Report on the Deliberation Results

September 14, 2016

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

Brand Name	Empliciti for I.V. Infusion 300 mg
	Empliciti for I.V. Infusion 400 mg
Non-proprietary Name	Elotuzumab (Genetical Recombination) (JAN*)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	December 24, 2015

Results of Deliberation

In its meeting held on September 9, 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 classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use results survey covering all Japanese patients treated with the drug product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 30, 2016
Pharmaceuticals and Medical Devices Agency

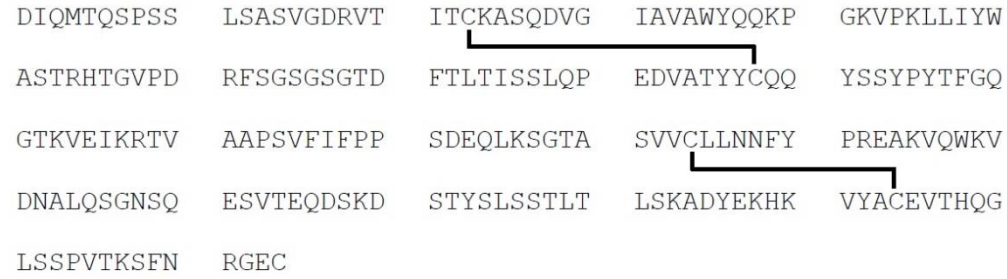
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Empliciti for I.V. Infusion 300 mg Empliciti for I.V. Infusion 400 mg
Non-proprietary Name	Elotuzumab (Genetical Recombination)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	December 24, 2015
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 340 or 440 mg of Elotuzumab (Genetical Recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Elotuzumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human signaling lymphocyte activation molecule family member 7 (SLAMF7) monoclonal antibody and framework regions and constant regions derived from human IgG1. Elotuzumab is produced in a mouse myeloma (NS0) cell line. Elotuzumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 449 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

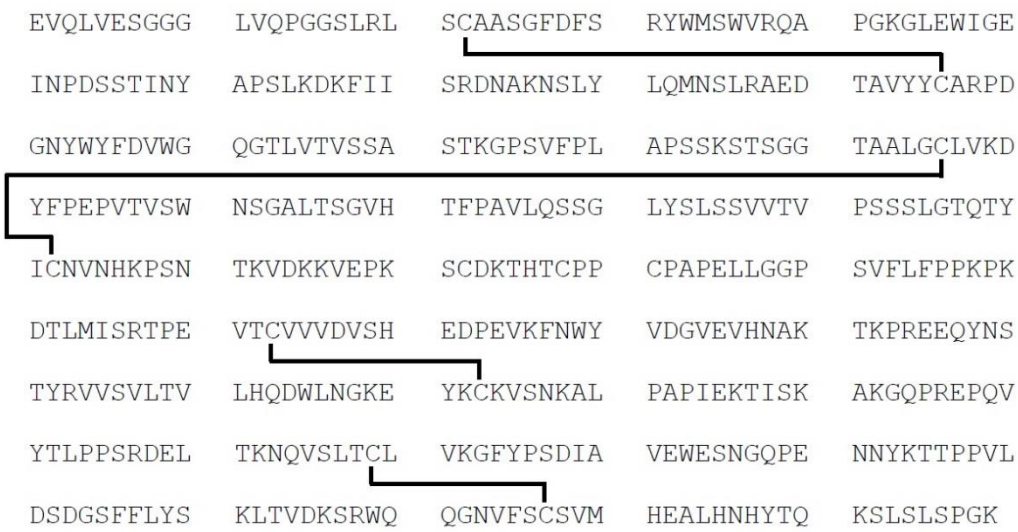
Structure

Amino acid sequence:

Light chain (L-chain)



Heavy chain (H-chain)



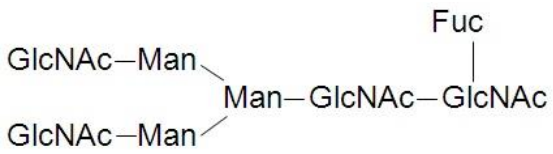
Intra-chain disulfide linkages: solid lines

Inter-chain disulfide linkages: between L-chain C214 and H-chain C222, H-chain C228 and H-chain C228, H-chain C231 and H-chain C231

Glycosylation: H-chain N299

Partial processing: H-chain K449

Deduced structure of major glycan



GlcNAc, *N*-acetylglucosamine; Man, Mannose; and Fuc, Fucose

Molecular formula: $C_{6476}H_{9982}N_{1714}O_{2016}S_{42}$ (protein moiety)

Molecular weight: ca. 148,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 367 of 2015 [*27 yaku*]; PSEHB/ELD Notification No. 1119-1 dated November 19, 2015, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

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 regulatory review, PMDA has concluded that the product may be approved for the following indication and dosage and administration, with the conditions for approval shown below. The following events should be further investigated through post-marketing surveillance: infusion reactions, infections, second primary malignancies, cataract, lymphopenia, and interstitial lung disease.

Indication

Relapsed or refractory multiple myeloma

Dosage and administration

In combination with lenalidomide and dexamethasone, the usual adult dosage of elotuzumab (genetical combination) is 10 mg/kg per dose, infused intravenously: once a week for the first two cycles (4 doses per 28-day cycle [Days 1, 8, 15, and 22]) and every 2 weeks for the third and subsequent cycles (2 doses per 28-day cycle [Days 1 and 15]).

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use results survey covering all Japanese patients treated with the drug product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

Attachment

Review Report (1)

July 8, 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 (PMDA).

Product Submitted for Approval

Brand Name	Empliciti for I.V. Infusion 300 mg Empliciti for I.V. Infusion 400 mg
Non-proprietary Name	Elotuzumab (Genetical Recombination)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	December 24, 2015
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 340 or 440 mg of Elotuzumab (Genetical Recombination)
Proposed Indication	Relapsed or refractory multiple myeloma
Proposed Dosage and Administration	In combination with lenalidomide and dexamethasone, the usual adult dosage of elotuzumab (genetical combination) is 10 mg/kg per dose, infused intravenously: once a week for the first two cycles (4 doses per 28-day cycle [Days 1, 8, 15, and 22]) and every 2 weeks for the third and subsequent cycles (2 doses per 28-day cycle [Days 1 and 15]).

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List of Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
[redacted]	[redacted]
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
Application	Application for marketing approval
Bd regimen	Combined regimen of bortezomib and dexamethasone
BTZ	Bortezomib
$C_{avg, ss}$	Average serum concentration at steady state
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CEX	Cation exchange chromatography
CI	Confidence interval
$C_{max, ss}$	Maximum serum concentration at steady state
$C_{min, ss}$	Minimum serum concentration at steady state
CQA	Critical quality attribute
CR	Complete response
CrCL	Creatinine clearance
DEX	Dexamethasone
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
EBMT criteria	Response criteria proposed by European Group for Blood and Marrow Transplantation (EBMT)
EBd regimen	Combined regimen of Elotuzumab (Genetical Recombination), bortezomib, and dexamethasone
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
ELd regimen	Combined regimen of Elotuzumab (Genetical Recombination), lenalidomide hydrate, and dexamethasone
ELISA	Enzyme-linked immunosorbent assay
EPCB	End-of-production cell bank
ESRD	End-stage renal disease
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
HRP	Horseradish peroxidase
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
IMWG criteria	Diagnostic criteria proposed by the International Myeloma Working Group (IMWG)
IRC	Independent review committee
ITT	Intent-to-treat
K_D	Dissociation constant
KIR	Killer-cell immunoglobulin-like receptors
[redacted]	[redacted]
[redacted]	[redacted]
LD regimen	Combined regimen of lenalidomide hydrate and high-dose dexamethasone
Ld regimen	Combined regimen of lenalidomide hydrate and dexamethasone
Lenalidomide	Lenalidomide hydrate
MCB	Master cell bank
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
MuLuc63	Murine anti-human SLAMF7 antibody
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-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query Multiple Myeloma and Other Plasma Cell Neoplasms
NE	Not evaluable
[redacted]	[redacted]
NK cell	Natural killer cell
NRF	Normal renal function
NZW rabbit	New Zealand White rabbit
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PPK	Population pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PS	Performance status
PT	Preferred term
QbD	Quality by design
QD	Quaque die
QTcF	QT interval corrected using Fridericia's formula
ΔQTcF	Change from baseline QTcF
QoL	Quality of life
QW	Once a week
Q2W	Once every 2 weeks
RAG	Recombination activating gene
SCID mouse	Severe combined immunodeficiency mouse
sCR	Stringent complete response
SD	Stable disease
SEC	Size exclusion chromatography
SLAMF7	Signaling lymphocyte activation molecule family member 7
SMQ	Standard MedDRA queries
SOC	System organ class
SPR	Surface plasmon resonance
SRI	Severe renal impairment
VC	Central volume of distribution
VGPR	Very good partial response
V_{max}	Maximum rate of Michaelis-Menten elimination
WCB	Working cell bank

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

1.1 Outline of the proposed product

Elotuzumab is a recombinant humanized monoclonal antibody of the IgG1 subclass targeting human CD319 (SLAMF7). It was developed by a US-based biopharmaceutical company, PDL BioPharma, Inc. (later Facet Biotech Corporation, and now AbbVie Biotherapeutics, Inc.).

It is considered that the anti-tumor effects of elotuzumab are exerted primarily by binding to SLAMF7, which is expressed at cell membranes of multiple myeloma (MM) cells, inducing antibody dependent cell mediated cytotoxicity (ADCC) activity against MM cells through Fc-receptor-mediated interaction with natural killer (NK) cells.

1.2 Development history etc.

From November 2006, a foreign phase I study (Study HuLuc63-1701) was conducted by a US-based biopharmaceutical company, Facet Biotech Corporation (now AbbVie Biotherapeutics, Inc.) in patients with relapsed or refractory MM to evaluate elotuzumab as a single agent. From August 2008, a phase I/II study (HuLuc63-1703) was conducted by the US-based AbbVie Biotherapeutics, Inc. in patients with relapsed MM to evaluate an elotuzumab, lenalidomide hydrate, and dexamethasone (ELd) regimen. Then, the following studies were conducted by the applicant: a phase I study (Study CA204007) in patients with MM to evaluate an ELd regimen from January 2012; and a phase III study (Study CA204004) in patients with relapsed or refractory MM to evaluate the ELd regimen from June 2011.

With the results from the pivotal CA204004 study and other studies, applications for approval of elotuzumab were filed in the US and EU in [redacted] 20[redacted], and [redacted] 20[redacted], respectively. In the US, elotuzumab was approved in November 2015 with the indication, “EMPLICITI is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies,” and in EU in May 2016 with the indication, “Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.”

As of June 2016, elotuzumab has been approved in 4 countries/regions with the indication for MM.

In Japan, a phase I study (Study CA204005) was conducted from February 2011 by the applicant in patients with relapsed or refractory MM to evaluate the ELd regimen. Patient registration for Study CA204004 started in [redacted] 20[redacted].

With the results from the pivotal CA204004 study and other studies, this application for approval of elotuzumab has been filed.

Elotuzumab was designated as an orphan drug (Orphan Drug Designation No. 367 of 2015 [*27 yaku*]) with the intended indication of “relapsed or refractory multiple myeloma” in November 2015.

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Hybridoma cells were produced by fusing mouse myeloma cells to mouse lymphocytes immunized with [redacted] of human SLAMF7 and human [redacted]. From the hybridomas, a clone that produces MuLuc63, monoclonal antibodies specific to human SLAMF7, was selected, and gene segments encoding the variable region of heavy and light chains prepared from the clone were inserted into plasmid containing the constant region of human IgG1 heavy and light chains to create an expression construct for elotuzumab. The expression construct was introduced into mouse myeloma cell line (NS0), and thus, master cell bank (MCB) and working cell bank (WCB) were prepared from a clone optimum for the production of elotuzumab.

Characterization and purity tests of MCB, WCB, and end-of-production cell bank (EPCB) were performed in accordance with ICH guidelines Q5A (R1), Q5B, and Q5D. The results confirmed the genetic stability of the cell banks during the manufacturing period. Although the results were positive for retroviruses that are generally found in rodent cell lines, no other viruses or non-viral infectious materials were detected within the scope of the tests conducted.

MCB and WCB are stored in the vapor phase of liquid nitrogen. While there is no plan to generate a new MCB, the WCB may be newly prepared on an as-needed basis.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of the following steps: expanded culture, seed bioreactor, production bioreactor, harvest/[redacted], [redacted], [redacted], [redacted], [redacted], virus filtration, [redacted], [redacted]/filling, freezing, testing, and storage processes. The drug substance obtained is stored in [redacted], at ≤[redacted]°C, and protected from light.

The following processes are defined as critical steps: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

With regard to the manufacturing process of the drug substance, process validation on production scale batches is conducted.

2.1.3 Safety evaluation of adventitious agents

No biological ingredients are used in the manufacturing process of the drug substance, except for the host cell, NS0 cell line.

Purity tests of MCB, WCB, and EPCB are conducted [see Section 2.1.1]. While endogenous retrovirus-like particles were detected in production scale batches of pre-harvest unprocessed bulk by transmission electron microscopy, contamination with other viral or non-viral adventitious agents was not detected

in the bioburden test, mycoplasma test, adventitious virus (*in vitro*) test, and mouse minute virus detection assay. The bioburden test, mycoplasma test, adventitious virus (*in vitro*) test, and mouse minute virus detection assay of pre-harvest unprocessed bulk are specified as in-process control tests.

The viral clearance study was performed using model viruses, and the results demonstrated that the purification process is capable of a certain degree of virus clearance (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Herpes simplex virus type 1	Mouse minute virus	Reovirus type 3
[redacted]	[redacted]	>[redacted]	[redacted]	[redacted]
[redacted]	>[redacted]	>[redacted]	[redacted]	[redacted]
[redacted]	>[redacted]	>[redacted]	>[redacted]	>[redacted]
Viral filtration	>[redacted]	[redacted]	>[redacted]	>[redacted]
Total virus reduction factor	>19.89	>21.81	>10.00	>10.75

2.1.4 Manufacturing process development

Major changes in the manufacturing process that occurred during the development of the drug substance are shown below (manufacturing methods are referred to as Methods A, B, C, C.1, and the proposed method):

- From Method A to Method B: Change of [redacted], and others.
- From Method B to Method C: Change of [redacted], and others.
- From Method C to Method C.1: Change of [redacted], and others.
- From Method C.1 to the proposed method: Addition of [redacted], and others.

Method A was used only at the beginning of the development stage. The formulation manufactured using the drug substance of Method C.1 was used in the pivotal global phase III study (Study CA204004), and the formulation manufactured using the drug substance of the proposed method was used in studies including a Japanese phase I study (Study CA204005) [see Section 6.1.2]. The comparability of the drug substances were verified based on the results of quality analysis before and after each change.

The quality by design (QbD) methodology was used for the development of the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 shows the characterization analyses that were conducted.

Table 2. Test items and procedures employed in the characterization analyses

Item		Test procedure
Primary structure	Amino acid sequence	[redacted]
	N-terminal and C-terminal amino-acid sequences	[redacted]
	Post-translational modification Oxidation Deamidation Glycation	[redacted] Peptide mapping ([redacted])
Higher-order structure	Secondary structure	Circular dichroism spectroscopy in the far-UV region
	Tertiary structure	[redacted]
	Disulfide linkage	[redacted]
	Free thiol group	[redacted]
	Thermal stability	Differential scanning calorimetry
Physicochemical properties	Molecular weight	Mass spectrometry [redacted]
	Absorption coefficient	[redacted] Ultraviolet absorption spectrum
	Molecular variants	SEC [redacted] Ultracentrifugal analysis SDS-polyacrylamide gel electrophoresis ([redacted]) CE-SDS ([redacted]) CEX [redacted]
Sugar chain structure	N-linked oligosaccharide distribution	[redacted]
	Non-glycosylated heavy chain	[redacted] Peptide mapping ([redacted])
Biological activity	SLAMF7 binding activity	ELISA
	SLAMF7 binding kinetics	SPR
	Fcγ receptor binding activity	SPR
	Neonatal Fc receptor binding activity	SPR
	Cell-based assay	ADCC activity CDC activity

Regarding the biological activity, the binding activity of elotuzumab to SLAMF7 was determined by enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR). The analysis of kinetics for the binding of elotuzumab to the Fc receptor (neonatal Fc receptor, and Fcγ receptors I, IIa, II b/c, and IIIa) was performed using SPR to calculate dissociation constant (K_D), and the results showed characteristic binding of IgG1.

The ADCC activity was assessed [redacted], and [redacted], and the results showed a dose-dependent ADCC activity. The complement dependent cytotoxicity

(CDC) activity was assessed [redacted], no CDC activity was detected in elotuzumab.

2.1.5.2 Product-related substances/product-related impurities

Based on the results of characterization in Section "2.1.5.1 Structure and characterization," [redacted], [redacted], [redacted] ([redacted] and [redacted]), [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. Impurities A, B, and C were identified as product-related impurities, which are adequately controlled by the specification and testing of the drug substance and drug product.

2.1.5.3 Process-related impurities

[redacted], [redacted], host cell proteins, host cell DNA, [redacted], endotoxins and microorganisms were specified as process-related impurities. It has been verified that any process-related impurities can be effectively eliminated in the manufacturing process. Endotoxins are controlled by the specifications and test methods (endotoxin testing) of the drug substance and drug product; while microorganisms are controlled by the specifications and test methods (microbial limit testing) of the drug substance.

2.1.6 Control of drug substance

The proposed specifications and test procedures for the drug substance include: content, description, identification ([redacted]), glycan profiles, osmotic pressure, pH, purity ([redacted], [redacted] [[redacted] and [redacted]], and [redacted]), endotoxin, microbial limit, biological activity ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows the main stability studies of the drug substance.

Table 3. Main stability studies of the drug substance

		Number of batches*	Storage conditions	Study period	Storage container
Long-term testing		3	[redacted] ± [redacted]°C	[redacted] months	[redacted]
Accelerated testing		3	[redacted] ± [redacted]°C	[redacted] months	
Stress testing	Temperature	1	[redacted] ± [redacted]°C/ [redacted] ± [redacted]% RH	[redacted] months	
	Photostability	1	Overall illumination of ≥1.2 million lux·h, and an integrated near ultraviolet energy of ≥200 W·h/m^2		

Note*, the drug substance was manufactured by the proposed manufacturing method

No significant change in quality attributes was observed over the long-term testing period.

In accelerated testing, the following were noted: a trend towards a decrease in [redacted], a trend towards an increase in Impurity A, a trend towards a decrease in [redacted], a decrease in [redacted], and an increase in [redacted].

In temperature stress tests, there was a trend towards an increase in [redacted] in addition to the changes observed in the accelerated tests.

The results of photostability stress tests showed that the drug substance was not photostable.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance when stored [redacted], protected from light at ≤ [redacted] °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, and each glass vial (20 mL) contains 340 or 440 mg of elotuzumab. The drug product contains sodium citrate hydrate, citric acid hydrate, sucrose, and polysorbate 80 as excipients. The actual volume contained in each vial slightly exceeds the content indicated on the label to ensure withdrawal of 300 or 400 mg of elotuzumab when reconstituted with 13.0 or 17.0 mL of water for injection (the protein concentration after reconstitution is 25 mg/mL for both volumes).

2.2.2 Manufacturing method

The manufacturing process of the drug product comprises thawing, mixing, aseptic filtration/filling, lyophilization, clamping, and packaging/labeling/storage/testing. [redacted] and [redacted] have been defined as critical steps.

Regarding the manufacturing process of the drug product, process validation on production scale batches is conducted.

2.2.3 Manufacturing process development

Major changes in the manufacturing process that occurred during the development of the drug product are as follows. These changes occurred at the same time as the changes in the manufacturing process of the drug substance occurred [see Section 2.1.4] (similarly to the changes for the drug substance, the manufacturing methods are referred to as Methods A, B, C, C.1, and the proposed method):

- From Method A to Method B: Change of [redacted], and others.
- From Method B to Method C: Change of [redacted], and others.
- From Method C to Method C.1: Change of [redacted], and others.
- From Method C.1 to the proposed method: Change of [redacted], and others, and addition of [redacted].

The comparability of the drug substances in terms of the quality attributes were evaluated at the time of the change in the manufacturing method for the drug product, and the comparability of the drug substance before and after each change has been verified.

The QbD methodology was used for the development of the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications and test procedures for the drug product include: content, description, identification ( ), pH, purity (appearance of solution, , [and], and), water content, endotoxin, uniformity of dosage unit, foreign insoluble matter, insoluble particulate matter, sterility, reconstitution time, biological activity ( ), and assay (ultraviolet-visible spectrophotometry). The specifications and test procedures for potency were changed during the review process from ( ) to biological activity ( ).

2.2.5 Stability of drug product

Table 4 shows the main stability studies of the drug product.

Table 4. Main stability studies of the drug product

		Formulation specification	Number of batches[*1]	Storage conditions	Study period	Storage container
Long-term testing		300 mg	3	5 ± 3°C	18 months[*2]	Butyl rubber stopper and glass vial
		400 mg			36 months	
Accelerated testing		300 mg	3	± °C/ ± % RH	months	
		400 mg				
Stress testing	Temperature	300 mg	3	± °C/ ± % RH	months	
		400 mg			months	
	Photostability	300 mg	1	Overall illumination of ≥1.2 million lux·h, and an integrated near ultraviolet energy of ≥200 W·h/m^2		
		400 mg				

*1, The drug substance and drug product were manufactured by the proposed manufacturing method.
*2, Stability testing is ongoing up to 36 months.

No significant change in quality attributes was observed over the long-term testing period for either of the formulations.

In accelerated testing, a trend towards a decrease in , and a trend towards an increase in Impurity A were observed for both formulations.

In temperature stress tests, a change in was observed for both formulations in addition to the changes observed in the accelerated tests.

The results of photostability stress tests showed that both formulations of the drug product were photostable.

Based on the above, a shelf life of 18 months and 36 months was proposed for the 300 mg and 400 mg formulations of the drug product, respectively, when stored protected from light at 2°C to 8°C, unfrozen, and using a butyl rubber stopper and in a glass vial.

2.3 QbD

The QbD methodology was used for the development of the manufacturing processes of the drug substance and drug product, and the control strategy for quality was formulated based on several considerations that included the following:

- Identification of critical quality attribute (CQA):
  Regarding quality attributes of product-related substances, process-related impurities, and pharmaceutical formulation, the following CQAs were identified based on the information obtained through the development of elotuzumab and related data:
  - CQA of the drug substance: [redacted], Impurity C, Impurity A, Impurity B, [redacted], host cell DNA, host cell proteins, [redacted], adventitious virus, bioburden, and endotoxins.
  - CQA of the drug product: [redacted], Impurity A, Impurity B, [redacted], endotoxins, and sterility.

- Characterization of the processes:
  Identification of processes that affect CQA, and identification of input variables (critical process parameters) and output variables (critical performance attributes) that have significant effects on CQA and the performance of these processes.
- Establishment of control method:
  Based on process knowledge including the above process characterizations, batch analysis results, stability study results, and other information, methods for control of process parameters and performance attributes, in-process control, and control of the quality attributes of the drug substance and drug product through a combination of specifications and testing methods were established [see Section "2.1.5.2 Product-related substances/product-related impurities" and "2.1.5.3 Process-related impurities" for the control of product-related impurities and process-related impurities, respectively].

2.R Outline of the review by PMDA

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

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

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics of elotuzumab to SLAMF7 (CTD 4.2.1.1-1 to 9)

An examination by the SPR method was performed to assess the binding of elotuzumab and its parent antibody MuLuc63 to hCS1-hFc or hCS1-mFc, fusion proteins of human SLAMF7 protein and an Fc fragment of human (hFc) or murine (mFc) IgG1 subclass. The results showed that elotuzumab bound to hCS1-hFc and hCS1-mFc with a K_D of 43.7 ± 6.5 and 28.9 ± 6.2 nmol/L, respectively (mean ± standard deviation, n = 4), and MuLuc63 bound to hCS1-hFc and hCS1-mFc with a K_D of 42.4 ± 2.4 and 28.5 ± 5.3 nmol/L, respectively (mean ± standard deviation, n = 4).

Binding of MuLuc63 to tumor cells of frozen tissue from MM patients was assessed by the immunohistochemistry (IHC) method. The results indicated that MuLuc63 bound to MM cells.

The binding of MuLuc63 to normal human tissues was assessed by the IHC method. The results showed that MuLuc63 bound to infiltrating leukocytes in each tissue; however, it did not bind to epithelium, smooth muscle cells, or blood vessels of major organs and tissues.

The binding of elotuzumab to leukocyte subsets was assessed by flow cytometry using whole blood samples of healthy adults. The results showed that elotuzumab bound to NK cells, NKT cells, and some CD8+ T cells, but did not bind to CD4+ T cells, monocytes, B cells, or granulocytes.

The binding of elotuzumab to SLAMF7 of chimpanzee, cynomolgus monkey, rhesus monkey, dog, miniature pig, mouse, rat, and rabbit was assessed by flow cytometry, ELISA, and the IHC method. Binding of elotuzumab to SLAMF7 did not occur in any of the animal species studied. The binding of elotuzumab to leukocyte subsets was studied using whole blood samples of chimpanzee, cynomolgus monkey, and rhesus monkey by flow cytometry. While binding of elotuzumab to leukocytes was not observed in samples from chimpanzee, it was found that elotuzumab bound to B cells in samples from cynomolgus and rhesus monkeys. However, the applicant explained that because elotuzumab did not bind to SLAMF7 of cynomolgus and rhesus monkeys, the binding of elotuzumab to B cells does not indicate a specific binding of elotuzumab to SLAMF7.

3.1.2 ADCC and CDC activities (CTD 4.2.1.1 to 10 and 4.2.1.1 to 11)

The ADCC activity of elotuzumab against human-MM L363 cell line was investigated using peripheral blood mononuclear cells (PBMCs) of MM-patients or healthy adults as effector cells based on lactate dehydrogenase activity as an indicator. The results indicated ADCC activity of elotuzumab.

The ADCC activity of elotuzumab against human-MM OPM2 and L363 cell lines was investigated using human PBMCs as effector cells by the chromium release assay. The results indicated ADCC activity in both cell lines. Further, the ADCC activity of elotuzumab against L363 cell line was investigated using PBMCs deprived of monocytes, B cells, T cells, or NK cells. The results showed that

compared with the case in which PBMCs were used as effector cells, a decrease in ADCC activity was observed when NK cells were removed from PBMCs ($P < 0.001$, Tukey's test).

The ADCC activity of elotuzumab against human embryonic kidney 293 (HEK 293) cell line, human prostate cancer (PC3) cell line, and human lung cancer 460 (H460) cell line was investigated in the presence of human PBMCs by the chromium release method. The results indicated no ADCC activity in any of the cell lines studied. The ADCC activity of elotuzumab against 293s-huCS1, PC3-huCS1, and H460-huCS1 cell lines was investigated, which were obtained by forced expression of human SLAMF7 protein in the HEK 293, PC3, and H460 cell lines, respectively. The results showed ADCC activity in all the cell lines.

The CDC activity of elotuzumab against L363 cell line was investigated in the presence of human serum using luciferase activity as an indicator. According to the results, no CDC activity was detected.

3.1.3 Anti-tumor activity of elotuzumab against human MM cells (CTD 4.2.1.1-13 to 17)

The anti-tumor activity of elotuzumab was investigated using severe combined immunodeficiency (SCID) mice subcutaneously inoculated with OPM2 cell line. The study started on the day of inoculation (Day 0), and the mice were given a total of 7 intraperitoneal doses of elotuzumab at 0.1, 0.5, 1, 5, or 10 mg/kg every third day from Day 19, and tumor volume was calculated (Figure 1). The results showed that from Day 23 onward a significant increase in anti-tumor activity was observed in the 0.5, 1, 5, and 10 mg/kg groups compared with the control (human IgG1 antibody) group ($P < 0.04$, Student's *t*-test).

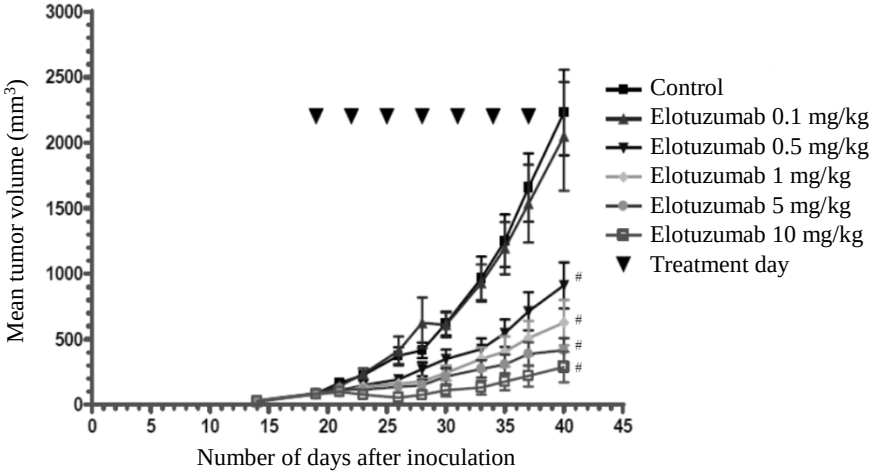

Figure 1. Anti-tumor activity of elotuzumab in mice subcutaneously inoculated with OPM2 cell line
Mean ± standard deviation, n = 9; #, $P < 0.04$ against control group (human IgG1 antibodies) (Student's *t*-test)

The anti-tumor activity of elotuzumab in combination with bortezomib (BTZ) was investigated using SCID mice subcutaneously inoculated with OPM2 cell line. The study started on the day of inoculation (Day 0), and the mice were intraperitoneally given elotuzumab (1 mg/kg twice a week from Day 22), and BTZ (in cycles starting from Day 19 consisting of 2-week treatment at 1 mg/kg twice a week followed by 1-week off treatment), and tumor volume was calculated. The results showed that at Day

38, a significant increase in anti-tumor activity was observed in the group that received elotuzumab in combination with BTZ, compared with the elotuzumab or BTZ monotherapy group ($P < 0.001$ for both, Tukey's test).

