Hematology*, thirteenth edition. (Lippincott Williams & Wilkins, 2013, the US): Carfilzomib was approved by FDA for the treatment of patients with relapsed or refractory MM who received prior therapy with an immunomodulatory agent and bortezomib. In addition, the development of several combination regimens with carfilzomib are underway.

PMDA's view:
The results of Study 009 showed increased PFS with an acceptable safety profile of carfilzomib in patients with relapsed or refractory MM who received carfilzomib in addition to the Ld regimen. Thus, the CLd regimen may be a treatment option for patients with relapsed or refractory MM. Carfilzomib monotherapy, however, is not recommended because of the results of Study 011, which did not demonstrate prolonged survival of patients in the carfilzomib monotherapy arm [see Section 7.1.2.6].

7.R.4.2 Target patient population of carfilzomib

The applicant's explanation about the efficacy of carfilzomib in Study 009 in relation to prior therapies:
Patients eligible for Study 009 were required to have 1 to 3 prior regimen(s) for MM and to meet at least 1 of the following criteria:

- Disease relapse or progression after any prior regimen (patients refractory to the most recent prior therapy[19] were eligible)

- A ≥25% decrease in M protein or total protein following at least 1 prior regimen

- No disease progression during prior bortezomib therapy, when relevant

- No disease progression within the first 3 months of prior therapy with the Ld regimen, when relevant, or no disease progression during the most recent prior therapy, if it was with the Ld regimen.

- No discontinuation of prior therapy with lenalidomide or DEX due to intolerance.

Table 44 shows the results of PFS in Study 009 by number of prior regimens. The study did not enroll patients with ≥4 prior regimens. In Study 05, the response rate was 100% (95% CI, 77.9%-100%) in subjects with 1 to 3 prior regimen(s) (12 subjects) and 78.6% (95% CI, 53.4%-93.9%) in those with ≥4 prior regimens (14 subjects).

[19] Defined as patients who had disease progression during or within 60 days after discontinuation of prior therapy, or those with a response lower than MR following prior therapy.

Table 44. The second interim analysis of progression-free survival (determined by the Independent Review Committee, intent-to-treat population, data cut-off on June 16, 2014)

Number of prior regimens	CLd		Ld		Hazard ratio [95% CI]
	N	Median PFS [95% CI] (months)	N	Median PFS [95% CI] (months)	
Total	396	26.3 [23.3-30.5]	396	17.6 [15.0-20.6]	0.69 [0.57-0.83]
1	184	29.6 [23.2-33.5]	157	17.6 [15.0-22.2]	0.71 [0.53-0.96]
2	120	26.2 [21.9-32.3]	139	18.5 [14.0-25.0]	0.74 [0.54-1.04]
3	92	24.1 [19.6-32.6]	100	14.8 [10.0-22.1]	0.68 [0.47-1.00]

PMDA asked the applicant to explain a benefit of the clinical use of carfilzomib in patients meeting the criteria listed below, who were excluded from Study 009. The applicant responded that there were no clinical study data on the efficacy and safety of carfilzomib in these patient populations at that time.

- Patients with MM experiencing disease progression during treatment with bortezomib.
- Patients with MM experiencing disease progression within the first 3 months of treatment with the Ld regimen.
- Patients with MM experiencing disease progression during treatment with the Ld regimen when it is the most recent prior therapy.

PMDA's view:
There are no available data to evaluate the efficacy and safety of carfilzomib in patients with MM who were excluded from Study 009, i.e., those who experienced disease progression during treatment with bortezomib, within the first 3 months of the Ld regimen, or during treatment with the Ld regimen. Therefore, use of carfilzomib in these patient populations is not recommended. However, given that carfilzomib is used by physicians knowledgeable and experienced in the treatment of haematopoietic malignancy, they should be able to identify eligible patients for the therapy based on the knowledge from advice appropriately given in the "Precautions for indication" section, including prior therapies of patients enrolled in Study 009. Accordingly, PMDA concluded that "relapsed or refractory multiple myeloma" is the appropriate indication of carfilzomib.

7.R.5 Dosage and administration

The proposed dosage and administration of carfilzomib was "Carfilzomib is usually administered to adult patients once daily on Days 1, 2, 8, 9, 15, and 16 followed by a 12-day rest period. This 28-day cycles is repeated. The dose is of carfilzomib 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1 and 27 mg/m^2 (body surface area) thereafter, and is administered intravenously over 10 minutes." The applicant noted that the "Precautions for dosage and administration" section will give advice to the following effect:

- For patients with a body surface area of >2.2 m^2, the dose should be determined based on the body surface area of 2.2 m^2.
- When using carfilzomib in combination with another antineoplastic drug, the package insert of the concomitant drug should be read carefully beforehand.
- In the combination therapy with lenalidomide and DEX, carfilzomib should be administered intravenously once daily on Days 1, 2, 15, and 16 from Cycle 13 onward.

- Treatment with carfilzomib should be suspended when CrCL has decreased to <15 mL/min or ≤50% from baseline, or to a level requiring dialysis. The resumption of treatment should be considered when CrCL has recovered to ≥15 mL/min or <25% from baseline, or to a level not requiring dialysis.

- Criteria for dose suspension, reduction, or discontinuation of carfilzomib following the occurrence of an adverse event.

- Instruction for reconstitution of carfilzomib.

Based on the discussions in the later subsections, PMDA concluded that appropriate descriptions in the "Dosage and administration" and "Precautions for dosage and administration" sections of the package insert are as follows:

Dosage and administration
In combination with lenalidomide plus dexamethasone, carfilzomib is usually administered to adult patients once daily by intravenous infusion on Days 1, 2, 8, 9, 15, and 16, followed by a 12-day rest period. This 28-day cycle is repeated until Cycle 12. From Cycles 13 onward, carfilzomib is administered once daily by intravenous infusion on Days 1, 2, 15, and 16, followed by a 12-day rest period. The dose of carfilzomib is 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1 and 27 mg/m^2 (body surface area) thereafter, and is administered as an intravenous infusion over 10 minutes. The dose may be reduced according to the patient's condition.

Precautions for dosage and administration
- The efficacy and safety of carfilzomib monotherapy have not been established.

- Lenalidomide and DEX should be administered with a good understanding of the "Clinical studies" section. The package insert of these concomitant drugs should be read thoroughly.

- The efficacy and safety of carfilzomib used in combination with antineoplastic drugs other than lenalidomide plus dexamethasone have not been established.

- The dose for patients with a body surface area of >2.2 m^2 should be determined based on the body surface area of 2.2 m^2.

- The efficacy and safety of carfilzomib administered for >18 cycles have not been established.

- The administration of carfilzomib should be suspended when creatinine clearance (CrCL) decreases to <15 mL/min. Treatment resumption should be considered when CrCL recovers to ≥15 mL/min. When dialysis is required, carfilzomib should be resumed at a dose of <20 mg/m^2 only after dialysis.

- Dose suspension or reduction or discontinuation of carfilzomib should be decided appropriately. If any of the following adverse events with a suspected causal relationship with carfilzomib (adverse drug reactions) occurs, treatment with carfilzomib should be suspended until resolution: hematotoxic events (Grade 4* platelet count decreased, lymphocyte count decreased, anaemia, or Grade ≥3* neutrophil count decreased) or Grade ≥3* non-hematotoxic events (excluding alopecia, and Grade 3* nausea, vomiting, diarrhoea, and fatigue). Treatment may be resumed, when appropriate, at a dose reduced according to the table below, with careful weighing of the risk and benefit associated with the use of carfilzomib. If an adverse drug reaction recurs causing another dose suspension, treatment should be resumed at a reduced dose or discontinued according to the table below.

* NCI-CTCAE ver. 4.0

Dose before adverse drug reaction	Recommended dose for treatment resumption
27 mg/m^2	20 mg/m^2
20 mg/m^2	15 mg/m^2
15 mg/m^2	Discontinue

- Kyprolis 10 mg should be reconstituted with 5 mL of water for injection, and Kyprolis 40 mg with 20 mL of water for injection, to make a 2-mg/mL injection solution. The required volume of the solution is calculated from the patient's body surface area, and it should be diluted with a 5% glucose solution.

7.R.5.1 Dosage and dose interval

The applicant's explanation about the dose and dose interval of carfilzomib:

Based on the evaluation results of 20S proteasome inhibition activity and tolerability following administration of carfilzomib to rats 5 or 2 times per week (*Cancer Res.* 2007;67:6383-91), 5-times-weekly treatment was evaluated in Study PX-171-001, and 2-times-weekly treatment in Part 1 of Study PX-171-002. Because carfilzomib was better tolerated in Part 1 of Study PX-171-002 than in Study PX-171-001, 2-times-weekly treatment was selected for clinical studies since then. Further, in Part 2 of Study PX-171-002, carfilzomib 20 mg/m^2 was administered in Cycle 1, and when tolerated, the dose was increased to 27 mg/m^2 from Cycle 2 onward. The incidence of adverse events attributable to oncolysis tended to be lower in Part 2 than in Part 1 of the study. Accordingly, in Part 2 (A1) of Study PX-171-003, carfilzomib was administered intravenously once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle at 20 mg/m^2 in Cycle 1, and at 27 mg/m^2 from Cycle 2 if tolerated as in Part 2 of Study PX-171-002.

In Part 2 (A1) of Study PX-171-003, 28 of 266 subjects (10.5%) were not able to proceed to Cycle 2 due to disease progression in Cycle 1. Therefore, clinical studies of carfilzomib started after Study PX-171-003 was designed to administer carfilzomib once daily in 28-day cycles at 20 mg/m^2 on Days 1 and 2 of Cycle 1 and at 27 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15, and 16 from Cycle 2 onward (20/27 mg/m^2).

Lenalidomide, when used in combination with bortezomib and DEX, was reported to have enhanced antiproliferative activity against human MM cell line (*Blood.* 2002;99:4525-30). Therefore, in Study PX-171-006, tolerability of carfilzomib was evaluated at 20/27 mg/m^2 in combination with lenalidomide at 10, 15, 20, or 25 mg plus DEX 40 mg. Because MTD was not achieved within the dose range studied in Study PX-171-006, the efficacy and safety of carfilzomib were evaluated at 20/27 mg/m^2 in combination with lenalidomide 25 mg plus DEX 40 mg in Studies 009 and 05. In Study PX-171-006, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 in Cycle1 to Cycle 12, but the omission of doses on Days 8 and 9 were allowed from Cycle 13 onward to reduce the occurrence of carfilzomib treatment-related adverse events, etc. In Studies 009 and 05, carfilzomib was administered on Days 1, 2, 15, and 16 only from Cycle 13 onward.

Accordingly, the proposed dosage and administration of carfilzomib was determined on the basis of that in Studies 009 and 05. However, the omission of carfilzomib 20/27 mg/m^2 in the combination therapy with lenalidomide 25 mg and DEX 40 mg on Days 8 and 9 from Cycle 13 onward should be highlighted in the "Precautions for dosage and administration" section.

PMDA asked the applicant to explain the rationale for the precautionary statement in the proposed "Precautions for dosage and administration" to the effect that dose for patients with a body surface area of >2.2 m^2 should be determined based on the body surface area of 2.2 m^2.

The applicant's rationale:

According to a published article (*Clin Oncol*. 2001;13:s211-248), upper limit doses of neoplastic drugs requiring body-surface-area-based dosing are determined based on a body surface area of 2.0 to 2.2 m^2 to prevent overdosing in obese patients. Therefore, in clinical studies conducted after Study PX-171-003 (foreign phase II study) the dose of carfilzomib for patients with a body surface area of >2.2 m^2 was calculated based on the body surface area of 2.2 m^2.

PMDA's view:
As per studies 009 and 05, the 28-day-cycle dosing schedule of carfilzomib may be specified as follows: 10-minute intravenous infusion at 20 mg/m^2 on Days 1 and 2 of Cycle 1 and at 27 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15, and 16 from Cycle 2 onward. Further, dosing on Days 1, 2, 15, and 16 from Cycle 13 onward should also be specified in the regimen.

The efficacy and safety of carfilzomib are clear only in the CLd regimen. Therefore, carfilzomib should be required to be administered in combination with lenalidomide and DEX in the regimen. The dosing regimens of lenalidomide and DEX in Studies 009 and 05 are important information for healthcare professionals in the use of carfilzomib and thus should be communicated through the "Precautions for dosage and administration" and "Clinical studies" sections.

In terms of the dose calculation based on the body surface area of 2.2 m^2 for patients with a body surface area of >2.2 m^2, the results of population pharmacokinetic analysis demonstrated no clear clinically significant effect of body surface area on the CL of carfilzomib [see Section 6.2.6]. Thus, there is no clinical pharmacological grounds for the upper limit of body surface area of 2.2 m^2 for dose calculation. However, the efficacy and safety of doses of carfilzomib without following this calculation rule are unknown. Therefore, the rule should be reminded in the "Precautions for dosage and administration" section.

7.R.5.2 Infusion rate and premedication
The applicant's explanation about the specifications on the infusion rate of carfilzomib and premedication with DEX to reduce IRR:
A rat study demonstrated the tolerability of an intravenous bolus of carfilzomib (*Cancer Res.* 2007;67:6383-91). Therefore, Study PX-171-001, Part 1 of Study PX-171-002, and Part 1 (A0) of Study PX-171-003 assessed carfilzomib infused over 1 to 2 minutes. The results of a pooled analysis for these studies showed that IRR occurred in 84 of 112 subjects (75.0%), including Grade ≥3 IRR occurring in 16 of 112 subjects (14.3%). Based on the results, the following were specified to alleviate IRR in Part 2 of Study PX-171-002 and subsequent clinical studies: (a) carfilzomib should be infused over 2 to 10 minutes (b) DEX 4 mg should be administered before carfilzomib; and (c) the starting dose of carfilzomib should be 20 mg/m^2, and, if tolerated, is increased to 27 mg/m^2 [see Section 7.R.5.1]. A total of 441 subjects participated in Part 2 of Study PX-171-002, Part 2 (A1) of Study PX-171-003, and Study PX-171-004. Of these, 337 subjects (76.4%) experienced IRR, including 51 subjects (11.6%) experiencing Grade ≥3 IRR. The results suggest that the incidence of Grade ≥3 IRR decreases by modifying the dosing regimen as mentioned above (a) to (c).

