Report on the Deliberation Results

June 4, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion
Non-proprietary Name	Isatuximab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	August 23, 2019

Results of Deliberation

In its meeting held on May 28, 2020, 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 product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

May 7, 2020
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	Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion
Non-proprietary Name	Isatuximab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	August 23, 2019
Dosage Form/Strength	Injection: Each vial (5 or 25 mL) contains 100 or 500 mg of Isatuximab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Isatuximab is a recombinant chimeric monoclonal antibody composed of variable regions derived from mouse antihuman CD38 antibody and constant regions derived from human IgG1. Isatuximab is produced in Chinese hamster ovary cells. Isatuximab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 450 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequences:

L-chain

DIVMTQSHLS MSTSLGDPVS ITCKASQDVS TVVAWYQQKP GQSPRRLIYS

ASYRYIGVPD RFTGSGAGTD FTFTISSVQA EDLAVYYCQQ HYSPPYTFGG

GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

LSSPVTKSFN RGEC

H-chain

QVQLVQSGAE VAKPGTSVKL SCKASGYTFT DYWMQWVKQR PGQGLEWIGT

IYPGDGDTGY AQKFQGKATL TADKSSKTVY MHLSSLASED SAVYYCARGD

YYGSNSLDYW GQGTSVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK

DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT

YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP

KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ

VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV

LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

Intra-chain disulfide bonds: Solid line

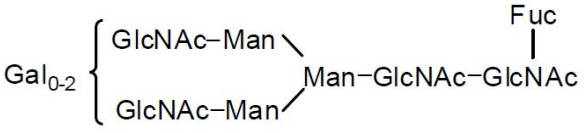
Inter-chain disulfide bonds: L-chain C214-H-chain C223, H-chain C229-H-chain C229, H-chain C232-H-chain C232

Pyroglutamic acid (partial): H-chain Q1

Glycosylation: H-chain N300

Partial processing: H-chain K450

Main proposed carbohydrate structure



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6456}H_{9938}N_{1702}O_{2026}S_{44}$ (protein moiety, 4 chains)

Molecular weight: ca. 148,000

Items Warranting Special Mention None
Reviewing Office Office of New Drug V

Results of Review

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

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of infusion reactions, myelosuppression, infections, and cardiac disorders need to be further investigated via post-marketing surveillance.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

Isatuximab in combination with pomalidomide and dexamethasone

The usual adult dose is 10 mg/kg of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

March 23, 2020

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	Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion
Non-proprietary Name	Isatuximab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	August 23, 2019
Dosage Form/Strength	Injection: Each vial (5 or 25 mL) contains 100 or 500 mg of Isatuximab (Genetical Recombination).
Proposed Indication	Relapsed or refractory multiple myeloma

Proposed Dosage and Administration

Isatuximab in combination with pomalidomide and dexamethasone

The usual adult dose is 10 mg/kg (body weight) of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. The treatment schedule must be followed. If a planned dose of isatuximab is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Isatuximab (Genetical Recombination) (isatuximab) is a chimeric monoclonal antibody composed of variable regions derived from mouse antihuman CD38 antibody and constant regions derived from human IgG1, discovered by ImmunoGen (the US).

Upon binding to CD38 expressed on the surface of multiple myeloma (MM) cells, isatuximab is thought to induce anti-tumor activity through antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) and by induction of apoptosis, etc.

1.2 Development history etc.

Overseas, Sanofi-Aventis (France) (a predecessor of Sanofi [France]) initiated a phase I/II study of single-agent isatuximab or isatuximab/dexamethasone (DEX) in patients with relapsed or refractory CD38-positive hematological malignancies (Study 10893) in June 2010. Then, Sanofi (France) initiated a global phase III study of isatuximab/pomalidomide and dexamethasone (Pd) in patients with relapsed or refractory MM (Study 14335) in January 2017.

US and EU applications were filed based mainly on the results from Study 14335 in April 2019. In the US, isatuximab was approved for the following indication in March 2020: "SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor." The EU application is under review.

As of March 2020, isatuximab has been approved for the indication of relapsed or refractory MM in the US only.

In Japan, the applicant initiated a phase I/II study of single-agent isatuximab in patients with relapsed or refractory MM (Study 14095) in September 2016. The above Study 14335 initiated patient enrollment in [redacted] 20[redacted].

The applicant has now submitted a marketing application for isatuximab based mainly on the results from Study 14335.

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

Hybridomas were generated by the fusion of spleen cells from mice immunized with [redacted] cell line expressing human CD38 with murine myeloma cells, and a suitable hybridoma clone was selected based on its biological activity such as [redacted], [redacted]

[redacted]. Expression constructs containing the genes encoding heavy and light chain variable regions obtained from this clone with the human IgG1 constant region genes were generated. The expression constructs were transfected into the Chinese hamster ovary (CHO) cell line, and a clone most suitable for the manufacture of isatuximab was selected and used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were characterized and subjected to purity tests in accordance with ICH Q5A (R1), Q5B, and Q5D guidelines. The results demonstrated the genetic stability of the production cell lines. No viral or non-viral adventitious agents were detected in any of the tests conducted.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of thawing of WCB, seed culture, cell expansion, production culture, harvest, [redacted] chromatography, [redacted] treatment, [redacted] chromatography, [redacted] chromatography, virus retentive filtration, [redacted] filtration, formulation, and dispensing/storage/testing.

[redacted], and [redacted] have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cell line, no raw materials of biological origin etc. are used in the drug substance manufacturing process.

The MCB, WCB, and CAL were subjected to purity tests [see Section 2.1.1]. [redacted] in CAL was subjected to tests for microbial contamination, mycoplasma, adventitious viruses, and minute virus of mice (MVM), and transmission electron microscopy. No viral or non-viral adventitious agents were detected in any of the tests conducted. Tests for bioburden, mycoplasma, adventitious viruses, and MVM are included as in-process controls for [redacted].

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})			
	Murine leukemia virus	MVM	Pseudorabies virus	Reovirus type 3
[redacted] treatment	>[redacted]	[redacted]	>[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	>[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	>[redacted]	>[redacted]
Virus retentive filtration	>[redacted]	[redacted]	>[redacted]	>[redacted]
Overall reduction factor	>16.65	9.24	>19.22	>9.97

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, the proposed commercial process). Process A was used in non-clinical studies. The drug product produced from the drug substance manufactured by Process B was used in phase I studies etc. The drug product produced from the drug substance manufactured by the proposed commercial process was used in phase I/II and III studies [see Section 6.1.2].

- Process A → Process B: changes in [redacted], [redacted], [redacted] step, etc.
- Process B → the proposed commercial process: changes in [redacted], [redacted], [redacted], [redacted] step, formulation, etc.

For the above process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

Quality by design (QbD) approaches were used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2.

Table 2. Characterization attributes

Primary structure/Conformation	Amino acid sequence, post-translational modifications ([redacted], [redacted], [redacted], [redacted]), disulfide bonds, free thiol group, [redacted], secondary structure, higher-order structure, [redacted]
Physicochemical properties	molecular weight, ultraviolet and visible absorption spectrum, [redacted], [redacted]
Carbohydrate structure	Determination of N-glycans profile
Biological properties	CD38 binding activity
	[redacted], [redacted] binding activity
	CDC activity, ADCC activity, [redacted]

With respect to the biological properties of isatuximab, the binding activity of isatuximab to CD38 was determined by [redacted], and the binding activities of isatuximab to [redacted] and [redacted] were determined by [redacted]. The CDC activity of isatuximab was evaluated by an assay using [redacted] cell lines and [redacted]. The ADCC activity of isatuximab was evaluated by an assay using [redacted] cell lines as [redacted] and [redacted] cell lines as [redacted]. [redacted] of isatuximab was determined by [redacted] assay using [redacted] cell lines. Isatuximab has been shown to have ADCP activity as well [see Section 3.1.3].