The anti-tumor activity of elotuzumab in combination with pomalidomide and dexamethasone (DEX) was investigated using SCID mice subcutaneously inoculated with OPM2 cell line. The study started on the day of inoculation (Day 0), and the mice were given elotuzumab (from Day 16, a total of 7 intraperitoneal doses, at 0.5 mg/kg twice a week), pomalidomide (from Day 16, a total of 10 oral doses, at 5 mg/kg 5 times a week), and DEX (from Day 16, a total of 7 intraperitoneal doses, at 5 mg/kg once daily) in monotherapies, combination therapies, or triple therapy, and tumor volume was calculated. According to the results, statistically significant anti-tumor activity was observed in the following groups (Mann-Whitney *U*-test): (1) combination therapy of elotuzumab and pomalidomide compared with elotuzumab monotherapy ($P = 0.0207$); (2) combination therapy of elotuzumab and pomalidomide compared with pomalidomide monotherapy ($P = 0.03823$); and (3) triple therapy of elotuzumab, pomalidomide, and DEX compared with combination therapy of pomalidomide and DEX ($P = 0.0002$).

The anti-tumor activity of elotuzumab in combination with an anti-human KIR2DL1/2/3 monoclonal antibody was investigated by subcutaneously inoculating OPM2 cell line into recombination activating gene (RAG) deficient mice, in which human KIR2DL3, a receptor mediating NK cell inactivation, is expressed on the NK cells. The study started on the day of inoculation (Day 0), and the mice were given elotuzumab (a total of 7 doses, at 0.5 mg/kg twice a week from Day 11) intraperitoneally and anti-human KIR2DL1/2/3 monoclonal antibody (at 15 mg/kg on Days 11 and 24) intravenously, and tumor volume was calculated. A trend towards an increase in anti-tumor activity was observed on Day 27 in the group receiving elotuzumab and anti-human KIR2DL1/2/3 monoclonal antibody in combination compared with the monotherapy groups of each agent.

The anti-tumor activity of elotuzumab in combination with anti-mouse CD137 monoclonal antibody, which targets CD137, a co-stimulatory molecule expressed on activated T cells and NK cells, was investigated using SCID mice inoculated with OPM2 cell line. The study started on the day of inoculation (Day 0), and the mice were intraperitoneally given elotuzumab 10 μg and anti-mouse CD137 monoclonal antibody 100 μg on Day 8, and tumor volume was calculated. A trend towards an increase in anti-tumor activity was observed in the group receiving elotuzumab and anti-mouse CD137 monoclonal antibody in combination compared with the monotherapy groups of each agent.

3.2 Safety pharmacology

In a single dose toxicity study, rhesus monkeys were given elotuzumab at 30 or 100 mg/kg to investigate the effects of elotuzumab on general signs, food consumption, weight, and other aspects [see Section 5.1.1]. No elotuzumab treatment-related effects were observed.

3.R Outline of the review by PMDA

Based on the submitted data and the following discussions, PMDA concluded that elotuzumab can be expected to be effective in the treatment of MM.

3.R.1 Mechanism of action of elotuzumab

The applicant's explanation of the mechanism of action of elotuzumab:

It has been reported that SLAMF7 is expressed in more than 95% of patients with MM (e.g., *Clin Cancer Res*. 2008;14:2775-84, *Blood.* 2008;112:1329-37).

It is considered that the anti-tumor effects of elotuzumab are exerted by binding to SLAMF7, which is expressed at cell membranes, especially those of MM cells, inducing ADCC activity against MM cells through Fc-receptor-mediated interaction with NK cells [see Sections 3.1.2 and 3.1.3]. SLAMF7 expressed at the cell membranes of NK cells is reported to be a receptor that mediates activation of NK cells (*J Immunol*. 2001;167:5517-21), and it has been suggested that elotuzumab activates NK cells by binding to SLAMF7 expressed at the cell membranes of NK cells (*Cancer Immunol Immunother*. 2013;62:1841-9); therefore, elotuzumab may exert its anti-tumor activity by the above-mentioned activation of NK cells.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics (PK) of elotuzumab in animals was evaluated in monkeys and mice.

4.1 Analytical methods

ELISA methods were used to quantify elotuzumab in monkey serum and mouse serum using fusion proteins prepared by fusing the extracellular domain of immobilized human SLAMF7 and Fc fragments of murine IgG1 subclass, as well as horseradish peroxidase (HRP)-labeled goat anti-human κ light chain antibody.

4.2 Absorption

4.2.1 Single-dose studies

A single intravenous dose of elotuzumab 30 or 100 mg/kg was administered to male and female monkeys to study the serum concentration of elotuzumab (Table 5). The exposure of elotuzumab (maximum serum concentration [C_{max}] and area under the plasma concentration-time curve from time zero extrapolated to the infinite time [AUC_{inf}]) increased roughly in a dose proportional manner, and no clear difference in exposure levels was observed between the sexes.

Table 5. Pharmacokinetic parameters of elotuzumab (male and female monkeys, single-dose intravenous administration)

Dose (mg/kg)	Sex	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (mg·h/mL)	CL (mL/h/kg)	V_1 (mL/kg)	$t_{1/2}$ (day)
30	M	640	1.00	194	0.155	46.3	14.8
	F	644	1.00	118	0.254	46.4	8.0

Dose (mg/kg)	Sex	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (mg·h/mL)	CL (mL/h/kg)	V_1 (mL/kg)	$t_{1/2}$ (day)
100	M	1657	2.00	335	0.299	61.5	8.4
	F	2065	8.00	447	0.224	49.9	9.7

n = 1; individual values

4.2.2 Repeated-dose studies

Elotuzumab was intraperitoneally administered to female mice at 0.1, 0.5, 1, 5, or 10 mg/kg every 3 days for a total of 7 doses, and the serum concentration of elotuzumab was assessed (Table 6). The serum concentration of elotuzumab increased roughly in a dose proportional manner over the dose range studied. The serum concentration of elotuzumab increased as the number of doses increased, suggesting that elotuzumab accumulates as a result of repeated administration.

Table 6. Pharmacokinetic parameters of elotuzumab (female mice, repeated-dose intraperitoneal administration)

Dose (mg/kg)	$C1_{max}$ *1 (μg/mL)	$C1_{min}$ (μg/mL)	$C6_{min}$ *1 (μg/mL)	$C7_{max}$ (μg/mL)	Terminal Bleed (μg/mL)
0.1	0.48 ± 0.19	0.13 ± 0.25*2	0.43 ± 0.96	0.87 ± 0.81*3	0.30 ± 0.56*4
0.5	3.55 ± 0.81	1.88 ± 1.09*2	6.90 ± 6.27	13.02 ± 7.23*2	7.05 ± 6.12*5
1	8.25 ± 2.09	3.15 ± 2.15*2	18.90 ± 10.20	23.84 ± 18.06*2	13.95 ± 11.00*5
5	43.08 ± 18.81	34.03 ± 6.22*2	126.99 ± 19.70	175.97 ± 36.98*2	108.91 ± 21.21*5
10	97.98 ± 24.81	68.51 ± 6.42*3	272.11 ± 55.86	429.08 ± 85.87*2	257.38 ± 54.89*5

Mean ± standard deviation; *1, n = 5; *2, n = 4; *3, n = 3; *4, n = 8; *5, n = 9; $C1_{max}$, 8 hours after administration of the first dose; $C1_{min}$, immediately before administration of the second dose; $C6_{min}$, immediately before administration of the seventh dose; $C7_{max}$, 8 hours after administration of the seventh dose; Terminal Bleed, 3 days after administration of the seventh dose

4.3 Distribution

Given that the volume of distribution of elotuzumab in the monkey single-dose study [see Section 4.2.1] was about the same as the plasma volume of monkeys, 44.8 mL/kg (*Pharm Res.* 1993;10:1093-5), it is considered that transfer of elotuzumab into tissue is insignificant, and that elotuzumab is primarily distributed in circulating blood. The applicant explained that for the above reason, the tissue distribution of elotuzumab was not studied.

Based on the following reasons and other aspects, the applicant also explained that elotuzumab, a humanized monoclonal antibody of IgG1 subclass, may be transferred across the placenta to the fetus, and that the rate of transfer of elotuzumab across the placenta may be higher in the third trimester than in the first and second trimesters.

- Human IgG1 can transfer across the placenta to the fetus mediated by neonatal Fc receptor.
- It has been suggested that the rate of transfer of human IgG1 may be higher in the third trimester than in the first and second trimesters (*Crit Rev Toxicol*. 2012;42:185-210, *Acta Pathol Microbiol Scand C.* 1977;85:314-6).

4.4 Metabolism and excretion

As elotuzumab is an antibody drug, it is assumed that elotuzumab is decomposed into low molecule peptides and amino acids, and is subsequently excreted or utilized for the synthesis of proteins or peptides in the body. The applicant explained that for this reason, no studies were performed for the

metabolism and excretion of elotuzumab in accordance with "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1, dated March 23, 2012).

The applicant also explained that it is possible that elotuzumab is transferred to breast milk, given that human IgG1 was reported to be transferred to breast milk (*Nutrients*. 2011;3:442-74); therefore, it plans to add a precautionary statement in the package insert to the effect that administration of elotuzumab to breastfeeding women should be avoided, and that if treatment is unavoidable, breastfeeding should be stopped.

4.R Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the explanations provided by the applicant regarding the absorption, distribution, metabolism, and excretion of elotuzumab are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

5.1.1 Single intravenous dose toxicity studies in rhesus monkeys (reference data)

Elotuzumab was administered by intravenous infusion over 30 minutes or more to rhesus monkeys (n = 1/sex/group) at 0 (vehicle control, an aqueous solution containing 0.05% Tween 80, 20-mmol/L sodium citrate, and 120-mmol/L sodium chloride), 30, or 100 mg/kg. Necropsies were performed on Day 45, and histopathological examination and other studies were performed. No elotuzumab treatment-related toxicological findings were noted at any dose levels. Based on the results, the approximate lethal dose was determined to be more than 100 mg/kg.

5.2 Repeat-dose toxicity

Based on the following reasons, no suitable animal species or animal models for the study of elotuzumab toxicity were identified, and therefore, no repeat-dose toxicity studies were conducted.

- Elotuzumab does not bind to SLAMF7 in the laboratory animals (chimpanzees, cynomolgus monkeys, rhesus monkeys, dogs, mini pigs, rabbits, rats, and mice) [see Section 3.1.1].
- The expression of SLAMF7 in human *SLAMF7* transgenic mice differs from the SLAMF7 expression in humans; therefore, transgenic mice were not considered a valid alternative animal model for the safety evaluation of elotuzumab.

5.3 Genotoxicity

Because elotuzumab is an antibody drug, it is unlikely to have a direct effect on DNA or other chromosome components; therefore, no genotoxicity tests were conducted.

5.4 Carcinogenicity

No carcinogenicity studies have been conducted because elotuzumab is an antineoplastic drug intended for the treatment of patients with advanced-stage cancer.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been conducted because no suitable animal species or animal models for the study of elotuzumab toxicity were identified [see Section 5.2].

5.6 Local tolerance

5.6.1 Local tolerance study in rabbits

A single intravenous bolus dose of elotuzumab 1 mL (5 mg/mL) was administered into the right auricular vein of New Zealand White (NZW) rabbits (6 females) at 1 mL/min. The same volume of vehicle (an aqueous solution containing 0.05% Tween 80, 20-mmol/L sodium citrate, and 120-mmol/L sodium chloride; pH 6.05) was administered into the left auricular vein of these animals. Necropsies were performed 30 minutes, 3 hours, and 24 hours after administration for 2 animals at a time, and macroscopic observation and histopathological examination were performed. No elotuzumab treatment-related effects were detected.

The applicant explained that the risk of elotuzumab causing local irritation would be low given the above results and the fact that the administration concentrations of elotuzumab in actual clinical use and in this study are about 2.4 to 3 mg/mL and 5 mg/mL, respectively.

5.7 Other toxicity studies

5.7.1 Cross-reactivity study of elotuzumab with human tissues

The binding of elotuzumab to human tissues was studied using a panel of human tissues. The results showed that elotuzumab bound to plasma cells and immunoblasts in the bone marrow, breast, colon, esophagus, small intestine, stomach, liver, lymph node, fallopian tube, pancreas, salivary gland, spleen, thymus, thyroid, tonsil, ureter, and uterus (endometrium of the body and cervix).

The applicant explained that although the above results suggest that SLAMF7 is expressed on plasma cells and immunoblasts, the function of SLAMF7 in cells is not understood except for NK cells; therefore, the effects of elotuzumab on plasma cells and immunoblasts are not clear.

5.7.2 Effects of elotuzumab *in vitro* on lymphocyte subsets in whole blood from healthy adults (reference data)

Whole blood samples from 8 healthy adults were incubated at 37°C for 24 hours in the presence of elotuzumab 100 or 200 µg/mL, and the absolute counts of leukocyte subsets were determined by flow cytometry. In the presence of elotuzumab 100 or 200 µg/mL, a decrease in NK cell counts (by about 20% to 44%) was observed in 5 of 8 whole blood samples; however, no effects were detected on the total lymphocyte counts, CD3+ T cell counts, CD4+ T cell counts, CD8+ T cell counts, B cell counts, and memory B cell counts.

5.7.3 Effects of elotuzumab on bone marrow stem cell differentiation potential (reference data)

Bone marrow cell samples from 3 healthy adults were cultured for 2 weeks in the presence of elotuzumab at 5, 20, 100, or 500 µg/mL, in a medium containing stem cell factor, granulocyte-

macrophage colony-stimulating factor, interleukin 3, and erythropoietin to investigate the effects of elotuzumab on bone marrow cell differentiation potential. No elotuzumab treatment-related effects were observed.

5.7.4 Hemolysis assay in human whole blood with elotuzumab

Whole blood (0.1 mL) from human donors was diluted with isotonic sodium chloride solution, and incubated in the presence of elotuzumab at 2, 5, or 10 mg/mL (5.0 mL) for about 60 minutes at 37 ± 2°C to investigate the potential for elotuzumab to induce hemolysis. The results showed that elotuzumab did not cause hemolysis of human whole blood. Based on the above results, the applicant concluded that elotuzumab has good human blood compatibility.

5.R Outline of the review by PMDA

Based on the submitted data and discussions in the following sections, PMDA concluded that in the non-clinical toxicity evaluation, no problems are associated with the clinical use of elotuzumab. Further, PMDA concluded that repeat-dose toxicity studies for elotuzumab can be omitted, because, along with the results from human experience with elotuzumab, no suitable animal species or animal models for the evaluation of pharmacological action-related toxicity of elotuzumab have been identified [see Section 5.2], and elotuzumab did not appear to bind to molecules other than SLAMF7 in the cross-reactivity study with human tissues [see Section 5.7.1].

5.R.1 Administration of elotuzumab to women who are or may be pregnant, and contraception

PMDA asked the applicant to explain the following: (a) treatment with elotuzumab in women who are or may be pregnant; and (b) need for effective contraception during and a certain period after treatment with elotuzumab. The applicant's response:

(a) Treatment with elotuzumab in women who are or may be pregnant:

Based on the points listed below, while the effects of elotuzumab on human fertility and embryonic development are not clear, there have been no clear findings that indicate elotuzumab would cause reproductive and developmental toxicity; therefore, it is considered that treatment with elotuzumab in women who are or may be pregnant is acceptable. However, given that treatment with elotuzumab in patients with relapsed or refractory MM involves coadministration with lenalidomide, a potential human teratogen [see Section 7.R.6], the ELd regimen should not be administered to women who are or may be pregnant.

- Because SLAMF7 deficient mice are born without abnormalities (*Nat Immunol*. 2009;10:297-305), SLAMF7 may not play a significant role in embryonic/fetal development and growth. However, the intracellular domain of SLAMF7 is different in mice and humans (*Crit Rev Oncol Hematol*. 2013;88:168-77, *Annu Rev Immunol*. 2011;29:665-705); therefore, it is not clear whether SLAMF7 is involved in human embryonic/fetal development and growth.
- Elotuzumab has the effect of activating NK cells in peripheral blood [see Section 3.R.1], and there have been reports that recurrent spontaneous abortion and a decrease in *in vitro* fertilization rate

were associated with NK cell activity in peripheral blood (e.g., *Hum Reprod.* 2000;15:1163-9, *Immunobiology.* 2015;220:649-55), suggesting a possibility that treatment with elotuzumab may cause spontaneous abortion. On the other hand, there have been reports including a large-scale cohort study (*Fertil Steril.* 2013;100:1629-34) that suggested no association between recurrent spontaneous abortion and the cytotoxic activity of NK cells in peripheral blood. Based on these results, it is considered that no clear evidence exists that activation of NK cells in peripheral blood affects normal embryonic/fetal development and growth.

(b) Need for effective contraception during and for a certain period after treatment with elotuzumab

Female patients of childbearing potential should use effective contraception during treatment and for a certain period after treatment with elotuzumab, because the effects of elotuzumab on embryos and fetuses are not known; moreover, elotuzumab is also administered to patients with relapsed or refractory MM in combination with lenalidomide [see Section 7.R.6].

On the other hand, based on the reasons listed below, it is not considered necessary for male patients to use contraception during treatment or for a certain period after treatment with elotuzumab. However, because patients with relapsed or refractory MM will be administered elotuzumab in combination with lenalidomide [see Section 7.R.6], male patients receiving the ELd regimen should use effective contraception measures.

- Based on the following points, the risk of elotuzumab treatment causing adverse effects on male fertility is considered low.
  - NK cells are present in testicular interstitium, and are considered to play a role in innate immunity (*Biol Reprod.* 1998;58:943-51, *Spermatogenesis*. 2013;3:e23870). However, there have been no reports on the effects of enhanced NK cell activation on male reproductivity.
  - Because elotuzumab is an antibody drug, it is unlikely that elotuzumab will have a direct effect on DNA; therefore, the risk of elotuzumab causing genetic mutation in germ cells is considered low.
  - Because elotuzumab is an antibody drug, it is unlikely that elotuzumab will pass the blood-testis barrier and have a direct effect on spermatogenesis.
- Because elotuzumab is an antibody drug, and it is considered that pregnant women or the embryo/fetus will be exposed to an extremely low level of elotuzumab through semen (e.g., *AIDS Res Hum Retroviruses.* 2000;16:583-94, *Reprod Toxicol*. 2014;48:124-37), the risk of elotuzumab causing adverse effects on embryonic/fetal development through semen following administration of elotuzumab to the male patient is considered low.

PMDA's view is as follows:

Regarding treatment of women who are or may be pregnant with elotuzumab, the currently available data on reproductive and developmental toxicity allow only a limited risk assessment of elotuzumab in relation to fertility and embryonic/fetal development in actual clinical use; therefore, it is considered that the risk of elotuzumab causing reproductive and developmental toxicity is not known. For this

reason, the administration of elotuzumab to female patients who are or may be pregnant is not acceptable, and therefore, it is concluded that elotuzumab should be contraindicated in female patients who are or may be pregnant.

Regarding contraception, PMDA accepted the applicant's explanation about female patients of childbearing potential. However, regarding male patients, the data currently available are insufficient for the assessment of the effects of elotuzumab on male fertility, and therefore, the effects are unclear. Accordingly, contraception is necessary during and for a certain period after treatment with elotuzumab, regardless of whether elotuzumab is administered with lenalidomide or not.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

6.1.1.1 Methods for measuring elotuzumab

The quantity of elotuzumab was determined by 2 ELISA methods using [redacted] and [redacted] ([a] the lower limit of quantitation, 75 ng/mL; [b] the lower limit of quantitation 190 ng/mL).

6.1.1.2 Methods for measuring anti-elotuzumab antibodies

The following methods were used to determine the quantity of anti-elotuzumab antibodies (a) and (b) (below) and anti-elotuzumab neutralizing antibodies (c) and (d) (below) in human serum:

(a) The electrochemiluminescence (ECL) method using [redacted], [redacted], and [redacted] (lower limit of quantitation, 24.7 ng/mL).

(b) The ECL method in which measurements are performed in the same manner as in the section (a), after separating elotuzumab and anti-elotuzumab antibodies by pretreatment using the solid phase extraction and acid dissociation methods (lower limit of quantitation, 6.19 ng/mL).

(c) The ECL method using [redacted] and [redacted] expressing the extracellular domain of human SLAMF7 (lower limit of quantitation, 271 ng/mL).

(d) The measurement method using [redacted], [redacted], and elotuzumab (lower limit of quantitation, 3.04 μg/mL).

The applicant explained the effects of elotuzumab in samples on the measurement of anti-elotuzumab antibody as follows:

The upper limit of the concentration of elotuzumab in serum which is known to have no influence on the measurement of anti-elotuzumab antibodies is 4.5 and 400 μg/mL for Methods (a) and (b) above, respectively. Given that in the clinical studies in which Methods (a) and (b) were used, the highest serum concentrations of elotuzumab at the time of measurements of anti-elotuzumab antibody were 436 and 1052 μg/mL, respectively, the possibility that measurements of anti-elotuzumab antibody were affected by elotuzumab in serum cannot be ruled out in either of the methods.

6.1.2 Changes in manufacturing processes of the drug substance and drug product during development

During the development stage, the manufacturing process of the drug substance was changed [see Section 2.1.4]. Table 7 shows manufacturing methods of formulations used in the clinical studies which were submitted in the application for approval.

Following changes in the manufacturing methods, from Method A up to the proposed method, the comparability of the quality attributes were evaluated, and the comparability of the drug substances were verified before and after each change [see Section 2.1.4].

Table 7. Manufacturing methods of formulations used in the clinical studies

Manufacturing method of drug substance	Study
A	Foreign phase I study (Study HuLuc63-1701), foreign phase I study (Study HuLuc63-1702)
B	Foreign phase I study (Study HuLuc63-1701), foreign phase I study (Study HuLuc63-1702), foreign phase Ib/II study (Study HuLuc63-1703)
C	Foreign phase I study (Study HuLuc63-1702), foreign phase Ib/II study (Study HuLuc63-1703), Japanese phase I study (Study CA204005)
C.1	International phase III study (Study CA204004), foreign phase Ib study (Study CA204007), foreign phase II study (Study CA204009), and foreign phase II study (Study CA204011)
Proposed method	Japanese phase I study (Study CA204005), foreign phase Ib study (Study CA204007), foreign phase II study (Study CA204009), foreign phase II study (Study CA204011)

6.2 Clinical pharmacology studies

The PK of elotuzumab in patients with MM was evaluated for elotuzumab monotherapy, combination therapy of elotuzumab with BTZ, the ELd regimen, and the elotuzumab, bortezomib, and dexamethasone (EBd) regimen.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study CA204005 [started in February 2011, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (n = 7, of these subjects, 6 subjects were included in the pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. In 28-day cycles, subjects received (1) intravenous doses of elotuzumab at 10 or 20 mg/kg *quaque* 1 week (QW) for Cycles 1 and 2, followed by *quaque* 2 weeks (Q2W) in subsequent cycles; (2) oral doses of lenalidomide 25 mg *quaque die* (QD) on Days 1 to 21; and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg), and the concentrations of elotuzumab in serum were evaluated.

Table 8 shows pharmacokinetic parameters of elotuzumab at 10 or 20 mg/kg. Over the dose range studied, the C_{max} and minimum serum concentration (C_{min}) increased slightly more than the dose-proportional amount in Cycles 1 and 2, and definitely more than the dose-proportional amount in Cycle 3.

Among 6 subjects tested for anti-elotuzumab antibodies, 3 subjects (50.0%) were found to have anti-elotuzumab antibodies in serum. Measurement of anti-elotuzumab neutralizing antibodies was not performed.

Table 8. Pharmacokinetic parameters of elotuzumab

Cycle	Measured date (Day)	Dose (mg/kg)	C_{max} (μg/mL)	C_{min} (μg/mL)
1	1	10	173 (9)	–
		20	376 (14)	–
	8	10	237 (19)	59 (28)
		20	549 (18)	165 (20)
	15	10	297 (10)	97 (12)
		20	652 (21)	252 (30)
	22	10	234 (14)	25 (87)
		20	521, 1004	175, 448
2	1	10	240 (28)	26 (95)
		20	671 (51)	240, 631
	22	10	270 (32)	58 (82)
		20	844 (26)	547 (41)
3	1	10	286 (32)	77 (78)
		20	972 (32)	579 (46)
	15	10	–	59 (78)
		20	–	466 (38)

Geometric mean (coefficient of variation, %), n = 3 (individual values for n = 2), –, not applicable

6.2.2 International studies

6.2.2.1 International phase III study (CTD 5.3.5.1-1, Study CA204004 [started in June 2011, ongoing, data cut-off on October 29, 2014])

An open-label, randomized study was conducted in patients with relapsed or refractory MM (n = 646, of these subjects, 318 subjects were included in the pharmacokinetic analysis set) to evaluate the efficacy and safety of elotuzumab. In 28-day cycles, subjects in the ELd regimen group received (1) intravenous doses of elotuzumab at 10 mg/kg QW for Cycles 1 and 2, and Q2W for subsequent cycles; (2) oral doses of lenalidomide 25 mg QD on Days 1 to 21; and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg, instead of an oral dose of DEX 40 mg), and the concentrations of elotuzumab in serum were evaluated.

The results showed that C_{min} (geometric mean [coefficient of variation]) was 72.3 μg/mL (55.3%) and 216 μg/mL (51.2%) on Cycle 1 Day 8 and Cycle 3 Day 1, respectively. The C_{min} (geometric mean [coefficient of variation]) was 204 μg/mL (71.2%) and 194 μg/mL (62.6%) on Cycle 15 Day 1 and Cycle 18 Day 1, respectively.

Among 299 subjects tested for anti-elotuzumab antibodies, 45 subjects (15.1%) were found to have anti-elotuzumab antibodies in serum, and 19 of them had anti-elotuzumab neutralizing antibodies.

6.2.3 Foreign clinical studies

6.2.3.1 Foreign phase I study (CTD 5.3.3.2-2, Study HuLuc63-1701 [November 2006 to July 2009])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (n = 35, of these subjects, 34 subjects were included in the pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. Subjects received a total of 4 intravenous doses of elotuzumab at 0.5, 1, 2.5, 5, 10, or 20 mg/kg Q2W, and the concentrations of elotuzumab in serum were evaluated.

Table 9 shows the pharmacokinetic parameters of elotuzumab. Following administration of the first dose, C_{max} increased roughly in a dose-proportional manner over the dose range studied, and AUC_{inf} increased more than the dose-proportional amount. Also, a decrease in clearance (CL) and a prolongation in apparent terminal half-life ($t_{1/2}$) were observed. The volume of distribution (V_Z) of elotuzumab was about the same as human plasma volume (about 3 L for body weight of 70 kg) (*Pharm Res*. 1993;10:1093-5).

The cumulative coefficient, the ratio of area under the plasma concentration-time curve in one dosing interval (AUC_{tau}) of repeat dose to AUC_{tau} of single dose, tended to increase with increase in dose. The applicant explained that this trend was considered attributable to the trend towards a decrease in CL associated with the increase in dose following repeat-dose administration.

Among 31 subjects tested for anti-elotuzumab antibodies, 12 subjects (38.7%) were found to have anti-elotuzumab antibodies in serum, and 11 of them had anti-elotuzumab neutralizing antibodies.