In Studies PX-171-006 and 009 designed for carfilzomib combination therapy with lenalidomide and DEX, carfilzomib was infused over 10 minutes. Premedication with DEX was scheduled on Days 1, 8, and 15 before dosing with carfilzomib. In Study PX-171-006, while carfilzomib was scheduled to be administered without DEX on Days 2, 9, and 16, premedication with DEX 4 mg was allowed. A total of 476 subjects participated in Studies PX-171-006 and 009. Of these, 305 subjects (64.1%) experienced IRR, including 51 subjects (10.7%) experiencing Grade ≥3 IRR. In Study 05, intravenous infusion of carfilzomib over 10 minutes, premedication with DEX 40 mg on Days 1, 8, and 15 (scheduled as days of co-administration of DEX), and premedication with DEX 4 mg on Days 2, 9, and 16, (not scheduled as days of co-administration of DEX) were required (and if IRR occurred in Cycle 1, premedication of DEX was to be continued in Cycle 2 onward).

Based on the infusion rate used in Studies 009 and 05, the proposed dosage and administration defined the duration of an intravenous infusion as over 10 minutes.

PMDA's view:
Along with the dosing regimen of DEX [see Section 7.R.5.1], the following requirements in Studies 009 and 05 should be communicated to healthcare professionals in an appropriate manner in the "Clinical studies" section of the package insert: on Days 1, 8, and 15, on which DEX was scheduled to be co-administered, the dose of DEX 40 mg should precede carfilzomib; on Days 2, 9, and 16, on which DEX was not scheduled to be co-administered, the dose of DEX 4 mg should precede carfilzomib (and if IRR occurred in Cycle 1, DEX premedication was to be continued in Cycle 2 onward).

Furthermore, based on the results of Studies 009 and 05, 10-minute intravenous infusion is acceptable as the dosage of carfilzomib.

7.R.5.3 Treatment cycles
PMDA asked the applicant to explain the rationale for the upper limit of carfilzomib treatment cycles defined as 18 cycles in Studies 009 and 05 and the necessity to specify the upper limit of treatment cycles in the dosing regimen.

The applicant's explanation:
When Study 009 was at the planning stage, Study PX-171-006 was underway to evaluate the combination regimen of carfilzomib 20/27 mg/m^2 with lenalidomide and DEX, no subject underwent treatment >19 cycles. Also, the maximum response duration according to the IMWG criteria (best overall response) was 354 days. Therefore, 18 cycles was specified as the upper limit for carfilzomib treatment in Study 009. The same specification was also used in Study 05.

In Study PX-171-006, 13 subjects were treated under the CLd regimen for >18 cycles (data cut-off on June 14, 2013). Of these 13 subjects, 1 subject had a new serious adverse event of multiple fractures in Cycle 19 or later, which had not occurred until Cycle 18. A causal relationship to carfilzomib was ruled out for the event. Response according to the IMWG criteria (best overall response) was observed in 9 of 13 subjects as of the end of Cycle 18. Given these facts, and because patients with relapsed or refractory MM have limited treatment options, treatment with carfilzomib for >18 cycles may offer a long-term treatment opportunity. Therefore, the number of treatment cycles is not necessary to be specified in the dosing regimen. In Studies 009 and 05, there were no subjects who received carfilzomib for >18 cycles.

PMDA's view:
The upper limit of carfilzomib treatment cycles for the combination regimen of carfilzomib 20/27 mg/m^2 with lenalidomide and DEX in Study 009 was defined as 18 cycles based on the evaluable data from Study PX-171-006. Considering that Study PX-171-006 was a study on long-term treatment of carfilzomib, which was underway when Study 009 was at the planning stage, there may be little need of specifying an upper limit of treatment cycles in the dosing regimen. However, due to the paucity of clinical data of patients treated with carfilzomib for >18 cycles, the "Precautions for dosage and administration" section should remind of unestablished efficacy and safety of carfilzomib treatment for >18 cycles. Study PX-171-010 is underway to evaluate the safety of carfilzomib in long-term treatment [see Section 7.2.2.5], and any study data indicating safety concerns in long-term treatment with carfilzomib should be provided promptly to healthcare professionals. Currently available evaluable data of patients treated with carfilzomib for >18 cycles should also be provided to healthcare professionals in an appropriate manner using written materials.

7.R.5.4 Dose modifications
(a) Dose modifications of carfilzomib based on CrCL
The applicant's explanation:
One of the inclusion criteria for Studies 009 and 05 was CrCL of ≥50 mL/min. The criteria for dose suspension in relation to CrCL were also specified as follows: Carfilzomib should be suspended when CrCL decreases to <15 mL/min. The treatment should be resumed when CrCL recovers to ≥15 mL/min. If dialysis is required, carfilzomib should be resumed at ≤20 mg/m^2, and it should be dosed after dialysis.

The criteria for dose suspension of carfilzomib due to decreased CrCL to <15 mL/min following treatment with carfilzomib and subsequent dose resumption, as in Studies 009 and 05, should be communicated through the "Precautions for dosage and administration" section. In actual clinical settings, carfilzomib may be used in patients with CrCL of <50 mL/min, and, therefore, the precautionary advice should also include guidelines on recommended dose modification for patients with CrCL of <50 mL/min and ≥15 mL/min: specifically, dose suspension following a decrease in CrCL by ≥50% from baseline or that requiring dialysis, and the resumption of treatment after recovery of CrCL to <25% from baseline or that not requiring dialysis.

According to the applicant, carfilzomib may be administered to patients with CrCL of <50 mL/min, who do not meet the inclusion criteria in Studies 009 and 05. The results from Study PX-171-005 showed that the exposure (AUC_{last}) to M14 and M15 in patients with renal impairment increased with increased severity of renal impairment [see Section 6.2.4]. PMDA asked the applicant to explain the effects of renal impairment on the safety of carfilzomib.

The applicant's explanation:
Tables 45 and 46 show the summary of safety data based on the severity (mild, moderate, or severe) of renal impairment in patients participated in Studies 009 and 011 (foreign phase III studies). In both studies, there were no obvious differences between the arms in the occurrence of adverse events by baseline severity of renal impairment.

Table 45. Summary of safety data by severity of renal impairment[*1] (Study 009)

	N (%)							
	CLd[*2]				Ld[*2]			
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe
	N = 197	N = 170	N = 24	N = 0	N = 203	N = 150	N = 30	N = 1
All adverse events	189 (95.9)	167 (98.2)	23 (95.8)	0	199 (98.0)	145 (96.7)	30 (100)	1 (100)
Grade ≥3 adverse events	154 (78.2)	151 (88.8)	22 (91.7)	0	161 (79.3)	125 (83.3)	24 (80.0)	1 (100)
Serious adverse events	102 (51.8)	115 (67.6)	18 (75.0)	0	101 (49.8)	86 (57.3)	20 (66.7)	0
Adverse events leading to treatment discontinuation	43 (21.8)	52 (30.6)	6 (25.0)	0	42 (20.7)	46 (30.7)	10 (33.3)	0

As specified in one of the inclusion criteria, patients must have a CrCL of ≥50 mL/min; [*1] baseline renal impairment (normal, CrCL of ≥80 mL/min; mild, ≥50 mL/min and <80 mL/min; moderate, ≥30 mL/min and <50 mL/min; and severe, <30 mL/min); [*2] Subjects with unclear baseline CrCL results, 1 and 5 subjects in the CLd and Ld arms, respectively, are excluded.

Table 46. Summary of safety data by severity of renal impairment[*1] (Study 011)

	N (%)							
	Carfilzomib				BSC[*2]			
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe
	N = 48	N = 64	N = 29	N = 16	N = 41	N = 58	N = 40	N = 13
All adverse events	46 (95.8)	63 (98.4)	29 (100)	16 (100)	37 (90.2)	53 (91.4)	39 (97.5)	13 (100)
Grade ≥3 adverse events	29 (60.4)	46 (71.9)	28 (96.6)	15 (93.8)	29 (70.7)	38 (65.5)	28 (70.0)	13 (100)
Serious adverse events	20 (41.7)	37 (57.8)	24 (82.8)	11 (68.8)	18 (43.9)	31 (53.4)	19 (47.5)	9 (69.2)
Adverse events leading to treatment discontinuation of treatment	2 (4.2)	12 (18.8)	5 (17.2)	4 (25.0)	6 (14.6)	14 (24.1)	7 (17.5)	4 (30.8)

As specified in one of the inclusion criteria, study included patients who had a CrCL of ≥15 mL/min and were not on dialysis; [*1] baseline renal impairment (normal, CrCL of ≥80 mL/min; mild, ≥50 mL/min and <80 mL/min; moderate, ≥30 mL/min and <50 mL/min; and severe, <30 mL/min); [*2] One subject with unclear baseline CrCL results is excluded.

PMDA's view:
The applicant presented the rationale for the recommended dose modification according to the change in CrCL following administration of carfilzomib for patients with CrCL of <50 mL/min and ≥15 mL/min. However, it mentioned only the possibility of the clinical use of carfilzomib in patients with CrCL of <50 mL/min without referring to the range of the change in CrCL. Therefore, whether the recommended dose modification needs to be advised is unclear. Because of this, the "Precautions for dosage and administration" section should provide the criteria used in Studies 009 and 05 for the suspension and resumption of carfilzomib for patients with CrCL decreasing to <15 mL/min following administration of carfilzomib, as recommended dose modification of carfilzomib based on CrCL.

CrCL of ≥50 mL/min was one of the criteria for inclusion of Studies 009 and 05, and there are only limited data on the safety of carfilzomib administered to patients with moderate or severe renal impairment under the CLd regimen. Therefore, precautionary advice should be given to healthcare professionals on the treatment with carfilzomib in patients with moderate to severe renal impairment, specifically, extra careful monitoring of patients for adverse events. The data on the occurrence of adverse events in Studies 009 and 011 (foreign phase III studies) based on the baseline severity of renal impairment will be useful reference for the CLd regimen. Healthcare professionals should be provided with relevant data appropriately through written materials.

(b) Dose modifications of carfilzomib following an adverse drug reaction
The applicant's explanation:
Recommended dose modification of carfilzomib following the onset of an adverse drug reaction was mentioned in the "Precautions for dosage and administration" section based on the criteria for dose reduction, suspension, and discontinuation used in Studies 009 and 05.

Hematotoxicity-related criteria for dose modification following an adverse drug reaction in Studies 009 and 05 were platelet or neutrophil count-related criteria. In the Japanese clinical studies (Studies 05 and 01). However, lymphocyte count decreased and haemoglobin decreased occurred more frequently than in the foreign clinical studies (Studies 009 and 011) [see Section 7.R.3.2]. Therefore, hematotoxicity–related criteria for dose modification should be established according to hematotoxicity classified in NCI-CTCAE, rather than limiting to platelet or neutrophil count-related criteria. While in Studies 009 and 05, the dose was reduced to 11 mg/m^2, which is 1-step lower than 15 mg/m^2, following the onset of an adverse event, and dose reduction of carfilzomib to 11 mg/m^2 was performed only in 2 subjects in Study 009 and 1 subject in Study 05. This precludes the evaluation of the safety of carfilzomib after dose reduction to 11 mg/m^2. Accordingly, when an adverse drug reaction occurred after dose reduction to 15 mg/m^2, carfilzomib treatment was to be discontinued to ensure safety.

PMDA's view:
Studies 009 and 05 required 1-step dose reduction of carfilzomib upon the recurrence of decreased platelet or neutrophil count after treatment with carfilzomib. This should be reminded in the "Precautions for dosage and administration" section. The rest of the applicant's explanation about dose modification of carfilzomib following an adverse drug reaction is acceptable.

7.R.5.5 Co-administration with other antineoplastic drugs
The applicant' explanation about the administration of carfilzomib in combination with antineoplastic drugs other than lenalidomide and DEX:
The efficacy and safety of carfilzomib used in combination with antineoplastic drugs other than lenalidomide and DEX are unknown, because of no data available at this point.

PMDA's view:
There are no available clinical study data on the efficacy and safety of carfilzomib used in combination with antineoplastic drugs other than lenalidomide and DEX in Japanese patients with relapsed or refractory MM. The combination use of carfilzomib with such drugs is therefore not recommended, and this should be reminded in the "Precautions for dosage and administration" section.

7.R.6 Post-marketing investigations
The applicant's explanation about the post-marketing surveillance plan:
The applicant has a plan to conduct post-marketing surveillance using the central registration method in patients with relapsed or refractory MM to investigate the safety of carfilzomib in post-marketing use.

Key survey items will be the following adverse events: cardiac disorder, lung disorder, pulmonary hypertension, dyspnoea, hypertension including hypertensive crisis, acute kidney injury, TLS, IRR, haemorrhage/thrombocytopenia, liver disorder, TMA, PRES, febrile neutropenia, and venous thromboembolism. These items are selected based on their incidences in the pooled analysis of clinical studies of carfilzomib in patients with relapsed or refractory MM (Studies PX-171-001, PX-171-002, PX-171-003, PX-171-004, PX-171-005, PX-171-006, PX-171-008, 009, 011, and 2011-002).

The target sample size of the surveillance was determined as 300, based on a ≥95% probability that 1 patient experiencing above-mentioned each adverse event (key survey item) is detected.
The occurrence of adverse events selected as key survey items was studied by treatment cycle based on the data from Studies 009, 011, 05, and 01. By the beginning of Cycle 7, 77.3% (839 of 1085) of the above adverse events occurred. Accordingly, the observation period was determined to be from the starting day of carfilzomib treatment through the day immediately before the beginning of Cycle 7.