2.1.5.2 Product-related substances/Product-related impurities

No product-related substances have been identified. On the basis of the results of characterization etc. in Section "2.1.5.1 Structure and properties," high molecular weight species, truncated forms, charge variants, deamidated forms, oxidized variants, and isomerized variants were considered product-related impurities. [redacted], [redacted], and [redacted] are controlled by the drug substance and drug product specifications. Meanwhile, [redacted], [redacted], and [redacted] are not controlled routinely because their [redacted] are low and do not affect [redacted] of isatuximab.

2.1.5.3 Process-related impurities

Host cell DNA, host cell protein (HCP), Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, and Impurity F were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process. [redacted] is controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of quantity, appearance, identification (peptide map), osmolarity, pH, charge heterogeneity (imaged capillary isoelectric focusing [icIEF]), glycans profile (HPLC), purity (size exclusion liquid chromatography [SEC], capillary electrophoresis-sodium dodecyl sulfate [CE-SDS] [non-reduced conditions], [redacted]), bacterial endotoxins, microbial limits, [redacted], potency ([redacted] activity), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

	No. of batches*	Storage conditions	Testing period	Storage package
Long-term	3	[redacted]±[redacted]°C	[redacted] months	[redacted] container
Accelerated	3	[redacted]±[redacted]°C	[redacted] months	
Stress (temperature)	3	[redacted]±[redacted]°C/[redacted]±[redacted]%RH	[redacted] months	

*: Drug substance manufactured by [redacted]

The long-term and accelerated testings showed no significant changes in quality attributes throughout the testing period.

Under the stress condition (temperature), no significant changes occurred up to [redacted] months, and changes in [redacted], an increase in [redacted] peak [redacted], an increase in [redacted] peak [redacted], and increases in [redacted] and [redacted] peaks due to [redacted] were observed by [redacted] months.

On the basis of the above, a shelf-life of [redacted] months has been proposed for the drug substance when stored in [redacted] container at [redacted]°C to [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection. Each glass vial (6 or 30 mL) contains either 100 mg/5.0 mL or 500 mg/25.0 mL of isatuximab. It contains the following excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of thawing of the drug substance, pooling and homogenization, [redacted] filtration, sterile filtration/filling/stoppering/capping, inspection, and packaging/labeling/storage/testing.

[redacted], [redacted], and [redacted] have been defined as critical steps.

Process validation of the commercial-scale manufacturing process has been performed.

2.2.3 Manufacturing process development

During the drug product development, changes were mainly made to the formulation ([redacted] concentration) and [redacted] (the manufacturing processes before and after the changes are referred to as Process I and the proposed commercial process, respectively [the drug substance was manufactured by Process B and by the proposed commercial process, respectively]). For these process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

QbD approaches were used to develop the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification ([redacted]), pH, charge heterogeneity (icIEF), purity (SEC, CE-SDS [non-reduced conditions]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], potency ([redacted] activity), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

		Presentations	No. of batches*	Storage conditions	Testing period	Storage package
Long-term		100 mg	3	5 ± 3°C	36 months	Glass vial with bromobutyl rubber stopper
		500 mg	3			
Accelerated		100 mg	3	[redacted]±[redacted]°C/[redacted]±[redacted]%RH	[redacted] months	
		500 mg	3			
Stress	Temperature	100 mg	3	[redacted]±[redacted]°C/[redacted]±[redacted]%RH	[redacted] months	
		500 mg	3			
	Light	100 mg	1	An overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		
		500 mg	1			

*: Drug product produced by [redacted]

Under the long-term condition, there were no significant changes in quality throughout the testing period.

Under the accelerated and stress conditions (temperature), a decrease in [redacted] and an increase in [redacted] peak due to [redacted], a decrease in [redacted] peak and an increase in [redacted] peak due to [redacted], and a decrease in [redacted] peak and an increase in [redacted] peak due to [redacted] were observed.

The stress testing (light) showed that the drug product is photosensitive.

On the basis of the above, a shelf-life of 36 months has been proposed for the drug product when primary packaged in a glass vial with a bromobutyl rubber stopper and stored in a carton to protect from light at 2°C to 8°C.

2.3 QbD

QbD approaches were used to develop the drug substance and the drug product, and a quality control strategy was established based on the following studies etc.

- Identification of critical quality attributes (CQAs)

  Concerning product-related impurities, process-related impurities [see Sections 2.1.5.2 and 2.1.5.3], and quality attributes including formulation attributes, the following CQAs were identified based on the information obtained during the development of isatuximab, the relevant knowledge, etc.

  - potency, protein content, appearance, identity, insoluble particulate matter, foreign insoluble matter, extractable volume, pH, osmolarity, [redacted], aggregates, truncated forms, charge heterogeneity, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], HCP, host cell DNA, Impurity A, Residual Impurity B, [redacted], Residual Impurity C, Residual Impurity E, [redacted], [redacted], [redacted], mycoplasma, bacterial endotoxins, viruses, sterility, container integrity, extractables/leachables, and polysorbate 80 concentration

- Process characterization

  Process steps that impact CQAs were identified, the process control parameters for these steps that have a significant impact on CQAs and process performance were chosen through risk assessment etc., and the proven acceptable ranges were determined.

- Development of method of control

  On the basis of process knowledge including the above process characterization, the results of batch analyses, stability study results, etc., the method of control of the quality attributes of isatuximab through the combination of the controls of process parameters and performance attributes, in-process controls, and the specifications was developed [for the controls of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and the 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 to CD38 (CTD 4.2.1.1-1)

Using the human Burkitt lymphoma cell line Ramos, the binding of isatuximab to human CD38 was determined by flow cytometry. The EC_{50} values of isatuximab (n = 2, individual values) were 0.227 and 0.240 nmol/L, respectively.

3.1.2 ADCC activity (CTD 4.2.1.1-4, 4.2.1.1-14)

The ADCC activity mediated by isatuximab against 15 different cell lines derived from human MM and malignant lymphoma was evaluated using natural killer (NK) cells prepared from human peripheral blood mononuclear cells (PBMCs) as effector cells by measuring lactate dehydrogenase (LDH) release. The EC_{50} values of isatuximab are shown in Table 5.

Table 5. ADCC activity by isatuximab against human MM and malignant lymphoma cell lines

Cell line	Derived from	n	EC_{50} values (ng/mL) (individual values)	Cell line	Derived from	n	EC_{50} values (ng/mL) (individual values)
LP-1	MM	2	2.50, 1.64	SU-DHL-8	DLBCL	2	0.34, 0.30
MOLP-8		2	0.11, 0.23	WSU-DLCL-2		1	0.38
NCI-H929		1	7.62	NALM-6	T-ALL	1	1.48
Ramos	Burkitt lymphoma	2	0.64, 0.36	DND-41		2	0.34, 0.14
Daudi		2	0.26, 0.10	TALL-1		1	0.16
Raji		2	1.54, 0.11	MOLT-4		1	0.15
Namalwa		2	0.47, 2.10	CCRF-CEM		1	0.10
JVM-13	CLL	1	0.87				

The ADCC activity mediated by isatuximab or daratumumab against the LP-1 and SU-DHL-8 cell lines was evaluated using NK cells prepared from human PBMCs as effector cells, based on esterase activity in viable cells. The EC_{50} values of isatuximab and daratumumab are shown in Table 6.