Table 9. Pharmacokinetic parameters of elotuzumab

Number of doses	Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} *1 (h)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_Z (mL/kg)	Cumulative coefficient*2
1	0.5	3	11.1 (26.4)	1.4 (1.3, 2.9)	523, 771	589, 796	52.8, 62.4	0.85, 0.63	65.8, 56.3	–
	1.0	4	17.0 (27.5)	1.5 (1.5, 1.5)	1799 (63.7)	1425*3 (15.8)	85.2*3 (43.1)	0.70*3 (16.98)	86.3*3 (60.9)	–
	2.5	6	43.7 (26.8)	2.9 (1.5, 4.0)	4725 (52.6)	5317 (61.8)	95.2 (44.4)	0.47 (63.18)	64.7 (40.9)	–
	5.0	4	86.9 (30.0)	5.2 (1.9, 5.2)	14,041*3 (28.4)	13,730	159.3	0.36	83.8	–
	10	3	383.9, 290.8	5.2 (1.5, 5.5)	34,442 (70.6)	37,198, 19,883	108, 110.4	0.27, 0.50	42.3, 80.8	–
	20	14	404.9 (21.7)	4.8 (3.4, 28.3)	64,560*4 (30.2)	105,270, 67,354	180.0, 192.0	0.19, 0.30	52.6, 77.4	–
4	0.5	2	5.7, 9.3	1.4, 5.1	387, 577	–	–	–	51.1, 71.7	0.7, 0.7
	1.0	3	21.5 (77.3)	1.6 (1.5, 3.0)	2256 (128.6)	–	–	–	81.2	1.1 (82.3)
	2.5	3	50.1 (2.1)	1.5 (1.5, 5.1)	6881 (48.1)	–	–	–	60.6, 52.2	1.2 (30.6)
	5.0	3	154.1 (36.7)	5.3 (1.8, 5.4)	46,395, 12,650	–	–	–	46.5	2.5, 1.2
	10	2	242.9, 190.3	5.8, 3.8	47,132, 26,476	–	–	–	53.4, 39.0	1.5, 1.5
	20	8	553.3 (20.0)	3.4 (3.2, 7.2)	124,300*5 (32.1)	–	–	–	38.1*3 (23.0)	1.8*5 (20.5)

Geometric mean (coefficient of variation %) (individual values for n = 1 or 2); –, not calculated; *1, median (range); *2, the ratio of AUC_{tau} of repeat dose to AUC_{tau} of single dose; *3, n = 3; *4, n = 5; and *5, n = 4

6.2.3.2 Foreign phase I/II study (CTD 5.3.3.2-3, Study HuLuc63-1702 [May 2008 to April 2012])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (n = 28, all the 28 subjects were included in the pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. In the phase I part of study, in 21-day cycles, subjects received intravenous doses of elotuzumab at 2.5, 5.0, 10, or 20 mg/kg QD on Days 1 and 11, and intravenous doses of BTZ 1.3 mg/m^2 QD on Days 1, 4, 8, and 11, and the concentrations of elotuzumab in serum were evaluated.

Table 10 shows the pharmacokinetic parameters of elotuzumab. In Cycles 1 and 4, C_{max} and AUC increased more than the dose-proportional amount in the dose range of 2.5 to 10 mg/kg, and roughly in a dose-proportional manner in the dose range of 10 to 20 mg/kg. Also, a decrease in CL and an increase in $t_{1/2}$ were observed with increase in dose.

Among 28 subjects tested for anti-elotuzumab antibodies, 5 subjects (17.9%) were found to have anti-elotuzumab antibodies in serum, and all 5 subjects had anti-elotuzumab neutralizing antibodies.

Table 10. Pharmacokinetic parameters of elotuzumab

Measuring time point	Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC*2 (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
Cycle 1 Day 1	2.5	3	38.5 (12.6)	2.9 (0.8, 3.0)	3906 (21.8)	4859 (39.3)	92 (48.0)	0.515 (37.7)	68.4 (13.6)
	5.0	3	95.3 (15.2)	3.0 (1.5, 5.4)	9640 (28.4)	12,111 (31.8)	107 (31.8)	0.413 (38.9)	63.8 (27.5)
	10	3	266.6 (4.6)	4.1 (3.6, 5.3)	32,926 (11.6)	49,347 (8.9)	140 (8.1)	0.203(9.1)	41.0 (10.0)
	20	19	485.2 (29.6)	4.5 (0, 6.6)	56,605*3 (43.2)	95,029*3 (44.3)	176*3 (33.9)	0.211*3 (39.6)	53.6*3 (32.2)
Cycle 4 Day 11	2.5	3	47.2 (26.8)	1.7 (1.5, 3.0)	10,936	–	–	–	–
	5.0	1	152.3	1.9	23,224	–	–	–	–
	10	2	512.4, 811.2	6.5, 6.9	110,258, 136,436	–	–	–	–
	20	12	980.2 (34.9)	3.5 (2.0, 240.0)	208,600*4 (50.6)	–	–	–	–

Geometric mean (coefficient of variation, %) (individual values for n = 1 or 2); –, not calculated; *1, median (range); *2, AUC_{last} on Cycle 1 Day 1, AUC_{tau} on Cycle 4 Day 11; *3, n = 16; *4, n = 7

The applicant explained the reason for the nonlinearity observed for part of the pharmacokinetic parameters of elotuzumab in the Japanese phase I (CA204005), foreign phase I (HuLuc63-1701), and foreign phase I/II (HuLuc63-1702) studies as follows:

Presumably, elotuzumab is eliminated in a process mediated by *in vivo* binding to the target antigen and in another process which is not dependent on the target antigen. It is considered that as the dose of elotuzumab increased, the target-binding-mediated elimination process was saturated, causing the decline in CL, which resulted in prolongation of $t_{1/2}$ and greater-than-proportional increases in exposure (e.g., C_{max} and AUC_{last}*).

* area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration

6.2.3.3 Foreign phase Ib/II study (CTD 5.3.5.2-1, Study HuLuc63-1703 [started in August 2008, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed MM (n = 102, of these subjects, 28 subjects in the phase Ib part, and 73 subjects in the phase II part were included in the pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. In 28-day cycles, subjects received (1) intravenous doses of elotuzumab 5, 10, or 20 mg/kg in the phase Ib part of study and 10 or 20 mg/kg in the phase II part of study, QW in Cycles 1 and 2 and Q2W in subsequent cycles for both parts of study; (2) oral doses of lenalidomide 25 mg QD on Days 1 to 21; and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of

DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg), and the concentrations of elotuzumab in serum were evaluated.

The results showed that the C_{min}[1] of elotuzumab at 5 mg/kg was 64 to 139 μg/mL and 65 to 87 μg/mL in Cycles 1 to 2 and subsequent cycles, respectively; the C_{min}[1] at 10 mg/kg was 124 to 214 μg/mL and 167 to 196 μg/mL in Cycles 1 to 2 and the subsequent cycles, respectively; and the C_{min}[1] at 20 mg/kg was 331 to 526 μg/mL and 332 to 401 μg/mL in Cycles 1 to 2 and subsequent cycles, respectively.

Among 99 subjects tested for anti-elotuzumab antibodies, 11 subjects (11.1%) were found to have anti-elotuzumab antibodies in serum, and all of them had anti-elotuzumab neutralizing antibodies.

6.2.3.4 Foreign phase II study (CTD 5.3.5.1-2, Study CA204009 [started in January 2012, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, randomized, controlled study was conducted in patients with relapsed or refractory MM (n = 152, of these subjects, 75 subjects were included in the pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. Each cycle consisted of 21 days for Cycles 1 to 8 and 28 days for the subsequent cycles. Subjects received (1) intravenous doses of elotuzumab 10 mg/kg QD on Days 1, 8, and 15 in Cycles 1 and 2, on Days 1 and 11 in Cycles 3 to 8, and on Days 1 and 15 in subsequent cycles; (2) intravenous or subcutaneous doses of BTZ 1.3 mg/m^2 QD on Days 1, 4, 8, and 11 in Cycles 1 to 8, and on Days 1, 8, and 15 in subsequent cycles; and (3) oral doses of DEX 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 15 in Cycles 1 and 2; on Days 1, 2, 4, 5, 8, 9, 11, and 12 in Cycles 3 to 8; and on Days 1, 2, 8, 9, 15, and 16 in subsequent cycles (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 8 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 20 mg), and the concentrations of elotuzumab in serum were evaluated.

The results showed that the C_{min}[1] of elotuzumab was 148 to 254 μg/mL, 228 to 284 μg/mL, and 290 to 339 μg/mL in Cycles 1 to 2, Cycles 3 to 8, and Cycle 9 and after, respectively.

Among 72 subjects tested for anti-elotuzumab antibodies, 20 subjects (27.8%) were found to have anti-elotuzumab antibodies. Measurement of anti-elotuzumab neutralizing antibodies was not performed.

6.2.3.5 Foreign phase II study (CTD 5.3.4.2-1, Study CA204011 [February 2012 to May 2014])

An open-label, uncontrolled study was conducted in patients with high-risk smoldering MM (n = 41, of these subjects, 31 subjects were included in pharmacokinetic analysis set) to evaluate the PK and other aspects of elotuzumab. In 28-day cycles, subjects received (1) intravenous doses of elotuzumab 10 mg/kg, QW in Cycles 1 and 2 followed by Q2W in subsequent cycles; or (2) intravenous doses of elotuzumab 20 mg/kg on Days 1 and 8 in Cycle 1 and on Day 1 in subsequent cycles, and the concentrations of elotuzumab in serum were evaluated.

[1] The minimum and maximum values of geometric mean for each cycle.

The results showed that at 10 mg/kg, the C_{min}[1] was 78 to 247 μg/mL and 76 to 275 μg/mL in Cycles 1 to 2 and the subsequent cycles, respectively, and at 20 mg/kg, the C_{min}[1] was 85 to 155 μg/mL and 32 to 73 μg/mL in Cycles 1 to 2 and the subsequent cycles, respectively.

Among 29 subjects tested for anti-elotuzumab antibodies, 12 subjects (41.4%) were found to have anti-elotuzumab antibodies in serum. Measurement of anti-elotuzumab neutralizing antibodies was not performed.

6.2.4 Foreign phase Ib study in MM patients with renal impairment (CTD 5.3.3.3-1, Study CA204007 [January 2012 to March 2014, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with MM (n = 26, and all the 26 subjects were included in the pharmacokinetic analysis set) to evaluate the effects of renal impairment on the pharmacokinetic parameters and other aspects of elotuzumab. In 28-day cycles, subjects received (1) intravenous doses of elotuzumab 10 mg/kg on Day 1 in Cycle 1, on Days 1, 8, 15, and 22 in Cycles 2 and 3, and on Days 1 and 15 in subsequent cycles; (2) oral doses of lenalidomide at a dose level which was determined based on the creatinine clearance (CrCL) on Day 1 of each cycle, QD on Days 1 to 21 (for patients with severe renal impairment [SRI], 15 mg every 48 hours); and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg), and the concentrations of elotuzumab in serum were evaluated.

Table 11 shows the pharmacokinetic parameters of elotuzumab in patients with renal impairment. The results suggest no statistically significant differences in C_{max}, AUC_{inf}, and other pharmacokinetic parameters of elotuzumab between the normal renal function (NRF) group and the SRI or end-stage renal disease (ESRD) group.

Further, the concentration of elotuzumab in serum in patients with ESRD was measured before and after hemodialysis performed 24 hours after administration on Cycle 1 Day 1 to evaluate the effects of hemodialysis on the pharmacokinetic parameters of elotuzumab. The geometric mean (coefficient of variation) of the concentration of elotuzumab in serum was 147 μg/mL (32%) before dialysis and 167 μg/mL (34%) after dialysis, showing no significant difference in the concentration of elotuzumab in serum before and after hemodialysis.

Among 16 subjects tested for anti-elotuzumab antibodies, 4 subjects (25.0%) were found to have anti-elotuzumab antibodies in serum. Measurement of anti-elotuzumab neutralizing antibodies was not performed.

Table 11. Pharmacokinetic parameters of elotuzumab in MM patients with renal impairment (Cycle 1 Day 1)

Renal function[*1]	n	C_{max} (mg/kg)	t_{max}[*2] (h)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_Z (mL/kg)
NRF	8	217 (24)	3.2 (2.9, 4.9)	39,559 (28)	46,401 (39)	147.3 (66)	0.215 (46)	59.4 (30)
SRI	7	226 (10)	3.9 (2.8, 6.8)	50,080 (20)	60,255 (31)	218.2 (46)	0.166 (28)	54.6 (20)
ESRD	8	218 (21)	3.3 (2.8, 25.9)	45,937 (31)	51,227 (39)	190.8 (45)	0.195 (54)	61.2 (43)

Geometric mean (coefficient of variation, %); *1, NRF, patients with normal renal function, with CrCL ≥90 mL/min; SRI, patients with severe renal impairment, with CrCL <30 mL/min, not requiring hemodialysis; ESRD, patients with end-stage renal function requiring hemodialysis; *2, median (range)

Based on the above results and the following points, the applicant considers that it is unlikely that lowered renal function has any effect on the pharmacokinetics of elotuzumab.

- It is thought that elotuzumab is eliminated in a process mediated by target-antigen binding and in another process not dependent on the target antigen; therefore, it is unlikely that lowered renal function has any effect on the elimination of elotuzumab.
- It is considered that elotuzumab is not eliminated by renal excretion because of the macromolecular structure (molecular weight, about 144,000).
- Based on the results of population pharmacokinetics (PPK) analysis, estimated glomerular filtration rate (eGFR) was not selected as a significant covariate for the pharmacokinetic parameters of elotuzumab [see Section 6.2.6].

6.2.5 Relationships between exposure and QT/QTc interval change

The relationships between ΔQTcF and the serum concentration of elotuzumab were investigated in a foreign phase II study (CA204011) by linear mixed-effects modeling. The results showed that no clear relationships exist between the serum concentration of elotuzumab and ΔQTcF. The upper limit of the 90% confidence interval (CI) for the mean change of ΔQTcF was below 10 msec over the serum concentration range of elotuzumab studied.

Based on the above results, the applicant explained that, when an intravenous dose of elotuzumab is administered at 10 or 20 mg/kg, it is unlikely that elotuzumab causes QT/QTc interval prolongation.

6.2.6 Population pharmacokinetic analysis

A PPK model was created by non-linear mixed-effects modeling (software program, *NONMEM* Ver. 7.3.0) using pharmacokinetic data for elotuzumab (375 subjects, 6958 measuring time points) obtained from the following 4 studies: a Japanese phase I study (CA204005), a global phase III study (CA204004), a foreign phase Ib study (CA204007), and a foreign phase II study (CA204011). Then, after integrating pharmacokinetic data (74 subjects, 476 measuring time points) from a foreign phase II study (CA204009), a population pharmacokinetic (PPK) analysis was performed. The PK of elotuzumab was described using a 2-compartment model with zero-order absorption, first-order elimination from the central compartment, Michaelis-Menten elimination, and target-mediated elimination from the peripheral compartment.

In the analysis, the following covariates were tested for their effects on (1) CL, (2) central volume of distribution (VC), and (3) maximum rate of Michaelis-Menten elimination (V_{max}): (1) sex, ethnicity (Asian or non-Asian), severity of hepatic impairment,[2] β2 microglobulin, serum M-protein, Eastern Cooperative Oncology Group (ECOG) performance status (PS), body weight, lenalidomide hydrate and

[2] Assessed in accordance with the hepatic function classification by NCI-ODWG.

dexamethasone (Ld) coadministration, age, albumin, eGFR, and lactate dehydrogenase (LDH); (2) body weight, sex, ethnicity (Asian or non-Asian), and β2 microglobulin; and (3) serum M-protein. As a result of the analysis, the following were selected as significant covariates: (1) body weight and Ld coadministration (for CL), (2) body weight, sex, ethnicity (Asian or non-Asian), and β2 microglobulin (for VC), and (3) serum M-protein (for V_{max}).

The applicant explained the effects of the covariates on CL, VC, and V_{max} of elotuzumab as follows:

- Regarding the effect of body weight, given that it was inferred that the CL and VC of elotuzumab would increase with increase in body weight, dosing based on body weight is considered to be appropriate.
- It was estimated that compared with elotuzumab monotherapy, the CL (geometric mean) of elotuzumab would decrease by 45%, and the maximum serum concentration at steady state ($C_{min, ss}$), maximum serum concentration at steady state ($C_{max, ss}$), area under the plasma concentration-time curve at steady state (AUC_{ss}), and average serum concentration at steady state ($C_{avg, ss}$) (geometric means) would increase by 80%, 13%, 40%, and 40%, respectively.
- Exposure to elotuzumab was evaluated for each quartile on the basis of baseline serum M-protein concentrations. For patients in the highest quartile, the $C_{avg, ss}$, $C_{max, ss}$, and $C_{min, ss}$ of elotuzumab were lower than those for patients in the lowest quartile by 39%, 32%, and 46%, respectively. A possible explanation for this result is as follows: Given that serum M-protein is secreted by tumor cells, it is suspected that the higher the serum M-protein concentrations, the higher the tumor burden in the body. Therefore, as the tumor burden increased, the rate of elimination mediated by binding to the target antigen of elotuzumab is considered to have increased, lowering the exposure to elotuzumab.
- Given that the effects of sex, ethnicity (Asian or non-Asian), and β2 microglobulin on the VC of elotuzumab were about the same as the inter-individual variation (19.9%), it is considered that the effects of these covariates on the PK of elotuzumab are limited.

6.2.7 Relationship between elotuzumab exposure and efficacy/safety

The relationship between exposure to elotuzumab and efficacy/safety was investigated based on the data obtained from the global phase III study (Study CA204004).

6.2.7.1 Relationship between elotuzumab exposure and efficacy

The relationship between exposure to elotuzumab ($C_{avg, ss}$[3]) and progression-free survival (PFS) was investigated by the Cox proportional hazard model. The results showed that a significant relationship exists between $C_{avg, ss}$ and PFS, suggesting that an increase in $C_{avg, ss}$ is associated with PFS prolongation (hazard ratio [95% CI]: 0.9985 [0.9979, 0.9991]).

The results of PPK analysis suggested that patients with higher baseline serum M-protein concentrations have higher V_{max} and lower exposure to elotuzumab [see Section 6.2.6]. Based on the results, the

[3] The mean concentration of elotuzumab in serum at steady state, estimated by PPK analysis [see Section 6.2.6]

applicant explained that the relationship between exposure to elotuzumab and PFS is likely confounded by baseline M-protein concentrations

6.2.7.2 Relationship between elotuzumab exposure and safety

The relationships of exposure to elotuzumab (C_{avg}[4]) and the incidence of adverse events of Grade 3 or greater, or adverse events that led to treatment discontinuation or death were analyzed by the Cox proportional hazard model. There was no trend that the incidence of Grade ≥3 adverse events or adverse events that led to treatment discontinuation or death increased due to high C_{avg} of elotuzumab (hazard ratio [95% CI]: 0.9999 [0.9992, 1.0000] and 0.9984 [0.9974, 0.9995], respectively).

6.2.8 Effects of hepatic impairment

No clinical studies have been conducted to investigate the PK of elotuzumab in patients with hepatic impairment.

Based on the following reasons, the applicant explained that it is unlikely that deterioration of hepatic function affects the PK of elotuzumab.

- It is unlikely that deterioration in hepatic function affects the elimination of elotuzumab, because it is considered that elotuzumab is eliminated in a process mediated by binding to the target antigen and in another process which is not dependent on the target antigen.
- Hepatic function (hepatic function classification by National Cancer Institute [NCI] Organ Dysfunction Working Group [ODWG]) was not selected as a significant covariate for the pharmacokinetic parameters of elotuzumab by PPK analysis [see Section 6.2.6].

6.R Outline of the review by PMDA

6.R.1 Pharmacokinetic interactions with lenalidomide or DEX

The applicant explained the pharmacokinetic interactions between elotuzumab and lenalidomide or DEX as follows:

Elotuzumab is an antibody drug, and therefore not considered to directly inhibit or induce drug-metabolizing enzymes and transporters. Because of this and other reasons, it is unlikely that elotuzumab affects the PK of lenalidomide and DEX in the ELd regimen. However, based on the following points, DEX may affect the PK of elotuzumab in the ELd regimen:

- The results of a comparison of concentrations of elotuzumab in serum indicated the following: the C_{min} decreased by 10% on Day 1 of Cycle 4 and increased by 17%, 71%, and 50% on Day 1 of Cycles 6, 9, and 12, respectively, in the ELd regimen of the Japanese phase I study (CA204005) and global phase III study (CA204004), compared with the C_{min} values for elotuzumab

[4] The mean concentration of elotuzumab in serum during the dosing interval at the onset of an adverse event, estimated by PPK analysis [see Section 6.2.6]

monotherapy in the foreign phase II study (CA204011).

- The results of the PPK analysis suggest that the CL of elotuzumab will decrease by 45% in the ELd regimen compared to elotuzumab monotherapy [see Section 6.2.6].
- It has been reported that drugs with immunosuppressive action cause effects on CL of antibody drugs (*AAPS J*. 2011;13:405-16).

PMDA's view:

It is difficult to draw firm conclusions regarding the pharmacokinetic interactions between elotuzumab and lenalidomide or DEX, because no pharmacokinetic interaction studies for the ELd regimen have been conducted. Therefore, information should be gathered continuously including published studies, and whenever new knowledge on the pharmacokinetic interactions of the ELd regimen becomes available, information needs to be provided to healthcare professionals in an appropriate manner.

6.R.2 Differences in PK of elotuzumab between Japanese and non-Japanese populations

The applicant explained the differences in the PK of elotuzumab between Japanese and non-Japanese populations as follows:

Table 12 shows the pharmacokinetic parameters of elotuzumab at 10 mg/kg in the Japanese phase I study (CA204005) and global phase III study (CA204004).

Table 12. The concentrations of elotuzumab in serum at elotuzumab 10 mg/kg (μg/mL)

	n	C_{max} (Cycle 1 Day 1)	n	C_{min} (Cycle 3 Day 1)	n	C_{min} (Cycle 4 Day 1)
Japanese*	34	198 (23)	32	227 (47)	31	182 (47)
Non-Japanese	271	195 (50)	238	224 (51)	241	158 (60)

Geometric mean (coefficient of variation, %); *, Japanese patients in Studies CA204005 and CA204004

Table 13 shows the estimated values of pharmacokinetic parameters following repeated intravenous administration of elotuzumab at 10 mg/kg to Japanese and non-Japanese patients after an estimation according to the final model obtained from the PPK analysis [see Section 6.2.6].

Table 13. Estimated values of pharmacokinetic parameters following repeated intravenous administration of elotuzumab 10 mg/kg

	n	$C_{min, ss}$ (μg/mL)	$C_{max, ss}$ (μg/mL)	$C_{avg, ss}$ (μg/mL)	AUC_{ss} (μg·h/mL)
Japanese	37	213 (47)	419 (30)	285 (39)	95,760 (39)
Non-Japanese	307	191 (53)	404 (34)	269 (43)	90,240 (43)

Geometric mean (coefficient of variation, %)

Based on the above results, it is considered that there are no marked differences in the pharmacokinetics of elotuzumab between Japanese and foreign populations.

PMDA's view:

Regarding the differences in the PK of elotuzumab between Japanese and non-Japanese populations following the administration of elotuzumab based on the proposed dosage and administration, the actual

data currently available for comparison are those of C_{max} and C_{min} only. With these data, it is difficult to make a definitive assessment of the difference between Japanese and non-Japanese populations; however, based on the submitted data, there appear to be no trends indicating obvious differences between the populations.

6.R.3 Effects of anti-elotuzumab antibodies on the PK of elotuzumab

The applicant explained the effects of anti-elotuzumab antibodies on the PK of elotuzumab as follows:

The effects of anti-elotuzumab antibodies on the PK of elotuzumab were evaluated based on the results from Studies CA204005, CA204004, CA204007, and CA204009, in which the ELd or EBd regimen was administered and Method (b) was used for the measurement of anti-elotuzumab antibodies [see Section 6.1.1.2]. Among 390 subjects[5] who were evaluable for anti-elotuzumab antibodies, 72 subjects (18.5%) were found to have anti-elotuzumab antibodies in serum after administration of elotuzumab. In CA204004, in which measurements of anti-elotuzumab neutralizing antibodies were performed, among the 45 subjects who tested positive for anti-elotuzumab antibodies in serum, 19 subjects (42.2%) were found to have anti-elotuzumab neutralizing antibodies. In Studies CA204005, CA204007, and CA204009, measurement of neutralizing antibodies was not performed.

Among clinical studies in which the ELd regimen was administered, for Studies CA204004 and CA204005, data on the serum concentrations of elotuzumab in subjects receiving elotuzumab at 10 mg/kg in the corresponding cycles are available (Table 14). At all measurement points for anti-elotuzumab antibodies, the serum concentrations of elotuzumab were lower in subjects who tested positive for anti-elotuzumab antibodies than in those who did not. From the above results, it is possible that anti-elotuzumab antibodies affected the PK of elotuzumab. However, given that the results were possibly confounded by the baseline serum M-protein concentrations, as suggested by the following points, it is difficult to conclude with certainty if anti-elotuzumab antibodies had any effect on the PK of elotuzumab.

- In Studies CA204004 and CA204005, the baseline serum M-protein concentration (median) at elotuzumab 10 mg/kg was higher (2.55 g/dL) in patients who tested positive for anti-elotuzumab antibodies than in those who did not (2.00 g/dL).
- The PPK analysis suggested that patients with higher baseline serum M-protein concentrations had lower elotuzumab exposure levels [see Section 6.2.6].

Table 14. The concentrations of elotuzumab in serum at elotuzumab 10 mg/kg (µg/mL)

Cycle No.	Patients who tested positive for anti-elotuzumab antibodies		Patients who tested negative for anti-elotuzumab antibodies	
	n	C_{min}	n	C_{min}
2	42	37.0 (99.4)	224	169.6 (46.2)
3	39	91.3 (72.0)	213	259.8 (45.1)
4	40	76.4 (77.4)	212	179.8 (55.1)

[5] Subjects whose anti-elotuzumab antibody level was determined at least once before the start of or during the period of elotuzumab treatment.

6	35	106.5 (69.4)	200	181.5 (54.5)
9	28	149.1 (67.2)	163	209.4 (50.0)
12	25	152.2 (71.4)	154	205.1 (52.9)

Geometric mean (coefficient of variation, %)

PMDA's view:

In addition to the above explanation by the applicant, the issue described in the following paragraph also makes it difficult to conclude with certainty if anti-elotuzumab antibodies have any effect on the PK of elotuzumab. Therefore, information should be gathered continuously with regard to the effects of anti-elotuzumab antibodies on the PK of elotuzumab, and whenever new knowledge becomes available, information needs to be provided to healthcare professionals in an appropriate manner.

- The methods employed in Studies CA204005, CA204004, CA204007, and CA204009 have been shown to determine the concentration of anti-elotuzumab antibodies correctly if the serum elotuzumab concentration in the sample is below certain level. This fact suggests that the concentrations of anti-elotuzumab antibody may have been incorrect in cases where the serum elotuzumab concentration in the sample exceeded this level [see Section 6.1.1.2].

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

As the efficacy and safety evaluation data, the results from the studies listed in Table 15 were submitted: a Japanese phase I study, a global phase III study, a foreign phase I study, a foreign phase Ib/II study, and a foreign phase Ib study. The results from 1 foreign phase I study, and 1 foreign phase IIa study, and 2 foreign phase II studies were also submitted as reference data (Table 15).

Table 15. Clinical studies used for the evaluation of efficacy and safety

Data category	Study location	Study	Phase	Population	Number of subjects enrolled	Summary of dosage and administration	Primary endpoints
Evaluation	Japan	CA204005	I	Relapsed or refractory MM	6	In 28-day cycles, subjects received elotuzumab IV at 10 or 20 mg/kg QW for Cycles 1 and 2, followed by Q2W in subsequent cycles; lenalidomide 25 mg PO QD on Days 1 to 21, and DEX 40 mg[*1] PO QW.	Safety PK
	International	CA204004	III	Relapsed or refractory MM	646[*2] (1) 321 (2) 325	(1) ELd: In 28-day cycles, subjects received elotuzumab IV 10 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles; lenalidomide 25 mg PO QD on Days 1 to 21; and DEX 40 mg[*1] PO QW. (2) Ld: In 28-day cycles, subjects received lenalidomide 25 mg PO QD on Days 1 to 21, and DEX 40 mg PO on Days 1, 8, 15, and 22	Efficacy Safety
	Foreign	HuLuc 63-1701	I	Relapsed or refractory MM	35	Subjects received a total of 4 IV doses of elotuzumab Q2W at 0.5, 1, 2.5, 5, 10, or 20 mg/kg	Safety PK
		HuLuc 63-1703	Ib/II	Relapsed MM	102 (1) 29 (2) 73	(1) Phase Ib part: In 28-day cycles, subjects received elotuzumab IV at 5, 10, or 20 mg/kg, QW in Cycles 1 and 2, and Q2W in the subsequent cycles; lenalidomide 25 mg PO QD on Days 1 to 21; and DEX 40 mg[*1] PO QW (2) Phase II part: In 28-day cycles, subjects received elotuzumab IV at 10 or 20 mg/kg, QW in Cycles 1 and 2, and Q2W in the subsequent cycles; lenalidomide 25 mg PO QD on Days 1 to 21; and DEX 40 mg[*1] PO QW	Efficacy Safety
		CA204007	Ib	MM patients (including those with renal impairment)	35	In 28-day cycles, subjects received elotuzumab IV at 10 mg/kg on Day 1 in Cycle 1, on Days 1, 8, 15, and 22 in Cycles 2 and 3, on Days 1 and 15 in Cycle 4 and after; lenalidomide at 5 to 25 mg PO QD (for patients with SRI, 15 mg every 48 hours); and DEX 40 mg[*1] PO QW	Safety PK
Reference	Foreign	HuLuc 63-1702	I	Relapsed or refractory MM	28	In 21-day cycles, subjects received elotuzumab IV at 2.5, 5, 10, or 20 mg/kg on Days 1 and 11; BTZ IV 1.3 mg/m^2 on Days 1, 4, 8, and 11	Efficacy Safety PK
		CA204009	II	Relapsed or refractory MM	152[*2] (1) 77 (2) 75	(1) EBd: in combination with the Bd regimen, in 21-day cycles for Cycles 1 to 8, subjects received elotuzumab IV at 10 mg/kg on Days 1, 8, and 15 in Cycles 1 and 2, on Days 1 and 11 in Cycles 3 to 8; and in 28-day cycles for Cycle 9 and after, elotuzumab IV at 10 mg/kg Q2W (2) Bd: In 21-day cycles for Cycles 1 to 8, subjects received BTZ 1.3 mg/m^2 IV or subcutaneously on Days 1, 4, 8, and 11; DEX 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, and 12; and in 28-day cycles for Cycle 9 and after, BTZ 1.3 mg/m^2 IV or SC QW; and DEX 20 mg PO on Days 1, 2, 8, 9, 15, and 16	Efficacy Safety
		CA204010	IIa	Relapsed or refractory MM	51	In 28-day cycles, subjects received elotuzumab IV at 10 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles; thalidomide 50 mg PO on Days 1 to 14 in Cycle 1, 100 mg on Days 15 to 28, and in Cycle 2 and after, 200 mg QD; DEX 40 mg[*1] PO QW	Safety
		CA204011	II	High-risk smoldering MM	31[*3] (1) 16 (2) 15	(1) 10 mg/kg: In 28-day cycles, subjects received elotuzumab IV at 10 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles (2) 20 mg/kg: In 28-day cycles, subjects received elotuzumab IV at 20 mg/kg on Days 1 and 8 in Cycle 1, on Day 1 in the subsequent cycles	Efficacy Safety

IV, intravenously; PO, *per os* (orally); Bd, bortezomib and dexamethasone; SC, subcutaneously.