PMDA's view:
Due to limited safety data on Japanese patients with relapsed or refractory MM treated under the CLd regimen, post-marketing surveillance should be conducted covering all patients receiving carfilzomib to obtain its safety data under actual use in Japan promptly and exhaustively.

In addition, based on the adverse events requiring attention during treatment with carfilzomib [see Section 7.R.3], infection, encephalopathy, and gastrointestinal perforation should be added to the proposed key survey items. Further, the following modifications should be made to the proposed items: (a) change "lung disorder" to "ILD," "thrombocytopenia" and "febrile neutropenia" to "haematotoxicity," and "acute kidney injury" to "renal disorder;" (b) classify "pericarditis" and "pericardial effusion" into "cardiac disorder"; and (c) collect data on dyspnoea not as a key survey item but as individual events including pulmonary hypertension, infection, etc., because dyspnoea is considered manifestation of these events. The target sample size and observation period should be reconsidered, in light of the occurrence of adverse events, i.e., key survey items, including those newly added ones.

7.3 Adverse events and other changes observed in clinical studies

The following subsections summarize major adverse events included in the results of clinical studies submitted for safety evaluation except death, which is described in Section 7.1 "Evaluation data" and Section 7.2 "Reference data."

7.3.1 Japanese phase I/II study (Study 01)

Adverse events occurred in all subjects (100%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 4 subjects (75.0%) in the 15 mg/m^2 arm, 5 of 6 subjects (83.3%) in the 20 mg/m^2 arm, 39 of 40 subjects (97.5%) in the 20/27 mg/m^2 arm. Table 47 lists adverse events that occurred at an incidence of ≥40% in any arm.

Table 47. Adverse events occurring at an incidence of ≥40% in any arm

SOC PT (MedDRA/J ver. 17.0)	N (%)					
	15 mg/m^2 N = 4		20 mg/m^2 N = 6		20/27 mg/ m^2 N = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	2 (50.0)	6 (100)	5 (83.3)	40 (100)	37 (92.5)
General disorders and administration site conditions						
Malaise	2 (50.0)	0	2 (33.3)	0	7 (17.5)	0
Investigations						
ALT increased	0	0	3 (50.0)	1 (16.7)	8 (20.0)	1 (2.5)
AST increased	0	0	4 (66.7)	2 (33.3)	9 (22.5)	2 (5.0)
Blood bilirubin increased	1 (25.0)	0	3 (50.0)	1 (16.7)	1 (2.5)	0
Blood creatinine increased	2 (50.0)	0	2 (33.3)	1 (16.7)	15 (37.5)	1 (2.5)
Blood LDH increased	0	0	4 (66.7)	1 (16.7)	12 (30.0)	0
Blood pressure increased	2 (50.0)	0	2 (33.3)	0	3 (7.5)	2 (5.0)
Blood urea increased	0	0	3 (50.0)	0	8 (20.0)	0
Haemoglobin decreased	1 (25.0)	0	2 (33.3)	1 (16.7)	17 (42.5)	11 (27.5)
Lymphocyte count decreased	3 (75.0)	1 (25.0)	6 (100)	5 (83.3)	33 (82.5)	27 (67.5)
Neutrophil count decreased	3 (75.0)	1 (25.0)	2 (33.3)	2 (33.3)	23 (57.5)	16 (40.0)
Platelet count decreased	0	0	4 (66.7)	1 (16.7)	30 (75.0)	12 (30.0)
White blood cell count decreased	2 (50.0)	0	2 (33.3)	1 (16.7)	21 (52.5)	12 (30.0)
White blood cell count increased	1 (25.0)	0	3 (50.0)	0	11 (27.5)	0
Metabolism and nutrition disorders						
Hyperglycaemia	2 (50.0)	0	4 (66.7)	2 (33.3)	9 (22.5)	0
Hypophosphataemia	0	0	1 (16.7)	0	16 (40.0)	3 (7.5)

Serious adverse events occurred in 2 of 6 subjects (33.3%) in the 20 mg/m^2 arm and 5 of 40 subjects (12.5%) in the 20/27 mg/m^2 arm. These serious events were TMA, cardiomyopathy, liver disorder, blood immunoglobulin A increased, and sensorimotor disorder (1 subject [16.7%] each) in the 20 mg/m^2 arm; and pneumonia, pneumonia viral, platelet count decreased, TLS, plasma cell myeloma, and spinal cord compression (1 subject [2.5%] each) in the 20/27 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for TMA, cardiomyopathy, liver disorder, and sensorimotor disorder (1 subject each) in the 20 mg/m^2 arm; and pneumonia, pneumonia viral, platelet count decreased, TLS, and plasma cell myeloma (1 subject each) in the 20/27 mg/m^2 arm.

Adverse events that led to discontinuation of the study drug in 1 of 4 subjects (25.0%) in the 15 mg/m^2 arm, 3 of 6 subjects (50.0%) in the 20 mg/m^2 arm, and 4 of 40 subjects (10.0%) in the 20/27 mg/m^2 arm. The reported events were pain (1 subject, 25.0%) in the 15 mg/m^2 arm; TMA, cardiomyopathy, liver disorder, AST increased, and blood immunoglobulin A increased (1 subject [16.7%] each) in the 20 mg/m^2 arm; and hypercalcaemia, muscular weakness, plasma cell myeloma, and spinal cord compression (1 subject [2.5%] each) in the 20/27 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for TMA, cardiomyopathy, and liver disorder (1 subject each) in the 20 mg/m^2 arm, and hypercalcaemia, muscular weakness, and plasma cell myeloma (1 subject each) in the 20/27 mg/m^2 arm.

7.3.2 Japanese phase I study (Study 05)

Adverse events occurred in all subjects (100%). For all of these events (100%), a causal relationship to the study drug could not be ruled out. Table 48 lists adverse events that occurred at an incidence of ≥30%.

Table 48. Adverse events occurring at an incidence of ≥30%

SOC PT (MedDRA/J ver. 18.0)	N (%) 26	
	All Grades	Grade ≥3
All adverse events	26 (100)	19 (73.1)
Gastrointestinal disorders		
Constipation	8 (30.8)	0
Investigations		
Lymphocyte count decreased	14 (53.8)	11 (42.3)
Platelet count decreased	14 (53.8)	6 (23.1)
White blood cell count decreased	8 (30.8)	3 (11.5)
Metabolism and nutrition disorders		
Hyperglycaemia	10 (38.5)	3 (11.5)
Hypophosphataemia	10 (38.5)	5 (19.2)
Skin and subcutaneous tissue disorders		
Rash	8 (30.8)	1 (3.8)

Serious adverse events occurred in 1 of 26 subjects (3.8%). The patient experienced pneumonia and respiratory tract infection (1 subject [3.8%] each). A causal relationship to the study drug could not be ruled out for either event.

An adverse event led to discontinuation of study drug in 1 of 26 subjects (3.8%), and the event was delirium (1 subject, 3.8%). A causal relationship to the study drug could not be ruled out for the event.

7.3.3 Foreign phase I study (Part 1 of Study PX-171-002)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for all events (100%). Adverse events that occurred at an incidence of ≥40% were: vision blurred, constipation, nausea, fatigue, malaise, and decreased appetite (2 of 3 subjects [66.7%] each) in the 1.2 mg/m^2 arm; anaemia (3 of 3 subjects, 100%) and upper respiratory tract infection (2 of 3 subjects, 66.7%) in the 2.4 mg/m^2 arm; thrombocytopenia, nausea, vomiting, fatigue, and pyrexia (3 of 4 subjects [75.0%] each), and constipation, diarrhoea, decreased appetite, headache, neuropathy peripheral, cough, and pruritus (2 of 4 subjects [50.0%] each) in the 4.0 mg/m^2 arm; anaemia, diarrhoea, vomiting, and oropharyngeal pain (2 of 3 subjects [66.7%] each) in the 6.0 mg/m^2 arm; cough (3 of 3 subjects, 100%), and constipation, nausea, bronchitis, hyperglycaemia, headache, acute kidney injury, and nasal congestion (2 of 3 subjects [66.7%] each) in the 8.4 mg/m^2 arm; vomiting and fatigue (3 of 4 subjects

[75.0%] each), and constipation, diarrhoea, nausea, musculoskeletal pain, cough, respiratory tract congestion, and alopecia (2 of 4 subjects [50.0%] each) in the 11.0 mg/m^2 arm; nausea and fatigue (3 of 3 subjects [100%] each), and anaemia, pyrexia, and dyspnoea (2 of 3 subjects [66.7%] each) in the 15.0 mg/m^2 arm; nausea (5 of 8 subjects, 62.5%), and anaemia and constipation (4 of 8 subjects [50.0%] each) in the 20.0 mg/m^2 arm; and arthralgia (5 of 6 subjects, 83.3%), anaemia, nausea, and cough (4 of 6 subjects [66.7%] each), and thrombocytopenia, constipation, chills, pyrexia, blood creatinine increased, decreased appetite, musculoskeletal pain anxiety, insomnia, and hypertension (3 of 6 subjects [50.0%] each) in the 27.0 mg/m^2 arm.

Serious adverse events occurred in 2 of 3 subjects (66.7%) in the 1.2 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 2.4 mg/m^2 arm, 3 of 4 subjects (75.0%) in the 4.0 mg/m^2 arm, 2 of 3 subjects (66.7%) in the 6.0 mg/m^2 arm, 2 of 3 subjects (66.7%) in the 8.4 mg/m^2 arm, 2 of 4 subjects (50.0%) in the 11.0 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 15.0 mg/m^2 arm, 3 of 8 subjects (37.5%) in the 20.0 mg/m^2 arm, and 4 of 6 subjects (66.7%) in the 27.0 mg/m^2 arm. Serious adverse events that occurred in ≥2 subjects in each arm were: bronchitis and acute kidney injury in 2 subjects each (66.7%) in the 8.4 mg/m^2 arm and acute kidney injury in 2 subjects (33.3%) in the 27.0 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for acute kidney injury (2 subjects) in the 27.0 mg/m^2 arm.

Adverse events led to discontinuation of carfilzomib occurred in 2 of 3 subjects (66.7%) in the 1.2 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 2.4 mg/m^2 arm, 1 of 4 subjects (25.0%) in the 4.0 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 6.0 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 8.4 mg/m^2 arm, 4 of 8 subjects (50.0%) in the 20.0 mg/m^2 arm, and 2 of 6 subjects (33.3%) in the 27.0 mg/m^2 arm. An adverse event leading to treatment discontinuation in ≥2 subjects in each arm was thrombocytopenia (2 subjects, 25.0%) in the 20.0 mg/m^2 arm. A causal relationship to carfilzomib could not be ruled out in 1 subject experiencing thrombocytopenia.

7.3.4 Foreign phase I study (Part 2 of Study PX-171-002)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for events occurring in 6 of 7 subjects (85.7%) in the carfilzomib arm and 4 of 4 subjects (100%) in the carfilzomib/DEX arm. Table 49 shows adverse events that occurred at an incidence of ≥40% in any arm.

Table 49. Adverse events occurring at an incidence of ≥40% in any arm

SOC PT (MedDRA/J ver. 15.1)	N (%)			
	Carfilzomib N = 7		Carfilzomib/DEX N = 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	7 (100)	5 (71.4)	4 (100)	4 (100)
Blood and lymphatic system disorders				
Anaemia	5 (71.4)	3 (42.9)	4 (100)	3 (75.0)
Neutropenia	1 (14.3)	0	2 (50.0)	1 (25.0)
Thrombocytopenia	4 (57.1)	1 (14.3)	3 (75.0)	3 (75.0)
Gastrointestinal disorders				
Diarrhoea	3 (42.9)	0	2 (50.0)	0
Nausea	3 (42.9)	0	0	0
General disorders and administration site conditions				
Fatigue	4 (57.1)	0	1 (25.0)	0
Oedema peripheral	3 (42.9)	1 (14.3)	0	0
Pyrexia	3 (42.9)	0	0	0

SOC PT (MedDRA/J ver. 15.1)	N (%)			
	Carfilzomib N = 7		Carfilzomib/DEX N = 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections and infestations				
Urinary tract infection	0	0	2 (50.0)	0
Metabolism and nutrition disorders				
Hypermagnesaemia	0	0	2 (50.0)	0
Psychiatric disorders				
Insomnia	3 (42.9)	0	1 (25.0)	0
Respiratory, thoracic and mediastinal disorders				
Cough	3 (42.9)	0	1 (25.0)	0

Serious adverse events occurred in 3 of 7 subjects (42.9%) in the carfilzomib arm and 2 of 4 subjects (50.0%) in the carfilzomib/DEX arm. The reported serious adverse events were upper gastrointestinal haemorrhage, multi-organ failure, pain, pain in extremity, pathological fracture, and tumour associated fever (1 subject [14.3%] each) in the carfilzomib arm, and hypoxia, pleural effusion, and hypotension (1 subject [25.0%] each) in the carfilzomib/DEX arm. A causal relationship to the study drug could not be ruled out for pain and tumour associated fever (1 subject each) in the carfilzomib arm and hypoxia (1 subject) in the carfilzomib/DEX arm.

Adverse events led to treatment discontinuation in 3 of 7 subjects (42.9%) in the carfilzomib arm and 1 of 4 subjects (25.0%) in the carfilzomib/DEX arm. The reported events were multi-organ failure, echinococciasis, pain in extremity, and pathological fracture (1 subject [14.3%] each) in the carfilzomib arm, and hypotension (1 subject, 25.0%) in the carfilzomib/DEX arm. A causal relationship to the study drug could not be ruled out for echinococciasis (1 subject) in the carfilzomib arm.

7.3.5 Foreign phase I study (Part 2 [A1] of Study PX-171-003)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events in 257 of 266 subjects (96.6%). Table 50 shows adverse events that occurred at an incidence of ≥30%.