Table 6. ADCC activity by isatuximab or daratumumab against different cell lines

Cell line	Derived from	EC_{50} value (ng/mL)	
		Isatuximab	Daratumumab
LP-1	MM	4.46 (51.40)	4.93 (28.70)
SU-DHL-8	DLBCL	7.11 (32.60)	7.64 (43.80)

Mean (coefficient of variation [CV] %), n = 3

3.1.3 ADCP activity (CTD 4.2.1.1-3)

The ADCP activity mediated by isatuximab 1 μg/mL against the human MM cell lines LP-1 and MOLP-8 and the human diffuse large B cell lymphoma (DLBCL) cell line SU-DHL-8 was evaluated using the human monocytic cell line THP-1, by measuring the percents phagocytosis of these cell lines.[1)] The percent

[1)] Percentages of the LP-1, MOLP-8, and SU-DHL-8 cell lines labeled with PKH67 phagocytosed by THP-1 cell line (CD14-positive cells)

phagocytosis of the LP-1, MOLP-8, and SU-DHL-8 cell lines were 34.86 ± 0.63%, 54.06 ± 7.21%, and 56.22 ± 0.86%, respectively.

3.1.4 CDC activity (CTD 4.2.1.1-4, 4.2.1.1-15)

The CDC activity of isatuximab against 15 different cell lines derived from human MM and malignant lymphoma was evaluated in the presence of human serum, based on reductase activity in viable cells. The EC_{50} values of isatuximab are shown in Table 7. The EC_{50} value of isatuximab could not be calculated for the NCI-H929, Namalwa, JVM-13, WSU-DLCL-2, NALM-6, TALL-1, MOLT-4, or CCRF-CEM cell line.

Table 7. CDC activity of isatuximab against different cell lines

Cell line	Derived from	EC_{50} values (μg/mL) (individual values)
LP-1	MM	0.019, 0.039
MOLP-8		0.262, 0.199
Ramos	Burkitt lymphoma	0.046, 0.013
Daudi		0.045, 0.065
Raji		0.031, 0.002
SU-DHL-8	DLBCL	0.156, 0.374
DND-41	T-ALL	0.016, 0.016

n = 2

The CDC activity of isatuximab or daratumumab against the human MM cell line U266.CD38 (transduction of human *CD38*), the human DLBCL cell line OCI-LY19.CD38 (transduction of human *CD38*), and the DND-41 cell line was evaluated in the presence of human serum, based on reductase activity in viable cells. The EC_{50} values of isatuximab and daratumumab are shown in Table 8.

Table 8. CDC activity of isatuximab or daratumumab against different cell lines

Cell line	Derived from	EC_{50} value (μg/mL) (individual value)	
		Isatuximab	Daratumumab
U266.CD38	MM	0.19	0.14
OCI-LY19.CD38	DLBCL	0.083	0.044
DND-41	T-ALL	0.052	0.031

n = 1

3.1.5 Apoptosis induction (CTD 4.2.1.1-4, 4.2.1.1-16)

The ability of isatuximab 0.01 μmol/L to induce apoptosis was tested in 15 different cell lines derived from human MM and malignant lymphoma, based on Annexin-V staining. The percentages of apoptotic cells in these cell lines[2)] are shown in Table 9.

[2)] Percentage of apoptotic cells (%) = (Percentage of apoptotic cells in the isatuximab group) − (Percentage of apoptotic cells in the untreated group)

Table 9. Percentages of apoptotic cells in different cell lines

Cell line	Derived from	n	Percentage of apoptotic cells (%)	Cell line	Derived from	n	Percentage of apoptotic cells (%)
LP-1	MM	1	0	SU-DHL-8	DLBCL	3	88.8 ± 2.0
MOLP-8		3	28.2 ± 2.0	WSU-DLCL-2		2	1.6, 0.75
NCI-H929		3	0	NALM-6	T-ALL	1	0
Ramos	Burkitt lymphoma	5	29.9 ± 3.9	DND-41		5	55.8 ± 5.7
Daudi		2	58.3, 49.2	TALL-1		1	3.0
Raji		2	13.5, 9.5	MOLT-4		1	4.3
Namalwa		1	19.3	CCRF-CEM		1	0.78
JVM-13	CLL	1	8.4				

Mean ± SD, Individual values are listed for n = 1 or 2.

The ability of isatuximab or daratumumab to induce apoptosis was tested in the human MM cell lines JJN3 (JJN3.CD38) and RPMI-8226 (RPMI-8226.CD38) (transduction of human *CD38*) and the SU-DHL-8 cell line, based on Annexin-V staining. The EC_{50} values of isatuximab in the JJN3.CD38, RPMI-8226.CD38, and SU-DHL-8 cell lines (n = 1, individual values) were 0.25, 0.42, and 0.03 μg/mL, respectively. The EC_{50} value of daratumumab could not be calculated for any of these cell lines.

3.1.6 Effect on enzymatic activity (CTD 4.2.1.1-17)

The effect of isatuximab or daratumumab on ADP ribosyl-cyclase activity in the LP-1 and RPMI-8226 cell lines was evaluated based on cADPR production. The EC_{50} values of isatuximab (mean [CV%], n = 3) were 1.41 (64.30) and 9.43 (74.60) ng/mL, respectively. The EC_{50} value of daratumumab could not be calculated for either cell line.

3.1.7 Anti-tumor activity against MM and malignant lymphoma cell lines

3.1.7.1 *In vivo*

3.1.7.1.1 MM cell line (CTD 4.2.1.1-23)

The anti-tumor activity of isatuximab or pomalidomide alone, or isatuximab/pomalidomide was evaluated in NSG mice[3)] with subcutaneously implanted MOLP-8 cell line (8/group). The day of implantation was designated as Study Day 0. Isatuximab 20 or 40 mg/kg was administered intravenously on Days 12, 16, 19, 24, and 26, and pomalidomide 5 or 10 mg/kg was administered intraperitoneally QD for 14 days, beginning from Day 12. Tumor volumes were calculated on Day 26. The T/C values[4)] for isatuximab or pomalidomide alone and isatuximab/pomalidomide are shown in Table 10.

Table 10. Anti-tumor activity in NSG mice with subcutaneously implanted MOLP-8 cell line

Dose (mg/kg)		T/C (%)
Isatuximab	Pomalidomide	
20	0	60.0
40	0	56.0
0	5	63.0
0	10	46.0
20	5	30.0*
20	10	30.0*
40	5	26.0*
40	10	22.0*

* $P \leq 0.0001$, vs. control (PBS) group (two-way ANOVA)

3) NOD/SCID mice having an IL-2 receptor γ chain deficiency

4) T/C (%) = {(median tumor volume of the isatuximab group)/(median tumor volume of the control group)} × 100

3.1.7.1.2 DLBCL cell line (CTD 4.2.1.1-22)

The anti-tumor activity of isatuximab was evaluated in SCID mice with subcutaneously implanted SU-DHL-8 cell line (9/group). The day of implantation was designated as Study Day 0. Isatuximab 2.5, 10, or 40 mg/kg was administered intravenously on Days 11, 14, 18, 21, and 26, and tumor volumes were calculated. The T/C values[4)] on Day 19 were 25.1%, 14.6%, and 5.0%, respectively. Isatuximab at all dose levels statistically significantly increased the time to reach a tumor volume of 1,000 mm^3 as compared to the control (PBS) group ($P < 0.0003$ for all doses vs. control, log-rank test).

3.2 Secondary pharmacodynamics (CTD 4.2.1.2-5, 4.2.1.2-11, 4.2.1.2-12, 4.2.1.2-14)

The following studies were conducted to evaluate the binding of isatuximab and 2 anti-CD38 antibodies that bind to cynomolgus monkey CD38 (ch38SB25 and chOKT10).

- The binding of isatuximab to human peripheral blood T cells, B cells, NK cells, and monocytes was assessed by flow cytometry, which showed that isatuximab binds to all of these cells.
- The binding of isatuximab to T cells, B cells, NK cells, and monocytes from cynomolgus monkey PBMCs and T cells, B cells, and NK cells from murine spleen was assessed by flow cytometry, which showed that isatuximab does not bind to any of these cells.
- Using the Ramos and CB1 cell lines, the binding affinities of isatuximab, ch38SB25, and chOKT10 to human and cynomolgus monkey CD38 were determined by flow cytometry. The K_D values of isatuximab, ch38SB25, and chOKT10 are shown in Table 11.