*1, On days with elotuzumab treatment, subjects received DEX 28 mg PO, and DEX 8 mg IV, instead of DEX 40 mg PO; *2, number of randomized subjects; and *3, number of subjects treated

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 study (CTD 5.3.3.2-1, Study CA204005 [started in February 2011, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 6 to 12 subjects) in 3 institutions in Japan to investigate the safety and PK of the ELd regimen.

In 28-day cycles, subjects received (1) intravenous doses of elotuzumab at 10 or 20 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles; (2) oral doses of lenalidomide 2.5 mg QD on Days 1 to 21; and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg).

Among 7 subjects enrolled in the dose ascending cohort, 6 subjects (3 subjects each at 10 and 20 mg/kg) who received at least 1 dose of elotuzumab were included in the safety analysis set.

In Cycle 1, the predefined dose limiting toxicity (DLT) assessment period, DLT was not observed and maximum tolerated dose (MTD) was not reached at either dose.

Regarding safety, there were no deaths during the study drug treatment or within 60 days of the end of treatment.

7.1.2 International clinical studies

7.1.2.1 International phase III study (CTD 5.3.5.1-1, Study CA204004 [started in June 2011, ongoing, data cut-off on October 29, 2014])

An open-label, randomized, controlled study was conducted in patients with relapsed or refractory MM (target sample size, 640 subjects) at 168 institutions in 21 countries including Japan to compare the efficacy and safety between the ELd regimen and the Ld regimen.

For the ELd regimen, in 28-day cycles, subjects received (1) intravenous doses of elotuzumab 10 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles; (2) oral doses of lenalidomide 25 mg QD on

Days 1 to 21; and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg). For the Ld regimen, in 28-day cycles, subjects received (1) oral doses of lenalidomide 25 mg QD on Days 1 to 21; and (2) oral doses of DEX 40 mg QW. In both the ELd and Ld regimens, treatment was to be continued until disease progression, or until the subject met the criteria for discontinuation.

All 646 subjects enrolled in the study and randomized (321 and 325 in the ELd and Ld groups) were included in the efficacy analysis set, and 635 of them who received the study drug (318 and 317 in the ELd and Ld groups) were included in the safety analysis set.

At the start of the study, the primary endpoint of the study was PFS as assessed by the independent review committee (IRC) according to the revised response criteria proposed by European Group for Blood and Marrow Transplantation (EBMT)[6]. However, because PFS events occurred late and for other reasons, the protocol was revised on [redacted], 20[redacted], before an interim analysis was performed, and the following changes were made: (1) an interim analysis of PFS should be conducted when 70% of the target number of PFS events (466 events) occurred and the follow-up period of ≥2 years ended to evaluate the efficacy of elotuzumab; and (2) response rate as assessed by the IRC according to the revised EBMT criteria, which was originally the secondary endpoint, should be included in the primary endpoint, and as a result of the addition, the significance levels of PFS and response rate were specified as two-tailed at 4.5% and 0.5%, respectively, for adjustment for multiplicity. Also, to adjust the probability of type I error associated with the interim analysis for PFS, the O'Brien-Fleming type alpha-spending function based on the Lan-DeMets method was to be used.

As is demonstrated by the results of the interim analysis for PFS as assessed by the IRC according to the revised EBMT criteria (Table 16), Kaplan-Meier plot (Figure 2), and the final analytical results for response rate (Table 17), a significant improvement in PFS for the ELd regimen was confirmed; accordingly, discontinuation of the study was recommended by the data monitoring committee held on [redacted], 20[redacted].

Table 16. Results of the interim analysis for PFS
(efficacy analysis set, determined by the IRC, data cut-off on October 29, 2014)

	ELd	Ld
Number of subjects	321	325
Died or progressed (%)	179 (55.8)	205 (63.1)
Median (95% CI) (months)	19.4 (16.6, 22.2)	14.9 (12.1, 17.2)
Hazard ratio*1 (95% CI)	0.70 (0.57, 0.85)	
P-value (two-sided)*2	0.0004	

*1, A stratified Cox proportional hazard model with the following stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); *2, stratified log-rank test, with the stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); two-sided significance level, 0.0239

[6] Criteria formulated by adding sCR and VGPR, which are the categories established by the IMWG (*Leukemia*. 2006;20:1467-73), to the EBMT criteria (*Br J Haematol.* 1998;102:1115-23)

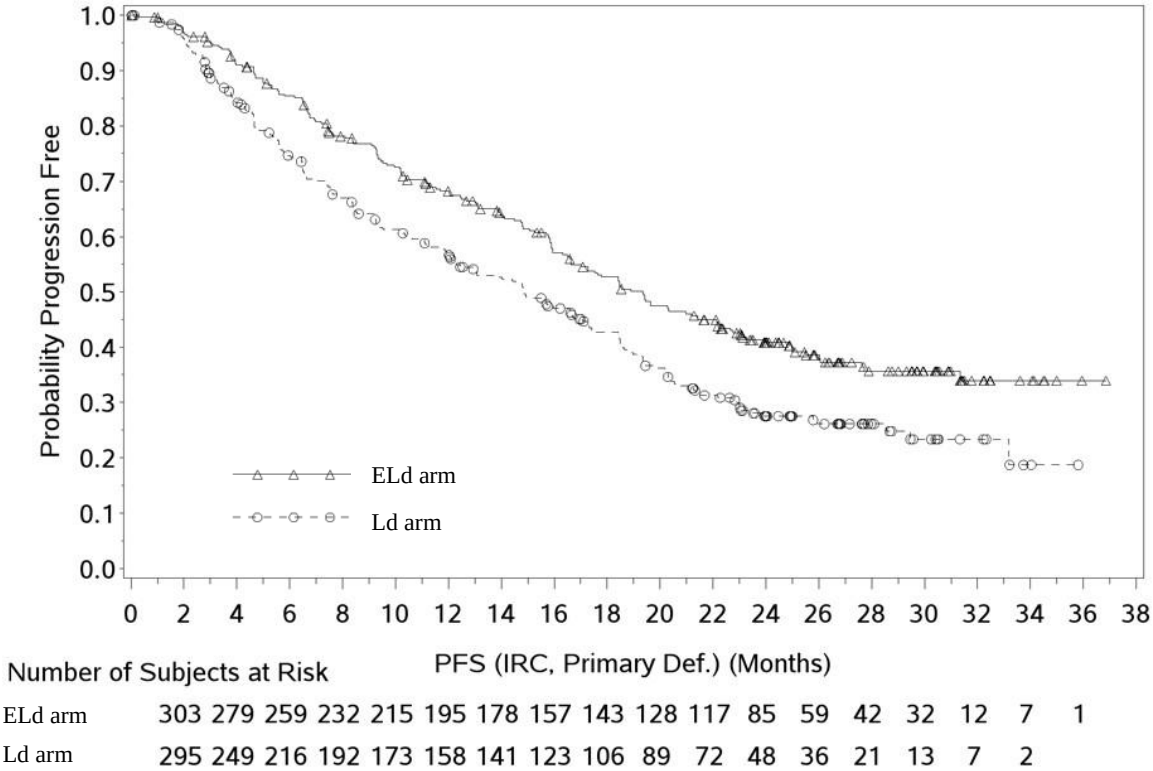

Figure 2. Kaplan-Meier plot of PFS in the interim analysis (efficacy analysis set, assessed by IRC, data cut-off on October 29, 2014)

Table 17. Best overall response and response rate (efficacy analysis set, determined by the IRC, data cut-off on October 29, 2014)

Best overall response	Number of subjects (%)	
	ELd 321 subjects	Ld 325 subjects
Stringent complete response (sCR)	9 (2.8)	5 (1.5)
Complete response (CR)	5 (1.6)	19 (5.8)
Very good partial response (VGPR)	91 (28.3)	67 (20.6)
Partial response (PR)	147 (45.8)	122 (37.5)
Minimal response (MR)	22 (6.9)	33 (10.2)
Stable disease (SD)	30 (9.3)	54 (16.6)
Progressive disease (PD)	8 (2.5)	8 (2.5)
Not evaluable (NE)	9 (2.8)	17 (5.2)
Response (sCR, CR, VGPR, or PR)	252	213
Response rate (%) (95% CI)	78.5% (73.6, 82.9)	65.5% (60.1, 70.7)
Odds ratio (95% CI)	1.94 (1.36, 2.77)	
P-value (two-sided)*	0.0002	

*, Cochran-Maentel-Haenszel test, stratified with β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); two-sided significance level, 0.005

During study drug treatment or within 60 days of the end of treatment, deaths occurred in 31 of 318 subjects (9.7%) in the ELd arm, and 39 of 317 subjects (12.3%) in the Ld arm. Besides disease progression (15 subjects in the ELd arm and 20 subjects in the Ld arm), causes of death were as follows: in the ELd arm, pneumonia (2 subjects), sepsis (2), meningitis staphylococcal (1), lung disorder (1), septic shock (1), influenza (1), gastrointestinal neoplasm (1), lower respiratory tract infection (1), pulmonary embolism (1), completed suicide (1), prerenal failure (1), lung neoplasm malignant (1), aortic aneurysm rupture (1), and unknown (1); in the Ld arm, general physical health deterioration (3), sepsis

(3), pneumocystis jirovecii pneumonia (1), pulmonary embolism (1), peritonitis (1), myocardial ischaemia/bronchopneumonia (1), road traffic accident/craniocerebral injury (1), encephalopathy (1), cardiac arrest (1), myocardial infarction (1), septic shock (1), cerebral haemorrhage (1), intestinal haemorrhage (1), malignant neoplasm of unknown primary site (1), and unknown (1). Among these events, a causal relationship to the study drug could not be ruled out for influenza (1), gastrointestinal neoplasm (1), lower respiratory tract infection (1), and pulmonary embolism (1) in the ELd arm; and sepsis (2), pneumocystis jirovecii pneumonia (1), pulmonary embolism (1), and peritonitis (1) in the Ld arm.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.3.2-2, Study HuLuc63-1701 [November 2006 to July 2009])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 18 to 42 subjects) at 11 institutions outside Japan to evaluate the safety and PK of elotuzumab.

Subjects received a total of 4 intravenous doses of elotuzumab at 0.5, 1, 2.5, 5, 10, or 20 mg/kg Q2W, and treatment was to be continued until disease progression or until the subject met the criteria for discontinuation on Day 52 or 56.

Among 35 subjects enrolled in the dose ascending cohort of the study, 34 subjects (3 at 0.5 mg/kg, 4 at 1 mg/kg, 6 at 2.5 mg/kg, 4 at 5 mg/kg, 3 at 10 mg/kg, and 14 at 20 mg/kg) were included in the safety analysis set.

In Cycle 1, the predefined DLT assessment period, DLT was observed in 1 of 6 subjects (Grade 3 blood creatinine increased) in the 2.5 mg/kg arm and 1 of 14 subjects (Grade 3 hypersensitivity) in the 20 mg/kg arm; however, MTD was not reached.

Deaths during treatment or within 60 days of the end of elotuzumab treatment occurred in 4 of 34 subjects (11.8%). The cause of death except disease progression (1 at 0.5 mg/kg, 1 at 5 mg/kg, and 1 at 20 mg/kg) was renal failure in 1 subject at 5 mg/kg, for which a causal relationship to elotuzumab was ruled out.

7.1.3.2 Foreign phase Ib/II study (CTD 5.3.5.2-1, Study HuLuc63-1703 [started in August 2008, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed MM (target sample size, 30 subjects at maximum in the phase Ib part, and about 70 subjects in the phase II part of the study) at 17 institutions outside Japan to evaluate the efficacy and safety of the ELd regimen.

In 28-day cycles, subjects received (1) intravenous doses of elotuzumab at 5, 10, or 20 mg/kg (phase Ib part), and intravenous doses of elotuzumab at 10 or 20 mg/kg (phase II part), QW in Cycles 1 and 2, and Q2W in the subsequent cycles; (2) oral doses of lenalidomide 25 mg QD on Days 1 to 21; and (3) oral

doses of DEX 40 mg QW (phase Ib part), and oral doses of DEX 40 mg QW (phase II part) (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg). The treatment was to be continued until disease progression or whenever the subject meets criteria for discontinuation.

The efficacy analysis set was the intent-to-treat (ITT) population, consisting of all 73 subjects enrolled in the phase II part of the study (36 at 10 mg/kg, and 37 at 20 mg/kg). Also, among 29 subjects enrolled in the phase Ib part of the study, 28 subjects who received the study drug (3 at 5 mg/kg, 3 at 10 mg/kg, and 22 at 20 mg/kg) and all 73 subjects enrolled in the phase II part of the study were included in the safety analysis set.

Table 18 shows the response rate[7] as assessed by the investigator according to the diagnostic criteria proposed by the International Myeloma Working Group (IMWG).

Table 18. Best overall response and response rate
(ITT population, determined by the investigator, data cut-off on [redacted])

Best overall response	Number of subjects (%)	
	10 mg/kg 36 subjects	20 mg/kg 37 subjects
Stringent complete response (sCR)	2 (5.6)	1 (2.7)
Complete response (CR)	4 (11.1)	3 (8.1)
Very good partial response (VGPR)	17 (47.2)	14 (37.8)
Partial response (PR)	10 (27.8)	10 (27.0)
No confirmed response*	3 (8.3)	9 (24.3)
Response (sCR, CR, VGPR, or PR)	33	28
Response rate (%) (95% CI)	91.7% (77.5, 98.2)	75.7% (58.8, 88.2)

*, Confirmed response requires the same or improved response to be confirmed by 2 consecutive assessments, and cases where the criteria are not met are defined here as "No confirmed response."

In Cycle 1 of the phase Ib part, the predefined DLT assessment period, DLT was not observed in any treatment group, and MTD was not reached.

During the study drug treatment or within 60 days of the end of treatment, deaths occurred in 1 of 28 subjects (3.6%) in the phase Ib part, and 3 of 73 subjects (4.1%) in the phase II part. The causes of death were: in the phase Ib part, gastrointestinal perforation/metabolic acidosis (1 subject) at 10 mg/kg; and in the phase II part, sepsis (1) at 10 mg/kg, and sepsis/cellulitis/pneumonia/multi-organ failure (1) and renal failure (1) at 20 mg/kg, and a causal relationship to the study drug was ruled out for all of these cases.

[7] The percentage of subjects assessed as sCR, CR, VGPR, or PR for the best overall response

7.1.3.3 Foreign phase Ib study (CTD 5.3.3.3-1, Study CA204007 [January 2012 to March 2014, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with MM (target sample size, 8 subjects each in the NRF, SRI, and ESRD arms[8]) at 8 institutions outside Japan to evaluate the safety and PK of the ELd regimen.

In 28-day cycles, subjects received (1) intravenous doses of elotuzumab 10 mg/kg on Day 1 in Cycle 1, and on Days 1, 8, 15, and 22 in Cycles 2 and 3, and on Days 1 and 15 in Cycle 4 and after; (2) oral doses of lenalidomide at a dose level which was determined based on the CrCL on Day 1 of each cycle, QD on Days 1 to 21 (for patients with SRI, 15 mg every 48 hours); and (3) oral doses of DEX 40 mg QW (only on days when elotuzumab treatment was given, subjects received an oral dose of DEX 28 mg and an intravenous dose of DEX 8 mg instead of an oral dose of DEX 40 mg).

Among 35 subjects enrolled in the study, 26 subjects who received the study drug (8 in the NRF, 9 in the SRI, and 9 in the ESRD arms) were included in the safety analysis set.

There were no deaths during the study drug treatment or within 60 days of the end of treatment.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase I study (CTD 5.3.3.2-3, Study HuLuc63-1702 [May 2008 to April 2012])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 15 to 42 subjects) at 7 institutions outside Japan to evaluate the efficacy, safety, and PK of the EBd regimen.

All 28 subjects enrolled in the study were included in the safety analysis set.

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

7.2.1.2 Foreign phase II study (CTD 5.3.5.1-2, Study CA204009 [started in January 2012, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, randomized, controlled study was conducted in patients with relapsed or refractory MM (target sample size, 150 subjects) at 53 institutions outside Japan to compare the efficacy and safety of the EBd regimen with the efficacy and safety of the Bd regimen.

Among 152 subjects who were enrolled in the study and randomized (77 in the EBd and 75 in the Bd arms), 150 subjects who received the study drug (75 each in the EBd and Bd arms) were included in the safety analysis set.

[8] NRF, patients with CrCL ≥90 mL/min; SRI, patients with CrCL <30 mL/min, not requiring hemodialysis; and ESRD, patients requiring hemodialysis

During the study drug treatment or within 60 days of the end of treatment, deaths occurred in 2 of 75 subjects (2.7%) in the EBd arm, and 6 of 75 subjects (8.0%) in the Bd arm. Besides disease progression (2 subjects each in the EBd and Bd arms), causes of death were: cardio-respiratory arrest (1 subject), cardio-respiratory arrest/gastrointestinal haemorrhage (1), sepsis (1), and subdural haematoma (1) in the Bd arm. A causal relationship to the study drug was ruled out for all of these cases.

7.2.1.3 Foreign phase IIa study (CTD 5.3.5.2-2, Study CA204010 [started in June 2012, ongoing, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory MM (target sample size, 15 to 42 subjects) at 10 institutions outside Japan to evaluate the safety of concurrent administration of elotuzumab, thalidomide, and DEX.

Among 51 subjects enrolled in the study, 40 subjects who received the study drug were included in the safety analysis set.

During the study drug treatment or within 60 days of the end of treatment, deaths occurred in 10 of 40 subjects (25.0%). Besides disease progression (1 subject), causes of death were: septic shock (2), sudden death (1), renal failure acute (1), cardiac death (1), aspiration bronchial (1), cardio-respiratory arrest (1), pulmonary oedema (1), and pulmonary embolism (1). A causal relationship to the study drug could not be ruled out for the case of sudden death (1).

7.2.1.4 Foreign phase II study (CTD 5.3.4.2-1, Study CA204011 [February 2012 to May 2014])

An open-label, uncontrolled study was conducted in patients with high-risk smoldering MM (target sample size, 30 subjects) at 8 institutions outside Japan to evaluate the efficacy and safety of elotuzumab.

Among 41 subjects enrolled in the study, 31 subjects who received elotuzumab were included in the safety analysis set.

There were no deaths during elotuzumab treatment or within 60 days of the end of treatment.

7.R Outline of the review by PMDA

7.R.1 Review policy

PMDA considers that, among the submitted evaluation data, Study CA204004, a global phase III study conducted in patients with relapsed or refractory MM, is the pivotal study in evaluating the efficacy and safety of elotuzumab, and decided that evaluation should be conducted based on the data from Study CA204004.

7.R.2 Efficacy

PMDA concluded that the efficacy of elotuzumab in the treatment of relapsed or refractory MM was demonstrated by the following review results.

7.R.2.1 Control arm

The applicant explained the reason for setting the control arm for CA204004 as follows:

Study CA204004 was started in 2011. At the time, the IMWG Guidelines for the management of MM patients (*Leukemia*. 2009;23:1716-30) recommended the lenalidomide hydrate and high-dose dexamethasone (LD) regimen[9] for patients with relapsed or refractory MM, the target population for Study CA204004, based on the results of foreign clinical studies (e.g., *New Engl J Med.* 2007;357:2123-32). However, in a foreign clinical study conducted in patients with newly diagnosed MM, (1) the overall survival (OS) tended to be longer, and (2) venous thrombosis events and infections occurred at lower rates (*Lancet Oncol*. 2010;11:29-37) in the Ld regimen[10] than in the LD regimen (for both results). Based on the above, the Ld regimen was set as a control arm for Study CA204004.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant explained the reason for selecting PFS and response rate as the primary endpoints for Study CA204004 as follows:

MM is a recurrent and refractory disease with existing treatments, and it has been reported that as the number of prior therapies for MM increases, the duration of response decreases (*Mayo Clin Proc.* 2004;79:867-74). While treatments for patients with relapsed or refractory MM are initiated to extend the lives of patients, it is expected that improvements in response rate and extension of PFS can lead to improvements of symptoms, hindering of disease progression, extension of time to next treatment, and other outcomes (*Leukemia*. 2006;20:1467-73). For this and other reasons, PFS and response rate were selected as the primary endpoints for Study CA204004.

PMDA's view:

While the applicant's explanation is reasonable for the most part, PMDA considers that OS is also an important factor when assessing the efficacy of treatments for patients with relapsed or refractory MM, for which standard treatments have not been established. Therefore, it was determined that the efficacy of elotuzumab was to be evaluated based primarily on PFS and response rate as assessed by the IRC according to the revised EBMT criteria, and that in addition to these primary endpoints, the OS results should also be taken into account.

7.R.2.3 Results of efficacy evaluation

In Study CA204004, the results for PFS and response rate assessed by the IRC using the revised EBMT criteria, the primary endpoints for the study, demonstrated the superiority of the ELd arm over the Ld arm [see Section 7.1.2]. The PFS and response rate determined by the investigator according to the revised EBMT criteria were analyzed as a sensitivity analysis. The results for PFS are shown in Table

[9] In 28-day cycles, subjects received lenalidomide 25 mg PO QD on Days 1 to 21 and DEX 40 mg on Days 1 to 4, Days 9 to 12, and Days 17 to 20 in Cycles 1 to 4, and on Days 1 to 4 in Cycle 5 and after.

[10] In 28-day cycles, subjects received lenalidomide 25 mg PO QD on Days 1 to 21 and DEX 40 mg PO QW.

19, and the results for response rate were as follows: 84.7% (95% CI, 80.3, 88.5) in the ELd arm, 73.5% (95% CI, 68.4, 78.3) in the Ld arm, with an odds ratio of 2.03 (95% CI, 1.37, 3.00).

Table 19. Results of PFS analysis
(efficacy analysis set, determined by the investigator, data cut-off on October 29, 2014)

	ELd	Ld
Number of subjects	321	325
Died or progressed (%)	167 (52.0)	201 (61.8)
Median (95% CI) (months)	22.7 (18.5, 25.8)	16.7 (13.4, 19.3)
Hazard ratio (95% CI)*1	0.65 (0.53, 0.80)	
P-value (two-sided)*2	<0.0001	

*1, A stratified Cox proportional hazard model with the following stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); *2, stratified log-rank test, with the stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other)

The results of the interim analysis[11] (data cut-off on October 29, 2015) in terms of OS, which was selected as one of the secondary endpoints, are summarized in Table 20, and the Kaplan-Meier plot is shown in Figure 3.

Table 20. The results of the interim analysis in terms of OS (efficacy analysis set, data cut-off on October 29, 2015)

	ELd	Ld
Number of subjects	321	325
Death (%)	136 (42.4)	159 (48.9)
Median (95% CI) (months)	43.7 (40.3, NE)	39.6 (33.3, NE)
Hazard ratio*1 (95% CI)	0.77 (0.61, 0.97)	
P-value (two-sided)*2	0.0257	

NE, not estimable; *1, Estimated with a stratified Cox proportional hazard model with the following stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); *2, stratified log-rank test, with the stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other); two-sided significance level, 0.014

[11] If the results of the interim analysis for PFS indicated a significant increase in PFS, another interim analysis was to be triggered for OS 1 year after the primary interim analysis. It was planned that the multiplicity problem between the PFS/response rate and OS would be adjusted by a closed testing procedure, and the significance level for the OS analysis was to be determined based on the results of analyses of the PFS and response rate. Also, to adjust the probability of type I error associated with the interim analysis, the O'Brien-Fleming type alpha-spending function based on Lan-DeMets method was to be used.

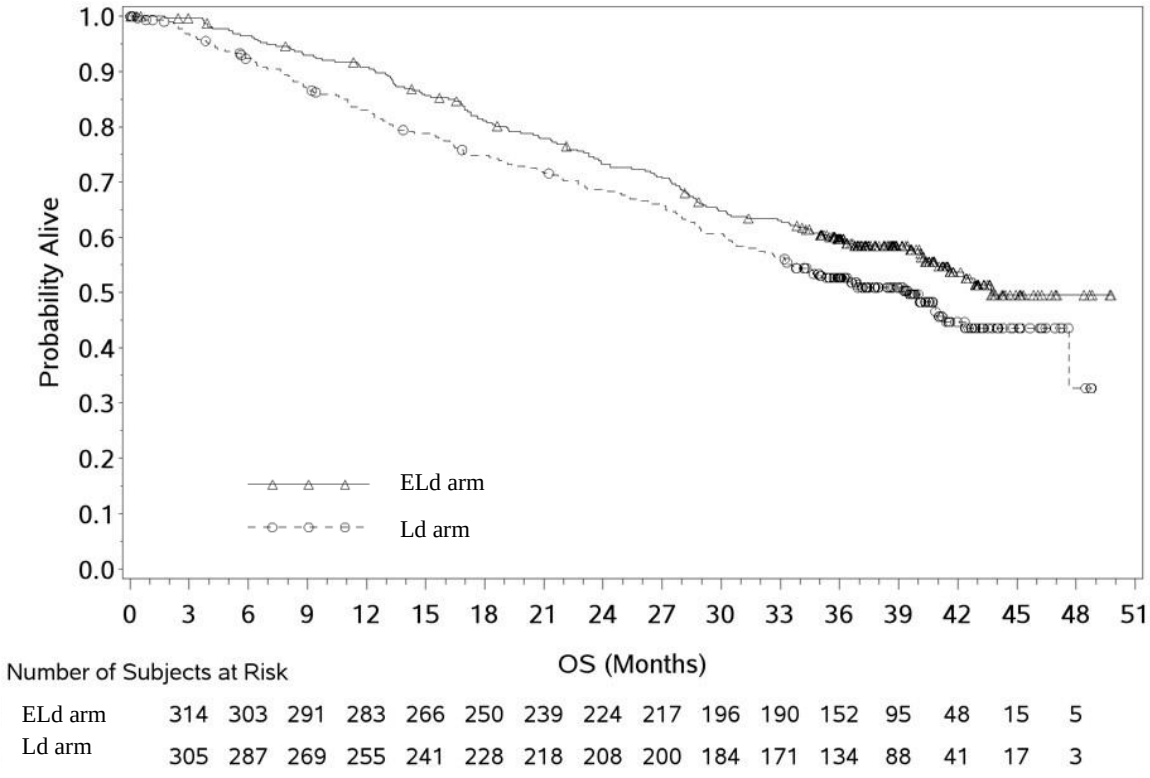

Figure 3. Kaplan-Meier plot of OS in the interim analysis (efficacy analysis set, data cut-off on October 29, 2015)

PMDA's view:

In Study CA204004, the PFS and response rate, the primary endpoints for the study, were assessed by the IRC using the revised EBMT criteria, and the analysis of the results demonstrated the superiority of the ELd arm over the Ld arm [see Section 7.1.2]. It is considered that the improvement in PFS is clinically meaningful. Regarding OS selected as a secondary endpoint, the results did not suggest that OS was shorter in the ELd arm than in the Ld arm.

Based on the above, it was concluded that the efficacy of elotuzumab in patients with relapsed or refractory MM has been demonstrated.

7.R.2.4 Efficacy of elotuzumab in Japanese patients

The PFS of Japanese patients in Study CA204004 was assessed by the IRC based on the revised EBMT criteria. The results of the PFS analysis are summarized in Table 21, and the Kaplan-Meier plot is shown in Figure 4. The response rate was also assessed by the IRC based on the revised EBMT criteria, and the results of the response rate analysis were: 83.9% (95% CI, 68.3, 94.5) in the ELd arm, 86.2% (95% CI, 68.3, 96.1) in the Ld arm, with an odds ratio of 0.68 (95% CI, 0.16, 2.90).