Table 50. Adverse events occurring at an incidence of ≥30%

SOC PT (MedDRA/J ver. 15.1)	N (%) 266	
	All Grades	Grade ≥3
All adverse events	266 (100)	231 (86.8)
Blood and lymphatic system disorders		
Anaemia	129 (48.5)	66 (24.8)
Thrombocytopenia	103 (38.7)	77 (28.9)
Gastrointestinal disorders		
Diarrhoea	87 (32.7)	2 (0.8)
Nausea	122 (45.9)	5 (1.9)
General disorders and administration site conditions		
Fatigue	130 (48.9)	20 (7.5)
Pyrexia	83 (31.2)	4 (1.5)

SOC	N (%)	
PT	266	
(MedDRA/J ver. 15.1)	All Grades	Grade ≥3
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	93 (35.0)	9 (3.4)

Serious adverse events occurred in 126 of 266 subjects (47.4%). Serious adverse events that occurred in ≥5 subjects were: pneumonia (25 subjects, 9.4%); renal failure acute (10 subjects, 3.8%); disease progression (9 subjects, 3.4%); cardiac failure congestive, pathological fracture, and MM (8 subjects [3.0%] each); pyrexia and hypercalcaemia (7 subjects [2.6%] each); spinal cord compression (6 subjects, 2.3%); and anaemia, dyspnoea, blood creatinine increased, and thrombocytopenia (5 subjects [1.9%] each). A causal relationship to the study drug could not be ruled out for pneumonia (21 subjects), renal failure acute (9 subjects), cardiac failure congestive (8 subjects), pyrexia (6 subjects), blood creatinine increased (5 subjects), thrombocytopenia and dyspnoea (4 subjects each), anaemia (3 subjects), MM and disease progression (2 subjects each), and spinal cord compression and hypercalcaemia (1 subject each).

Adverse events led to treatment discontinuation in 74 of 266 subjects (27.8%). Adverse events leading to treatment discontinuation occurring in ≥3 subjects were disease progression (7 subjects, 2.6%); hypercalcaemia (6 subjects, 2.3%); cardiac arrest, cardiac failure congestive, pneumonia, spinal cord compression, and dyspnoea (4 subjects [1.5%] each); thrombocytopenia, blood creatinine increased, and acute kidney injury (3 subjects [1.1%] each). A causal relationship to the study drug could not be ruled out for cardiac arrest, cardiac failure congestive, and dyspnoea (4 subjects each), thrombocytopenia and blood creatinine increased (3 subjects each), acute kidney injury, pneumonia, and disease progression (2 subjects each), and hypercalcaemia (1 subject).

7.3.6 Foreign phase Ib study (Study PX-171-006)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events occurring in 4 of 6 subjects (66.7%) in Cohort 1 (carfilzomib 15 mg/m^2, lenalidomide 10 mg, DEX 40 mg), 6 of 6 subjects (100%) in Cohort 2 (15 mg/m^2, 15 mg, 40 mg), 8 of 8 subjects (100%) in Cohort 3 (15 mg/m^2, 20 mg, 40 mg), 5 of 6 subjects (83.3%) in Cohort 4 (20 mg/m^2, 20 mg, 40 mg), 6 of 6 subjects (100%) in Cohort 5 (20 mg/m^2, 25 mg, 40 mg), 51 of 52 subjects (98.1%) in Cohorts 6 and 7 combined (20/27 mg/m^2, 25 mg, 40 mg). Adverse events occurring at an incidence of ≥40% in each cohort were: neutropenia (4 of 6 subjects, 66.7%), anaemia, thrombocytopenia, diarrhoea, and fatigue (3 of 6 subjects [50.0%] each) in Cohort 1; cough (5 of 6 subjects, 83.3%), neutropenia, fatigue, oedema peripheral, decreased appetite, and muscle spasms (4 of 6 subjects [66.7%] each), leukopenia, lymphopenia, thrombocytopenia, diarrhoea, nausea, upper respiratory tract infection, hypokalaemia, back pain, hypoaesthesia, paraesthesia, insomnia, and dyspnoea (3 of 6 subjects [50.0%] each) in Cohort 2; anaemia (6 of 8 subjects, 75.0%), fatigue, upper respiratory tract infection, and pyrexia (5 of 8 subjects [62.5%] each), neutropenia, sinusitis, muscle spasms, pain in extremity, and rash (4 of 8 subjects [50.0%] each) in Cohort 3; diarrhoea (4 of 6 subjects, 66.7%), fatigue, pyrexia, hyperglycaemia, musculoskeletal pain, and headache (3 of 6 subjects [50.0%] each) in Cohort 4; neutropenia (5 of 6 subjects; 83.3%), diarrhoea and fatigue (4 of 6 subjects, 66.7%), anaemia, thrombocytopenia, oedema peripheral, cough, and dyspnoea (3 of 6 subjects, 50.0%) in Cohort 5; and fatigue (36 of 52 subjects, 69.2%), diarrhoea (30 of 52 subjects, 57.7%), lymphopenia (27 of 52 subjects, 51.9%), pyrexia (23 of 52 subjects, 44.2%), and cough (21 of 52 subjects, 40.4%) in Cohorts 6 and 7.

Serious adverse events occurred in 3 of 6 subjects (50.0%) in Cohort 1, 3 of 6 subjects (50.0%) in Cohort 2, 4 of 8 subjects (50.0%) in Cohort 3, 4 of 6 subjects (66.7%) in Cohort 4, 3 of 6 subjects (50.0%) in Cohort 5, 28 of 52 subjects (53.8%) in Cohorts 6 and 7. Serious adverse events that occurred in ≥2 subjects in each cohort were: disease progression (2 subjects, 33.3%) in Cohort 1, pyrexia (2 subjects, 25.0%) in Cohort 3; pneumonia (5 subjects, 9.6%), anaemia, gastrointestinal haemorrhage, and acute kidney injury (2 subjects [3.8%] each) in Cohorts 6 and 7. A causal relationship to the study drug could

not be ruled out for the following: pyrexia (1 subject) in Cohort 3; and pneumonia (5 subjects), and anaemia and gastrointestinal haemorrhage (1 subject each) in Cohorts 6 and 7.

Adverse events led to treatment discontinuation in 1 of 6 subjects (16.7%) in Cohort 1, 2 of 6 subjects (33.3%) in Cohort 2, 3 of 8 subjects (37.5%) in Cohort 3, 4 of 6 subjects (66.7%) in Cohort 4, 2 of 6 subjects (33.3%) in Cohort 5, 21 of 52 subjects (40.4%) in Cohorts 6 and 7. Adverse events leading to treatment discontinuation occurring in ≥2 subjects in each group were disease progression (3 subjects; 5.8%), abdominal pain, nausea, fatigue, and mood altered (2 subjects [3.8%] each) in Cohorts 6 and 7. A causal relationship to the study drug could not be ruled out for abdominal pain, nausea, fatigue, and mood altered (2 subjects each) in Cohorts 6 and 7.

7.3.7 Foreign phase III study (Study 009)

Adverse events occurred in 380 of 392 subjects (96.9%) in the CLd arm and 380 of 389 subjects (97.7%) in the Ld arm. A causal relationship to the study drug could not be ruled out for the events occurring in 332 of 392 subjects (84.7%) in the CLd arm and 329 of 389 subjects (84.6%) in the Ld arm. Table 51 shows adverse events occurring at an incidence of ≥20% in any arm.

Table 51. Adverse events occurring at an incidence of ≥20% in any arm

SOC PT (MedDRA/J ver. 15.1)	N (%)			
	CLd N = 392		Ld N = 389	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	380 (96.9)	328 (83.7)	380 (97.7)	316 (81.2)
Blood and lymphatic system disorders				
Anaemia	169 (43.1)	70 (17.9)	155 (39.8)	69 (17.7)
Neutropenia	148 (37.8)	116 (29.6)	131 (33.7)	103 (26.5)
Thrombocytopenia	115 (29.3)	66 (16.8)	89 (22.9)	48 (12.3)
Gastrointestinal disorders				
Constipation	79 (20.2)	1 (0.3)	67 (17.2)	2 (0.5)
Diarrhoea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
General disorders and administration site conditions				
Fatigue	129 (32.9)	30 (7.7)	120 (30.8)	25 (6.4)
Oedema peripheral	85 (21.7)	5 (1.3)	75 (19.3)	2 (0.5)
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Infections and infestations				
Nasopharyngitis	84 (21.4)	1 (0.3)	63 (16.2)	0
Upper respiratory tract infection	112 (28.6)	7 (1.8)	76 (19.5)	4 (1.0)
Metabolism and nutrition disorders				
Hypokalaemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Musculoskeletal and connective tissue disorders				
Back pain	69 (17.6)	5 (1.3)	80 (20.6)	8 (2.1)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	113 (28.8)	1 (0.3)	69 (17.7)	0

Serious adverse events occurred in 235 of 392 subjects (59.9%) in the CLd arm and 210 of 389 subjects (54.0%) in the Ld arm. Serious adverse events occurring in ≥5 subjects in each arm were: pneumonia (56 subjects, 14.3%), respiratory tract infection (15 subjects, 3.8%), pyrexia (14 subjects, 3.6%), pulmonary embolism (12 subjects, 3.1%), deep vein thrombosis (9 subjects, 2.3%), anaemia, febrile neutropenia, and bronchitis (8 subjects [2.0%] each), thrombocytopenia, atrial fibrillation, myocardial infarction, diarrhoea, and renal failure acute (6 subjects [1.5%] each), cardiac failure congestive, bronchopneumonia, basal cell carcinoma, and dyspnoea (5 subjects [1.3%] each) in the CLd arm; pneumonia (43 subjects, 11.1%), anaemia (10 subjects, 2.6%), diarrhoea and pyrexia (9 subjects [2.3%] each), disease progression and pulmonary embolism (8 subjects, 2.1%), atrial fibrillation, bronchopneumonia, and cerebrovascular accident (7 subjects [1.8%] each), bronchitis, respiratory tract infection, and deep vein thrombosis (6 subjects [1.5%] each), and neutropenia (5 subjects, 1.3%) in the Ld arm. A causal relationship to the study drug could not be ruled out for the following: pneumonia (22 subjects), pulmonary embolism (10 subjects), deep vein thrombosis (9 subjects), febrile neutropenia (8 subjects), anaemia (6 subjects), pyrexia (5 subjects), thrombocytopenia and respiratory tract infection (4 subjects each), dyspnoea (3 subjects), atrial fibrillation, cardiac failure congestive, diarrhoea, basal cell carcinoma, and renal failure acute (2 subjects each), and bronchitis and bronchopneumonia (1 subject each) in the CLd arm; pneumonia (17 subjects), pulmonary embolism (7 subjects), deep vein thrombosis (6 subjects), anaemia (5 subjects), neutropenia, atrial fibrillation, diarrhoea, and cerebrovascular accident (4 subjects each), pyrexia, bronchitis, and respiratory tract infection (3 subjects each), and bronchopneumonia (1 subject) in the Ld arm.

Adverse events led to treatment discontinuation in 102 of 392 subjects (26.0%) in the CLd arm and 98 of 389 subjects (25.2%) in the Ld arm. These events were thrombocytopenia (5 subjects, 1.3%), neutropenia, pneumonia, upper respiratory tract infection, and insomnia (4 subjects [1.0%] each), myocardial infarction, diarrhoea, pyrexia, and hypocalcaemia (3 subjects [0.8%] each) in the CLd arm; and thrombocytopenia (5 subjects, 1.3%), anaemia, myelodysplastic syndrome, and insomnia (4 subjects [1.0%] each), diarrhoea, pneumonia, tremor, and pulmonary embolism (3 subjects [0.8%] each) in the Ld arm. A causal relationship to the study drug could not be ruled out for thrombocytopenia (5 subjects, 1.3%), neutropenia and insomnia (4 subjects each), diarrhoea and upper respiratory tract infection (3 subjects each), pyrexia, pneumonia, and hypocalcaemia (2 subjects each) in the CLd arm; thrombocytopenia and insomnia (4 subjects each), diarrhoea, tremor, and pulmonary embolism (3 subjects each), anaemia and myelodysplastic syndrome (2 subjects each), and pneumonia (1 subject) in the Ld arm.

7.3.8 Foreign phase III study (Study 011)

Adverse events occurred in 154 of 157 subjects (98.1%) in the carfilzomib arm and 143 of 153 subjects (93.5%) in the BSC arm. A causal relationship to the study drug could not be ruled out for the events occurring in 96 of 157 subjects (61.1%) in the carfilzomib arm and 76 of 153 subjects (49.7%) in the BSC arm. Table 52 shows adverse events that occurred at an incidence of ≥20% in any arm.