Table 11. Binding affinities of isatuximab, ch38SB25, and chOKT10 to human and cynomolgus monkey CD38

	K_D value (nmol/L)			
	n	Human CD38	n	Cynomolgus monkey CD38
Isatuximab	4	0.29 ± 0.11	2	—
ch38SB25	4	0.84 ± 0.47	2	5.50, 1.80
chOKT10	3	1.20 ± 1.35	1	4.40

Geometric mean ± SD, Individual values are listed for n = 1 or 2. —, Not calculable

The ADCC activity mediated by isatuximab, ch38SB25, or chOKT10, and their abilities to induce apoptosis were tested as follows.

- The ADCC activity mediated by 10 μg/mL of isatuximab, ch38SB25, or chOKT10 against the LP-1 cell line was evaluated using NK cells prepared from human PBMCs as effector cells, by measuring LDH release. The ADCC activities (percentage of cell lysis[5)]) mediated by isatuximab, ch38SB25, and chOKT10 (n = 1, individual value) were 41%, 55%, and 60%, respectively.
- The ability of 0.01 μmol/L of isatuximab, ch38SB25, or chOKT10 to induce apoptosis was tested in the Ramos, Daudi, and DND-41 cell lines, based on Annexin-V staining. The percentages of apoptotic cells[2)] in (1) Ramos, (2) Daudi, and (3) DND-41 cell lines after incubation with isatuximab (n = 2, individual values) were (1) 31% and 36%, (2) 44% and 52%, and (3) 30% and 39%. On the other hand, ch38SB25 or chOKT10 did not induce apoptosis in these cell lines.

[5)] Percentage of cell lysis (%) = { (LDH release in the isatuximab group) − (LDH release in the untreated group)}/{(LDH release in the 10% TritonX-100 group) − (LDH release in the untreated group)} × 100

3.3 Safety pharmacology

In a 3-week repeated intravenous dose toxicity study in cynomolgus monkeys, the effects of isatuximab 20, 50, and 100 mg/kg on ECG, blood pressure, gross behavior profile, respiratory function, etc. were assessed. There were no isatuximab-related effects [see Section 5.2].

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of isatuximab, excluding the considerations in the following section, is acceptable.

3.R.1 Mechanism of action of isatuximab and its efficacy in treatment of MM

The applicant's explanation about the mechanism of action of isatuximab and its efficacy in the treatment of MM:

Upon binding to CD38 expressed on the surface of MM cells [see Section 3.1.1], isatuximab is thought to induce anti-tumor activity through ADCC, ADCP, and CDC and by induction of apoptosis [see Sections 3.1.2, 3.1.3, 3.1.4, and 3.1.5]. Since isatuximab inhibited CD38 enzymatic activity in the human MM cell lines [see Section 3.1.6] etc., this may also contribute to its anti-tumor activity.

Given the above mechanisms of action, and the anti-tumor activities of isatuximab alone and isatuximab/pomalidomide observed in NSG mice[3)] bearing subcutaneously implanted human MM cell line [see Section 3.1.7] etc., the efficacy of isatuximab in the treatment of MM is expected.

The applicant's explanation about differences in pharmacological properties between isatuximab and daratumumab, another anti-CD38 monoclonal antibody approved in Japan:

Isatuximab and daratumumab both bind to CD38 and induce ADCC, ADCP, and CDC. On the other hand, isatuximab is different from daratumumab with regard to the induction of apoptosis in the absence of effector cells etc. [see Section 3.1.5].

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, the association between inhibition of CD38 enzymatic activity and anti-MM activity, etc. are not fully understood at present. Since this information and the findings on the pharmacological properties of isatuximab including dissimilarities between isatuximab and daratumumab may be beneficial in terms of selecting appropriate patients in the clinical use of isatuximab, an investigation should be continued, and if a new finding becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

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

The non-clinical PK of isatuximab were studied in mice and monkeys.

4.1 Analytical method

4.1.1 Isatuximab assays

The following assays were used to quantify isatuximab in (1) mouse and (2) monkey plasma.

(1) An enzyme-linked immunosorbent assay (ELISA) using solid phased recombinant CD38-Fc fusion protein and horseradish peroxidase (HRP)-conjugated goat anti-human IgG antibody

(2) An assay using solid phased streptavidin, biotinylated rabbit anti-isatuximab antibody, and fluorescence-labeled CD38

4.1.2 Anti-isatuximab antibody assay

An electrochemiluminescence (ECL) immunoassay using ruthenium-conjugated isatuximab was used to detect anti-isatuximab antibodies in monkey plasma.

4.2 Absorption

4.2.1 Single-dose study

Following a single intravenous administration of isatuximab 40 mg/kg in female mice, plasma isatuximab concentrations were determined. The AUC_{inf}, $t_{1/2Z}$, CL, and V_{ss} of isatuximab were 11,900 μg·day/mL, 23.5 days, 0.0759 mL/day, and 2.44 mL, respectively.[6)]

4.2.2 Repeated-dose study

Male and female monkeys received isatuximab at 20, 50, or 100 mg/kg intravenously QW for 3 weeks, and plasma isatuximab concentrations were determined (Table 12). Isatuximab exposure on Days 1 and 15 increased in an approximately dose-proportional manner over the dose range tested. No obvious gender-related differences in isatuximab exposure were observed.

Anti-isatuximab antibody was not detected in any of the animals.

Table 12. PK parameters of isatuximab (male and female monkeys, 3-week repeated intravenous administration)

Sampling day (Day)	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	AUC_{3day} (μg·day/mL)	AUC_{7day} (μg·day/mL)
1	20	M	3	634 (12)	1,040 (14)	1,930 (19)
		F	3	519 (4)	959 (3)	1,870 (5)
	50	M	3	1,300 (17)	2,160 (16)	4,060 (13)
		F	3	1,450 (20)	2,350 (15)	4,490 (15)
	100	M	3	2,390 (8)	4,430 (8)	8,540 (8)
		F	3	2,840 (1)	4,560 (1)	8,600 (1)
15	20	M	3	1,020 (27)	1,920 (20)	—
		F	3	994 (7)	2,040 (2)	—
	50	M	3	2,040 (8)	4,140 (12)	—
		F	3	2,800 (35)	5,540 (36)	—
	100	M	3	4,360 (3)	9,670 (5)	—
		F	3	4,250 (5)	9,290 (4)	—

Mean (CV%), —: not calculated

[6)] PK parameters were calculated based on the mean plasma isatuximab concentration at each time point (n = 5).

4.3 Distribution

The applicant's explanation:

Given the V_{ss} of isatuximab in a single intravenous dose study in mice [see Section 4.2.1] and blood volume in mice (1.7 mL) (*Pharm Res*. 1993;10:1093-5), isatuximab is considered to have low tissue distribution and be distributed predominantly into circulation, etc. Thus, a tissue distribution study of isatuximab was not conducted.

As human IgG has been reported to cross the placenta into the fetus (*Am J Gstroenterol*. 2009;43:613-6), isatuximab, which bears the constant regions of human IgG, also has the potential to cross the placenta into the fetus.

4.4 Metabolism and excretion

The applicant's explanation:

Since isatuximab is an antibody drug and is expected to be eliminated by proteolytic catabolism etc., no metabolism or excretion studies of isatuximab were conducted, based on "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

Given that human IgG has been reported to be excreted in milk (*Clin Transl Immunology*. 2013;2:e3, etc.), isatuximab, which bears the constant regions of human IgG, also has the potential to be excreted in milk.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of isatuximab is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, saline was used as vehicle. Since a relevant species for preclinical safety testing does not exist, etc. [see Section 5.2], toxicology studies with isatuximab were limited to (1) a toxicity study in cynomolgus monkeys in order to evaluate potential off-target toxicity etc. [see Section 5.2], (2) a local tolerance study in rabbits or cynomolgus monkeys [see Section 5.6], (3) an *in vitro* hemocompatibility and hemolytic potential study with human plasma and whole blood [see Section 5.7.2], etc.