Table 21. Analytical results for PFS in Japanese patients (efficacy analysis set, determined by the IRC, data cut-off on October 29, 2014)

	ELd	Ld
Number of subjects	31	29
Died or progressed (%)	16 (51.6)	23 (79.3)
Median (95% CI) (months)	22.2 (17.5, NE)	18.5 (11.1, 21.2)
Hazard ratio (95% CI)*	0.51 (0.25, 1.06)	

*1, A stratified Cox proportional hazard model with the following stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), number of prior regimens (1, 2, or 3), and prior treatment with immunostimulatory drugs (none, thalidomide only, or other)

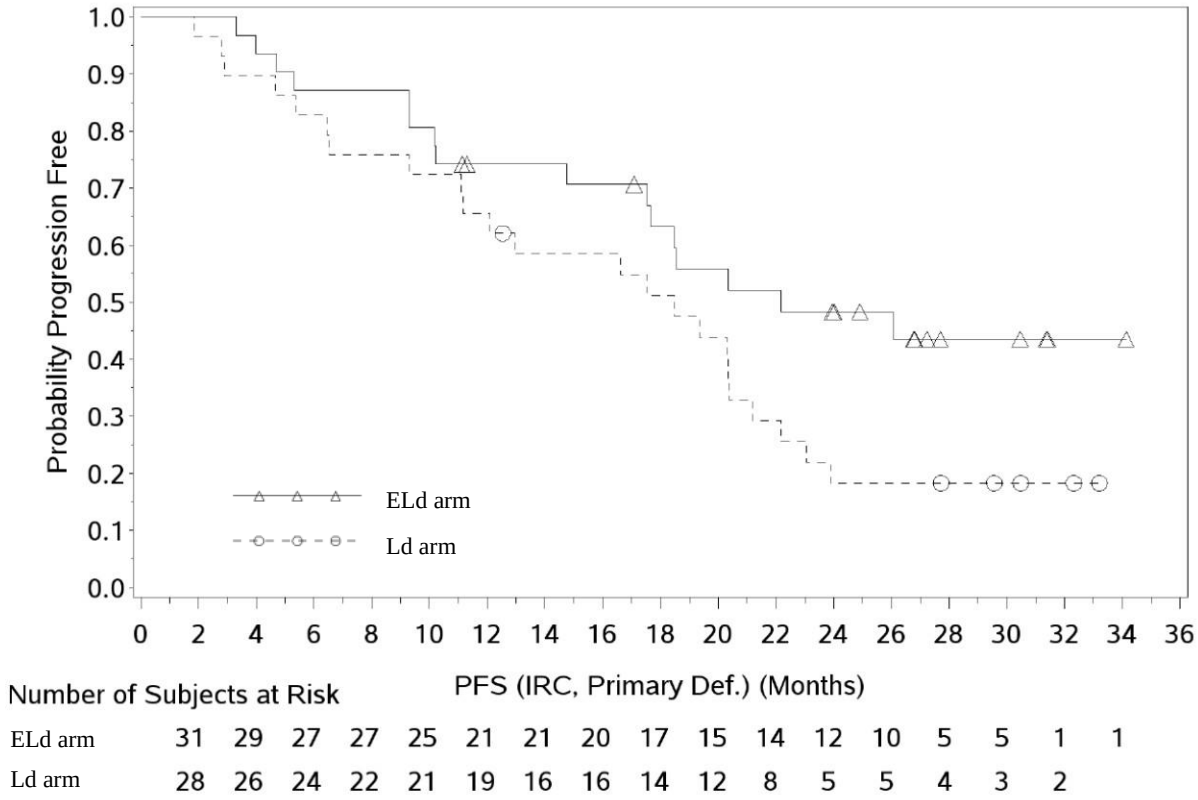

Figure 4. Kaplan-Meier plot for PFS in Japanese patients (efficacy analysis set, determined by the IRC, data cut-off on October 29, 2014)

PMDA's view:

While the evaluation is limited by the small number of Japanese patients enrolled in Study CA204004, the results for Japanese patients did not differ markedly from those of the entire study population in terms of PFS and response rate. Therefore, it is concluded that elotuzumab will be as effective in Japanese patients as it was in the entire study population.

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

Based on the review results shown in the following sections, PMDA considers that adverse events of particular concern when administering elotuzumab for the treatment of patients with relapsed or refractory MM are: infusion reactions, infections, second primary malignancies, cataract, and lymphopenia. Vigilance should be exercised regarding the occurrence of these adverse events when using elotuzumab.

In addition to the above adverse events, careful monitoring is required for any occurrence of hepatic impairment when administering elotuzumab; however, PMDA concluded that elotuzumab is tolerable provided that appropriate steps including monitoring and control of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies. Note that it is necessary to gather safety information continuously after market launch because of the paucity of currently available data for elotuzumab treatment in Japanese patients [see Section 7.R.7].

7.R.3.1 Safety profile of elotuzumab

Based on the safety data obtained from Study CA204004, the applicant explained the safety profile of elotuzumab as follows:

Table 22 summarizes the safety data of Study CA204004.

Table 22. Summary of safety data (Study CA204004)

	Number of subjects (%)	
	ELd 318 subjects	Ld 317 subjects
Adverse events total	316 (99.4)	314 (99.1)
Adverse event (Grade ≥3)	278 (87.4)	247 (77.9)
Adverse events that resulted in death	31 (9.7)	39 (12.3)
Serious adverse event	208 (65.4)	179 (56.5)
Adverse event that led to discontinuation of treatment	83 (26.1)	85 (26.8)
Adverse event that led to dose interruption	250 (78.6)	217 (68.5)
Adverse event that led to dose reduction	166 (52.2)	134 (42.3)

Table 23 shows adverse events that occurred with an incidence of ≥20% in at least 1 group in Study CA204004.

Table 23. Adverse events that occurred with an incidence of ≥20% in at least 1 group (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	316 (99.4)	278 (87.4)	314 (99.1)	247 (77.9)
Fatigue	149 (46.9)	27 (8.5)	123 (38.8)	26 (8.2)
Diarrhoea	149 (46.9)	16 (5.0)	114 (36.0)	13 (4.1)
Anaemia	124 (39.0)	48 (15.1)	117 (36.9)	52 (16.4)
Pyrexia	119 (37.4)	8 (2.5)	78 (24.6)	9 (2.8)
Constipation	113 (35.5)	4 (1.3)	86 (27.1)	1 (0.3)
Neutropenia	107 (33.6)	79 (24.8)	135 (42.6)	105 (33.1)
Cough	100 (31.4)	1 (0.3)	57 (18.0)	0
Muscle spasms	95 (29.9)	1 (0.3)	84 (26.5)	3 (0.9)
Back pain	90 (28.3)	16 (5.0)	89 (28.1)	14 (4.4)
Thrombocytopenia	86 (27.0)	37 (11.6)	72 (22.7)	36 (11.4)
Nausea	76 (23.9)	3 (0.9)	68 (21.5)	2 (0.6)
Oedema peripheral	82 (25.8)	4 (1.3)	70 (22.1)	1 (0.3)
Nasopharyngitis	78 (24.5)	0	61 (19.2)	0
Insomnia	73 (23.0)	6 (1.9)	82 (25.9)	8 (2.5)
Upper respiratory tract infection	72 (22.6)	2 (0.6)	55 (17.4)	4 (1.3)
Asthenia	70 (22.0)	15 (4.7)	53 (16.7)	12 (3.8)
Dyspnoea	69 (21.7)	6 (1.9)	59 (18.6)	11 (3.5)
Decreased appetite	66 (20.8)	5 (1.6)	40 (12.6)	4 (1.3)

Adverse events of all grades with an incidence higher in the ELd arm than in the Ld arm by ≥10% were: cough (100 of 318 subjects [31.4%] in the ELd arm, 57 of 317 subjects [18.0%] in the Ld arm; the same applies hereinafter in this paragraph for the order of the arms), pyrexia (119 of 318 subjects [37.4%], 78 of 317 subjects [24.6%]), and diarrhoea (149 of 318 subjects [46.9%], 114 of 317 subjects [36.0%]). Grade 3 or higher adverse events with an incidence higher in the ELd arm than in the Ld arm by ≥2% were: lymphopenia (28 of 318 subjects [8.8%], 10 of 317 subjects [3.2%]), pneumonia (33 of 318 subjects [10.4%], 23 of 317 subjects [7.3%]), cataract (20 of 318 subjects [6.3%], 9 of 317 subjects [2.8%]), deep vein thrombosis (18 of 318 subjects [5.7%], 7 of 317 subjects [2.2%]), and hyperglycaemia (23 of 318 subjects [7.2%], 14 of 317 subjects [4.4%]). Serious adverse events with an incidence higher in the ELd arm than in the Ld arm by ≥2% were: pneumonia (35 of 318 subjects [11.0%], 27 of 317 subjects [8.5%]) and pyrexia (22 of 318 subjects [6.9%], 15 of 317 subjects [4.7%]). Adverse events with an incidence higher in the ELd arm than in the Ld arm by ≥2%, which led to dose interruption of the study drug were: respiratory tract infection (20 of 318 subjects [6.3%], 9 of 317 subjects [2.8%]), pneumonia (35 of 318 subjects [11.0%], 23 of 317 subjects [7.3%]), fatigue (17 of 318 subjects [5.3%], 7 of 317 subjects [2.2%]), cough (11 of 318 subjects [3.5%], 2 of 317 subjects [0.6%]), thrombocytopenia (30 of 318 subjects [9.4%], 21 of 317 subjects [6.6%]), asthenia (9 of 318 subjects [2.8%], 1 of 317 subjects [0.3%]), and bronchopneumonia (8 of 318 subjects [2.5%], 1 of 317 subjects [0.3%]). There were no cases of adverse events with an incidence higher in the ELd arm than in the Ld arm by ≥2% which resulted in death, dose reduction of the study drug, or study drug discontinuation.

PMDA's view:

Vigilance should be exercised regarding the occurrence of adverse events with an incidence higher in the ELd arm than in the Ld arm in Study CA204004, as these adverse events are likely to occur following

administration of elotuzumab, and therefore information on the status of occurrence of these events needs to be provided to healthcare professionals in an appropriate manner.

7.R.3.2 Differences in the safety of elotuzumab between Japanese and non-Japanese populations

Based on the safety data obtained from Study CA204004, the applicant explained the differences in the safety of elotuzumab between Japanese and non-Japanese populations as follows:

Table 24 shows the summary of safety data for Japanese and non-Japanese patients in Study CA204004.

Table 24. Summary of safety data for Japanese and non-Japanese patients (Study CA204004)

	Number of subjects (%)			
	Japanese patients		Non-Japanese patients	
	ELd 31 subjects	Ld 29 subjects	ELd 287 subjects	Ld 288 subjects
Adverse events total	31 (100)	29 (100)	285 (99.3)	285 (99.0)
Adverse events (Grade ≥3)	29 (93.5)	23 (79.3)	249 (86.8)	224 (77.8)
Adverse events that resulted in death	0	1 (3.4)	31 (10.8)	38 (13.2)
Serious adverse events	25 (80.6)	18 (62.1)	183 (63.8)	161 (55.9)
Adverse events that led to discontinuation of treatment	5 (16.1)	4 (13.8)	78 (27.2)	81 (28.1)
Adverse events that led to dose interruption	27 (87.1)	26 (89.7)	223 (77.7)	191 (66.3)
Adverse events that led to dose reduction	14 (45.2)	10 (34.5)	152 (53.0)	124 (43.1)

In the ELd arm of Study CA204004, adverse events with an incidence higher in the Japanese patient group than in the non-Japanese patient group by ≥15% were: nasopharyngitis (15 of 31 subjects [48.4%] in Japanese patients, 63 of 287 subjects [22.0%] in non-Japanese patients; the same applies hereinafter in this paragraph for the order of the patient groups), rash (11 of 31 subjects [35.5%], 47 of 287 subjects [16.4%]), upper respiratory tract inflammation (5 of 31 subjects [16.1%], 0 subjects), pneumonia (9 of 31 subjects [29.0%], 39 of 287 subjects [13.6%]), malaise (6 of 31 subjects [19.4%], 12 of 287 subjects [4.2%]). Grade 3 or higher adverse events with an incidence higher in Japanese patients than in non-Japanese patients by ≥10% were: cataract (6 of 31 subjects [19.4%], 14 of 287 subjects [4.9%]) and lymphopenia (6 of 31 subjects [19.4%], 22 of 287 subjects [7.7%]). Serious adverse events with an incidence higher in Japanese patients than in non-Japanese patients by ≥10% were: pneumonia (9 of 31 subjects [29.0%], 26 of 287 subjects [9.1%]) and cataract (4 of 31 subjects [12.9%], 1 of 287 subjects [0.3%]). Adverse events with an incidence higher in Japanese patients than in non-Japanese patients by ≥10%, which led to dose interruption of the study drug were: pneumonia (9 of 31 subjects [29.0%], 26 of 287 subjects [9.1%]) and pyrexia (6 of 31 subjects [19.4%], 23 of 287 subjects [8.0%]). Adverse events with an incidence higher in Japanese patients than in non-Japanese patients by ≥10%, which led to dose reduction of the study drug were: creatinine renal clearance decreased (4 of 31 subjects [12.9%], 8 of 287 subjects [2.8%]). There were no cases of adverse events which resulted in death with an incidence higher in Japanese patients than in non-Japanese patients, or which resulted in study drug discontinuation with an incidence higher in Japanese patients than in non-Japanese patients by ≥10%.

Based on the above results, while some adverse events occurred at a higher incidence in Japanese patients than in non-Japanese patients, given that the study involved only a limited number of Japanese patients, and that there are no clear differences in the PK of elotuzumab between Japanese and non-Japanese populations [see Section 6.R.2], it is considered that at present, there is no evidence showing a difference in the safety of elotuzumab between Japanese and non-Japanese populations.

PMDA's view:

Due to the limited number of Japanese patients, it is difficult to determine with certainty whether there are differences in the safety profile of elotuzumab between Japanese and non-Japanese populations based on the results from Study CA204004. However, vigilance is required regarding the incidence of

serious or Grade ≥3 adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients, and information on the occurrence of these events should be provided to healthcare professionals in an appropriate manner using information materials. Because of the limited amount of safety data on elotuzumab in Japanese patients, information should be gathered continuously after market launch, and when new findings become available, the information needs to be provided to healthcare professionals in an appropriate manner.

In the following sections, PMDA examined the safety results mainly from Study CA204004, focusing on the following: adverse events that resulted in death in ≥2 subjects in the ELd arm (pneumonia and sepsis), serious adverse events that occurred with an incidence higher in the ELd arm than in the Ld arm, serious or Grade ≥3 adverse events that occurred with an incidence higher in Japanese patients than in non-Japanese patients, and adverse events that have been listed in the warnings and precautions section of package inserts in other countries (infusion reactions, infections, second primary malignancies, and hepatic impairment).

7.R.3.3 Infusion reactions

(a) Incidence and timing of the occurrence

The applicant explained the incidence and the timing of occurrence of infusion reactions following administration of elotuzumab as follows:

From the data of the ELd arm of Study CA204004, those of 126 infusion reaction-related events that occurred from the start of infusion until the next day were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT)[12] (MedDRA ver. 17.0). Data on these adverse events were not collected for the Ld arm as patients in this arm did not receive drugs parenterally.

Table 25 shows infusion reactions with an incidence of ≥5% in the ELd arm of Study CA204004.

[12] Acute respiratory failure, allergic cough, allergic oedema, allergic respiratory symptom, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, angioedema, apnoea, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, lip oedema, lip swelling, myocardial infarction, nausea, oedema, oedema mouth, oropharyngeal spasm, oropharyngeal swelling, oxygen saturation decreased, palpitations, periorbital oedema, pharyngeal oedema, pruritus, blood pressure systolic decreased, bradycardia, bronchial oedema, bronchospasm, cardiac arrest, cardiac failure acute, cardio-respiratory arrest, cardio-respiratory distress, cardiovascular insufficiency, chest discomfort, nausea, choking sensation, circulatory collapse, circumoral oedema, cough, diastolic hypotension, dizziness, drug hypersensitivity, dysphonia, dyspnoea, erythema, eye oedema, eye swelling, eyelid oedema, face oedema, first use syndrome, fixed eruption, flushing, generalised erythema, headache, heart rate increased, hot flush, pruritus allergic, pruritus generalised, pyrexia, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash pruritic, rash pustular, respiratory arrest, respiratory distress, respiratory failure, respiratory rate increased, reversible airways obstruction, sensation of foreign body, shock, sinus tachycardia, skin reaction, skin swelling, sneezing, stridor, swelling, swelling face, swollen tongue, syncope, tachycardia, tachypnoea, throat irritation, throat tightness, tongue oedema, hyperhidrosis, hyperpyrexia, hypersensitivity, hyperventilation, hypotension, hypoxia, influenza like illness, infusion-related reaction, Kounis syndrome, laryngeal dyspnoea, laryngeal oedema, laryngospasm, laryngotracheal oedema, tracheal obstruction, tracheal oedema, type I hypersensitivity, type II hypersensitivity, type IV hypersensitivity reaction, upper airway obstruction, urticaria, urticaria papular, vasculitic rash, vasculitis, vomiting, wheezing, asthenia, dyspepsia, chest pain, dysgeusia, vision blurred, myalgia, diarrhoea, hypertension, tremor, feeling cold, and cardiac failure congestive.

Table 25. Infusion reactions with an incidence of ≥5% (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)	
	ELd 318 subjects	
	All Grades	Grade ≥3
Infusion reaction	230 (72.3)	27 (8.5)
Diarrhoea	68 (21.4)	8 (2.5)
Asthenia	46 (14.5)	6 (1.9)
Cough	44 (13.8)	0
Dyspnoea	40 (12.6)	3 (0.9)
Pyrexia	40 (12.6)	1 (0.3)
Nausea	33 (10.4)	1 (0.3)
Headache	27 (8.5)	0
Dizziness	26 (8.2)	0
Hypertension	22 (6.9)	4 (1.3)
Tremor	20 (6.3)	1 (0.3)
Dyspepsia	20 (6.3)	0
Dysphonia	19 (6.0)	0
Hyperhidrosis	18 (5.7)	0
Pruritus	18 (5.7)	0
Vision blurred	17 (5.3)	1 (0.3)
Hypotension	16 (5.0)	0

There were no cases of infusion reaction that resulted in death. Serious infusion reactions occurred in 12 of 318 subjects (3.8%). These events were classified as pyrexia (5 subjects), diarrhoea (3), dyspnoea (2), cardiac failure congestive (1), chest pain (1), nausea (1), and vomiting (1) (including overlaps). Among these cases a causal relationship to elotuzumab could not be ruled out for pyrexia (3), diarrhoea (2), cardiac failure congestive (1), chest pain (1), and nausea (1). Infusion reactions that led to study drug discontinuation, dose interruption, and dose reduction occurred in 7 of 318 subjects (2.2%), 32 of 318 subjects (10.1%), and 28 of 318 subjects (8.8%), respectively.

Table 26 shows the occurrence of infusion reactions cycle-by-cycle following administration of elotuzumab in Study CA204004.

Table 26. Occurrence of infusion reactions on a cycle-by-cycle basis (Study CA204004)

Time of treatment (Cycle)	Number of subjects	Number of subjects (%)		
		All Grades	Grade ≥3	First occurrence in each subject (all grades)
1	318	149 (46.9)	11 (3.5)	149 (46.9)
2	312	69 (22.1)	4 (1.3)	25 (7.9)
3	307	32 (10.4)	2 (0.7)	8 (2.5)
4	298	27 (9.1)	1 (0.3)	6 (1.9)
5	287	24 (8.4)	6 (2.1)	4 (1.3)
6	278	20 (7.2)	0	5 (1.6)
7 and after	268	125 (46.6)	4 (1.5)	33 (10.4)

(b) Management of infusion rate

The applicant explained the infusion rate for elotuzumab in Study CA204004 as follows:

At the beginning of Study CA204004 (June 2011), the infusion rate for elotuzumab was specified as shown in Table 27. Subsequently, the protocol was revised in [redacted] 20[redacted] to shorten the infusion time of elotuzumab: for Cycle 1 Dose 2, elotuzumab should be administered initially at an infusion rate of 3

mL/min and at 4 mL/min from 30 minutes after the start of administration; and for Cycle 1 Dose 3 and all subsequent cycles, elotuzumab should be administered at an infusion rate of 5 mL/min.

Table 27. Infusion rate for elotuzumab at the beginning of Study CA204004

Time of treatment		Infusion rate (mL/min)		
		0 to 30 min after the start of infusion	30 to 60 min after the start of infusion	≥60 min after the start of infusion
Cycle 1	Initial treatment*	0.5	1	2
	Doses 2 to 4 *	1	2	
Cycle 2 and after		2		

*, If no infusion reactions have occurred within a prescribed time, the infusion rate for elotuzumab may be increased by 1 step.

Further, the following steps were specified regarding the infusion rate for elotuzumab in the event of an infusion reaction during administration of elotuzumab:

- For a Grade 1 infusion reaction, elotuzumab infusion may be continued, but the infusion rate should be decreased to 0.5 mL/min until the reaction resolves. Once the reaction has resolved, the infusion rate may be escalated in a stepwise manner about every 30 minutes by 0.5 mL/min. However, the maximum infusion rate of elotuzumab should not exceed 2 mL/min.
- For a Grade 2 or 3 infusion reaction, elotuzumab infusion must be interrupted. Once the reaction has resolved to Grade ≤1, elotuzumab can be restarted at the initial infusion rate of 0.5 mL/min. If symptoms of infusion reaction do not recur within 30 minutes after the restart, the infusion rate may be escalated gradually every 30 minutes by 0.5 mL/min after sufficiently confirming that the patient can tolerate the dose administered. The infusion rate should not exceed either the rate at which the infusion interruption occurred or 2 mL/min, whichever is lower. If an infusion reaction has occurred after resuming elotuzumab infusion, infusion must be interrupted again, and appropriate medical measures should be instituted; infusion must not be restarted for the day.
- For a Grade 4 infusion reaction, elotuzumab infusion must be discontinued permanently.

The "Precautions for dosage and administration" section included precautions on the infusion rate specified in the revised protocol mentioned above. PMDA asked the applicant to explain the occurrence of infusion reactions after the revision and the appropriateness of the precautions, and the applicant responded as follows:

At the time of protocol revision, all patients enrolled in Study CA204004 had already advanced to Cycle 4 or later; and therefore, no patients received elotuzumab at the infusion rate specified according to the revised protocol. Yet, it is considered possible to specify the infusion rates of elotuzumab according to the revised protocol for Study CA204004 in the "Precautions for dosage and administration" section based on the following reasons:

- In Study CA204004, infusion reactions occurred most frequently following administration of the first dose in Cycle 1, and the incidence decreased thereafter.
- In Study CA204004, elotuzumab was administered at an infusion rate of 5 mL/min in 8 of 318 subjects (the 8 subjects including 4 Japanese subjects [2 doses, 1 subject; 1 dose, 3 subjects] received 11 of the 12,851 doses), but these subjects did not experience infusion reactions.

(c) Pre-medication

In Study CA204004, 30 to 90 minutes before administration of elotuzumab, an antihistamine, an H_2 blocker, and an antipyretic analgesic were to be administered. On the days when subjects received elotuzumab, an oral dose of DEX 28 mg (3 to 24 hours prior to administration of elotuzumab) and an intravenous dose of DEX 8 mg (administration should be completed at least 45 minutes prior to administration of elotuzumab) were administered instead of an oral dose of DEX 40 mg.

PMDA asked the applicant to explain the incidence of infusion reactions in patients in the ELd arm of Study CA204004 who continued receiving elotuzumab despite postponement, interruption, or discontinuation of DEX treatment. The applicant responded as follows:

In Study CA204004, 18 subjects received elotuzumab without receiving pre-medication of DEX, and infusion reactions of Grade ≤2 occurred in 3 subjects (16.7%). The study drug treatment was interrupted in the subject with Grade 2 infusion reaction, while the treatment with elotuzumab was continued without any change in the subjects with Grade 1 infusion reaction.

PMDA's view:

Given that in Study CA204004, infusion reactions occurred in approximately 70% of subjects in the ELd arm, and that there were cases of infusion reactions that led to treatment discontinuation, as well as cases of serious infusion reactions, vigilance should be exercised regarding the occurrence of infusion reactions when using elotuzumab. Further, there were patients who had an infusion reaction for the first time after several cycles of treatment, or who experienced an infusion reaction more than once. It is therefore necessary to examine the status of the occurrence of infusion reactions in clinical studies including the above cases, and the information should be provided to healthcare professionals in an appropriate manner using materials such as the package insert.

To call attention to the infusion rate and pre-medication in an appropriate manner, the dosage and administration used for these drugs in Study CA204004 should be included in the "Precautions for dosage and administration" section. With regard to the infusion rate, given that no patients received elotuzumab at the infusion rate specified in the revised protocol for Study CA204004, it is concluded that the caution should be based on the dosage and administration specified at the start of the study (June 2011).

7.R.3.4 Infections

The applicant explained the occurrence of infections following administration of elotuzumab as follows:

As infection-related adverse events, data corresponding to MedDRA PTs under MedDRA system organ class (SOC) (MedDRA ver. 17.0) "Infections and infestations" were tabulated.

Table 28 shows the occurrence of infections in Study CA204004.

Table 28. Occurrence of infections with an incidence of ≥2% in at least one of the arms (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections	259 (81.4)	97 (30.5)	236 (74.4)	84 (26.5)
Nasopharyngitis	78 (24.5)	0	61 (19.2)	0
Upper respiratory tract infection	72 (22.6)	2 (0.6)	55 (17.4)	4 (1.3)
Bronchitis	55 (17.3)	5 (1.6)	51 (16.1)	7 (2.2)
Pneumonia	48 (15.1)	35 (11.0)	37 (11.7)	23 (7.3)
Respiratory tract infection	34 (10.7)	8 (2.5)	30 (9.5)	4 (1.3)
Lower respiratory tract infection	27 (8.5)	4 (1.3)	17 (5.4)	4 (1.3)
Urinary tract infection	27 (8.5)	4 (1.3)	31 (9.8)	7 (2.2)
Rhinitis	23 (7.2)	0	12 (3.8)	0
Sinusitis	20 (6.3)	1 (0.3)	14 (4.4)	1 (0.3)
Herpes zoster	19 (6.0)	5 (1.6)	9 (2.8)	2 (0.6)
Influenza	19 (6.0)	3 (0.9)	21 (6.6)	4 (1.3)
Oral herpes	17 (5.3)	0	13 (4.1)	0
Pharyngitis	17 (5.3)	1 (0.3)	12 (3.8)	1 (0.3)
Viral infection	14 (4.4)	1 (0.3)	8 (2.5)	0
Gastroenteritis	13 (4.1)	2 (0.6)	10 (3.2)	2 (0.6)
Cellulitis	12 (3.8)	5 (1.6)	7 (2.2)	1 (0.3)
Conjunctivitis	12 (3.8)	0	12 (3.8)	0
Oral candidiasis	11 (3.5)	0	7 (2.2)	0
Bronchopneumonia	10 (3.1)	6 (1.9)	4 (1.3)	3 (0.9)
Infection	8 (2.5)	3 (0.9)	15 (4.7)	3 (0.9)
Lung infection	8 (2.5)	2 (0.6)	7 (2.2)	1 (0.3)
Cystitis	7 (2.2)	0	6 (1.9)	0
Herpes virus infection	7 (2.2)	0	0	0
Sepsis	5 (1.6)	5 (1.6)	7 (2.2)	6 (1.9)
Tooth infection	4 (1.3)	0	9 (2.8)	0
Localised infection	1 (0.3)	0	7 (2.2)	0

Infections that resulted in death occurred in 8 of 318 subjects (2.5%) and 7 of 317 subjects (2.2%) in the ELd and Ld arms, respectively. These events were classified as pneumonia (2 subjects), sepsis (2), influenza (1), lower respiratory tract infection (1), meningitis staphylococcal (1), and septic shock (1) in the ELd arm, and sepsis (3), septic shock (1), bronchopneumonia (1), peritonitis (1), and pneumocystis jirovecii pneumonia (1) in the Ld arm. Among these events, a causal relationship to the study drug could not be ruled out for influenza (1) and lower respiratory tract infection (1) in the ELd arm, and sepsis (2), peritonitis (1), and pneumocystis jirovecii pneumonia (1) in the Ld arm. Serious infections occurred in 99 of 318 subjects (31.1%) in the Ld arm and 80 of 317 subjects (25.2%) in the Ld arm, and among these cases, a causal relationship to the study drug could not be ruled out in 48 subjects (15.1%) and 32 subjects (10.1%) in the ELd and Ld arms, respectively. Infections that led to study drug discontinuation occurred in 11 of 318 subjects (3.5%) in the ELd arm and 13 of 317 subjects (4.1%) in the Ld arm. Infections that led to study drug dose interruption occurred in 139 of 318 subjects (43.7%) in the ELd arm and 108 of 317 subjects (34.1%) in the Ld arm. Infections that led to study drug dose reduction occurred in 3 of 318 subjects (0.9%) in the ELd arm and 6 of 317 subjects (1.9%) in the Ld arm.

PMDA asked the applicant to explain the occurrence of herpes zoster, tuberculosis, and hepatitis B reactivation in Study CA204004, and the applicant responded as follows:

Herpes zoster (including oral herpes and herpes virus infections) occurred in 43 of 318 subjects (13.5%) and 21 of 317 subjects (6.6%) in the ELd and Ld arms, respectively. Grade ≥3 herpes zoster (including

oral herpes and herpes virus infections) occurred in 5 of 318 subjects (1.6%) and 2 of 317 subjects (0.6%) in the ELd and Ld arms, respectively. There were no cases of tuberculosis or hepatitis B reactivation. Also, no prophylactic medication for infection had been specified in Study CA204004.

PMDA's view:

Given the following considerations, vigilance should be exercised regarding the occurrence of infections when administering elotuzumab, and information should be provided to healthcare professionals in an appropriate manner with regard to the occurrence of infections in clinical studies: the incidence of infections of all grades or Grade ≥3 was higher in the ELd arm than in the Ld arm in Study CA204004; there were cases of infections that resulted in death as well as cases of serious infections, for which a causal relationship to elotuzumab could not be ruled out; and serious pneumonia occurred at a higher incidence in Japanese patients than in non-Japanese patients [see Section 7.R.3.2].