Table 52. Adverse events occurring at an incidence of ≥20% in any arm

SOC PT (MedDRA/J ver. 15.1)	N (%)			
	Carfilzomib N = 157		BSC N = 153	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events total	154 (98.1)	118 (75.2)	143 (93.5)	109 (71.2)
Blood and lymphatic system disorders				
Anaemia	88 (56.1)	40 (25.5)	74 (48.4)	47 (30.7)
Thrombocytopenia	59 (37.6)	38 (24.2)	46 (30.1)	34 (22.2)
Gastrointestinal disorders				
Nausea	32 (20.4)	2 (1.3)	14 (9.2)	2 (1.3)

SOC PT (MedDRA/J ver. 15.1)	N (%)			
	Carfilzomib N = 157		BSC N = 153	
	All Grades	Grade ≥3	All Grades	Grade ≥3
General disorders and administration site conditions				
Pyrexia	44 (28.0)	5 (3.2)	30 (19.6)	0

Serious adverse events occurred in 92 of 157 subjects (58.6%) in the carfilzomib arm and 78 of 153 subjects (51.0%) in the BSC arm. Serious adverse events occurring in ≥3 subjects in each arm were: renal failure acute (15 subjects, 9.6%), disease progression (13 subjects, 8.3%), pneumonia (10 subjects, 6.4%), hypercalcaemia (7 subjects, 4.5%), pyrexia, bronchopneumonia, and back pain (6 subjects [3.8%] each), anaemia (4 subjects, 2.5%), febrile neutropenia, thrombocytopenia, cardiac failure, bronchitis, sepsis, urinary tract infection, TLS, and renal failure (3 subjects [1.9%] each) in the carfilzomib arm; pneumonia (18 subjects, 11.8%), disease progression (17 subjects, 11.1%), anaemia (8 subjects, 5.2%), renal failure acute (6 subjects, 3.9%), thrombocytopenia and bronchopneumonia (5 subjects [3.3%] each), respiratory tract infection, and hypercalcaemia (4 subjects [2.6%] each), neutropenia, cardiac failure congestive, septic shock and back pain (3 subjects [2.0%] each) in the BSC arm. A causal relationship to the study drug could not be ruled out for the following: febrile neutropenia, pneumonia, and TLS (3 subjects each), pyrexia (2 subjects), anaemia, thrombocytopenia, cardiac failure, bronchopneumonia, urinary tract infection, hypercalcaemia, and renal failure acute (1 subject each) in the carfilzomib arm; pneumonia (5 subjects), anaemia (3 subjects), neutropenia (2 subjects, 1.3%), cardiac failure congestive (2 subjects, 1.3%), bronchopneumonia (2 subjects, 1.3%), renal failure acute (2 subjects, 1.3%), and septic shock (1 subject) in the BSC arm.

Adverse events led to treatment discontinuation in 23 of 157 subjects (14.6%) in the carfilzomib arm and 31 of 153 subjects (20.3%) in the BSC arm. Adverse events leading to treatment discontinuation occurring in ≥3 subjects in each arm were renal failure acute (5 subjects, 3.2%) in the carfilzomib arm, and pneumonia (5 subjects, 3.3%) and neutropenia (3 subjects, 2.0%) in the BSC arm. A causal relationship to the study drug could not be ruled out for pneumonia (2 subjects) and neutropenia (1 subject) in the BSC arm.

7.3.9 Foreign phase I study (Study PX-171-001)

Adverse events occurred in all subjects (100%). For all of these events (100%), a causal relationship to the study drug could not be ruled out. Adverse events that occurred with an incidence of ≥40% in each arm were: diarrhoea, nausea, fatigue, and hypoaesthesia (2 of 3 subjects [66.7%] each) in the 1.2 mg/m^2 arm; fatigue, pyrexia, dyspnoea exceptional, and pruritus (2 of 3 subjects [66.7%] each) in the 2.4 mg/m^2 arm; diarrhoea, nausea, fatigue, oedema peripheral, pyrexia, and pruritus (2 of 3 subjects [66.7%] each) in the 4.0 mg/m^2 arm; constipation and nausea (2 of 3 subjects [66.7%] each) in the 6.0 mg/m^2 arm; nausea and hypertension (2 of 3 subjects [66.7%] each) in the 8.4 mg/m^2 arm; nausea and fatigue (2 of 3 subjects [66.7%] each) in the 11.0 mg/m^2 arm; oedema peripheral (3 of 6 subjects, 50.0%) in the 15.0 mg/m^2 arm; nausea, pyrexia, hypoaesthesia, and dyspnoea (3 of 5 subjects [60.0%] each), diarrhoea, chills, fatigue, infusion site pain, urinary tract infection, dizziness, paraesthesia, cough, productive cough, and erythema (2 of 5 subjects [40.0%] each) in the 20.0 mg/m^2 arm.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 2.4 mg/m^2 arm; 2 of 3 subjects (66.7%) in the 4.0 mg/m^2 arm; 1 of 3 subjects (33.3%) in the 11.0 mg/m^2 arm; 2 of 5 subjects (40.0%) in the 20.0 mg/m^2 arm. The reported events were bronchitis (1 subject, 33.3%) in the 2.4 mg/m^2 arm; abdominal pain, disease progression, infected skin ulcer, skin infection, and mycosis fungoides (1 subject [33.3%] each) in the 4.0 mg/m^2 arm; gastrointestinal haemorrhage (1 subject, 33.3%) in the 11.0 mg/m^2 arm; febrile neutropenia, neutropenia, thrombocytopenia, diplopia, gastric haemorrhage, gastrointestinal angiodysplasia, haematemesis, chills, MM, and nervous system disorder (1 subject [20.0%] each) in the 20.0 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for bronchitis (1 subject)

in the 2.4 mg/m^2 arm; abdominal pain, disease progression, infected skin ulcer, skin infection, and mycosis fungoides (1 subject each) in the 4.0 mg/m^2 arm; gastrointestinal haemorrhage (1 subject) in the 11.0 mg/m^2 arm; and febrile neutropenia, neutropenia, thrombocytopenia, and chills (1 subject each) in the 20.0 mg/m^2 arm.

Adverse events led to treatment discontinuation in 2 of 3 subjects (66.7%) in the 4.0 mg/m^2 arm, 1 of 3 subjects (33.3%) in the 11.0 mg/m^2 arm, and 1 of 5 subjects (20.0%) in the 20.0 mg/m^2 arm. The reported events were abdominal pain, disease progression, infected skin ulcer, skin infection, and mycosis fungoides (1 subject [33.3%] each) in the 4.0 mg/m^2 arm; gastrointestinal haemorrhage (1 subject [33.3%]) in the 11.0 mg/m^2 arm; thrombocytopenia, gastric haemorrhage, gastrointestinal angiodysplasia, haematemesis, MM, and nervous system disorder (1 subject [20.0%] each) in the 20.0 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for the following: abdominal pain (1 subject), disease progression, infected skin ulcer, skin infection, and mycosis fungoides (1 subject each) in the 4.0 mg/m^2 arm; gastrointestinal haemorrhage (1 subject) in the 11.0 mg/m^2 arm; and thrombocytopenia (1 subject) in the 20.0 mg/m^2 arm.

7.3.10 Foreign phase Ib study (Study PX-171-008)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events in 13 of 17 subjects (76.5%). Table 53 shows adverse events that occurred with an incidence of ≥30%.

Table 53. Adverse events occurring at an incidence of ≥30%

SOC PT (MedDRA/J ver. 15.1)	N (%) 17	
	All Grades	Grade ≥3
All adverse events	17 (100)	5 (29.4)
Gastrointestinal disorders		
Nausea	9 (52.9)	0
General disorders and administration site conditions		
Fatigue	9 (52.9)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	6 (35.3)	0

Serious adverse events occurred in 5 of 17 subjects (29.4%). Details of these events were pneumonia (2 subjects, 11.8%), pain, urinary tract infection, haematuria, renal failure acute, hypertension, and hypotension (1 subject [5.9%] each). A causal relationship to the study drug could not be ruled out for renal failure acute and hypotension (1 subject each).

Adverse events led to treatment discontinuation in 5 of 17 subjects (29.4%). These events were pneumonia (2 subjects, 11.8%), pain, haematuria, renal failure acute, hypertension, and hypotension (1 subject [5.9%] each). A causal relationship to the study drug could not be ruled out for renal failure acute and hypotension (1 subject each).

7.3.11 Foreign phase Ib/II study (Study PX-171-007)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events occurring in 2 of 3 subjects (66.7%) in the 20 mg/m^2 arm; 3 of 4 subjects (75.0%) in the 20/27 mg/m^2 arm; 7 of 7 subjects (100%) in the 20/36 mg/m^2 arm (Phase Ib), 61 of 65 subjects (93.8%) in the 20/36 mg/m^2 arm (Phase II). Adverse events that occurred at an incidence of ≥40% in each arm were: hypomagnesaemia (2 of 3 subjects, 66.7%) in the 20 mg/m^2 arm; fatigue and back pain (2 of 4 subjects [50.0%] each) in the 20/27 mg/m^2 arm; nausea, vomiting, asthenia, and headache (4 of 7 subjects [57.1%] each), lymphopenia, diarrhoea, fatigue, pyrexia, hypokalaemia, and insomnia (3 of 7 subjects [42.9%] each) in the 20/36 mg/m^2 arm (Phase Ib); fatigue (38 of 65 subjects, 58.5%), nausea

(28 of 65 subjects, 43.1%), decreased appetite (26 of 65 subjects, 40.0%) in the 20/36 mg/m^2 arm (Phase II).

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 20 mg/m^2 arm, 1 of 4 subjects (25.0%) in the 20/27 mg/m^2 arm, 4 of 7 subjects (57.1%) in the 20/36 mg/m^2 arm (Phase Ib), 27 of 65 subjects (41.5%) in the 20/36 mg/m^2 arm (Phase II). Serious adverse events occurring in ≥2 subjects in each arm were: disease progression (5 subjects, 7.7%), pain, pneumonia, hyponatraemia, spinal cord compression, renal failure acute, chronic obstructive pulmonary disease, and deep vein thrombosis (2 subjects [3.1%] each) in the 20/36 mg/m^2 arm (Phase II). A causal relationship to the study drug could not be ruled out for pneumonia, renal failure acute, deep vein thrombosis (2 subjects each), pain, disease progression, and hyponatraemia (1 subject each) in the 20/36 mg/m^2 arm (Phase II).

Adverse events led to treatment discontinuation in 1 of 4 subjects (25.0%) in the 20/27 mg/m^2 arm, 3 of 7 subjects (42.9%) in the 20/36 mg/m^2 arm (Phase Ib), and 8 of 65 subjects (12.3%) in the 20/36 mg/m^2 arm (Phase II). These adverse events were: pneumonia aspiration (1 subject, 25.0%) in the 20/27 mg/m^2 arm; diarrhoea, metastases to meninges, and skin lesion (1 subject [14.3%] each) in the 20/36 mg/m^2 arm (Phase Ib); and cardiac failure congestive, infusion related reaction, hepatorenal failure, pneumonia, septic shock, hyponatraemia, malignant pleural effusion, neuritis, and spinal cord compression (1 subject [1.5%] each) in the 20/36 mg/m^2 arm (Phase II). A causal relationship to the study drug could not be ruled out for the following: pneumonia aspiration (1 subject) in the 20/27 mg/m^2 arm; diarrhoea (1 subject) in the 20/36 mg/m^2 arm (Phase Ib); and cardiac failure congestive, infusion related reaction, hepatorenal failure, pneumonia, septic shock, hyponatraemia, and malignant pleural effusion (1 subject each) in the 20/36 mg/m^2 arm (Phase II).

7.3.12 Foreign phase I study (Part 1 [A0] of Study PX-171-003)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events occurring in 45 of 46 subjects (97.8%). Table 54 shows adverse events that occurred at an incidence of ≥30%.

Table 54. Adverse events occurring at an incidence of ≥30%

SOC PT (MedDRA/J ver. 15.1)	N (%) 46	
	All Grades	Grade ≥3
All adverse events	46 (100)	41 (89.1)
Blood and lymphatic system disorders		
Anaemia	34 (73.9)	17 (37.0)
Lymphopenia	17 (37.0)	14 (30.4)
Thrombocytopenia	23 (50.0)	12 (26.1)
Gastrointestinal disorders		
Diarrhoea	15 (32.6)	0
Nausea	16 (34.8)	0
General disorders and administration site conditions		
Fatigue	32 (69.6)	4 (8.7)
Pyrexia	14 (30.4)	2 (4.3)
Infections and infestations		
Upper respiratory tract infection	16 (34.8)	1 (2.2)
Investigations		
Blood creatinine increased	18 (39.1)	2 (4.3)
Metabolism and nutrition disorders		

SOC PT (MedDRA/J ver. 15.1)	N (%) 46	
	All Grades	Grade ≥3
Hypocalcaemia	16 (34.8)	3 (6.5)
Decreased appetite	14 (30.4)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	14 (30.4)	4 (8.7)

Serious adverse events occurred in 20 of 46 subjects (43.5%). Serious adverse events occurring in ≥2 subjects were pneumonia (5 subjects, 10.9%), renal failure acute (4 subjects, 8.7%), disease progression (3 subjects, 6.5%), cardiac failure congestive, bacteraemia, hypercalcaemia, TLS, and plasmacytoma (2 subjects [4.3%] each). A causal relationship to the study drug could not be ruled out for the following pneumonia (4 subjects), renal failure acute (3 subjects), cardiac failure congestive, disease progression, and TLS (2 subjects each).

Adverse events led to treatment discontinuation in 16 of 46 subjects (34.8%). Adverse events leading to treatment discontinuation in ≥2 subjects were: disease progression (3 subjects, 6.5%), pyrexia, bone pain, and renal failure acute (2 subjects [4.3%] each). A causal relationship to the study drug could not be ruled out for disease progression (2 subjects), renal failure acute (2), pyrexia (1), and bone pain (1).

7.3.13 Foreign phase II study (Study PX-171-004)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for the events occurring in 35 of 35 subjects (100%) in the 20 mg/m^2 arm (Part 1), 58 of 59 subjects (98.3%) in the 20 mg/m^2 arm (Part 2), and 68 of 70 subjects (97.1%) in the 20/27 mg/m^2 arm. Table 55 shows adverse events occurring at an incidence of ≥30% in any arm.