5.1 Single-dose toxicity

Although no single-dose toxicity study was conducted with isatuximab, the acute off-target toxicity etc. of isatuximab was assessed based on the findings after the first dose in a repeated intravenous dose toxicity study in cynomolgus monkeys [see Section 5.2], and the approximate lethal dose was determined to be >100 mg/kg (Table 13).

Table 13. Single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	IV	0, 20, 50, 100	Acute toxicity was assessed in a 3-week repeated intravenous dose toxicity study. No toxic signs	>100	4.2.3.2-2

5.2 Repeated-dose toxicity

For the following reasons etc., the applicant considered that a relevant species for preclinical safety testing does not exist.

- The percentages of identity with the human CD38 sequence were high with the chimpanzee, rhesus monkey, and cynomolgus monkey, and low with other species (marmoset, mouse, rat, rabbit, dog, pig).
- Isatuximab did not bind to lymphocytes etc. from cynomolgus monkey PBMCs or murine spleen [see Section 3.2].
- A tissue cross-reactivity study with normal tissues from a wide range of animal species (mouse, rat, hamster, guinea pig, rabbit, ferret, mini pigs, dog, cynomolgus monkey, rhesus monkey, marmoset, baboon, chimpanzee) demonstrated specific binding of isatuximab to tissues from the chimpanzee with a comparable staining pattern as in human [see Section 5.7.1.1], but the chimpanzee was not considered an appropriate species from animal welfare and ethical perspectives etc.

Moreover, (1) no adequate transgenic mouse model was available, and (2) given the pattern of binding of surrogate antibodies that bind to cynomolgus monkey CD38 (ch38SB25 and chOKT10) in a tissue cross-reactivity study [see Section 5.7.1.2] and the results of *in vitro* studies [see Section 3.2], safety assessment using the surrogate antibodies was considered to provide only limited information on safety in humans. Thus, no non-clinical safety studies have been conducted in such model or with the surrogate antibodies.

A 3-week repeated intravenous dose toxicity study in cynomolgus monkeys was conducted to evaluate the potential off-target toxicity of isatuximab etc. (Table 14). No toxicological findings were observed in any group. Isatuximab exposure (C_{max} and AUC_{3day}) at the no-observed-adverse-effect level (NOAEL) in the study (100 mg/kg) was 4,305 μg/mL and 9,480 μg·day/mL, respectively, which were 8.0- to 9.1-fold and 2.2- to 4.6-fold the human exposure,[7)] respectively.

Table 14. Repeated-dose toxicity study

Test system	Route of administration	Duration of dosing	Dose (mg/kg/week)	Principal findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV	3 weeks (QW)	0, 20, 50, 100	No toxic signs	100	4.2.3.2-2

[7)] On the basis of the data from a phase I/II study in Japanese patients with relapsed or refractory MM (Study 14095), plasma concentrations in Japanese patients were simulated based on the PPK model (POH0504). Following intravenous administration of isatuximab 10 mg/kg QW for 3 weeks, the C_{max} was 471 μg/mL, and the AUC_{7day} was 2,069 μg·day/mL. Following intravenous administration of isatuximab 10 mg/kg QW for 4 weeks followed by Q2W for 16 weeks, the steady-state C_{max} was 540 μg/mL, and the steady-state AUC_{14day} was 4,389 μg·day/mL.

5.3 Genotoxicity

No genotoxicity studies were conducted because isatuximab is an antibody drug, and it is not expected that isatuximab would interact directly with DNA or other chromosomal material.

5.4 Carcinogenicity

No carcinogenicity studies were conducted because isatuximab is an anti-neoplastic drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted because a relevant species for preclinical safety testing does not exist [see Section 5.2] etc.

The applicant's explanation about the effects of isatuximab on embryo-fetal development:
For the following reasons etc., isatuximab has the potential to affect embryo-fetal development.

- Isatuximab is an IgG1 monoclonal antibody, and placental transfer of IgG1 monoclonal antibodies has been reported (*Birth Defects Res*. (Part B) 2009;86:328-44).
- Given the mechanism of action of isatuximab, the reported effects on the immune system and bone in *CD38*-deficient mice (*FASEB J*. 2003;17:369-75) etc., isatuximab has the potential to affect the fetal immune system and bone.

Since isatuximab has the potential to affect embryo-fetal development as described above, the applicant explained about (1) the use of isatuximab in pregnant women or women who may be pregnant and (2) contraception requirements during treatment with isatuximab and for a certain period of time after the last dose of isatuximab.
(1) Use of isatuximab in pregnant women or women who may be pregnant
Although the use of isatuximab in pregnant women or women who may be pregnant is not actively recommended, considering that MM is a disease with poor prognosis, etc., the use of isatuximab in pregnant women or women who may be pregnant is permitted, only if the expected therapeutic benefits outweigh the possible risks, on the premise that the physician and the patient fully understand the potential risk to the fetus associated with isatuximab. On the basis of the above, the package insert etc. will include the above information.

(2) Contraception requirements during treatment with isatuximab and for a certain period of time after the last dose of isatuximab
The package insert etc. will advise that females with reproductive potential should use an effective method of contraception during treatment with isatuximab and for a certain period of time after the last dose of isatuximab. On the other hand, contraceptive use during treatment with isatuximab and for a certain period of time after the last dose of isatuximab is unnecessary for male patients with female partners of reproductive potential, because, given the following points etc., the risk to embryo-fetal development associated with isatuximab exposure via semen of a male patient is low.

- Since isatuximab is an antibody drug and would not interact directly with DNA, it is unlikely to induce gene mutations in germ cells.
- Seminal transport and absorption from the vagina of antibody drugs are considered very limited, and antibody drugs undergo degradation caused by vaginal and cervical enzymes (*Reprod Toxicol.* 2015;58:213-21).

5.6 Local tolerance

A local tolerance study was conducted in rabbits (Table 15). No changes indicative of local irritation were observed via any route of administration. A repeated intravenous dose toxicity study in cynomolgus monkeys [see Section 5.2] assessed the effect of isatuximab on the injection sites, and no changes indicative of local irritation were noted at any dose level up to the highest dose tested of 100 mg/kg/week (20 mg/mL/week; 5 mL/kg).

Table 15. Local tolerance study

Test system	Application site	Test method	Principal findings	Attached document CTD
Female rabbits (New Zealand white)	intravenous, intra-arterial	Single injection of 1 mL of isatuximab 0, 1 or 5 mg/mL	No toxic signs	4.2.3.6-1
	intramuscular, subcutaneous	Single injection of 0.5 mL of isatuximab 0, 1 or 5 mg/mL	No toxic signs	
	paravenous	Single injection of 0.05 mL of isatuximab 0, 1 or 5 mg/mL	No toxic signs	

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity studies

5.7.1.1 Tissue cross-reactivity studies of isatuximab

Tissue cross-reactivity studies of isatuximab with normal tissues from the human and a wide range of animal species were conducted (Table 16). Isatuximab specific binding was detected in the human lymphoid tissues and in the bone marrow, as well as in the non-lymphoid tissues (prostate gland, pituitary gland, bronchi, brain). On the other hand, there was no observed isatuximab binding in tissues from the other tested species, except in the chimpanzee (prostate gland and lymph node), hamster (prostate gland), and ferret (pulmonary bronchial glands).

The applicant's explanation:
With regard to the above unintended binding to non-lymphoid tissues (prostate gland, pituitary gland, bronchi, brain), no evident effects related to isatuximab have been observed in these tissues in clinical use.