7.R.3.5 Second primary malignancies

The applicant explained second primary malignancies associated with elotuzumab treatment as follows: As adverse events of second primary malignancies, data of all events classified under the standard MedDRA queries (SMQ) term (MedDRA ver. 17.0) "Neoplasms benign, malignant and unspecified (including cysts and polyps)" (except those corresponding to MedDRA PTs "malignant neoplasm progression," "plasma cell myeloma," and "plasmacytoma"), as well as data of "skin neoplasm excision," were tabulated by MedDRA PT.

Table 29 shows the occurrence of second primary malignancies in Study CA204004.

Table 29. Second primary malignancies that occurred in ≥2 subjects in at least one of the arms (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Second primary malignancies	32 (10.1)	20 (6.3)	19 (6.0)	14 (4.4)
Squamous cell carcinoma of skin	6 (1.9)	4 (1.3)	2 (0.6)	1 (0.3)
Basal cell carcinoma	5 (1.6)	5 (1.6)	3 (0.9)	3 (0.9)
Lipoma	3 (0.9)	0	0	0
Skin papilloma	3 (0.9)	0	1 (0.3)	0
Lung neoplasm malignant	2 (0.6)	2 (0.6)	0	0
Myelodysplastic syndrome	2 (0.6)	2 (0.6)	3 (0.9)	3 (0.9)

Second primary malignancies that resulted in death occurred in 2 of 318 subjects (0.6%) and 1 of 317 subjects (0.3%) in the ELd and Ld arms, respectively. Among these cases, a causal relationship to the study drug could not be ruled out for the case of gastrointestinal neoplasm in the ELd arm. Serious second primary malignancies occurred in 23 of 318 subjects (7.2%) and 17 of 317 subjects (5.4%) in the ELd and Ld arms, respectively. Among these cases, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma of skin (2 subjects), myelodysplastic syndrome (2), basal cell carcinoma (2), gastrointestinal neoplasm (1), squamous cell carcinoma (1), erythroleukaemia (1), and lipoma of breast (1) in the ELd arm. In the ELd and Ld arms, second primary malignancies that led to study drug discontinuation occurred in 9 of 318 subjects (2.8%) and 6 of 317 subjects (1.9%),

respectively; and dose interruption in 1 of 318 subjects (0.3%) and 2 of 317 subjects (0.6%), respectively. There were no second primary malignancies that led to study drug dose reduction.

Table 30 shows a list of patients who developed second primary malignancies in Study CA204004.

Table 30. List of patients who developed second primary malignancies (Study CA204004)

	Age	Sex	MedDRA PT	Grade	Seriousness	Onset (Day)[*1]	Causal relationship to study drug	Study drug discontinuation / interruption	Outcome
ELd arm	6[redacted]	M	Squamous cell carcinoma of skin	3	Serious	218	Yes	No	Resolved
	5[redacted]	M	Squamous cell carcinoma of skin	2	Serious	409	No	Discontinued	Resolved
	7[redacted]	M	Squamous cell carcinoma of skin	3	Serious	316	No	No	Resolved
			Squamous cell carcinoma of skin	3	Serious	657	Yes	No	Resolved
			Skin cancer	1	Non-serious	316	No	No	Unknown
			Squamous cell carcinoma	3	Serious	567	Yes	No	Resolved
			Basal cell carcinoma	3	Serious	657	Yes	No	Resolved
	7[redacted]	M	Squamous cell carcinoma of skin	1	Serious	395	No	No	Resolved
	7[redacted]	M	Squamous cell carcinoma of skin	3	Serious	505	No	No	Resolved
	8[redacted]	M	Squamous cell carcinoma of skin	3	Serious	331	No	No	Resolved
			Squamous cell carcinoma of skin	3	Serious	630	No	No	Resolved
			Seborrhoeic keratosis	1	Non-serious	219	No	No	Unknown
	7[redacted]	M	Basal cell carcinoma	3	Serious	78	No	No	Resolved
	5[redacted]	F	Basal cell carcinoma	3	Serious	726	No	No	Resolved
	7[redacted]	M	Basal cell carcinoma	3	Non-serious	903	No	No	Unknown
	6[redacted]	F[*2]	Basal cell carcinoma	3	Serious	505	Yes	Interrupted	Resolved
	6[redacted]	M	Lipoma	1	Non-serious	45	No	No	Unknown
	5[redacted]	F	Lipoma	1	Non-serious	29	No	No	Unknown
	6[redacted]	F	Lipoma	1	Non-serious	370	No	No	Unknown
			Breast fibroma	1	Non-serious	344	No	No	Unknown
	8[redacted]	M	Skin papilloma	2	Non-serious	266	No	No	Unknown
	4[redacted]	M	Skin papilloma	1	Non-serious	336	No	No	Unknown
	6[redacted]	M	Skin papilloma	1	Non-serious	225	No	No	Unknown
	6[redacted]	M	Lung neoplasm malignant	4	Serious	191	No	No	Not resolved
	7[redacted]	F	Lung neoplasm malignant	5	Serious	412	No	No	Fatal
	7[redacted]	M[*2]	Myelodysplastic syndrome	4	Serious	281	Yes	Discontinued	Fatal
	7[redacted]	M	Myelodysplastic syndrome	4	Serious	911	Yes	Discontinued	Not resolved
			Chronic lymphocytic leukaemia	4	Serious	43	No	No	Not resolved
	7[redacted]	M[*2]	Adenocarcinoma of colon	4	Serious	357	No	No	Resolved
	7[redacted]	M	Bladder transitional cell carcinoma	3	Serious	15	No	No	Resolved
	7[redacted]	F	Breast cancer	3	Serious	633	No	Discontinued	Not resolved
	6[redacted]	M	Erythroleukaemia	4	Serious	781	Yes	Discontinued	Not resolved

	Age	Sex	MedDRA PT	Grade	Seriousness	Onset (Day)[*1]	Causal relationship to study drug	Study drug discontinuation / interruption	Outcome
	6[redacted]	M	Gastrointestinal neoplasm	5	Serious	209	Yes	Discontinued	Fatal
	8[redacted]	M	Meningioma	4	Serious	526	No	Discontinued	Not resolved
	7[redacted]	M	Mesothelioma	3	Serious	85	No	Discontinued	Not resolved
	6[redacted]	M	Prostatic adenoma	1	Serious	974	No	No	Resolved
	5[redacted]	M	Lipoma of breast	1	Non-serious	420	Yes	No	Unknown
	7[redacted]	M	Malignant pleural effusion	2	Serious	235	No	Discontinued	Resolved
	7[redacted]	M	Thyroid neoplasm	1	Non-serious	672	No	No	Unknown
	7[redacted]	M	Skin neoplasm excision [*3]	3	Serious	563	No	No	Resolved
Ld arm	6[redacted]	F	Basal cell carcinoma	3	Serious	85	No	No	Resolved
	5[redacted]	M	Basal cell carcinoma	3	Serious	703	Yes	No	Not resolved
	6[redacted]	M	Basal cell carcinoma Myelodysplastic syndrome	3 4	Serious Serious	561 632	No No	No No	Not resolved Fatal
	7[redacted]	F	Myelodysplastic syndrome	4	Serious	562	Yes	Discontinued	Unknown
	5[redacted]	M	Myelodysplastic syndrome	3	Serious	566	Yes	Discontinued	Not resolved
	7[redacted]	F	Squamous cell carcinoma of skin	2	Serious	601	No	No	Not resolved
	7[redacted]	M	Squamous cell carcinoma of skin	3	Serious	401	No	No	Resolved
	6[redacted]	M	Adenocarcinoma of colon	4	Serious	84	No	No	Fatal
	5[redacted]	F	Endometrial cancer	4	Serious	407	No	Discontinued	Not resolved
	6[redacted]	M	Haemangioma of bone	3	Serious	367	No	No	Resolved
	8[redacted]	M	Lung cancer metastatic	3	Serious	61	No	Discontinued	Not resolved
	5[redacted]	M	Malignant neoplasm of unknown primary site	5	Serious	43	No	Discontinued	Fatal
	6[redacted]	M	Prostate cancer	4	Serious	1	No	No	Not resolved
	6[redacted]	M	Tonsil cancer	4	Serious	493	Yes	Discontinued	Fatal
	6[redacted]	M[*2]	Tumour associated fever	3	Serious	381	No	No	Resolved
	7[redacted]	M	Haemangioma	2	Serious	204	No	Interrupted	Resolved
	4[redacted]	M	Malignant melanoma in situ	1	Serious	589	Yes	Interrupted	Resolved
	5[redacted]	M[*2]	Skin papilloma	1	Non-serious	729	No	No	Unknown
	6[redacted]	M	Prostatic adenoma Prostatic adenoma	2 2	Non-serious Serious	326 337	No No	No No	Unknown Resolved
	7[redacted]	F	Seborrhoeic keratosis	1	Non-serious	336	No	No	Unknown

*1, Number of days elapsed from the start of treatment; *2, Japanese patient; and *3, excision of squamous cell carcinoma of the skin

PMDA's view:

In Study CA204004, the incidence of second primary malignancies was higher in the ELd arm than in the Ld arm based on both all-grade and Grade ≥3 second primary malignancies, and there were cases of second primary malignancies that resulted in death as well as cases of serious second primary malignancies, for which a causal relationship to elotuzumab could not be ruled out. Based on these and other considerations, it was concluded that when administering elotuzumab, vigilance should be exercised regarding the occurrence of second primary malignancies, and information needs to be

provided to healthcare professionals in an appropriate manner with regard to the occurrence of these events in clinical studies by using the package insert or other materials.

7.R.3.6 Cataract

The applicant explained the occurrence of cataract associated with elotuzumab treatment as follows:
As cataract-related adverse events, data corresponding to MedDRA PTs (MedDRA ver. 17.0) "cataract" and "cataract nuclear" were tabulated.

Table 31 shows the occurrence of cataract in Study CA204004.

Table 31. Occurrence of cataract (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cataract	39 (12.3)	21 (6.6)	21 (6.6)	10 (3.2)
Cataract	38 (11.9)	20 (6.3)	20 (6.3)	9 (2.8)
Cataract nuclear	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

Serious cataract occurred in 6 of 318 subjects (1.9%) and 4 of 317 subjects (1.3%) in the ELd and Ld arms, respectively. These events were classified as cataract (5 subject) and cataract nuclear (1) in the ELd arm, and cataract (4) in the Ld arm. Among these events, a causal relationship to the study drug could not be ruled out for cataract (2) and cataract nuclear (1) in the ELd arm, and cataract (2) in the Ld arm. There were no cases of cataract that led to study drug discontinuation in either arm. In the ELd and Ld arms, cataract that led to dose interruption occurred in 4 of 318 subjects (1.3%) and 1 of 317 subjects (0.3%), respectively; and dose reduction in 7 of 318 subjects (2.2%) and 3 of 317 subjects (0.9%), respectively.

Table 32 shows the first occurrence of cataract in each subject cycle-by-cycle following administration of elotuzumab in Study CA204004.

Table 32. First occurrence of cataract in each subject on a cycle-by-cycle basis (Study CA204004)

Time of treatment (Cycle)	Number of subjects (%)	
	ELd 318 subjects	Ld 317 subjects
1 to 6	5 (1.6)	4 (1.3)
7 to 12	5 (1.9)	1 (0.3)
13 to 18	12 (3.8)	5 (1.6)
19 to 24	10 (3.1)	7 (2.2)
25 to 30	4 (1.3)	2 (0.6)
31 to 36	3 (0.9)	2 (0.6)
37 and after	0	0

PMDA's view:
In Study CA204004, the incidence of cataract was higher in the ELd arm than in the Ld arm both for all-grade cataract and Grade ≥3 cataract; and Grade ≥3 cataract occurred with an incidence higher in Japanese patients than in non-Japanese patients [see Section 7.R.3.2]. Based on these and other

considerations, vigilance should be exercised regarding the occurrence of cataract when administering elotuzumab. Information that includes the following should be provided to healthcare professionals in an appropriate manner using the package insert or other materials: the occurrence of the events in clinical studies; and the finding that there were many patients who developed cataract in Cycle 13 (about 1 year after the start of elotuzumab treatment) and subsequent cycles.

7.R.3.7 Myelosuppression

The applicant explained the occurrence of myelosuppression associated with elotuzumab treatment as follows:

As myelosuppression-related adverse events, data corresponding to MedDRA PTs (MedDRA ver. 17.0) "anaemia," "neutropenia," "thrombocytopenia," "lymphopenia," "leukopenia," "platelet count decreased," "haemoglobin decreased," "pancytopenia," "neutrophil count decreased," "white blood cell count decreased," "lymphocyte count decreased," "granulocytopenia," "monocytopenia," "bone marrow failure," and "eosinopenia" were tabulated.

Table 33 shows the occurrence of myelosuppression in Study CA204004.

Table 33. Occurrence of myelosuppression (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%) Study CA204004			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	208 (65.4)	143 (45.0)	193 (60.9)	144 (45.4)
Anaemia	124 (39.0)	48 (15.1)	117 (36.9)	52 (16.4)
Neutropenia	107 (33.6)	79 (24.8)	135 (42.6)	105 (33.1)
Thrombocytopenia	86 (27.0)	37 (11.6)	72 (22.7)	36 (11.4)
Lymphopenia	42 (13.2)	28 (8.8)	22 (6.9)	10 (3.2)
Leukopenia	24 (7.5)	13 (4.1)	25 (7.9)	12 (3.8)
Platelet count decreased	15 (4.7)	4 (1.3)	5 (1.6)	1 (0.3)
Haemoglobin decreased	10 (3.1)	2 (0.6)	8 (2.5)	4 (1.3)
Pancytopenia	8 (2.5)	4 (1.3)	0	0
Neutrophil count decreased	8 (2.5)	3 (0.9)	6 (1.9)	5 (1.6)
White blood cell count decreased	8 (2.5)	4 (1.3)	4 (1.3)	1 (0.3)
Lymphocyte count decreased	2 (0.6)	1 (0.3)	0	0
Bone marrow failure	1 (0.3)	1 (0.3)	0	0
Granulocytopenia	1 (0.3)	0	0	0
Monocytopenia	0	0	1 (0.3)	0

There were no cases of myelosuppression that resulted in death in either the ELd arm or the Ld arm. Serious myelosuppression occurred in 15 of 318 subjects (4.7%) and 11 of 317 subjects (3.5%) in the ELd and Ld arms, respectively. These events were classified as anaemia (9 subjects), thrombocytopenia (5), bone marrow failure (1), neutropenia (1), and pancytopenia (1) in the ELd arm; and anaemia (6), neutropenia (3), thrombocytopenia (2), and haemoglobin decreased (1) in the Ld arm. Among these cases, a causal relationship to the study drug could not be ruled out for anaemia (1) and thrombocytopenia (1) in the ELd arm, and neutropenia (2) in the Ld arm. In the ELd and Ld arms, myelosuppression that led to study drug discontinuation occurred in 8 of 318 subjects (2.5%) and 11 of 317 subjects (3.5%), respectively; dose interruption in 94 of 318 subjects (29.6%) and 100 of 317

subjects (31.5%), respectively; and dose reduction in 27 of 318 subjects (8.5%) and 29 of 317 subjects (9.1%), respectively.

Among all myelosuppression adverse events, the incidence of lymphopenia was higher in the ELd arm than in the Ld arm both for all-grade and Grade ≥3 events; therefore, PMDA asked the applicant to explain the relationship between lymphopenia and infections, and the applicant responded as follows:
In the ELd and Ld arms of Study CA204004, infections occurred concurrently with lymphopenia (including lymphocyte count decreased) in 23 of 318 subjects (7.2%) and 7 of 317 (2.2%), respectively; and infections occurred concurrently with Grade ≥3 lymphopenia in 17 of 318 subjects (5.3%) and 4 of 317 subjects (1.3%), respectively. Because of the small percentage of patients who developed infections concurrently with lymphopenia, it is considered that there is no obvious relationship between infections and lymphopenia.

PMDA's view:
The incidence of Grade ≥3 myelosuppression was about the same in both the ELd and Ld arms in Study CA204004. However, based on the following and other findings on lymphopenia, vigilance should be exercised regarding the occurrence of lymphopenia when administering elotuzumab: the incidence of lymphopenia was higher in the ELd arm than in the Ld arm both for all-grade and Grade ≥3 events; the incidence of Grade ≥3 lymphopenia was higher in Japanese patients than in non-Japanese patients [see Section 7.R.3.2]; and the incidence of infections that occurred concurrently with Grade ≥3 lymphopenia was higher in the ELd arm than in the Ld arm. It is concluded that information on the occurrence of these events in clinical studies needs to be provided to healthcare professionals in an appropriate manner by using the package insert or other materials.

7.R.3.8 Hepatic impairment

The applicant explained the occurrence of hepatic impairment associated with elotuzumab treatment as follows:
As hepatic-impairment related adverse events, data corresponding to MedDRA PTs under MedDRA SOC (MedDRA ver. 17.0) "Hepatobiliary disorders" were tabulated.

Table 34 shows the occurrence of hepatic impairment in Study CA204004.

Table 34. Hepatic-impairment related adverse events that occurred in ≥2 subjects in at least one of the arms (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic impairment	26 (8.2)	9 (2.8)	11 (3.5)	0
Hyperbilirubinaemia	9 (2.8)	2 (0.6)	5 (1.6)	0
Hepatic function abnormal	4 (1.3)	0	3 (0.9)	0
Cholecystitis	3 (0.9)	2 (0.6)	0	0
Cholelithiasis	3 (0.9)	1 (0.3)	1 (0.3)	0
Hepatomegaly	2 (0.6)	0	1 (0.3)	0

There were no cases of hepatic impairment that resulted in death either in the ELd arm or in the Ld arm. Serious hepatic impairment occurred in 9 of 318 subjects (2.8%) and 1 of 317 subjects (0.3%) in the ELd and Ld arms, respectively. Table 35 shows a list of patients who had hepatic impairment, and there were no Japanese patients who developed hepatic impairment. In the ELd and Ld arms, hepatic impairment that led to study drug discontinuation occurred in 1 of 318 subjects (0.3%) and 1 of 317 subjects (0.3%), dose interruption in 8 of 318 subjects (2.5%) and 2 of 317 subjects (0.6%), respectively; and there were no cases of hepatic impairment that led to study drug dose reduction. The laboratory values of the patient who developed hepatitis[13] in the ELd arm met the criteria for Hy's law (based on the definition in *Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation* [U.S. Department of Health and Human Services, Food and Drug Administration; July 2009]).

Table 35. List of patients who developed serious hepatic impairment (Study CA204004)

	Age	Sex	MedDRA PT	Grade	Onset (Day)*	Causal relationship to study drug	Study drug discontinuation/ interruption	Outcome
ELd arm	7[redacted]	F	Hyperbilirubinaemia	3	690	No	Interrupted	Resolved
	7[redacted]	F	Hyperbilirubinaemia	4	106	No	No	Resolved
	6[redacted]	M	Cholangitis	3	5	No	Interrupted	Resolved
	6[redacted]	M	Cholecystitis	3	788	No	Interrupted	Resolved
	6[redacted]	F	Cholecystitis acute	2	298	No	Interrupted	Not resolved
	5[redacted]	M	Cholecystitis chronic	3	72	No	No	Resolved
	6[redacted]	F	Cholelithiasis	3	454	No	No	Resolved
	7[redacted]	M	Hepatic failure	3	246	No	No	Not resolved
	5[redacted]	M	Hepatitis	3	211	Yes	Discontinued	Resolved
Ld arm	7[redacted]	M	Hepatic function abnormal	2	58	No	Discontinued	Not resolved

*, Number of days elapsed from the start of treatment

PMDA's view:

In Study CA204004, although hepatic impairment was not rare in the ELd arm, serious hepatic impairment did not occur in Japanese patients. Moreover, many of the patients who developed serious hepatic impairment recovered regardless of whether the study drug was continued or interrupted. Therefore, it is difficult to draw a definite conclusion on the relationship between elotuzumab treatment and the occurrence of hepatic impairment. Nevertheless, based on the report of serious hepatitis following administration of elotuzumab and other considerations, it was concluded that information on the occurrence of hepatic impairment in clinical studies needs to be provided to healthcare professionals in an appropriate manner by using information materials. In addition, information should be gathered continuously on the occurrence of hepatic impairment, and whenever new knowledge becomes available, information needs to be provided to healthcare professionals in an appropriate manner.

[13] Elotuzumab treatment was discontinued when serious hepatitis occurred in Cycle 8 (211 days after the start of study drug treatment). The liver biopsy results indicated that the patient had chronic hepatitis graded as moderately active, accompanied by cirrhosis and biliary ductopenia, suggesting drug-induced liver injury. Subsequently, hepatitis resolved. A causal relationship to elotuzumab could not be ruled out. It was confirmed that the patient had had hepatic steatosis before the start of study drug treatment.

7.R.4 Anti-elotuzumab antibodies

The applicant explained the effects of anti-elotuzumab antibodies on the efficacy and safety of elotuzumab as follows:

In Study CA204004, 45 of 299 subjects (15.1%) tested positive and 254 of 299 subjects (84.9%) tested negative for anti-elotuzumab antibodies. Of the 45 anti-elotuzumab antibody-positive subjects, 19 subjects had anti-elotuzumab neutralizing antibodies (of the 19 subjects, 2 subjects had a persistently positive response).

The overall response rate in the subjects who tested positive for anti-elotuzumab neutralizing antibodies was 78.9% (15 of 19 subjects), which is about the same as that in all subjects for the study, 78.5%. In the anti-elotuzumab antibody-positive patients, immunogenicity was transient and lasted 2 to 3 months, developing at an early stage and resolving by 2 to 4 months after the start of elotuzumab treatment.

The safety profiles of subjects who tested positive for anti-elotuzumab neutralizing antibodies did not differ significantly from those of subjects who tested negative.

Based on the above results, it is considered unlikely that anti-elotuzumab antibodies have a clinically significant effect on the efficacy and safety of elotuzumab.

PMDA's view:

There have been no results so far that indicate that anti-elotuzumab antibodies affect the efficacy and safety of elotuzumab. On the other hand, because of the small number of patients who tested positive for anti-elotuzumab antibodies in the clinical studies, the effect of anti-elotuzumab antibodies on the efficacy and safety of elotuzumab is difficult to be determined. Therefore, it is considered necessary to provide information in an appropriate manner to healthcare professionals that there were patients who tested positive for anti-elotuzumab neutralizing antibody in clinical studies. This information should be provided in the package insert. In addition, information regarding the effects of anti-elotuzumab antibodies on the efficacy and safety of elotuzumab should be continuously gathered including published studies after market launch, and whenever new knowledge becomes available, the information should be provided to healthcare professionals in an appropriate manner.

7.R.5 Clinical positioning and indications

In the application for marketing approval, the proposed indication for elotuzumab has been stated as the treatment of "relapsed or refractory multiple myeloma." Also, the "Precautions for indication" section has included a statement to the effect that elotuzumab is indicated for the treatment of patients who have not responded to 1 or more lines of prior standard therapy, or patients with MM that has recurred after initial treatment.

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and in the following sections, PMDA concluded that the indication for elotuzumab should be "relapsed or refractory multiple

myeloma," the same as the proposed indication, and that the "Precautions for indication" section should include statements to the effect that:

- Elotuzumab is indicated for the treatment of patients who have not responded to 1 or more lines of prior standard therapy, or patients with MM that has recurred after initial treatment.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of elotuzumab and of the information in the "Clinical Studies" section regarding prior treatments of patients enrolled in the clinical studies.

7.R.5.1 Clinical positioning of elotuzumab

The information on the administration of elotuzumab in the treatment of patients with relapsed or refractory MM contained in the clinical practice guidelines and representative hematology and clinical oncology textbooks published in Japan and other countries are summarized below. On the other hand, there was no reference to elotuzumab in the following guidelines and textbooks: *The Hematopoietic Tumor Guidelines 2013* [in Japanese] (Kanehara Shuppan, 2013); Japanese Society of Medical Oncology. *New Clinical Oncology*, 4th revised ed. [in Japanese] (Nankodo; 2015) (one of the representative textbooks on clinical oncology); and *Wintrobe's Clinical Hematology*, 13th ed. (USA: Lippincott Williams & Wilkins; 2013) (one of the representative textbooks on hematology).

Clinical practice guidelines

- National Comprehensive Cancer Network (NCCN) Guidelines (v3.2016): As a treatment option for patients with relapsed or refractory MM, the ELd regimen is recommended (Category 1).[14]
- US NCI Physician Data Query (PDQ) (May 27, 2016 edition): In a randomized controlled study in patients with relapsed or refractory MM, the PFS was higher in the ELd regimen than in the Ld regimen.
- Japanese Society of Myeloma. *Guideline for the treatment of multiple myeloma*, 3rd ed. [in Japanese] (Bunkodo; 2012): Outside Japan, a phase II study in patients with relapsed or refractory MM demonstrated that the ELd regimen has high anti-tumor activity, and currently, a phase III study is underway in patients with relapsed or refractory MM.

Textbooks

- Williams Hematology, 9th Edition (USA: The McGraw-Hill Companies, Inc.; 2015): In a randomized study in patients with relapsed or refractory MM, the PFS was longer in the ELd regimen than in the Ld regimen.

PMDA's view:

The results of Study CA204004 demonstrated that add-on therapy of elotuzumab to the Ld regimen has clinical benefit in the treatment of patients with relapsed or refractory MM [see Sections 7.R.2 and 7.R.3]; therefore, it was concluded that the ELd regimen can be positioned as a treatment option for patients with relapsed or refractory MM.

[14] Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

7.R.5.2 Indicated patient population and indication of elotuzumab

The applicant, after comparing the efficacy of elotuzumab according to the number of prior regimens and examining clinical benefit of elotuzumab in patients who did not meet the inclusion criteria of Study CA204004, explains the target population and indication of elotuzumab as follows:

For patients with relapsed or refractory MM to be eligible for inclusion in Study CA204004, they had to have received 1 to 3 prior regimens. Further, prior exposure to lenalidomide was permitted if they met the following criteria:

- Best overall response achieved was PR or better.
- The subject did not discontinue treatment due to a Grade ≥3 adverse event that is related to lenalidomide.
- The subject did not receive more than 9 cycles of lenalidomide, and the disease did not progress during treatment or within 9 months of the end of treatment.

Table 36 shows the results of PFS analysis for subgroups defined according to the number of prior regimens in Study CA204004.

Table 36. Results of the interim analysis in terms of PFS (efficacy analysis set, determined by IRC, data cut-off on October 29, 2014)

Number of prior regimens	ELd arm		Ld arm		Hazard ratio (95% CI)
	Number of subjects	Median PFS (95% CI) (months)	Number of subjects	Median PFS (95% CI) (months)	
Total	321	19.4 (16.6, 22.2)	325	14.9 (12.1, 17.2)	0.70 (0.57, 0.85)
1 regimen	151	18.5 (15.7, 20.3)	159	16.0 (11.9, 18.9)	0.75 (0.56, 1.00)
2 regimens	118	21.4 (16.3, 26.0)	114	16.7 (12.3, 19.4)	0.74 (0.52, 1.04)
3 or more regimens	52	17.8 (10.2, 27.6)	52	8.5 (5.7, 15.5)	0.51 (0.32, 0.82)

Given that the PFS results for all the subgroups that were defined according to the number of prior regimens in Study CA204004 were similar to those for the overall study population, it is considered that elotuzumab treatment can be recommended for patients with 1 to 3 prior regimens, the criteria for Study CA204004.

Given that no data from clinical studies are currently available with regard to the clinical benefits of elotuzumab for patients with relapsed or refractory MM who do not meet the criteria of Study CA204004, it is considered that administration of elotuzumab to this patient population is not recommended

Based on the above, it is considered that the target population of elotuzumab is the same as the study population of Study CA204004; therefore, the proposed indication for elotuzumab was specified as "relapsed or refractory multiple myeloma," and at the same time, a statement to the effect that elotuzumab is indicated for the treatment of patients who have not responded to 1 or more lines of prior standard therapy, or patients with MM that has recurred after the initial treatment was included in the "Precautions for indication" section.

PMDA's view:

The applicant's explanation is largely acceptable. However, with regard to the statement that elotuzumab treatment is recommended for the patient population of Study CA204004, PMDA concluded that it is appropriate to include detailed information such as prior treatments of patients enrolled in Study CA204004 in the "Clinical studies" section of the package insert in addition to the proposed statement, and to include a statement to the following effect in the "Precautions for indication" section:

- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of elotuzumab and of the information in the "Clinical Studies" section regarding prior treatments of patients enrolled in the clinical studies.

7.R.6 Dosage and administration

The proposed dosage and administration of elotuzumab was "In combination with lenalidomide and dexamethasone, the usual adult dosage of elotuzumab (genetical combination) is 10 mg/kg per dose, infused intravenously: once a week for the first two cycles (4 doses per 28-day cycle [Days 1, 8, 15, and 22]) and every 2 weeks for the third and subsequent cycles (2 doses per 28-day cycle [Days 1 and 15])." Also, statements to the following effect were included in the "Precautions for dosage and administration" section:

- Administration of lenalidomide and DEX should be undertaken only after the information included in the "Clinical studies" section, especially on the dosage and administration, is fully understood. Read the package inserts of the agents to be co-administered thoroughly.
- The efficacy and safety of elotuzumab monotherapy have not been established.
- With the exception of lenalidomide and DEX, the efficacy and safety of elotuzumab in combination with other antineoplastic drugs have not been established.
- Pre-medication of DEX or other agents to reduce infusion reactions.
- The infusion rate for elotuzumab.
- Measures against infusion reactions.
- Treatment schedule of the other agents when dose postponement, interruption, or discontinuation of elotuzumab or agent to be co-administered has occurred.
- Instruction for reconstitution and preparation of elotuzumab.