Table 55. Adverse events occurring at an incidence of ≥30% in any arm

SOC PT (MedDRA/J ver. 15.1)	N (%) Part 1 N = 35		Part 2 20 mg/m^2 N = 59		Part 2 20/27 mg/m^2 N = 70	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	35 (100)	22 (62.9)	59 (100)	36 (61.0)	70 (100)	56 (80.0)
Blood and lymphatic system disorders						
Anaemia	13 (37.1)	6 (17.1)	27 (45.8)	7 (11.9)	29 (41.4)	14 (20.0)
Lymphopenia	6 (17.1)	2 (5.7)	20 (33.9)	8 (13.6)	13 (18.6)	13 (18.6)
Neutropenia	10 (28.6)	4 (11.4)	18 (30.5)	7 (11.9)	23 (32.9)	11 (15.7)
Thrombocytopenia	11 (31.4)	7 (20.0)	21 (35.6)	10 (16.9)	19 (27.1)	8 (11.4)
Gastrointestinal disorders						
Diarrhoea	13 (37.1)	0	21 (35.6)	1 (1.7)	19 (27.1)	1 (1.4)
Nausea	21 (60.0)	1 (2.9)	33 (55.9)	0	31 (44.3)	0
Vomiting	15 (42.9)	1 (2.9)	15 (25.4)	1 (1.7)	14 (20.0)	1 (1.4)
General disorders and administration site conditions						
Fatigue	22 (62.9)	1 (2.9)	42 (71.2)	7 (11.9)	39 (55.7)	1 (1.4)
Oedema peripheral	6 (17.1)	0	18 (30.5)	0	18 (25.7)	0
Pyrexia	9 (25.7)	0	21 (35.6)	0	23 (32.9)	1 (1.4)

SOC PT (MedDRA/J ver. 15.1)	N (%)					
	Part 1		Part 2			
	N = 35		20 mg/m^2 N = 59		20/27 mg/m^2 N = 70	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections and infestations						
Upper respiratory tract infection	11 (31.4)	2 (5.7)	20 (33.9)	1 (1.7)	19 (27.1)	0
Investigations						
Blood creatinine increased	12 (34.3)	1 (2.9)	14 (23.7)	0	10 (14.3)	0
Nervous system disorders						
Headache	9 (25.7)	1 (2.9)	19 (32.2)	1 (1.7)	23 (32.9)	0
Respiratory, thoracic and mediastinal disorders						
Cough	8 (22.9)	0	23 (39.0)	0	21 (30.0)	0
Dyspnoea	13 (37.1)	2 (5.7)	30 (50.8)	3 (5.1)	21 (30.0)	4 (5.7)

Serious adverse events occurred in 12 of 35 subjects (34.3%) in the 20 mg/m^2 arm (Part 1), 18 of 59 subjects (30.5%) in the 20 mg/m^2 arm (Part 2), and 28 of 70 subjects (40.0%) in the 20/27 mg/m^2 arm. Serious adverse events occurring in ≥2 subjects in each arm were: pneumonia (3 subjects, 8.6%), pyrexia and hypercalcaemia (2 subjects [5.7%] each) in the 20 mg/m^2 arm (Part 1); pneumonia (6 subjects; 10.2%), cardiac failure congestive, TLS, renal failure acute, and pulmonary embolism (2 subjects [3.4%] each) in the 20 mg/m^2 arm (Part 2); pneumonia (6 subjects, 8.6%), anaemia, pyrexia, and renal failure acute (3 subjects [4.3%] each), neutropenia, cardiac failure congestive, and dyspnoea (2 subjects [2.9%] each) in the 20/27 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for pneumonia (3 subjects), pyrexia (2 subjects), hypercalcaemia (1 subject) in the 20 mg/m^2 arm (Part 1); pneumonia (5 subjects), cardiac failure congestive, TLS, renal failure acute, and pulmonary embolism (2 subjects each) in the 20 mg/m^2 arm (Part 2); and pneumonia (5 subjects), renal failure acute (3 subjects), anaemia, neutropenia, cardiac failure congestive, pyrexia, and dyspnoea (2 subjects) in the 20/27 mg/m^2 arm.

Adverse events led to treatment discontinuation in 8 of 35 subjects (22.9%). Adverse events leading to treatment discontinuation in ≥2 subjects in each arm were: hypercalcaemia (2 subjects, 5.7%) in the 20 mg/m^2 arm (Part 1); mitral valve incompetence and pneumonia (2 subjects [3.4%] each) in the 20 mg/m^2 arm (Part 2); renal failure acute and dyspnoea (2 subjects [2.9%] each) in the 20/27 mg/m^2 arm. A causal relationship to the study drug could not be ruled out for hypercalcaemia (1 subject) in the 20 mg/m^2 arm (Part 1).

7.3.14 Foreign phase II study (Study PX-171-005)

Adverse events occurred in all subjects (100%). A causal relationship to the study drug could not be ruled out for events occurring in all subjects (100%). Table 56 shows adverse events occurring at an incidence of ≥30%.

Table 56. Adverse events occurring at an incidence of ≥30%

SOC PT (MedDRA/J ver. 15.1)	N (%) 50	
	All Grades	Grade ≥3
All adverse events	50 (100)	49 (98.0)
Blood and lymphatic system disorders		
Anaemia	30 (60.0)	20 (40.0)
Lymphopenia	16 (32.0)	11 (22.0)
Thrombocytopenia	23 (46.0)	17 (34.0)
Gastrointestinal disorders		
Constipation	20 (40.0)	0
Diarrhoea	23 (46.0)	2 (4.0)
Nausea	22 (44.0)	2 (4.0)
General disorders and administration site conditions		
Fatigue	33 (66.0)	8 (16.0)
Oedema peripheral	17 (34.0)	1 (2.0)
Metabolism and nutrition disorders		
Hypokalaemia	18 (36.0)	4 (8.0)
Hypomagnesaemia	16 (32.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	22 (44.0)	7 (14.0)

Serious adverse events occurred in 37 of 50 subjects (74.0%). Serious adverse events occurring in ≥2 subjects were: pneumonia (10 subjects, 20.0%), disease progression (6 subjects, 12.0%), dehydration, mental status changes, and renal failure acute (4 subjects [8.0%] each), cardiac failure congestive, renal failure, dyspnoea, and respiratory failure (3 subjects [6.0%] each), and atrial fibrillation, diarrhoea, pyrexia, non-cardiac chest pain, bronchitis, urinary tract infection, H1N1 Influenza, pathological fracture, and deep vein thrombosis (2 subjects [4.0%] each). A causal relationship to the study drug could not be ruled out for pneumonia (5 subjects), cardiac failure congestive, non-cardiac chest pain, dehydration, renal failure, deep vein thrombosis (2 subjects each), diarrhoea, pyrexia, disease progression, bronchitis, H1N1 Influenza, pathological fracture, mental status changes, dyspnoea, and respiratory failure (1 subject each).

Adverse events led to treatment discontinuation in 22 of 50 subjects (44.0%). Adverse events leading to treatment discontinuation in ≥2 subjects were disease progression (7 subjects, 14.0%), mental status changes, renal failure acute, and respiratory failure (2 subjects [4.0%] each). A causal relationship to the study drug could not be ruled out for disease progression and respiratory failure (1 subject each).

7.3.15 Foreign phase II study (Study PX-171-010)

Adverse events occurred in 32 of 59 subject (54.2%). A causal relationship to the study drug could not be ruled out for the events occurring in 23 of 59 subjects (39.0%). No adverse events occurred at an incidence of ≥30%.

Serious adverse events occurred in 13 of 59 subjects (22.0%). The reported events were infection, pneumonia, and cerebrovascular accident (2 subjects [3.4%] each), diarrhoea, pain, pyrexia, influenza, lobar pneumonia, pathological fracture, headache, dyspnoea, asthenia, bronchitis, syncope, cardiomyopathy, sepsis, arthralgia, and renal failure acute (1 subject [1.7%] each). A causal relationship to the study drug could not be ruled out for diarrhoea, pyrexia, infection, influenza, cerebrovascular

accident, headache, dyspnoea, asthenia, bronchitis, pneumonia, syncope, and cardiomyopathy (1 subject each).

Adverse events led to treatment discontinuation in 7 of 59 subjects (11.9%). These events were disease progression (2 subjects), blood creatinine increased (1 subject, 1.7%), failure to thrive (1 subject, 1.7%), cardiomyopathy (1 subject, 1.7%), ascites (1 subject, 1.7%), and arthralgia (1 subject, 1.7%). A causal relationship to the study drug could not be ruled out for blood creatinine increased and cardiomyopathy (1 subject each).

7.3.16 Foreign compassionate use study (Study 2011-002)

Adverse events occurred in 318 of 328 subjects (97.0%). A causal relationship to the study drug could not be ruled out for the events occurring in 232 of 328 subjects (70.7%). Table 57 shows adverse events that occurred at an incidence of ≥30%.

Table 57. Adverse events occurring at an incidence of ≥30%

SOC	N (%)	
PT	328	
(MedDRA/J ver. 15.1)	All Grades	Grade ≥3
All adverse events	318 (97.0)	245 (74.7)
Blood and lymphatic system disorders		
Anaemia	142 (43.3)	82 (25.0)
Thrombocytopenia	126 (38.4)	94 (28.7)
General disorders and administration site conditions		
Fatigue	133 (40.5)	10 (3.0)

Serious adverse events occurred in 155 of 328 subjects (47.3%). Serious adverse events occurring in ≥5 subjects were MM (21 subjects, 6.4%), pneumonia (19 subjects, 5.8%), disease progression and renal failure acute (14 subjects [4.3%] each), dyspnoea (11 subjects, 3.4%), hypercalcaemia (9 subjects, 2.7%), cardiac failure congestive (8 subjects, 2.4%), sepsis (7 subjects, 2.1%), thrombocytopenia, and hypertension (6 subjects [1.8%] each), anaemia, febrile neutropenia, and pyrexia (5 subjects [1.5%] each). A causal relationship to the study drug could not be ruled out for cardiac failure congestive (6 subjects), pneumonia, dyspnoea (5 subjects each), renal failure acute, hypertension (4 subjects each), thrombocytopenia (3), pyrexia (2), anaemia, febrile neutropenia, and sepsis (1 subject each).

Adverse events led to treatment discontinuation in 45 of 328 subjects (13.7%). Adverse events leading to treatment discontinuation in ≥3 subjects were renal failure acute (5 subjects, 1.5%) and sepsis (3 subjects, 0.9%). A causal relationship to the study drug could not be ruled out for renal failure acute (2 subjects) and sepsis (1).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion on concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1, 5.3.5.2-12) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of carfilzomib in the treatment of relapsed or refractory MM and acceptable safety in view of the benefits indicated by the data submitted. Carfilzomib is a drug with a new active ingredient that binds to the chymotrypsin-like active sites of the 20S proteasome in the ubiquitin-proteasome system, inhibiting 20S proteasome activity to induce apoptosis of tumor cells and thereby suppressing tumor growth. Carfilzomib is clinically significant because it offers a new treatment option for patients with relapsed or refractory MM. PMDA will further discuss indications, dosing regimens, post-marketing investigations, etc. in the Expert Discussion.

PMDA has concluded that carfilzomib may be approved if carfilzomib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 12, 2016

Product Submitted for Approval

Brand name	Kyprolis for Intravenous Injection 10 mg
	Kyprolis for Intravenous Injection 40 mg
Non-proprietary Name	Carfilzomib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 26, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA concluded that the efficacy of carfilzomib in the treatment of patients with relapsed or refractory multiple myeloma (MM) has been demonstrated as a result of the review described in Section "7.R.2 Efficacy" of Review Report (1), based on the results of in a foreign phase III study (Study PX-171-009; hereinafter referred to as "Study 009") conducted in patients with relapsed or refractory MM. Progression free survival (PFS), the primary endpoint of the study, was longer in patients receiving carfilzomib in combination with lenalidomide hydrate (lenalidomide) plus dexamethasone (DEX) (CLd arm) than in those receiving the control regimen of lenalidomide plus DEX (Ld arm).

The conclusion of PMDA described above was supported by the expert advisors at the Expert Discussion.

1.2 Safety

After the discussion in Section "7.R.3 Safety" of Review Report (1), PMDA concluded that patients should be carefully monitored during treatment with carfilzomib for cardiac disorder, interstitial lung disease (ILD), pulmonary hypertension, haematotoxicity, infection, liver disorder, renal disorder, haemorrhage, infusion related reaction (IRR), tumour lysis syndrome (TLS), hypertension including hypertensive crisis, venous thromboembolism, posterior reversible encephalopathy syndrome (PRES)/encephalopathy, thrombotic microangiopathy (TMA), gastrointestinal perforation, pericarditis, and pericardial effusion. PMDA also concluded that carfilzomib may be tolerable when appropriate actions including monitoring and control of adverse events are taken by physicians knowledgeable and experienced in the treatment of hematopoietic malignancy.

During the preparation of the Review Report (1), PMDA asked the applicant to provide the latest data on the occurrence, etc. of haemorrhagic events associated with venous thromboembolism and thrombocytopenia following carfilzomib treatment.

The applicant's explanation:
Onyx Therapeutics, Inc. in the US received an inquiry from Health Canada about venous thromboembolism and haemorrhage following carfilzomib treatment after filing an application for marketing approval in Canada on May 12, 2015. The company began investigation to obtain updated occurrence data of venous thromboembolism and haemorrhage.

The results of data summary using the database provided by Amgen Inc. in the US showed that venous thromboembolism occurred following carfilzomib treatment in 285 patients in foreign and Japanese

clinical studies and foreign post-marketing use results data (data cut-off on February 17, 2016). (Unless otherwise specified, the occurrence of events from Japanese and foreign clinical studies and foreign post-marketing use results mentioned hereinafter in Section "1.2 Safety" of Review Report (2) refers to that based on above-mentioned database. However, a foreign phase II study (Study PX-171-010) was an extension study and its results were combined with data from the prior study.) Venous thromboembolism resulted in death in 7 subjects. All fatal events were pulmonary embolism, and a causal relationship to carfilzomib could not be ruled out for the event of 3 of the 7 subjects. Serious venous thromboembolism occurred in 175 subjects. Serious venous thromboembolism occurring in ≥3 subjects were pulmonary embolism (94 subjects), deep vein thrombosis (63 subjects), and retinal vein occlusion (3 subjects) (a single subject may have ≥1 event). A causal relationship to carfilzomib could not be ruled out for pulmonary embolism (61 subjects), deep vein thrombosis (30 subjects), and retinal vein occlusion (2 subjects).