Table 16. Tissue cross-reactivity studies of isatuximab

Test system	Test method	Principal findings	Attached document CTD
Normal human tissues	Isatuximab 2.1 or 21.1 μg/mL was applied to cryosections, and binding to a panel of tissues[a)] was detected by IHC.	At ≥2.1 μg/m, isatuximab specific binding was detected in the lymphoid tissues (spleen, thymus, lymph node, tonsil), bone marrow, lymphocytes or macrophages in most tissues, Kupffer cell subpopulations in the liver, etc. In addition, isatuximab binding was detected in endothelial cells lining the sinusoids in the pituitary glands and epithelial cells of the acini in the prostate.	4.2.1.2-1
Normal human tissues	Isatuximab 0.32 μg/mL was applied to cryosections, and binding to tissues (26 tissues) was detected by IHC.	Isatuximab specific binding was detected in the lymphoid tissues (T-cell zones of the thymus and lymph nodes, T-cell zone and germinal center of the tonsil), splenic red pulp, bone marrow cells, glandular epithelium of the prostate, pulmonary bronchial epithelium, Kupffer cells in the liver, astrocytes in the brain, etc. Isatuximab binding to infiltrating and inflammatory cells was observed in the mammary gland, esophagus, stomach, colon, small intestine, ovary, and endometrium. Isatuximab binding was not detected in other tissues. Very faint binding to the optic nerve was seen in 1 of 3 specimens.	4.2.1.2-2 (non-GLP)
Normal tissues from various laboratory animals	Isatuximab 2.85, 5.70, or 11.40 μg/mL was applied to cryosections, and binding to a panel of tissues[b)] was detected by IHC.	Specific binding of isatuximab to the prostate gland and lymph node from the chimpanzee was observed. Isatuximab binding was detected in the prostate gland from the hamster (epithelial surface and secreted material only) and the pulmonary bronchial glands from the ferret (epithelial cytoplasm). There was no observed isatuximab binding in tissues from the other tested species.	4.2.1.2-13 (non-GLP)

a) A list of tissues recommended in the published article (*J Immunother*. 1997;20:214-43), b) Prostate glands, lungs/bronchi, spleens, pituitary glands, hearts, livers, brains, and kidneys from the mouse, rat, hamster, rabbit, guinea pig, ferret, dog, mini pig, marmoset, cynomolgus monkey, and rhesus monkey, prostate gland and lymph node from the chimpanzee, prostate gland from the baboon, bladder from the marmoset, pancreas from the rhesus monkey, prostate gland, spleen, and lymph node from the human (positive control), and Ramos cell line (for validation of CD38 recognition)

5.7.1.2 Tissue cross-reactivity study of surrogate antibodies

A tissue cross-reactivity study of surrogate antibodies (ch38SB25 and chOKT10) with normal tissues from the cynomolgus monkey, rhesus monkey, baboon, mouse, rat, and human was conducted (Table 17). There was no cross-reactivity with mouse or rat tissues. Although there was cross-reactivity with cynomolgus and rhesus monkey tissues, the pattern of tissue cross-reactivity of the surrogate antibodies in cynomolgus and rhesus monkey tissues was different from the pattern of tissue cross-reactivity observed with isatuximab in human tissues [see Section 5.7.1.1], with regards to vascular endothelial cell staining observed in most tissues.

Table 17. Tissue cross-reactivity study of surrogate antibodies

Test system	Test method	Principal findings	Attached document CTD
Normal tissues from the cynomolgus monkey, rhesus monkey, baboon, mouse, rat, and human	Surrogate antibodies (ch38SB25 and chOKT10) were applied to cryosections, and binding to a panel of tissues[a)] was detected by IHC.	Specific binding was detected in the vascular endothelial cells in most tissues, in addition to lymphoid cells in the spleen, Kupffer cells in the liver, and cerebral white matter from the cynomolgus monkey and rhesus monkey. Specific binding of surrogate antibodies was detected in the prostate gland from the baboon, and the spleen, lymph node, and glandular epithelium in the prostate from the human. Surrogate antibodies were shown to recognize human CD38, while there was no observed binding of surrogate antibodies in mouse or rat tissues.	4.2.1.2-15 (non-GLP)

a) Prostate glands, lungs/bronchi, spleens, pituitary glands, hearts, livers, brains, and kidneys from the cynomolgus monkey, rhesus monkey (excluding prostate gland), mouse, and rat, prostate gland from the baboon, prostate gland, spleen, and lymph node from the human, and Ramos cell line (for validation of CD38 recognition)

5.7.2 *In vitro* hemocompatibility and hemolytic potential study with human plasma and whole blood

An *in vitro* hemocompatibility and hemolytic potential study of isatuximab with human plasma and whole blood was conducted (Table 18). Isatuximab did not induce hemolysis of human whole blood, and was compatible with human plasma at concentrations up to a maximum final isatuximab concentration in blood or plasma of 2.5 mg/mL (corresponding to isatuximab 5 mg/mL).

Table 18. *In vitro* hemocompatibility and hemolytic potential study with human plasma and whole blood

Type of study	Test method	Principal findings	Attached document CTD
In vitro hemocompatibility and hemolytic potential study with human plasma and whole blood	Human plasma or whole blood was diluted by a factor of 2 or 10, respectively, and incubated for 15 minutes at room temperature or for 45 minutes at 37°C, respectively, in the presence of vehicle[a)] or isatuximab 0.1, 0.2, 0.5, 1, or 2.5 mg/mL to assess for precipitate formation or hemolysis, respectively.	The incubation of human plasma or whole blood with isatuximab did not result in precipitation or hemolysis.	4.2.3.7.7-1

a) 10 mmol/L histidine solution containing10% (w/v) sucrose and 0.005% (w/v) polysorbate 80 (pH 6.5)

5.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the toxicity of isatuximab is acceptable.

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 method

6.1.1.1 Isatuximab assay

An ELISA using solid phased rabbit anti-isatuximab antibody, biotinylated CD38, and HRP-conjugated streptavidin was used to quantify isatuximab in human plasma (lower limit of quantification, 0.500 ng/mL).

6.1.1.2 Anti-isatuximab antibody assay

An ECL immunoassay using ruthenium-conjugated isatuximab was used to detect anti-isatuximab antibodies in human plasma (detection sensitivity, 50.0 ng/mL[8)]).

The applicant's explanation about the potential interference of isatuximab in samples with anti-isatuximab antibody assay results:

The drug tolerance limit of the above anti-isatuximab antibody assay was 4,000 μg/mL. Given that the isatuximab concentrations in samples collected for this assay were mostly <4,000 μg/mL[9)] in clinical studies, the presence of isatuximab in these samples did not generally interfere with anti-isatuximab antibody assay results.

8) Plasma samples from Study 14335 were analyzed using an assay with a detection sensitivity of 75.0 ng/mL.
9) In a Japanese phase I/II study (Study 14095), the plasma isatuximab concentrations in 3 samples collected for the anti-isatuximab antibody assay exceeded 4,000 μg/mL. These samples were obtained from 2 patients treated with isatuximab 20 mg/kg QW.

6.1.2 Changes made to the drug substance and drug product manufacturing processes during development

Changes were made to the drug substance and drug product manufacturing processes during development [see Sections 2.1.4 and 2.2.3]. The following drug products were used in the clinical studies submitted in the present application: The drug product produced by Process I was used in foreign phase Ib studies (Study 14079 Part A, Study 11863, Study 13983) and a foreign phase I/II study (Study 10893 Phase I and Phase II Stage 1), and the drug product produced by the proposed commercial process was used in a foreign phase I study (Study 14154 Part A), foreign phase Ib studies (Studies 14079 and 13983), a foreign phase I/II study (Study 10893 Phase II Stage 2), a Japanese phase I/II study (Study 14095), and a global phase III study (Study 14335).

For the drug substance and drug product manufacturing process changes, comparability of quality attributes between pre-change and post-change drug substances and drug products has been demonstrated [see Sections 2.1.4 and 2.2.3].