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and in the following sections, PMDA concluded that it is appropriate to specify the "Dosage and administration" section as proposed by the applicant, and at the same time, include the following statements in the "Precautions for dosage and administration" section:

Precautions for dosage and administration

- Administration of lenalidomide and DEX, agents co-administered with elotuzumab, should be undertaken only after the information included in the "Clinical studies" section is fully understood. Read the package inserts of the agents to be co-administered thoroughly.
- The efficacy and safety of elotuzumab monotherapy have not been established.
- With the exception of lenalidomide and DEX, the efficacy and safety of elotuzumab in combination

with other antineoplastic drugs have not been established.

- To reduce infusion reactions that may occur during elotuzumab treatment, pre-medication consisting of an antihistamine (e.g., diphenhydramine), an H_2 blocker (e.g., ranitidine), and an antipyretic analgesic (e.g., acetaminophen) should be administered prior to any elotuzumab dose. Dexamethasone, which is co-administered with elotuzumab, should be administered as a split dose of 28 mg orally (3 to 24 hours prior to elotuzumab infusion) and 8 mg intravenously (DEX infusion should be completed 45 minutes prior to elotuzumab infusion).
- Initiate elotuzumab infusion at a rate of 0.5 mL/min. If well tolerated, the infusion rate may be increased in a stepwise manner as shown in the table below, while monitoring the patient's condition. The infusion rate should not exceed 2 mL/min.

Time of treatment		Infusion rate (mL/min)		
		0 to 30 min after the start of infusion	30 to 60 min after the start of infusion	≥60 min after the start of infusion
Cycle 1	Initial treatment	0.5	1	2
	Doses 2 to 4	1	2	
Cycle 2 and after		2		

- Discontinue elotuzumab treatment immediately if a Grade 4 infusion reaction occurs. If a Grade 3 infusion reaction occurs, interrupt elotuzumab treatment immediately, and in principle, elotuzumab treatment should not be resumed. If a Grade 2 infusion reaction occurs, interrupt elotuzumab treatment immediately. If the reaction resolves to Grade ≤1, elotuzumab may be restarted at 0.5 mL/min. If the infusion reaction recurs after restarting the treatment, stop the infusion immediately and do not restart infusion for the day. If a Grade 1 infusion reaction occurs, the infusion rate should be maintained at 0.5 mL/min until resolution of the infusion reaction. If elotuzumab at 0.5 mL/min is well tolerated, the infusion rate may be increased incrementally by 0.5 mL/min every 30 minutes. However, the infusion rate must not exceed the rate at which the infusion reaction occurred that day.
- If administration of DEX is postponed or discontinued, decide whether to administer elotuzumab on the basis of the risk of infusion reactions.
- Elotuzumab for 300 mg injection should be reconstituted with 13 mL of water for injection, and elotuzumab for 400 mg injection should be reconstituted with 17 mL of water for injection to make a 25-mg/mL solution. Calculate the dose from the body weight of the patient, and dilute the corresponding amount of the solution normally with 230 mL of isotonic sodium chloride solution or 5% glucose solution for injection.

7.R.6.1 Dosage and administration of elotuzumab

The applicant explained the dosage and administration of elotuzumab as follows:

In Study HuLuc63-1703, which was conducted in patients with relapsed MM to evaluate the efficacy and safety of the ELd regimen, the dosage and administration of elotuzumab was specified as follows:

- It was decided that elotuzumab was to be administered in 28-day cycles, to match the cycle of the Ld regimen, which was to be co-administered with elotuzumab. To prevent infusion reactions, on

days of elotuzumab infusion, DEX was to be administered at a split dose of 28 mg orally and 8 mg intravenously instead of an oral dose of 40 mg.

- In order to rapidly reach the minimum effective elotuzumab concentration,[15] at which binding of elotuzumab to SLAMF7 expressed on the MM cell membrane is saturated, it was planned for elotuzumab to be administered QW in Cycles 1 and 2 and Q2W in the subsequent cycles.

The results showed (1) that elotuzumab was tolerated at doses of up to 20 mg/kg; (2) that elotuzumab may be clinically beneficial at 10 and 20 mg/kg, and that there were no obvious differences in efficacy and safety between the dose levels [see Section 7.1.3.2]. The dosage and administration used in Study CA204004 was determined as follows: in 28-day cycles, elotuzumab is administered at 10 mg/kg QW in Cycles 1 and 2, and Q2W in the subsequent cycles.

Study CA204004 was conducted according to the above regimen, and the results demonstrated that elotuzumab had a clinical benefit in patients with relapsed or refractory MM; accordingly, the proposed dosage and administration of elotuzumab was determined on the basis of those used in these studies.

PMDA accepted the applicant's explanation.

7.R.6.2 Elotuzumab monotherapy and co-administration with other antineoplastic drugs

The applicant gave the following explanation regarding elotuzumab monotherapy and co-administration with antineoplastic drugs other than DEX and lenalidomide:

Data are unavailable from clinical studies in patients with relapsed or refractory MM that evaluated the efficacy and safety of elotuzumab monotherapy or co-administration with antineoplastic drugs other than the Ld regimen; therefore, administration of elotuzumab either as monotherapy or with other antineoplastic drugs is not recommended. Based on the above, in the "Dosage and administration" section, a statement to the effect that elotuzumab should be administered in combination with lenalidomide plus DEX will be included; and at the same time, in the "Precautions for dosage and administration" section, a statement will be included to the effect that the efficacy and safety of elotuzumab monotherapy have not been established, or when used in combination with antineoplastic drugs with the exception of lenalidomide and DEX.

PMDA accepted the applicant's explanation.

7.R.7 Post-marketing investigations

The applicant explained the post-marketing surveillance plan as follows:

The applicant has planned to conduct a post-marketing surveillance covering all patients who receive elotuzumab after market launch to investigate safety and other aspects of elotuzumab under actual use conditions.

[15] The threshold value of the concentration of elotuzumab in serum (C_{min} ≥70 μg/mL), at which the maximum anti-tumor effect was reached based on the results of a non-clinical study using mice subcutaneously inoculated with human MM cell line [see Section 3.1.3].

Infusion reactions were specified as a key survey item, because these reactions occurred in 230 of 318 subjects (72.3%) in Study CA204004, and these were considered to be adverse events unique to elotuzumab.

It was determined that the target sample size would be 330 patients, as this will allow about the same number of infusion reaction events to be detected as occurred in Study CA204004.

Among 230 subjects who had infusion reactions in Study CA204004, the event occurred within 6 cycles (24 weeks) of the start of elotuzumab treatment in 197 subjects (85.7%), and a trend towards an increase in the incidence of infusion reactions was not observed in Cycle 7 and after; therefore, it was determined that the observation period would be 6 cycles (24 weeks) from the start of elotuzumab treatment.

PMDA's view:
Due to the paucity of safety data on Japanese patients with relapsed or refractory MM who received elotuzumab, it is necessary to conduct a post-marketing surveillance covering all patients who receive elotuzumab for a specific period after market launch to collect safety data quickly and comprehensively and to provide the obtained safety information promptly to healthcare professionals.

It is appropriate to select infusion reactions, infections, second primary malignancies, cataract, and lymphopenia, which are the adverse events of particular concern when administering elotuzumab, as the key survey items for the post-marketing surveillance, based on the incidence of adverse events observed in clinical studies both in and outside Japan.

The target sample size and the duration of the observation period should be re-examined based on the details of the key survey items.

7.3 Adverse events and other findings observed in clinical studies

The following sections describe major adverse events included in the results of clinical studies submitted for safety evaluation, except the results for death, which are described in Sections "7.1 Evaluation data" and "7.2 Reference data."

7.3.1 Japanese phase I study (CA204005)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out also occurred in all subjects. Table 37 shows adverse events that occurred with an incidence of ≥40% in at least one of the arms.

Table 37. Adverse events that occurred with an incidence of ≥40% in at least one of the arms

SOC PT (MedDRA/J ver. 16.1)	Number of subjects (%)			
	10 mg/kg 3 subjects		20 mg/kg 3 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	3 (100)	3 (100)	3 (100)	3 (100)
Blood and lymphatic system disorders				
Leukopenia	3 (100)	1 (33.3)	3 (100)	0
Lymphopenia	3 (100)	3 (100)	3 (100)	2 (66.7)
Neutropenia	3 (100)	1 (33.3)	2 (66.7)	1 (33.3)
Thrombocytopenia	2 (66.7)	0	0	0
Gastrointestinal disorders				
Constipation	2 (66.7)	0	2 (66.7)	0
Dental caries	0	0	2 (66.7)	0
Diarrhoea	0	0	2 (66.7)	0
Nausea	2 (66.7)	0	0	0
General disorders and administration site conditions				
Pyrexia	3 (100)	0	1 (33.3)	0
Malaise	0	0	2 (66.7)	0
Infections and infestations				
Nasopharyngitis	2 (66.7)	0	2 (66.7)	0
Investigations				
ALT increased	1 (33.3)	0	2 (66.7)	1 (33.3)
AST increased	1 (33.3)	0	2 (66.7)	1 (33.3)
Nervous system disorders				
Dysgeusia	2 (66.7)	0	3 (100)	0
Skin and subcutaneous tissue disorders				
Rash	2 (66.7)	0	2 (66.7)	0
Dry skin	0	0	2 (66.7)	0
Psychiatric disorders				
Insomnia	2 (66.7)	0	1 (33.3)	0
Vascular disorders				
Flushing	0	0	2 (66.7)	0

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 10 mg/kg arm and 3 of 3 subjects (100%) in the 20 mg/kg arm. These events were classified as hepatitis (1 subject; 33.3%) in the 10 mg/kg arm, and cataract, bronchopneumonia, ALT increased, AST increased, blood ALP increased, and GGT increased (1 subject each; 33.3% each) in the 20 mg/kg arm. A causal relationship to the study drug could not be ruled out for hepatitis (1 subject) in the 10 mg/kg arm and cataract (1) in the 20 mg/kg arm.

There were no adverse events that led to study drug discontinuation.

7.3.2 International phase III study (Study CA204004)

Adverse events occurred in 316 of 318 subjects (99.4%) in the ELd arm and 314 of 317 subjects (99.1%) in the Ld arm, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 293 of 318 subjects (92.1%) in the ELd arm and 277 of 317 subjects (87.4%) in the Ld arm. Table 38 shows adverse events with an incidence of ≥30% in at least one of the arms.

Table 38. Adverse events with an incidence of ≥30% in at least one of the arms

SOC PT (MedDRA/J ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	316 (99.4)	278 (87.4)	314 (99.1)	247 (77.9)
General disorders and administration site conditions				
Fatigue	149 (46.9)	27 (8.5)	123 (38.8)	26 (8.2)
Pyrexia	119 (37.4)	8 (2.5)	78 (24.6)	9 (2.8)
Gastrointestinal disorders				
Diarrhoea	149 (46.9)	16 (5.0)	114 (36.0)	13 (4.1)
Constipation	113 (35.5)	4 (1.3)	86 (27.1)	1 (0.3)
Blood and lymphatic system disorders				
Anaemia	124 (39.0)	48 (15.1)	117 (36.9)	52 (16.4)
Neutropenia	107 (33.6)	79 (24.8)	135 (42.6)	105 (33.1)
Respiratory, thoracic and mediastinal disorders				
Cough	100 (31.4)	1 (0.3)	57 (18.0)	0

Serious adverse events occurred in 208 of 318 subjects (65.4%) in the ELd arm and 179 of 317 subjects (56.5%) in the Ld arm. Serious adverse events that occurred in ≥5 subjects in each arm were: in the ELd arm, pneumonia (35 subjects; 11.0%), pyrexia (22 subjects; 6.9%), disease progression (13 subjects; 4.1%), pulmonary embolism (10 subjects, 3.1%), respiratory tract infection (10 subjects, 3.1%), anaemia (9 subjects; 2.8%), renal failure acute (8 subjects; 2.5%), bronchitis (7 subjects; 2.2%), atrial fibrillation, general physical health deterioration, bronchopneumonia, squamous cell carcinoma of skin (6 subjects each; 1.9% each), diarrhoea, sepsis, plasma cell myeloma, back pain, malignant neoplasm progression, febrile neutropenia, deep vein thrombosis, cataract, thrombocytopenia, and cellulitis (5 subjects each; 1.6% each); in the Ld arm, pneumonia (27 subjects; 8.5%), pyrexia (15 subjects; 4.7%), disease progression (10 subjects; 3.2%), pulmonary embolism, atrial fibrillation, diarrhoea (8 subjects each; 2.5% each), bronchitis (7 subjects; 2.2%), anaemia, renal failure acute, sepsis (6 subjects each; 1.9% each), plasma cell myeloma, back pain, renal failure, urinary tract infection, influenza, and septic shock (5 subjects each; 1.6% each). Among these cases, a causal relationship to the study drug could not be ruled out for the following cases: pneumonia (18 subjects), pyrexia (8), pulmonary embolism (8), respiratory tract infection (6), diarrhoea (5), deep vein thrombosis (5), febrile neutropenia (3), bronchitis (2), squamous cell carcinoma of skin (2), sepsis (2), cataract (2), anaemia (1), renal failure acute (1), general physical health deterioration (1), bronchopneumonia (1), thrombocytopenia (1), and cellulitis (1) in the ELd arm; pneumonia (8), pulmonary embolism (6), pyrexia (5), sepsis (3), bronchitis (2), renal failure acute (2), septic shock (2), atrial fibrillation (1), diarrhoea (1), renal failure (1), urinary tract infection (1), and influenza (1) in the Ld arm.

Adverse events that led to discontinuation of study drug treatment occurred in 83 of 318 subjects (26.1%) in the ELd arm and 85 of 317 subjects (26.8%) in the Ld arm. Adverse events that led to discontinuation of study drug treatment in ≥3 subjects in each arm were: in the ELd arm, disease progression (10 subjects; 3.1%), anaemia, pulmonary embolism, hyperglycaemia, and diarrhoea (3 subjects each; 0.9% each); and in the Ld arm, thrombocytopenia (6 subjects; 1.9%), fatigue, general physical health deterioration, neutropenia (5 subjects each; 1.6% each), disease progression, anaemia, and anaemia (4 subjects each; 1.3% each), pulmonary embolism, pneumonia, renal failure, and sepsis

(3 subjects each; 0.9% each). Among these cases, a causal relationship to the study drug could not be ruled out for the following cases: pulmonary embolism (3 subjects), hyperglycaemia (2), and diarrhoea (3) in the ELd arm; and neutropenia (5), and fatigue (5), thrombocytopenia (4), pulmonary embolism (3), general physical health deterioration (2), asthenia (2), sepsis (2), and anaemia (1).

7.3.3 Foreign phase I study (Study HuLuc63-1701)

Adverse events occurred in 30 of 34 subjects (88.2%), and a causal relationship to elotuzumab could not be ruled out for 18 of 34 subjects (52.9%). Adverse events with an incidence of ≥20% were: chills, fatigue, pyrexia (13 subjects each; 38.2% each), cough, headache (10 subjects each; 29.4% each), anaemia (9 subjects; 26.5%), nausea (8 subjects; 23.5%), and back pain (7 subjects; 20.6%). Among these, anaemia (8 subjects), fatigue (1), and pyrexia (1) were Grade ≥3.

Serious adverse events occurred in 15 of 34 subjects (44.1%). These events were classified as pyrexia, pneumonia, sepsis, urinary tract infection (2 subjects each; 5.9% each), anaemia, febrile neutropenia, bradycardia, cardiac failure congestive, tachycardia, melena, chest discomfort, chest pain, chills, hypersensitivity, bacteraemia, staphylococcal bacteraemia, accidental overdose, spinal compression fracture, hypercalcaemia, muscular weakness, migraine, renal failure, renal failure acute, renal failure acute, respiratory failure, and orthostatic hypotension (1 subject each; 2.9% each). Among these cases, a causal relationship to elotuzumab could not be ruled out for pyrexia (1 subject), bradycardia (1), chest discomfort (1), chills (1), hypersensitivity (1), and renal failure acute (1).

Adverse events that led to elotuzumab treatment discontinuation occurred in 2 of 34 subjects (5.9%). These events were classified as migraine, cardiac failure congestive, and hypersensitivity (1 subject each; 2.9% each), and a causal relationship to elotuzumab could not be ruled out for hypersensitivity (1 subject).

7.3.4 Foreign phase Ib/II study (Study HuLuc63-1703)

7.3.4.1 Phase Ib part

Adverse events occurred in all subjects and a causal relationship to the study drug could not be ruled out in any of these subjects. Table 39 shows adverse events with an incidence of ≥40% in at least one of the arms.

Table 39. Adverse events with an incidence of ≥40% in at least one of the arms

SOC PT (MedDRA/J ver. 16.1)	Number of subjects (%)					
	5 mg/kg 3 subjects		10 mg/kg 3 subjects		20 mg/kg 22 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	3 (100)	2 (66.7)	3 (100)	3 (100)	22 (100)	19 (86.4)
Gastrointestinal disorders						
Diarrhoea	1 (33.3)	0	2 (66.7)	2 (66.7)	14 (63.6)	2 (9.1)
Constipation	1 (33.3)	0	2 (66.7)	1 (33.3)	11 (50.0)	0
Nausea	0	0	3 (100)	0	11 (50.0)	0
General disorders and administration site conditions						
Fatigue	1 (33.3)	1 (33.3)	2 (66.7)	0	15 (68.2)	3 (13.6)
Pyrexia	0	0	0	0	10 (45.5)	0
Chills	2 (66.7)	0	2 (66.7)	0	1 (4.5)	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	1 (33.3)	0	1 (33.3)	0	10 (45.5)	0
Arthralgia	0	0	2 (66.7)	0	7 (31.8)	1 (4.5)
Blood and lymphatic system disorders						
Anaemia	2 (66.7)	0	2 (66.7)	1 (33.3)	10 (45.5)	2 (9.1)
Neutropenia	2 (66.7)	1 (33.3)	3 (100)	3 (100)	7 (31.8)	7 (31.8)
Thrombocytopenia	1 (33.3)	1 (33.3)	2 (66.7)	2 (66.7)	5 (22.7)	5 (22.7)
Psychiatric disorders						
Insomnia	2 (66.7)	0	1 (33.3)	0	6 (27.3)	0

Serious adverse events occurred in 3 of 3 subjects (100%) in the 10 mg/kg arm and 12 of 22 subjects (54.5%) in the 20 mg/kg arm. These events were classified as febrile neutropenia, atrial fibrillation, diarrhoea, diverticular perforation, gastrointestinal haemorrhage, gastrointestinal perforation, metabolic acidosis, and renal failure acute (1 subject each; 33.3% each) in the 10 mg/kg arm; and lung disorder (2 subjects; 9.1%), febrile neutropenia, atrial fibrillation, haematemesis, chest pain, anaphylactic reaction, aspergillus infection, pneumonia, sepsis, urinary tract infection, gastroenteritis radiation, arthralgia, pulmonary embolism, stridor, and deep vein thrombosis (1 subject each; 4.5% each) in the 20 mg/kg arm. Among these events, a causal relationship to the study drug that could not be ruled out for the following: diverticular perforation (1 subject) in the 10 mg/kg arm; and lung disorder (1), atrial fibrillation (1), haematemesis (1), anaphylactic reaction (1), pneumonia (1), urinary tract infection (1), pulmonary embolism (1), and stridor (1) in the 20 mg/kg arm.

Adverse events that led to study drug discontinuation occurred in 2 of 3 subjects (66.7%) in the 10 mg/kg arm and 5 of 22 subjects (22.7%) in the 20 mg/kg arm. These events were classified as atrial fibrillation, gastrointestinal haemorrhage, metabolic acidosis, renal failure acute, and diverticular perforation (1 subject each; 33.3% each) in the 10 mg/kg arm; and atrial fibrillation, bradycardia, aspergillus infection, anaphylactic reaction, glaucoma, stridor, and urticaria (1 subject each; 4.5% each) in the 20 mg/kg arm. Among these cases, a causal relationship to the study drug could not be ruled out for: diverticular perforation (1 subject) in the 10 mg/kg arm, and anaphylactic reaction (1), glaucoma (1), stridor (1), and urticaria (1) in the 20 mg/kg arm.

7.3.4.1 Phase II part

Adverse events occurred in all subjects. A causal relationship to the study drug could not be ruled out for 36 of 36 subjects (100%) in the 10 mg/kg arm and 35 of 37 subjects (94.6%) in the 20 mg/kg arm. Table 40 shows adverse events with an incidence of ≥40% in at least one of the arms.

Table 40. Adverse events with an incidence of ≥40% in at least one of the arms

SOC PT (MedDRA/J ver. 16.1)	Number of subjects (%)			
	10 mg/kg 36 subjects		20 mg/kg 37 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	36 (100)	32 (88.9)	37 (100)	25 (67.6)
General disorders and administration site conditions				
Fatigue	24 (66.7)	3 (8.3)	17 (45.9)	2 (5.4)
Pyrexia	14 (38.9)	1 (2.8)	17 (45.9)	1 (2.7)
Gastrointestinal disorders				
Diarrhoea	24 (66.7)	5 (13.9)	24 (64.9)	2 (5.4)
Constipation	18 (50.0)	0	19 (51.4)	0
Nausea	18 (50.0)	0	17 (45.9)	1 (2.7)
Infections and infestations				
Upper respiratory tract infection	19 (52.8)	1 (2.8)	15 (40.5)	1 (2.7)
Musculoskeletal and connective tissue disorders				
Muscle spasms	22 (61.1)	2 (5.6)	23 (62.2)	0
Back pain	17 (47.2)	3 (8.3)	13 (35.1)	1 (2.7)
Blood and lymphatic system disorders				
Anaemia	17 (47.2)	6 (16.7)	12 (32.4)	5 (13.5)
Psychiatric disorders				
Insomnia	10 (27.8)	0	15 (40.5)	2 (5.4)

Serious adverse events occurred in 21 of 36 subjects (58.3%) in the 10 mg/kg arm and 21 of 37 subjects (56.8%) in the 20 mg/kg arm. These events were classified as follows: in the 10 mg/kg arm, pneumonia (4 subjects; 11.1%), sepsis (3 subjects; 8.3%), bronchitis, bronchitis, syncope (2 subjects each; 5.6% each), febrile neutropenia, neutropenia, myelodysplastic syndrome, squamous cell carcinoma, transient ischaemic attack, pulmonary embolism, bradycardia, tachycardia, constipation, clostridium difficile immunisation, H1N1 influenza, herpes zoster, influenza, localised infection, pneumonia viral, postoperative wound infection, hypokalaemia, back pain, bone pain, musculoskeletal pain, spinal pain, malignant melanoma, cerebrovascular accident, grand mal convulsion, renal colic, renal failure acute, dyspnoea, lung disorder, rash, accelerated hypertension, and phlebitis superficial (1 subject each; 2.8% each) ; in the 20 mg/kg arm, pneumonia (5 subjects; 13.5%), pyrexia, confusional state, renal failure (2 subjects each; 5.4% each), sepsis, bronchitis, cellulitis, febrile neutropenia, neutropenia, myelodysplastic syndrome, squamous cell carcinoma, transient ischaemic attack, pulmonary embolism, lymphopenia, atrial fibrillation, nausea, varices oesophageal, vomiting, multi-organ failure, cholecystitis, lung infection, meningitis, visceral leishmaniasis, hypercalcaemia, bladder transitional cell carcinoma, lobular breast carcinoma in situ, prostate cancer, transient global amnesia, benign prostatic hyperplasia, prostatitis, acute respiratory failure, pneumonitis, deep vein thrombosis, and phlebitis (1 subject each; 2.7% each). Among these events, a causal relationship to the study drug could not be ruled out for the following cases: in the 10 mg/kg arm, pneumonia (4 subjects), sepsis (2), bronchitis (2), syncope (1), febrile neutropenia (1), neutropenia (1), myelodysplastic syndrome (1), squamous cell carcinoma (1), pulmonary embolism (1), bradycardia (1), constipation (1), herpes zoster (1), influenza (1),

postoperative wound infection (1), pneumonia viral (1), malignant melanoma (1), cerebrovascular accident (1), lung disorder (1), and rash (1); in the 20 mg/kg arm, pneumonia (1), febrile neutropenia (1), neutropenia (1), myelodysplastic syndrome (1), pulmonary embolism (1), lymphopenia (1), atrial fibrillation (1), nausea (1), varices oesophageal (1), vomiting (1), visceral leishmaniasis (1), prostate cancer (1), transient global amnesia (1), deep vein thrombosis (1), and phlebitis (1).

Adverse events that led to study drug discontinuation occurred in 6 of 36 subjects (16.7%) in the 10 mg/kg arm and 10 of 37 subjects (27.0%) in the 20 mg/kg arm. These events were classified as sepsis, myelodysplastic syndrome, dermatitis allergic, bone pain, fall, muscular weakness, and interstitial lung disease (1 subject each; 2.8% each) in the 10 mg/kg arm; and sepsis, myelodysplastic syndrome, bladder transitional cell carcinoma, thrombocytopenia, febrile neutropenia, leukopenia, neutropenia, rash maculo-papular, prostate cancer, glomerulonephritis, visceral leishmaniasis, C-reactive protein increased, multi-organ failure, cellulitis, pneumonia, and meningitis (1 subject each; 2.7% each) in the 20 mg/kg arm. Among these events, a causal relationship to the study drug could not be ruled out for the following cases: myelodysplastic syndrome (1 subject), dermatitis allergic (1), fall (1), muscular weakness (1), and interstitial lung disease (1) in the 10 mg/kg arm; and myelodysplastic syndrome (1), thrombocytopenia (1), febrile neutropenia (1), leukopenia (1), neutropenia (1), rash maculo-papular (1), prostate cancer (1), glomerulonephritis (1), visceral leishmaniasis (1), and C-reactive protein increased (1) in the 20 mg/kg arm.

7.3.5 Foreign phase Ib study (Study CA204007)

Adverse events occurred in all subjects. A causal relationship to the study drug could not be ruled out in 21 of 26 subjects (80.8%). Adverse events with an incidence of ≥30% were: fatigue (16 subjects; 61.5%), diarrhoea (11 subjects; 42.3%), back pain, constipation, anaemia (10 subjects each; 38.5% each), pyrexia, oedema peripheral (9 subjects each; 34.6% each), thrombocytopenia, and hyperglycaemia (8 subjects each; 30.8% each). Among these events, Grade ≥3 events were: hyperglycaemia (4 subjects), diarrhoea (2), fatigue (2), anaemia (2), thrombocytopenia (2), and back pain (1).

Serious adverse events occurred in 15 of 26 subjects (57.7%). These events were classified as pneumonia, upper respiratory tract infection (2 subjects each; 7.7% each), sepsis, pulmonary embolism, pneumonia respiratory syncytial viral, soft tissue infection, gout, hyperglycaemia, abdominal pain, cholecystitis, hypertensive crisis, chest discomfort, chest pain, pyrexia, bronchitis, influenza, staphylococcal bacteraemia, hypercalcaemia, hyperkalaemia, febrile neutropenia, atrial fibrillation, tachycardia, hypothyroidism, diarrhoea, blood creatinine increased, dyspnoea, and deep vein thrombosis (1 subject each; 3.8% each). Among these events, a causal relationship to the study drug could not be ruled out for pneumonia (1 subject), upper respiratory tract infection (1), sepsis (1), pulmonary embolism (1), soft tissue infection (1), hyperglycaemia (1), hypertensive crisis (1), staphylococcal bacteraemia (1), febrile neutropenia (1), and deep vein thrombosis (1).

Adverse events that led to study drug discontinuation occurred in 4 of 26 subjects (15.4%). These events were classified as infusion related reaction, soft tissue infection, blood creatinine increased, agitation,

and drug eruption (1 subject each; 3.8% each). Among these events, a causal relationship to the study drug could not be ruled out for infusion related reaction (1 subject), soft tissue infection (1), agitation (1), and drug eruption (1).

7.3.6 Foreign phase I study (Study HuLuc63-1702)

Adverse events occurred in all subjects. A causal relationship to the study drug could not be ruled out in 23 of 28 subjects (82.1%). Adverse events with an incidence of ≥30% were: fatigue (24 subjects; 85.7%), diarrhoea (21 subjects; 75.0%), anaemia (19 subjects; 67.9%), thrombocytopenia, nausea (18 subjects each; 64.3% each), hyperglycaemia (16 subjects; 57.1%), lymphopenia (15 subjects; 53.6%), leukopenia, neutropenia, constipation, neuropathy peripheral (13 subjects each; 46.4% each), headache (11 subjects; 39.3%), vomiting, pyrexia, upper respiratory tract infection (10 subjects each; 35.7% each), and chills (9 subjects; 32.1%). Among these events, Grade ≥3 events were: lymphopenia (7 subjects), thrombocytopenia (4), fatigue (4), neutropenia (3), hyperglycaemia (3), neuropathy peripheral (3), anaemia (2), leukopenia (2), vomiting (1), and upper respiratory tract infection (1).