The data from foreign and Japanese clinical studies and foreign post-marketing use results (data cut-off on February 17, 2016) revealed that haemorrhage occurred following carfilzomib treatment in 1066 patients. Fatal haemorrhagic events occurred in 40 patients and were namely, haemorrhage intracranial (10 patients), subdural haematoma (8 patients), cerebral haemorrhage, subarachnoid haemorrhage, and gastrointestinal haemorrhage (3 patients each), haemorrhage, disseminated intravascular coagulation, and haematemesis (2 patients each), thrombotic thrombocytopenic purpura, duodenal ulcer haemorrhage, haemorrhagic stroke, post procedural haemorrhage, cerebral haematoma, pulmonary haemorrhage, upper gastrointestinal haemorrhage, and gastric haemorrhage (1 patient each) (a single patient may have ≥1 event). A causal relationship to carfilzomib could not be ruled out for haemorrhage intracranial (6 patients), subarachnoid haemorrhage and subdural haematoma (2 patients each), gastrointestinal haemorrhage, thrombotic thrombocytopenic purpura, haematemesis, cerebral haemorrhage, and disseminated intravascular coagulation (1 patient each). Serious haemorrhagic events occurred in 233 patients. Serious haemorrhagic events occurring in ≥3 patients were as follows: gastrointestinal haemorrhage (29 patients), haemoglobin decreased (23 patients), rectal haemorrhage (15 patients), haemorrhage intracranial (14 patients), subdural haematoma and epistaxis (13 patients each), red blood cell count decreased (12 patients), thrombotic thrombocytopenic purpura (11 patients), haematuria (10 patients), cerebral haemorrhage, upper gastrointestinal haemorrhage, gastric haemorrhage, and haemoptysis (7 patients each), haematemesis (6 patients), haematoma (5 patients), subarachnoid haemorrhage, pulmonary haemorrhage, disseminated intravascular coagulation, and haemorrhage (4 patients each), haematocrit decreased, post procedural haemorrhage, and haematochezia (3 patients each) (a single patient may have ≥1 event). A causal relationship to carfilzomib could not be ruled out for haemoglobin decreased (17 patients), gastrointestinal haemorrhage (14 patients), thrombotic thrombocytopenic purpura (11 patients), red blood cell count decreased (9 patients), haemorrhage intracranial (8 patients), epistaxis (7 patients), rectal haemorrhage (6 patients), upper gastrointestinal haemorrhage and haemoptysis (5 patients each), cerebral haemorrhage, haematemesis, and subdural haematoma (4 patients each), subarachnoid haemorrhage, disseminated intravascular coagulation, haematocrit decreased, and haematuria (3 patients each), gastric haemorrhage, haematoma, haematochezia, haemorrhage, and pulmonary haemorrhage (2 patients each).

Table 58 shows the occurrence of haemorrhage with concomitant platelet count decreased in comparative foreign phase III studies, Studies 009, PX-171-011 ("Study 011"), and 2011-003, conducted in patients with MM.

Table 58. Haemorrhage with or without concomitant platelet count decreased

Concomitant platelet count decreased*	N (%)					
	Study 009		Study 011		Study 2011-003	
	CLd N = 392	Ld N = 389	Carfilzomib N = 157	BSC N = 153	Cd N = 463	Vd N = 456
With	23/119 (19.3)	17/99 (17.2)	21/96 (21.9)	21/93 (22.6)	37/133 (27.8)	25/115 (21.7)
Without	52/273 (19.0)	51/290 (17.6)	8/61 (13.1)	6/60 (10.0)	46/330 (13.9)	51/341 (15.0)

BSC, Best supportive care; Cd, carfilzomib co-administered with DEX; Vd, bortezomib co-administered with DEX
* $<150 \times 10^9$/L

PMDA's view:
Venous thromboembolism and haemorrhage with a suspected causal relationship to carfilzomib had a fatal outcome. Updated information on the occurrence of venous thromboembolism and haemorrhage following carfilzomib treatment should be provided to healthcare professionals in an appropriate manner, along with the fact that haemorrhagic events occurred following treatment with carfilzomib regardless of with or without concomitant platelet count decreased.

The above conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following comments were made by the expert advisors:

- Bortezomib is a proteasome inhibitor similar to carfilzomib and caused fatal ILD. Therefore, updated information on the occurrence of ILD following carfilzomib treatment, including that in foreign post-marketing use should be checked.

- Major pulmonary hypertension-related adverse events were dyspnoea [see Section 7.R.3.5 of Review Report (1)]. However, dyspnoea is associated with not only pulmonary hypertension but also many other diseases. Therefore, patient records should be carefully checked for complications, a history of heart disease or lung disease, or availability of diagnostic echocardiography to find out if the patient has been conclusively diagnosed to have pulmonary hypertension.

PMDA asked the applicant to explain the update status of the occurrence of ILD following carfilzomib treatment.

The applicant's explanation:
Following carfilzomib treatment, ILD occurred in 89 patients in foreign and Japanese clinical studies and post-marketing use in foreign countries (data cut-off on February 17, 2016). Fatal ILD occurred in 9 patients and were, namely, acute respiratory distress syndrome (6 patients), ILD, pneumonitis, and pulmonary toxicity (1 patient each). A causal relationship to carfilzomib could not be ruled out for acute respiratory distress syndrome (3 patients), ILD, pneumonitis, and pulmonary toxicity (1 patient each). Serious ILD occurred in 69 patients. Serious ILD occurring in ≥3 patients were acute respiratory distress syndrome and pneumonitis (20 patients each), ILD (7 patients), pulmonary fibrosis and lung infiltration (5 patients each), and pulmonary toxicity (3 patients) (a single patient may have ≥1 event). A causal relationship to carfilzomib could not be ruled out for pneumonitis (16 patients), acute respiratory distress syndrome (13 patients), ILD and lung infiltration (5 patients each), and pulmonary toxicity (2 patients).

PMDA asked the applicant to elaborate complications or a history of heart disease or lung disease, or availability of a diagnostic echocardiography result of patients who developed pulmonary hypertension following carfilzomib treatment.

The applicant's explanation:

Clinical studies conducted in and outside the US and post-marketing use results in foreign countries (data cut-off on February 17, 2016) revealed that 1303 patients had experienced pulmonary hypertension following carfilzomib treatment [see Section 7.R.3.5 of Review Report (1)]. Of these, 816 patients were the participants of clinical studies, and they were the focus of investigation on their history or complications that could have caused pulmonary hypertension. Based on the "Guidelines for Treatment of Pulmonary Hypertension: Guidelines for Diagnosis/Treatment of Cardiovascular Diseases, 2012 revised edition" (Report of FY2011 Joint Research Group), data of patients who developed pulmonary hypertension following carfilzomib treatment were reviewed to see if the patient had a history or complications that could have caused pulmonary hypertension. A total of 646 patients had no relevant history or complications while 170 patients did. Relevant histories or complications found in ≥3 patients were deep vein thrombosis (86 patients), chronic obstructive pulmonary disease (46 patients), sleep apnoea syndrome (27 patients), pulmonary hypertension (11 patients), mitral valve incompetence (8 patients), pulmonary fibrosis (5 patients), and hypoxia (3 patients).

Of the 816 patients experiencing pulmonary hypertension in clinical studies, 16 patients had serious events other than dyspnoea and dyspnoea exceptional, and were, namely, pulmonary hypertension (12 subjects) and right ventricular failure and pulmonary arterial hypertension (2 subjects each). Of the 16 patients experiencing serious events, 12 patients had an event (pulmonary hypertension [10 patients] and right ventricular failure and pulmonary arterial hypertension [1 subject each]), for which a causal relationship to carfilzomib could not be ruled out. The 12 patients were the focus of investigation on the availability of echocardiography result, etc. Of these, 3 patients had a confirmed diagnosis of pulmonary hypertension based on echocardiography or cardiac catheterization.

PMDA's view:
The updated status of the occurrence of ILD, including the fact that fatal ILD with a suspected causal relationship to carfilzomib occurred, should be communicated to healthcare professionals in an appropriate manner.

Some patients were confirmed to have pulmonary hypertension based on echocardiography or cardiac catheterization. Therefore, the updated status of the occurrence of pulmonary hypertension should be communicated to healthcare professionals in an appropriate manner.

Accordingly, PMDA instructed the applicant to take appropriate actions as per above. The applicant agreed with the instruction.

1.3 Clinical positioning and indications

PMDA concluded, after the discussion in Section "7.R.4 Clinical positioning and indications" of Review Report (1), that carfilzomib combined with the Ld regimen can be a treatment option for patients with relapsed or refractory MM. The indication of carfilzomib should be specified as "relapsed or refractory multiple myeloma" as proposed by the applicant. At the same time, the "Clinical studies" section of the package insert should mention prior treatments, etc. of subjects enrolled in Study 009, and the precautionary statements written below should be appeared in the "Precautions for indication" section. Further, the use of carfilzomib as a single agent is not recommended, because the results of Study 011, a foreign phase III study conducted in patients with relapsed or refractory MM, did not demonstrate improvement in overall survival (primary endpoint) in patients in the carfilzomib monotherapy arm as compared to the control (best supportive care) arm.

Precautions for indication

- Carfilzomib should be administered to patients who have not responded to at least 1 prior standard therapy or patients in a recurring condition after prior therapy.

- Before selecting eligible patients, healthcare professionals should understand the efficacy and safety of carfilzomib well through a careful review of the "Clinical studies" section that elaborates prior therapies, etc. of patients enrolled in the clinical studies.

The above conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to describe the "Indications" and "Precautions for indication" sections as stated above. The applicant agreed.

1.4 Dosage and administration

After the discussion described in Section "7.R.5 Dosage and administration" of Review Report (1), PMDA concluded that the "Precautions for dosage and administration" section should give the precautionary statements below, along with dosage and administration of carfilzomib described as: "In combination with lenalidomide plus dexamethasone, carfilzomib is usually administered to adult patients once daily by intravenous infusion on Days 1, 2, 8, 9, 15, and 16 followed by a 12-day rest period. This 28-day cycle is repeated until Cycle 12. From Cycle 13 onward, carfilzomib is administered once daily by intravenous infusion on Days 1, 2, 15, and 16 followed by a 12-day rest period. The dose of carfilzomib is 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1 and 27 mg/m^2 (body surface area) thereafter, and is administered as an intravenous infusion over 10 minutes. The dose may be reduced according to the patient's condition."

- The efficacy and safety of carfilzomib monotherapy have not been established.

- Lenalidomide and DEX should be administered with a good understanding of the "Clinical studies" section. The package insert of these concomitant drugs should be read thoroughly.

- The efficacy and safety of carfilzomib used in combination with antineoplastic drugs other than lenalidomide plus dexamethasone have not been established.

- The dose for patients with a body surface area of >2.2 m^2 should be determined based on the body surface area of 2.2 m^2.

- The efficacy and safety of carfilzomib administered >18 cycles have not been established.

- The administration of carfilzomib should be suspended when creatinine clearance (CrCL) decreases to <15 mL/min. Treatment resumption should be considered when CrCL recovers to ≥15 mL/min. When dialysis is required, carfilzomib should be resumed at a dose of <20 mg/m^2 only after dialysis.

- Dose suspension or reduction or discontinuation of carfilzomib should be decided appropriately. If any of the following adverse drug reactions occurs, treatment with carfilzomib should be suspended until resolution: hematotoxic events (Grade 4* platelet count decreased, lymphocyte count decreased, anaemia, or Grade ≥3* neutrophil count decreased) or Grade ≥3* non-hematotoxic events (excluding alopecia, and Grade 3* nausea, vomiting, diarrhoea, and fatigue). Treatment may be resumed, when appropriate, at a dose reduced according to the table below, with careful weighing of the risk and benefit associated with the use of carfilzomib. If an adverse drug reaction recurs causing another dose suspension, treatment should be resumed at a reduced dose or discontinued according to the table below.

* NCI-CTCAE ver. 4.0

Dose before adverse drug reaction	Recommended dose for treatment resumption
27 mg/m^2	20 mg/m^2
20 mg/m^2	15 mg/m^2
15 mg/m^2	Discontinue carfilzomib treatment

- Kyprolis 10 mg should be reconstituted with 5 mL of water for injection, and Kyprolis 40 mg with 20 mL of water for injection, to make a 2-mg/mL injection solution. The required volume of the

solution is calculated from the patient's body surface area, and it should be diluted with a 5% glucose solution.

The expert advisors in the Expert Discussion supported PMDA's decision described above and made the following comment:

- The different dosing schedules of carfilzomib, lenalidomide, and DEX are a cause of complexity of the regimen. Further, in Study 009, the administration of lenalidomide was suspended in patients with a CrCL of ≥15 mL/min and <30 mL/min. However, this instruction differs from that in the guidelines for lenalidomide dose adjustment for patients with renal impairment in its package insert. Therefore, the dosing regimens of lenalidomide and DEX in Study 009 should be communicated to healthcare professionals to ensure the proper use of carfilzomib in the combination therapy with lenalidomide plus DEX.

PMDA's view:
The efficacy and safety of carfilzomib, lenalidomide, and DEX are known only under the dosing regimens used in Study 009. Therefore, the Study 009 regimens should be communicated to healthcare professionals in an appropriate manner through written materials.

Accordingly, PMDA instructed the applicant to define the dosing regimens and modify the descriptions in the "Precautions for dosage and administration" section as above, and the applicant agreed.

1.5 Risk Management Plan (draft)

The applicant has a plan of post-marketing surveillance in patients who will be receiving carfilzomib for the treatment of relapsed or refractory MM to investigate the safety, etc. of carfilzomib in post-marketing use. The target sample size is 300 and the observation period will end immediately before Cycle 7

After the discussion described in Section "7.R.6 Post-marketing investigations" of Review Report (1), PMDA concluded that post-marketing surveillance should be conducted covering all patients who will be receiving carfilzomib. Meanwhile, the following should be considered in planning the surveillance.