6.2 Clinical pharmacology

The PK of isatuximab were investigated in patients with cancer when given as a single agent or in combination with Pd.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I/II study (CTD 5.3.3.2-7, Study 14095 Phase I [ongoing since September 2016 (data cutoff date of July 31, 2018)])

An open-label, uncontrolled study was conducted in 8 patients with relapsed or refractory MM (8 subjects included in PK analysis) to evaluate the PK etc. of isatuximab. Treatment was to be administered in 28-day cycles. Isatuximab 10 or 20 mg/kg was to be administered intravenously QW in the first cycle and Q2W thereafter. Plasma isatuximab concentrations were determined.

The PK parameters of isatuximab following the first dose of isatuximab are shown in Table 19.

Table 19. PK parameters of isatuximab

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} *1 (h)	AUC_{1week} (μg·h/mL)
10	3	124 (18)	2.68 (2.32, 7.25)	9,300 (32)
20	4*2	280 (23)	5.56 (3.28, 8.48)	21,300 (26)

Mean (CV%), *1, Median (range), *2, Excluding 1 subject who had his/her first infusion interrupted

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I/II study (CTD 5.3.3.2-3, Study 10893 Phase I [June 2010 to August 2016])

An open-label, uncontrolled study was conducted in 89 patients with relapsed or refractory CD38-positive hematological malignancies or MM (88 subjects included in PK analysis) to evaluate the PK etc. of isatuximab. Treatment was to be administered in 14-day cycles. Isatuximab 0.0001 to 20 mg/kg[10)] was to be administered

[10)] Plasma isatuximab concentrations at different time points were generally below the lower limit of quantification over the dose range of 0.0001-0.03 mg/kg.

intravenously Q2W, or isatuximab 10 or 20 mg/kg was to be administered intravenously QW. Plasma isatuximab concentrations were determined.

The PK parameters of isatuximab are shown in Table 20. The AUC_{last} of isatuximab increased more than dose-proportionally over the Q2W dose range tested. The applicant explained that this result was obtained because target mediated non-linear CL due to binding to the target antigen contributed to isatuximab clearance.

Table 20. PK parameters of isatuximab

Dosing regimen	Cycle	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{1week} (μg·h/mL)	AUC_{last} (μg·h/mL)
0.3 mg/kg Q2W	1	6	2.09 (31)	2.49 (1.42, 3.43)	16.5 (73)	16.5 (73)
1 mg/kg Q2W	1	3	13.5 (45)	4.35 (3.13, 6.33)	460 (81)	630, 717*2
3 mg/kg Q2W	1	4	55.3 (28)	6.99 (4.58, 8.00)	3,110 (14)	3,120 (14)
5 mg/kg Q2W	1	2	88.0, 181	5.13, 10.2	3,930, 14,400	4,180, 24,200
10 mg/kg Q2W	1	20	180 (40)	4.75 (2.15, 30.1)	14,400 (44)	22,200 (50)*3
20 mg/kg Q2W	1	3	469 (28)	5.87 (5.78, 9.90)	33,300 (46)	49,900 (53)
10 mg/kg QW	1	3	183 (20)	2.25 (2.20, 7.50)	17,000 (22)	17,400 (23)
	3	4	326 (67)	4.30 (2.57, 27.5)	37,100 (66)	40,600 (61)
20 mg/kg QW	1	6	356 (29)	6.83 (3.98, 10.5)	32,900 (31)*4	33,500 (34)*4
	3	6	737 (27)	8.07 (2.87, 29.0)	86,600 (43)*4	85,800 (43)*4

Mean (CV%) (Individual values are listed for n = 2), *1, Median (range); *2, n = 2; *3, n = 18; *4, n = 5

6.2.2.2 Foreign phase Ib study (CTD 5.3.3.2-4, Study 14079 Part A [May 2015 to November 2017])

An open-label, uncontrolled study was conducted in 45 patients with relapsed or refractory MM (45 subjects included in PK analysis) to evaluate the PK etc. of isatuximab. Treatment was to be administered in 28-day cycles. Isatuximab 5, 10, or 20 mg/kg was to be administered intravenously QW in the first cycle and Q2W thereafter, in combination with Pd.[11)] Plasma isatuximab concentrations were determined.

The PK parameters of isatuximab are shown in Table 21. Following administration of isatuximab 10 mg/kg, the accumulation ratios based on C_{trough} and C_{max}[12)] were 3.36 and 2.96, respectively.

Table 21. PK parameters of isatuximab

Dose (mg/kg)	Cycle	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{1week} (μg·h/mL)	AUC_{last} (μg·h/mL)
5	1	5	91.3 (21.7)	2.42 (2.13, 3.83)	6,100 (46.5)	6,100 (46.4)
	3	6	167 (20.6)	5.97 (1.83, 7.25)	—	30,900 (35.1)
10	1	18	141 (13.3)	3.41 (2.30, 28.0)	12,800 (18.9)*2	13,000 (18.1)*2
	3	24	403 (40.4)	6.36 (2.00, 23.7)	—	74,000 (49.1)*3
20	1	6	297 (5.6)	5.22 (4.28, 8.93)	27,000 (20.8)	27,600 (21.8)
	3	6	648 (38.0)	7.52 (4.25, 48.2)	—	155,000 (58.4)*4

Mean (CV%), *1, Median (range); *2, n = 16; *3, n = 20; *4, n = 5; —, not calculated

6.2.2.3 Foreign phase I study (CTD 5.3.3.2-6, Study 14154 Part A [ongoing since October 2015 (data cutoff date of July 21, 2017)])

An open-label, uncontrolled study was conducted in 26 patients with relapsed or refractory MM (23 subjects included PK analysis) to evaluate the PK etc. of isatuximab. Treatment was to be administered in 28-day cycles.

11) Pomalidomide 4 mg was to be administered orally QD on Days 1-21 of each 28-day cycle, and DEX 40 mg (20 mg for patients aged ≥75 years) was to be administered orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle.
12) The ratio of C_{trough} or C_{max} on Day 1 of Cycle 3 to C_{trough} on Day 8 of Cycle 1 or C_{max} on Day 1 of Cycle 1

Isatuximab 10 or 20 mg/kg was to be administered intravenously QW in the first cycle and Q2W thereafter. Plasma isatuximab concentrations were determined.

The PK parameters of isatuximab following the first dose of isatuximab are shown in Table 22.

Table 22. PK parameters of isatuximab

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} *1 (h)	AUC_{1week} (μg·h/mL)
10	4*2	182 (34.1)	5.78 (3.08, 8.75)	14,600 (22.5)
20	6*3	265 (42.2)	6.38 (3.08, 8.72)	19,900 (35.7)

Mean (CV%), *1, Median (range); *2, Excluding 7 subjects who had their first infusion interrupted; *3, Excluding 6 subjects who had their first infusion interrupted

6.2.3 Relationship between exposure and change in QT/QTc interval

The relationship between plasma isatuximab concentrations and ΔQTcF was assessed using a linear mixed effects model, based on the data from Phase I part of a foreign phase I/II study (Study 10893). There was no clear relationship between plasma isatuximab concentrations and ΔQTcF. The applicant explained that prolongation of the QT/QTc interval is unlikely in clinical use of isatuximab based on the above.

6.2.4 PPK analysis

A population pharmacokinetic analysis (PPK) was performed by non-linear mixed-effects modeling, based on isatuximab PK data from foreign clinical studies (Studies 10893, 14154, and 14079) and a global phase III study (Study 14335) (7,697 PK samples from 476 subjects) (software used, MONOLIX Version 2018R1). The PK of isatuximab were described by a 2-compartment model with linear and Michaelis-Menten eliminations.

The PK parameters and covariates tested in this analysis are shown in Table 23.