Serious adverse events occurred in 10 of 28 subjects (35.7%). These events were classified as pneumonia (4 subjects; 14.3%), vomiting, sepsis, acute myocardial infarction, hypercalcaemia, dehydration, chest pain, gastroenteritis, influenza, ileus, and metabolic encephalopathy (1 subject each; 3.6% each). Among these events, a causal relationship to the study drug could not be ruled out for sepsis (1 subject), chest pain (1), gastroenteritis (1), and ileus (1).

Adverse events that led to study drug discontinuation occurred in 9 of 28 subjects (32.1%). These events were classified as neuropathy peripheral, weight decreased (2 subjects each; 7.1% each), sepsis, acute myocardial infarction, gastroenteritis, pain in extremity, metabolic encephalopathy, and peripheral sensory neuropathy (1 subject each; 3.6% each). Among these events, a causal relationship to the study drug could not be ruled out for neuropathy peripheral (2 subjects), weight decreased (1), sepsis (1), gastroenteritis (1), pain in extremity (1), and peripheral sensory neuropathy (1).

7.3.7 Foreign phase II study (Study CA204009)

Adverse events occurred in 75 of 75 subjects (100%) in the EBd arm and 72 of 75 subjects (96.0%) in the Bd arm. A causal relationship to the study drug could not be ruled out for 63 of 75 subjects (84.0%) in the EBd arm and 63 of 75 subjects (84.0%) in the Bd arm. Table 41 shows adverse events that occurred with an incidence of ≥30% at least one of the arms.

Table 41. Adverse events that occurred with an incidence of ≥30% at least one of the arms

SOC PT (MedDRA/J ver. 17.0)	Number of subjects (%)			
	EBd 75 subjects		Bd 75 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	75 (100)	55 (73.3)	72 (96.0)	51 (68.0)
Gastrointestinal disorders				
Diarrhoea	32 (42.7)	6 (8.0)	25 (33.3)	3 (4.0)
Constipation	29 (38.7)	1 (1.3)	22 (29.3)	0
General disorders and administration site conditions				
Pyrexia	25 (33.3)	0	20 (26.7)	3 (4.0)
Nervous system disorders				
Neuropathy peripheral	26 (34.7)	6 (8.0)	25 (33.3)	7 (9.3)
Respiratory, thoracic and mediastinal disorders				
Cough	29 (38.7)	1 (1.3)	17 (22.7)	0
Blood and lymphatic system disorders				
Anaemia	28 (37.3)	5 (6.7)	21 (28.0)	5 (6.7)

Serious adverse events occurred in 35 of 75 subjects (46.7%) in the EBd arm and 31 of 75 subjects (41.3%) in the Bd arm. Serious adverse events that occurred in ≥2 subjects in each arm were: pneumonia (6 subjects; 8.0%), diarrhoea (4 subjects; 5.3%), syncope (3 subjects; 4.0%), abdominal pain, nausea, and malignant neoplasm progression, renal failure, cellulitis, hyperglycaemia, and oedema peripheral (2 subjects each; 2.7% each) in the EBd arm; and pneumonia (4 subjects; 5.3%), pyrexia (3 subjects; 4.0%), sepsis, vomiting, small intestinal obstruction, cardio-respiratory arrest, and renal failure acute (2 subjects each; 2.7% each) in the Bd arm. Among these events, a causal relationship to the study drug could not be ruled out for diarrhoea (2 subjects) and hyperglycaemia (2) in the EBd arm and vomiting (1) in the Bd arm.

Adverse events that led to study drug discontinuation occurred in 21 of 75 subjects (28.0%) in the EBd arm and 26 of 75 subjects (34.7%) in the Bd arm. Adverse events that led to study drug discontinuation in ≥2 subjects were neuropathy peripheral, thrombocytopenia (3 subjects each; 4.0% each), renal failure, neuralgia, anaemia, back pain, diarrhoea, and blood creatinine increased (2 subjects each; 2.7% each) in the EBd arm; and neuropathy peripheral (6 subjects; 8.0%), paraesthesia, pyrexia, pneumonia (3 subjects each; 4.0% each), cardio-respiratory arrest, and orthostatic hypotension (2 subjects each; 2.7% each) in the Bd arm. Among these events, a causal relationship to the study drug could not be ruled out for neuropathy peripheral (3 subjects), neuralgia (2), diarrhoea (2), and thrombocytopenia (1) in the EBd arm, and neuropathy peripheral (4), paraesthesia (2), and orthostatic hypotension (2) in the Bd arm.

7.3.8 Foreign phase IIa study (Study CA204010)

Adverse events occurred in all subjects. A causal relationship to the study drug could not be ruled out in 30 of 40 subjects (75.0%). Table 42 shows adverse events with an incidence of ≥20%.

Table 42. Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver. 16.1)	Number of subjects (%) 40 subjects	
	All Grades	Grade ≥3
Adverse events total	40 (100)	27 (67.5)
General disorders and administration site conditions		
Asthenia]	14 (35.0)	0
Oedema peripheral	10 (25.0)	1 (2.5)
Pyrexia	10 (25.0)	0
Infections and infestations		
Respiratory tract infection	9 (22.5)	3 (7.5)
Nervous system disorders		
Neuropathy peripheral	9 (22.5)	1 (2.5)
Musculoskeletal and connective tissue disorders		
Back pain	8 (20.0)	2 (5.0)
Gastrointestinal disorders		
Constipation	8 (20.0)	1 (2.5)
Blood and lymphatic system disorders		
Anaemia	15 (37.5)	5 (12.5)

Serious adverse events occurred in 23 of 40 subjects (57.5%). These events were classified as respiratory tract infection, pneumonitis (3 subjects each; 7.5% each), pneumonia, septic shock, malignant neoplasm progression, confusional state (2 subjects each; 5.0% each), aspergillus infection, bronchopulmonary aspergillosis, cellulitis, herpes zoster, lung infection, epistaxis, pulmonary embolism, pulmonary oedema, cardiac death, disease progression, sudden death, cardio-respiratory arrest, myocarditis, femur fracture, spinal fracture, renal failure, renal failure acute, pancreatitis, aspiration bronchial, spinal pain, and hypertension (1 subject each; 2.5% each). Among these events, a causal relationship to the study drug could not be ruled out for confusional state (2 subjects; 5.0%), pneumonia, pulmonary embolism, sudden death, and myocarditis (1 subject each).

Adverse events that led to study drug discontinuation occurred in 13 of 40 subjects (32.5%). These events were classified as septic shock (2 subjects; 5.0%), respiratory tract infection, pneumonitis, pulmonary oedema, rales, cardio-respiratory arrest, myocarditis, renal failure, renal failure acute, thrombocytopenia, pancreatitis, cardiac death, and femur fracture (1 subject each; 2.5% each). Among these events, a causal relationship to the study drug could not be ruled out for myocarditis (1 subject).

7.3.9 Foreign phase II study (Study CA204011)

Adverse events occurred in 29 of 31 subjects (93.5%). A causal relationship to elotuzumab could not be ruled out in 17 of 31 subjects (54.8%). Adverse events with an incidence of ≥20% were upper respiratory tract infection (12 subjects; 38.7%), fatigue, and insomnia (9 subjects each; 29.0% each). Among these events, Grade ≥3 events were upper respiratory tract infection (1 subject), fatigue (1), and insomnia (1).

Serious adverse events occurred in 12 of 31 subjects (38.7%). These events were classified as pneumonia (2 subjects; 6.5%), upper respiratory tract infection, urosepsis, asthenia, infusion related reaction, pathological fracture, transient ischaemic attack, rectal abscess, prostate cancer, renal cell carcinoma, dyspnoea, respiratory failure, vertigo, dehydration, and renal failure acute (1 subject each; 3.2% each).

Among these events, a causal relationship to elotuzumab could not be ruled out for pneumonia (1 subject), infusion related reaction (1), and dyspnoea (1).

Adverse events that led to elotuzumab treatment discontinuation occurred in 5 of 31 subjects (16.1%). These events were classified as asthenia, chills, local swelling, malaise, oedema peripheral, cushingoid, abdominal distension, urosepsis, pathological fracture, alopecia, and renal cell carcinoma (1 subject each; 3.2% each), and a causal relationship to elotuzumab was ruled out for all of these events.

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

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

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical and Medical Device Act for the data submitted in the new drug application. The inspection and assessment revealed no particular problems. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical and Medical Device Act for the data submitted in the new drug application (CTD 5.3.3.2-1, 5.3.5.1-1). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. However, the following issue was found regarding some clinical study institutions, albeit with no major impact on the overall study evaluation, and was notified to the directors of the institutions as an issue to be improved.

Issues to be improved

Clinical study institutions

- Deviation from the protocol (non-compliance with the specifications on the infusion rate of the study drug, or the specifications on the dosage and administration of agents that were co-administered during the study period)

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

On the basis of the data submitted, PMDA has concluded that elotuzumab has efficacy in the treatment of relapsed or refractory MM, and that elotuzumab has acceptable safety in view of its benefits. Elotuzumab is a drug with a new active ingredient, and it is considered that the anti-tumor effects of elotuzumab are exerted primarily by binding to SLAMF7, which is expressed at cell membranes, especially those of MM cells, inducing ADCC activity against MM cells through Fc-receptor-mediated interaction with NK cells. Elotuzumab is thus considered to be a clinically significant treatment option for relapsed or refractory MM. PMDA considers that further discussions are necessary regarding the indications, dosage and administration, post-marketing investigations, and other issues of elotuzumab.

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

Review Report (2)

August 30, 2016

Product Submitted for Approval

Brand Name	Empliciti for I.V. Infusion 300 mg Empliciti for I.V. Infusion 400 mg
Non-proprietary Name	Elotuzumab (Genetical Recombination)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	December 24, 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 below. 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

In a global phase III study (Study CA204004) conducted in patients with relapsed or refractory multiple myeloma (MM), the progression free survival, the primary endpoint, was significantly longer in the treatment arm (the ELd regimen arm: elotuzumab [genetical recombination] + lenalidomide hydrate [lenalidomide] + dexamethasone [DEX]) than in the control arm (the Ld regimen arm: lenalidomide + DEX). In view of this finding and based on the review presented in Section "7.R.2 Efficacy" of Review Report (1), PMDA concluded that elotuzumab was shown to be effective in the treatment of relapsed or refractory MM.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following issue was raised by the expert advisors:

- Elotuzumab can be detected by tests that measure serum M-proteins (i.e., serum protein electrophoresis [SPEP] and immunofixation electrophoresis [IFE]), and thereby may interfere with the assessment of complete response. This information should be provided to healthcare professionals.

PMDA's view:

It is beneficial for healthcare professionals to know that elotuzumab may interfere with the assessment of complete response. Accordingly, this information should be provided to healthcare professionals in an appropriate manner using the package insert or other materials.

Based on the above, PMDA instructed the applicant to take appropriate actions regarding this issue, and the applicant agreed with the instruction.

1.2 Safety

Based on the discussion presented in Section "7.R.3 Safety" of Review Report (1), PMDA concluded that special attention should be paid to the following adverse events in patients treated with elotuzumab: infusion reactions, infections, second primary malignancies, cataract, and lymphopenia.

PMDA concluded that elotuzumab can be tolerated, provided that appropriate steps, including monitoring and control of adverse events, are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following issue was raised by the expert advisors:

- The incidence of herpes virus infections (including herpes zoster) in patients receiving or not receiving prophylactic medication in Study CA204004 is important in determining whether prophylactic medication is necessary. Therefore, this information should be provided to healthcare professionals using information materials.

PMDA asked the applicant to discuss the incidence of herpes virus infections (including herpes zoster) in patients receiving or not receiving prophylactic medication.

The applicant's response:

Table 43 shows the incidence of herpes virus infections (including herpes zoster) in Study CA204004.

Table 43. Herpes virus infections (including herpes zoster) (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	With prophylactic medication		Without prophylactic medication	
	ELd 73 subjects	Ld 84 subjects	ELd 245 subjects	Ld 233 subjects
Herpes virus infections	1 (1.4)	0	42 (17.1)	21 (9.0)
Herpes zoster	1 (1.4)	0	18 (7.3)	9 (3.9)
Oral herpes	0	0	17 (6.9)	13 (5.6)
Herpes virus infection	0	0	7 (2.9)	0

PMDA's view:

The protocol of Study CA204004 did not require prophylactic medication for herpes virus infections. Further, in Study CA204004, the incidence of Grade ≥3 herpes zoster was low in the ELd arm [see Section 7.R.3.4 of Review Report (1)], and herpes virus infections was controllable by dose interruption and other measures. PMDA therefore considers that, at this point, prophylactic medication to prevent herpes virus infections is not mandatory for patients receiving elotuzumab. However, healthcare professionals should be informed, through information materials, of the incidence of herpes virus infections (including herpes zoster) in patients receiving or not receiving prophylactic medication in Study CA204004.

In addition, after Expert Discussion, the applicant reported a case of patient death[16] due to interstitial lung disease (ILD). This patient had been receiving the ELd regimen in an ongoing Japanese phase II study (Study CA204116) in patients with untreated MM. PMDA asked the applicant to provide the latest information on the incidence of ILD associated with elotuzumab.

The applicant's response:
Table 44 shows the incidence of ILDs (events corresponding to the SMQ term "Interstitial lung disease") in Study CA204004.

Table 44. ILDs (Study CA204004)

MedDRA PT (MedDRA ver. 17.0)	Number of subjects (%)			
	ELd 318 subjects		Ld 317 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD	7 (2.2)	1 (0.3)	7 (2.2)	3 (0.9)
Pneumonitis	4 (1.3)	0	3 (0.9)	2 (0.6)
ILD	1 (0.3)	0	4 (1.3)	1 (0.3)
Obliterative bronchiolitis	1 (0.3)	1 (0.3)	0	0
Bronchiolitis	1 (0.3)	0	0	0

There were no cases of ILDs that resulted in death in the ELd arm or in the Ld arm. Serious ILDs occurred in 2 of 318 subjects (0.6%) and 4 of 317 subjects (1.3%) in the ELd and Ld arms, respectively. These events were classified as pneumonitis (1 subject) and obliterative bronchiolitis (1) in the ELd arm, and pneumonitis (2) and ILD (2) in the Ld arm. Among these events, a causal relationship to the study drug could not be ruled out for obliterative bronchiolitis (1) in the ELd arm, and pneumonitis (2) and ILD (1) in the Ld arm. In the ELd and Ld arms, ILDs that led to study drug discontinuation occurred in 1 of 318 subjects (0.3%) and 1 of 317 subjects (0.3%), respectively; and ILDs that led to dose interruption in 3 of 318 subjects (0.9%) and 2 of 317 subjects (0.6%), respectively. There were no cases of ILDs that led to dose reduction of study drug.

Interstitial lung diseases occurred in 13 of 729 subjects (1.8%) who received elotuzumab in the following studies: a Japanese phase I study (CA204005), Study CA204004, a foreign phase I study (HuLuc63-1701), a foreign phase Ib/II study (HuLuc63-1703), a foreign phase Ib study (CA204007), a foreign phase I study (HuLuc63-1702), a foreign phase II study (CA204009), a foreign phase IIa study (CA204010), a foreign phase II study (CA204011), and a foreign phase II study (CA204112). There were no cases of ILDs that resulted in death. Serious ILDs occurred in 7 of 729 subjects (1.0%). ILDs that led to study drug discontinuation occurred in 3 of 729 subjects (0.4%).

[16] A male patient aged 7[redacted], who was hospitalized due to dyspnoea exertional 122 days after the start of Eld regimen (Cycle 5). (The patient received the last doses of elotuzumab, lenalidomide, and DEX at 121, 121, and 120 days after the start of treatment, respectively.) The patient was treated by pulse steroid therapy; however, his ILD became worse, and the patient died of ILD 50 days after discontinuation of the ELd regimen. While a causal relationship to lenalidomide could not be ruled out, a causal relationship to elotuzumab and to DEX was ruled out.

In ongoing clinical studies[17] and a clinical study that reported ILD after database lock (Study CA204005), serious ILDs occurred in 10 subjects. There was 1 subject[16] with ILD that resulted in death. Grade ≥3 ILDs occurred in 9 subjects, and a causal relationship to the study drug could not be ruled out in 4 of the 9 subjects.

PMDA's view:
At present, a definite conclusion cannot be drawn on the relationship between ILDs and elotuzumab treatment, because the incidence of ILDs did not differ greatly between the ELd and Ld arms in Study CA204004. However, given that 1 Japanese patient died of ILD in Study CA204116, the applicant should inform healthcare professionals of the incidence of ILDs in an appropriate manner using the package insert and other materials, and continue to collect relevant data after market launch.

Based on the above, PMDA instructed the applicant to take appropriate actions regarding this issue, and the applicant agreed with the instruction.

1.3 Clinical positioning and indications
Based on the discussion presented in Section "7.R.5 Clinical positioning and indications" of Review Report (1), PMDA concluded that elotuzumab in combination with the Ld regimen can be used as a treatment option for patients with relapsed or refractory MM. PMDA therefore concluded that the indication of elotuzumab should be "relapsed or refractory multiple myeloma," as proposed by the applicant, and that the package insert should include (a) information on prior treatments etc. of patients enrolled in Study CA204004 (in the "Clinical studies" section) and (b) the following precautionary statements (in the "Precautions for indication" section).

- Elotuzumab is indicated for the treatment of patients who have not responded to 1 or more lines of prior standard therapy, or patients with MM that has recurred after initial treatment.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of elotuzumab and of the information in the "Clinical Studies" section regarding prior treatments of patients enrolled in the clinical studies.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the indication presented above and include the above statements in the "Precautions for indication" section. The applicant agreed with the instruction.

[17] Study CA204116, a foreign phase I/II study (SWOG S1211), a foreign phase III study (CA204006), and a foreign compassionate use study (CA204022).

1.4 Dosage and administration

Based on the discussion presented in Section "7.R.6 Dosage and administration" of Review Report (1), PMDA concluded that the precautionary statements listed below should be included in the "Precautions for dosage and administration" section of the package insert, and that the dosage and administration for elotuzumab should be as follows (as proposed by the applicant): "In combination with lenalidomide and dexamethasone, the usual adult dosage of elotuzumab (genetical combination) is 10 mg/kg per dose, infused intravenously: once a week for the first two cycles (4 doses per 28-day cycle [Days 1, 8, 15, and 22]) and every 2 weeks for the third and subsequent cycles (2 doses per 28-day cycle [Days 1 and 15])."

Precaution for Dosage and Administration

- Administration of lenalidomide and DEX, agents co-administered with elotuzumab, should be undertaken only after the information included in the "Clinical studies" section is fully understood. Read the package inserts of the agents to be co-administered thoroughly.
- The efficacy and safety of elotuzumab monotherapy have not been established.
- With the exception of lenalidomide and DEX, the efficacy and safety of elotuzumab in combination with other antineoplastic drugs have not been established.
- To reduce infusion reactions that may occur during elotuzumab treatment, pre-medication consisting of an antihistamine (e.g., diphenhydramine), an H_2 blocker (e.g., ranitidine), and an antipyretic analgesic (e.g., acetaminophen) should be administered prior to any elotuzumab dose. Dexamethasone, which is co-administered with elotuzumab, should be administered as a split dose of 28 mg orally (3 to 24 hours prior to elotuzumab infusion) and 8 mg intravenously (DEX infusion should be completed 45 minutes prior to elotuzumab infusion).
- Initiate elotuzumab infusion at a rate of 0.5 mL/min. If well tolerated, the infusion rate may be increased in a stepwise manner as shown in the table below, while monitoring the patient's condition. The infusion rate should not exceed 2 mL/min.

Time of treatment		Infusion rate (mL/min)		
		0 to 30 min after the start of infusion	30 to 60 min after the start of infusion	≥60 min after the start of infusion
Cycle 1	Initial treatment	0.5	1	2
	Doses 2 to 4	1	2	
Cycle 2 and after		2		

- If infusion reactions occur following administration of elotuzumab, discontinue or interrupt elotuzumab treatment, change the infusion rate, or take other actions as shown below.

Grading according to NCI-CTCAE*	Action
Grade 4	Discontinue elotuzumab immediately.
Grade 3	Interrupt elotuzumab immediately. In principle, do not restart elotuzumab.
Grade 2	Interrupt elotuzumab immediately. Upon resolution to Grade ≤1, elotuzumab may be restarted at 0.5 mL/min. If elotuzumab at 0.5 mL/min is well tolerated, the infusion rate may be increased incrementally by 0.5 mL/min every 30 minutes. However, the infusion rate must not exceed the rate at which the infusion reaction occurred that day. If the infusion reaction recurs after restarting the treatment, stop the infusion immediately, and do not restart infusion for the day.

Grade 1	The infusion rate should remain 0.5 mL/min until resolution of the infusion reaction. If elotuzumab at 0.5 mL/min is well tolerated, the infusion rate may be increased incrementally by 0.5 mL/min every 30 minutes.

*, Graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0

- If administration of DEX is postponed or discontinued, decide whether to administer elotuzumab on the basis of the risk of infusion reactions.
- Empliciti for I.V. Infusion 300 mg and 400 mg, respectively, should be reconstituted with 13 and 17 mL of water for injection, to make a 25 mg/mL solution. Calculate the required volume of the solution from the body weight of the patient, and dilute the solution with 230 mL of saline or 5% glucose solution before infusion.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the dosage and administration presented above and include the above information in "Precautions for dosage and administration" section. The applicant agreed with the instruction.

1.5 Risk Management Plan (draft)

The applicant plans to conduct post-marketing surveillance covering all patients who receive elotuzumab to investigate the safety and other aspects of elotuzumab in routine clinical practice. The target sample size is 330. The observation period is 6 cycles (24 weeks) after the start of elotuzumab treatment.

Based on the discussion presented in Section "7.R.7 Post-marketing investigations" of Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance covering all patients who receive elotuzumab for a specific period of time after market launch to collect safety data quickly and evenly, and provide the obtained safety information promptly to healthcare professionals. In addition, the following issues were identified regarding the surveillance plan.

- Key survey items should include infections, second primary malignancies, cataract, and lymphopenia, in addition to the items selected by the applicant.
- The target sample size and the duration of the observation period should be re-examined based on the details of the key survey items.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to re-examine the post-marketing surveillance plan based on the discussion presented in Section "1.2 Safety" and the above issues.

The applicant's response:

- Infections, second primary malignancies, cataract, lymphopenia, and ILD will be added to the key

survey items.

- The target sample size will be 330 patients, in order to make a comparison of the incidence of the events included in the key survey items between surveillance patients and subjects receiving ELd in Study CA204004.
- The duration of the observation period will be 18 cycles of treatment because, in the ELd arm of Study CA204004, the adverse events included in the key survey items occurred generally at ≤18 cycles of treatment.

PMDA accepted the applicant's response.

In view of Section "1.2 Safety" and the discussion above, PMDA has concluded that the risk management plan (draft) for elotuzumab should include the safety and efficacy specifications presented in Table 45, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 46.

Table 45. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reactions • Infections • Second primary malignancies • Cataract • Lymphopenia	• ILD	None
Efficacy specification		
• Efficacy of elotuzumab in routine clinical practice		

Table 46. 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 • Specified use-results survey (all-case surveillance) • Post-marketing clinical study (the extension study of CA204004) • Post-marketing clinical study (the extension study of CA204005) • Post-marketing clinical study (the extension study of CA204220*)	• Disseminate information gathered during early post-marketing phase vigilance • Prepare and distribute materials designed for healthcare professionals

* This clinical trial is conducted as an expanded access program, with Study CA204004 being the main clinical study.

Table 47. Outline of post-marketing surveillance plan (draft)

Objective	To review the safety and other aspects of elotuzumab in clinical practice after market launch
Survey method	All-case surveillance
Population	All patients who receive elotuzumab
Observation period	18 cycles of elotuzumab treatment
Planned sample size	330 patients
Main survey items	Key survey items: infusion reactions, infections, second primary malignancies, cataract, lymphopenia, and ILD Other main survey items: patient characteristics (e.g., performance status, date of diagnosis, disease stage, prior treatments), treatment status of elotuzumab, co-administered drugs, adverse events, and others

1.6 Others

1.6.1 Storage method and shelf life of 300 mg formulation

The applicant submitted the results of long-term storage study (up to 24 months) for the 300 mg formulation (Empliciti for I.V. Infusion 300 mg). (The study was underway at the time of preparation for Review Report (1)). The applicant explained the storage conditions and shelf life of the 300 mg formulation based on the study results.

The applicant's explanation:
No significant change was observed in any parameters over the testing period in all 3 batches of the 300 mg formulation. Therefore the shelf-life of the 300 mg formulation is 24 months when it is stored in a glass vial sealed with a butyl rubber stopper, protected from light at 2°C to 8°C, unfrozen.

PMDA accepted the applicant's explanation.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication and dosage and administration shown below, under the conditions of approval listed below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is used properly under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancy at medical institutions that can adequately respond to emergencies. As the product is designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

In combination with lenalidomide and dexamethasone, the usual adult dosage of elotuzumab (genetical combination) is 10 mg/kg per dose, infused intravenously: once a week for the first two cycles (4 doses per 28-day cycle [Days 1, 8, 15, and 22]) and every 2 weeks for the third and subsequent cycles (2 doses per 28-day cycle [Days 1 and 15]).

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use results survey covering all Japanese patients treated with the drug product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

Warnings

Elotuzumab should be administered only to patients eligible for elotuzumab therapy by physicians with sufficient knowledge and experience in treating hematopoietic malignancy at medical institutions that can adequately respond to emergencies. Elotuzumab therapy should be initiated only after the patient or their family has provided consent after being fully informed of the efficacy and risks of elotuzumab.

Contraindications

(1) Patients who have a history of hypersensitivity to any ingredient of the product
(2) Women who are or may be pregnant

Precautions for Indication

(1) Elotuzumab is indicated for the treatment of patients who have not responded to 1 or more lines of prior standard therapy, or patients with MM that has recurred after initial treatment.
(2) Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of elotuzumab and of the information in the "Clinical Studies" section regarding prior treatments of patients enrolled in the clinical studies.

Precautions for Dosage and Administration

(1) Administration of lenalidomide and dexamethasone, agents co-administered with elotuzumab, should be undertaken only after the information included in the "Clinical studies" section is fully understood. Read the package inserts of the agents to be co-administered thoroughly.
(2) The efficacy and safety of elotuzumab monotherapy have not been established.
(3) With the exception of lenalidomide and dexamethasone, the efficacy and safety of elotuzumab in combination with other antineoplastic drugs have not been established.
(4) To reduce infusion reactions that may occur during elotuzumab treatment, pre-medication consisting of an antihistamine (e.g., diphenhydramine), an H_2 blocker (e.g., ranitidine), and an antipyretic analgesic (e.g., acetaminophen) should be administered prior to any elotuzumab dose. Dexamethasone, which is co-administered with elotuzumab, should be administered as a split dose of 28 mg orally (3 to 24 hours prior to elotuzumab infusion), and 8 mg intravenously (dexamethasone infusion should be completed 45 minutes prior to elotuzumab infusion).
(5) Initiate elotuzumab infusion at a rate of 0.5 mL/min. If well tolerated, the infusion rate may be increased in a stepwise manner as shown in the table below, while monitoring the patient's condition. The infusion rate should not exceed 2 mL/min.

<table>
<tr><td colspan="2" rowspan="2">Time of treatment</td><td colspan="3">Infusion rate (mL/min)</td></tr>
<tr><td>0 to 30 min after the start of infusion</td><td>30 to 60 min after the start of infusion</td><td>≥60 min after the start of infusion</td></tr>
<tr><td rowspan="2">Cycle 1</td><td>Initial treatment</td><td>0.5</td><td>1</td><td>2</td></tr>
<tr><td>Doses 2 to 4</td><td>1</td><td colspan="2">2</td></tr>
<tr><td colspan="2">Cycle 2 and after</td><td colspan="3">2</td></tr>
</table>

(6) If infusion reactions occur following administration of elotuzumab, discontinue or interrupt elotuzumab treatment, change the infusion rate, or take other actions as shown below.

Grading according to NCI-CTCAE*	Action
Grade 4	Discontinue elotuzumab immediately.
Grade 3	Interrupt elotuzumab immediately. In principle, do not restart elotuzumab.
Grade 2	Interrupt elotuzumab immediately. Upon resolution to Grade ≤1, elotuzumab may be restarted at 0.5 mL/min. If elotuzumab at 0.5 mL/min is well tolerated, the infusion rate may be increased incrementally by 0.5 mL/min every 30 minutes. However, the infusion rate must not exceed the rate at which the infusion reaction occurred that day. If the infusion reaction recurs after restarting the treatment, stop the infusion immediately, and do not restart infusion for the day.
Grade 1	The infusion rate should remain 0.5 mL/min until resolution of the infusion reaction. If elotuzumab at 0.5 mL/min is well tolerated, the infusion rate may be increased incrementally by 0.5 mL/min every 30 minutes.

*, Graded according to NCI-CTCAE v4.0

(7) If administration of dexamethasone is postponed or discontinued, decide whether to administer elotuzumab on the basis of the risk of infusion reactions.

(8) Empliciti for I.V. Infusion 300 mg and 400 mg, respectively, should be reconstituted with 13 and 17 mL of water for injection, to make a 25 mg/mL solution. Calculate the required volume of the solution from the body weight of the patient, and dilute the solution with 230 mL of saline or 5% glucose solution before infusion.