- Infection, encephalopathy, and gastrointestinal perforation should be added to the key survey items.

- The following modifications should be made in the proposed key survey items before investigate the occurrence of relevant events: "lung disorder" to "ILD," "thrombocytopenia" and "febrile neutropenia" to "haematotoxicity," "acute kidney injury" to "renal disorder," and "pericarditis" and "pericardial effusion" to be included in "cardiac disorder."

- Dyspnoea should be excluded from the key survey items. Dyspnoea may a sign of pulmonary hypertension, infection, etc. Upon the onset of dyspnoea, relevant data, including its causative disorders, should be collected in an appropriate manner.

- The target sample size and the observation period should be reconsidered after the above-mentioned modifications are made, based on the occurrence of the events defined as key survey items including the new ones.

The above conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following comments were made by the expert advisors:

- Bortezomib, a proteasome inhibitor like carfilzomib, is known to have a risk of herpes zoster. The clinical studies of carfilzomib required premedication with an antiviral drug. However, the study data did not elucidate the details of prophylactic treatment with antiviral drugs. Whether prophylactic antiviral drugs are used and the occurrence of herpes virus infections associated with the post-marketing use of carfilzomib should be clarified through data collection, and knowledge from the data should be communicated to healthcare professionals, once available.

PMDA instructed the applicant to reconsider their post-marketing surveillance plan according to the advice given above, and the applicant agreed. PMDA reviewed the target sample size and observation period after adding new key survey items, and concluded that there is no need for modifying the target number of patients and observation period.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for carfilzomib should include the safety and efficacy specifications presented in Table 2, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 3.

Table 59. Safety and efficacy specifications for the Risk Management Plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiac disorders (cardiac failure, myocardial infarction, QT prolongation, pericarditis, and pericardial effusion) • ILD • Pulmonary hypertension • Haematotoxicity • Infection • Hepatic failure/hepatic impairment • Acute kidney injury • Haemorrhage • IRR • TLS • Hypertension/ hypertensive crisis • Venous thromboembolism • TMA	• PRES and encephalopathy • Gastrointestinal perforation	• Not specified
Efficacy specification		
• Efficacy in the treatment of patients with relapsed or refractory MM in actual use		

Table 60. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing clinical study* • Post-marketing surveillance (all case surveillance)	• Prepare and disseminate a written guide on the use of the product for healthcare professionals • Disseminate data gathered during early post-marketing phase vigilance

* After approval, the ongoing Japanese phase I study (Study ONO-7057-05) will be classified as a post-marketing clinical study and will continue until November 2019.

Table 61. Outline of post-marketing surveillance plan (draft)

Objective	To review safety and other aspects of carfilzomib under actual use conditions after the market launch
Survey method	Central registration method (all-case surveillance)
Target patients	All patients treated with carfilzomib
Observation period	Until immediately before the start of Cycle 7
Planned sample size	300 subjects

Main survey items	Key survey items: Cardiac disorders (cardiac failure, myocardial infarction, QT prolongation, pericarditis, and pericardial effusion), ILD, pulmonary hypertension, hypertension including hypertensive crisis, renal disorder, TLS, IRR, haemorrhage, haematotoxicity, hepatic failure/hepatic impairment, TMA, PRES/encephalopathy, venous thromboembolism, infection, and gastrointestinal perforation Other main survey items: patient characteristics, status of use of carfilzomib and concomitant drugs, adverse events, etc.

1.6 Other

During the preparation of the Review Report (1), PMDA asked the applicant to explain differences in pharmacokinetics (PK) of carfilzomib between Japanese and non-Japanese patients including the PK data following a 30-minute intravenous infusion.

The applicant's explanation:
After a 10-minute intravenous infusion of carfilzomib 15 mg/m^2, C_{max} tended to be lower in Japanese patients than in non-Japanese patients [see Section 6.R.3 of Review Report (1)]. However, in Japanese patients, PK was evaluated based on the data not only from Day 1 of Cycle 1 but also from Day 16 of Cycle 1. Because C_{max} on Day 16 ranged from 539 to 1630 ng/mL, there are no clear differences in the distribution (range) of individual values of C_{max} between Japanese and non-Japanese patients. There was only 1 non-Japanese patient who received an intravenous carfilzomib 20 mg/m^2 on Day 1 of Cycle 1, and this precluded comparison of PK data between the 2 patient populations.

On the other hand, PK data following a 30-minute intravenous infusion of carfilzomib were evaluated in an additional cohort in Study ONO-7057-02 (Japanese phase I study) and Study PX-171-007 (foreign phase Ib/II study) in patients with relapsed or refractory MM [see the section 6.R.3 of Review Report (1)] (Table 5). There were no clear differences in C_{max}, AUC_{last}, and $t_{1/2}$ between Japanese and non-Japanese patients following administration of carfilzomib 20, 45, or 56 mg/m^2.

Based on the above, there are no clear differences in the PK of carfilzomib between Japanese and non-Japanese patients.

Table 62. PK parameters in Japanese and non-Japanese patients following a 30-minute intravenous infusion of carfilzomib

	Study	Dose (mg/m^2)	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
Japanese	ONO-7057-02	20[*1]	7	856 ± 155	369 ± 50.1	0.797 ± 0.319
		45[*2]	3	2070 ± 1040	790 ± 162	0.784 ± 0.119
		56[*2]	3	2110 ± 587	1040 ± 180	0.892 ± 0.132
Non-Japanese	PX-171-007	20[*1]	30	866 ± 666	305 ± 161	0.882 ± 0.284[*4]
		45[*3]	4	1802 ± 477	756 ± 182	1.02 ± 0.0616
		56[*3]	12	2298 ± 1361	1000 ± 370	0.918 ± 0.363[*5]

Arithmetic mean ± standard deviation, [*1] Day 1 of Cycle 1, [*2] Day 16 of Cycle 1, [*3] Day 16 of Cycle 2, [*4] N = 28, [*5] N = 10

PMDA asked the applicant to explain the safety of carfilzomib in the additional cohort in Studies ONO-7057-02 and PX-171-007.

The applicant's explanation:
Table 6 shows the summary of safety data in 7 patients who received carfilzomib intravenously over 30 minutes in Study ONO-7057-02 (3 subjects[20] in the 20/45 mg/m^2 arm and 4 subjects[20] in the

[20] The dose of carfilzomib was titrated in 2 steps. Each treatment cycle consisted of 28 days. Before titration, carfilzomib was administered at 20 mg/m^2 once daily on Days 1 and 2 of Cycle 1. Then, the dose titrated to 36, 45, 56, or 70 mg/m^2 was administered once daily on Days 8, 9, 15, and 16 of Cycle 1 and Days 1, 2, 8, 9, 15, and 16 of Cycle 2 onward.

20/56 mg/m^2 arm), and 105 subjects[20] who received carfilzomib intravenously over 30 minutes in Study PX-171-007 (40 subjects[21] in the solid tumor cohort, 55 subjects in the MM cohort, and 10 subjects in the malignant lymphoma cohort).

Table 63. Summary of safety data (Studies ONO-7057-02 and PX-171-007)

	N (%)	
	ONO-7057-02 N = 7	PX-171-007 N = 105
All adverse events	7 (100)	105 (100)
Grade ≥3 adverse events	7 (100)	84 (80.0)
Adverse events resulting in death*	0	8 (7.6)
Serious adverse events	2 (28.6)	51 (48.6)
Adverse events leading to treatment discontinuation	2 (28.6)	20 (19.0)
Adverse events leading to dose suspension	5 (71.4)	4 (3.8)
Adverse events leading to dose reduction	0	19 (18.1)

Patients who received carfilzomib by intravenous infusion over 30 minutes (Data cut-off on [redacted], 20[redacted] in Study ONO-7057-02, and on [redacted], 20[redacted] in Study PX-171-007); *deaths during the treatment period or within 30 days after the end of the treatment

In Study PX-171-007, 8 subjects died during the treatment or within 30 days after the end of the treatment. Other than 6 subjects died due to disease progression, 1 subject (45 mg/m^2 arm) died from chronic liver disease and another 1 (20/70 mg/m^2 arm) from pneumonitis. A causal relationship to carfilzomib could not be ruled out for either event.

PMDA's view:
The data submitted show no clear differences in the PK of carfilzomib between Japanese and non-Japanese patients. However, the available PK data of carfilzomib following 10-minute intravenous infusion, as per the proposed dosing regimen, are insufficient for comparison of differences between Japanese and non-Japanese patients. Relevant data on the proposed dosing regimen should be further collected through the survey and from published literature. The safety issues of carfilzomib identified in the additional cohort in Study ONO-7057-02 and Study PX-171-007 are unlikely to require additional safety measures because of the following points:

- The deaths of subjects in Study PX-171-007 should be highlighted as ILD and liver disorder requiring attention during treatment with carfilzomib [see Section 1.2 of Review Report (2)].

- The types of adverse events observed the additional cohort in Studies ONO-7057-02 and PX-171-007 did not suggest any new safety concerns.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with "Conditions of approval" shown below after the modification of the proposed indication and dosage and administration as shown below, provided that necessary precautionary statements are included in the package insert and information concerning the proper use of carfilzomib is appropriately disseminated after the market launch; and provided that the product is used under the supervision of physicians with sufficient knowledge and experience in treating hematopoietic malignancy at medical institutions capable of emergency response. The product is an orphan drug, and the re-examination period for the

[21] Only the solid tumor cohort was designed with the dose titration regimens at 20/45 mg/m^2 (6 subjects), 20/56 mg/m^2 (10 subjects), and 20/70 mg/m^2 (11 subjects) and additional regimens of carfilzomib 36 mg/m^2 (6 subjects) and 45 mg/m^2 (7 subjects) administered once daily on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle.

product is 10 years. The drug substance and the drug product are both classified as poisonous drugs, and neither is classified as a biological product or a specified biological product.

Indication
Relapsed or refractory multiple myeloma

Dosage and Administration
In combination with lenalidomide plus dexamethasone, carfilzomib is usually administered to adult patients once daily by intravenous infusion on Days 1, 2, 8, 9, 15, and 16 followed by a 12-day rest period. This 28-day cycle is repeated until Cycle 12. From Cycle 13 onward, carfilzomib is administered once daily by intravenous infusion on Days 1, 2, 15, and 16 followed by a 12-day rest period. The dose of carfilzomib is 20 mg/m^2 (body surface area) only on Days 1 and 2 of Cycle 1 and 27 mg/m^2 (body surface area) thereafter, and is administered as an intravenous infusion over 10 minutes. The dose may be reduced according to the patient's condition.

Conditions of approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited number of subjects in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use results survey covering all patients treated with the product until data from a specified number of patients are collected, in order to understand the characteristics of patients and to promptly collect safety and efficacy data of the product. Based on the collected data, necessary measures should be taken to ensure correct use of the product.

Warnings
Kyprolis should be administered only to patients for whom its administration is considered appropriate by physicians with sufficient knowledge and experience in treating hematopoietic malignancy at medical institutions capable of providing sufficient emergency care. Administration of Kyprolis should be initiated only after the benefits and risks have been sufficiently explained to patients or their families and their consent has been obtained.

Contraindications
1. Patients who have a history of hypersensitivity to the ingredients of Kyprolis

2. Pregnant or possibly pregnant women

Precautions for Indication
1. Kyprolis should be administered to patients who have not responded to at least 1 prior standard therapy or patients in a recurring condition after prior therapy.

2. Before selecting eligible patients, healthcare professionals should understand the efficacy and safety of Kyprolis well through a careful review of the “Clinical studies” section that elaborates prior therapies, etc. of patients enrolled in the clinical studies.

Precautions for dosage and administration
1. The efficacy and safety of Kyprolis in monotherapy have not been established.

2. Lenalidomide and DEX should be administered with a good understanding of the “Clinical studies” section. The package insert of these concomitant drugs should be read thoroughly.

3. The efficacy and safety of Kyprolis used in combination with antineoplastic drugs other than lenalidomide plus dexamethasone have not been established.

4. The dose for patients with a body surface area of >2.2 m^2 should be determined based on the body surface area of 2.2 m^2.

5. The efficacy and safety of Kyprolis administered for >18 cycles have not been established.

6. The administration of Kyprolis should be suspended when creatinine clearance (CrCL) decreases to <15 mL/min. Treatment resumption should be considered when CrCL recovers to ≥15 mL/min. When dialysis is required, Kyprolis should be resumed at a dose <20 mg/m^2 only after dialysis.

7. Dose suspension or reduction or treatment discontinuation should be decided appropriately. If any of the following adverse drug reactions occurs, treatment with Kyprolis should be suspended until resolution: hematotoxic events (Grade 4* platelet count decreased, lymphocyte count decreased, and anaemia; Grade 3* or higher neutrophil count decreased), or Grade ≥3* non-hematotoxic events (excluding alopecia, and Grade 3* nausea and vomiting, diarrhoea, and fatigue). Treatment may be resumed, when appropriate, at the dose reduced according to the table below, with careful weighing of the risk and benefit associated with the use of the product. If an adverse drug reaction recurs causing another dose suspension, treatment should be resumed at a reduced dose or discontinued according to the table below.

* NCI-CTCAE ver. 4.0

Dose before adverse drug reaction	Recommended dose for treatment resumption
27 mg/m^2	20 mg/m^2
20 mg/m^2	15 mg/m^2
15 mg/m^2	Discontinue carfilzomib treatment

8. Kyprolis 10 mg should be reconstituted with 5 mL of water for injection, and Kyprolis 40 mg with 20 mL of water for injection, to make a 2-mg/mL injection solution. The required volume of the solution is calculated from the patient's body surface area, and it should be diluted with a 5% glucose solution before injection.