Table 23. Covariates tested

PK parameters	Covariates
CL_{inf}, CL_m, KCL, V1, V_m	age, albumin, alkaline phosphatase, ALT, AST, β_2 microglobulin, bilirubin, BMI, bone marrow plasma cells, body surface area, CrCL, eGFR, LDH, the number of prior lines of therapy, lymphocyte count, serum M protein concentration, body weight, dose,*1 coadministration with Pd, performance status, formulation, hepatic impairment,*2 ISS, clinical study, myeloma type (IgG vs. non-IgG), obesity, race, renal impairment,*3 IgG patients with serum M protein >5 g/L vs. other patients, sex
V2, Q	body weight, body surface area

*1, Covariate effects on CL_{inf} and V_m only were evaluated. *2, Categorized based on bilirubin and AST. *3, Categorized based on CrCL or eGFR.

(1) Body weight, β_2 microglobulin, and myeloma type (IgG vs. non-IgG), (2) myeloma type (IgG vs. non-IgG), (3) body weight, race (Asian vs. non-Asian), sex, and formulation, and (4) body weight were identified as significant covariates influencing (1) CL_{inf}, (2) KCL, (3) V1, and (4) V2 and Q of isatuximab.

The applicant's explanation:
Since the magnitude of impact of each covariate on isatuximab exposure (AUC at steady state) was limited etc., these covariates are unlikely to have clinically meaningful effects on the PK of isatuximab.

The $t_{1/2}$ at steady state was estimated to be 28 days based on the above PPK analysis.

6.2.5 Exposure-efficacy/safety relationship

6.2.5.1 Exposure-efficacy relationship

On the basis of the results from a global phase III study (Study 14335), isatuximab exposure[13] (C_{trough} after the 4th weekly dose) was divided into 4 quartiles[14] to assess the relationship between isatuximab exposure and progression-free survival (PFS). PFS tended to increase with increasing isatuximab exposure.

6.2.5.2 Exposure-safety relationship

On the basis of the results from a foreign phase Ib study (Study 14079) Part A and a global phase III study (Study 14335), isatuximab exposure[13] (C_{max} on Day 1 of Cycle 1) was divided into 4 quartiles[15] to assess the relationship between isatuximab exposure and the incidence of infusion reactions. In addition, isatuximab exposure[13] (C_{max} from Cycle 1 Day 1 to Cycle 2 Day 1) was divided into 4 quartiles[16] to assess the relationship between isatuximab exposure and the incidences of arrhythmia, cardiac and nervous system disorders, Grade ≥2 infections and respiratory adverse events, and Grade ≥3 thrombocytopenia, neutropenia, anemia, lymphopenia, infections, and respiratory adverse events. There was a trend towards decreasing incidence of Grade ≥3 anemia as isatuximab exposure increased. The incidence of Grade ≥3 infections tended to be lower in patients in the high-exposure quartiles (Q3 and Q4) than in patients in the low-exposure quartiles (Q1 and Q2). On the other hand, there was no clear relationship between the incidences of other events and isatuximab exposure.

6.2.6 Impact of decreased renal or hepatic function on PK of isatuximab

No clinical studies to evaluate the PK of isatuximab in patients with renal or hepatic impairment have been conducted. However, the applicant explained that given the following points, decreased renal or hepatic function is unlikely to affect the PK of isatuximab.

- Isatuximab is considered to be eliminated via a target mediated pathway due to binding to the target antigen and a proteolytic catabolism pathway.
- In the PPK analysis, eGFR, bilirubin, ALT, or AST was not identified as a significant covariate on the PK parameters of isatuximab [see Section 6.2.5].

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[13] Predicted by PPK analysis [see Section 6.2.4].
[14] The ranges of C_{trough} (μg/mL) in the quartiles were <86.0, ≥86.0 and <142.4, ≥142.4 and <187.5, and ≥187.5 and ≤357.1.
[15] The ranges of C_{max} (μg/mL) in the quartiles were <149.9, ≥149.9 and <174.6, ≥174.6 and <210.1, and ≥210.1 and ≤777.1.
[16] The ranges of concentration (μg/mL) in the quartiles were <249.6, ≥249.6 and <316.3, ≥316.3 and <382.4, and ≥382.4 and ≤931.3.

6.2.7 Isatuximab PK differences between Japanese and non-Japanese populations

The applicant's explanation:

Since there were no clear differences in the C_{max} or AUC_{1week} following administration of single-agent isatuximab between a Japanese phase I/II study (Study 14095) and a foreign phase I study (Study 14154) Part A [see Sections 6.2.1.1 and 6.2.2.3] etc., no clear differences in the PK of isatuximab between Japanese and non-Japanese populations were observed.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of isatuximab is acceptable, except for the considerations in the following section.

6.R.1 Impact of anti-isatuximab antibodies on PK of isatuximab

The incidence of anti-isatuximab antibodies was determined in all clinical studies submitted in the present application. Anti-isatuximab antibodies were detected in 17 of 600 patients evaluable for anti-isatuximab antibodies (2.8%).

The applicant's explanation:

The time-matched PK/anti-isatuximab antibody assay data[17)] from patients treated with the proposed dosing regimen of isatuximab in Studies 11863 and 10893 showed no trend towards clear differences in the plasma isatuximab concentration between anti-isatuximab antibody-positive patients (n = 2) (individual values, 67.9 and 891 μg/mL) and antibody-negative patients (n = 9) (range, 26.2-449 μg/mL). Taking account of this finding etc., anti-isatuximab antibodies are unlikely to impact the PK of isatuximab.

PMDA's discussion:

Given that the number of anti-isatuximab antibody-positive patients was limited, it is difficult to draw a definitive conclusion on the impact of anti-isatuximab antibodies on the PK of isatuximab. Thus, it is necessary to continue to collect information on the impact of anti-isatuximab antibodies on the PK of isatuximab and appropriately provide any new finding to healthcare professionals in clinical practice.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from a total of 3 studies presented in Table 24: 1 Japanese phase I/II study, 1 global phase III study, and 1 foreign phase Ib study. The applicant also submitted the results from a total of 4 studies presented in Table 24 as reference data: 1 foreign phase I study, 2 foreign phase Ib studies, and 1 foreign phase I/II study.

17) Pre-dose on Day 1 of Cycle 6

Table 24. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study Identifier	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	14095	I/II	Patients with relapsed or refractory MM	Phase I: 8 Phase II: 28	Treatment was administered in 28-day cycles. (1) Isatuximab 10 or 20 mg/kg in Phase I or (2) Isatuximab 20 mg/kg in Phase II intravenously QW in the first cycle and Q2W thereafter	Efficacy Safety PK
	Global	14335	III	Patients with relapsed or refractory MM	(1) 154 (2) 153	Treatment was administered in 28-day cycles. (1) Isatuximab/Pd group: Isatuximab 10 mg/kg intravenously QW in the first cycle and Q2W thereafter, in combination with Pd[11)] (2) Pd group: Pd[11)]	Efficacy Safety
	Foreign	14079	Ib	Patients with relapsed or refractory MM	Part A: 54 Part B: 54	Treatment was administered in 28-day cycles. Isatuximab was used in combination with Pd.[11)] Isatuximab 5, 10, or 20 mg/kg in Part A or Isatuximab 10 mg/kg in Part B intravenously QW in the first cycle and Q2W thereafter	Safety PK
Reference	Foreign	14154	I	Patients with relapsed or refractory MM	26	Treatment was administered in 28-day cycles. Isatuximab 10 or 20 mg/kg intravenously QW in the first cycle and Q2W thereafter	Safety PK
		11863	Ib	Patients with relapsed or refractory MM	57	Treatment was administered in 28-day cycles. Isatuximab was used in combination with Ld.[18)] Isatuximab 3.0, 5.0, or 10 mg/kg intravenously Q2W, or Isatuximab 10 or 20 mg/kg intravenously QW in the first cycle and Q2W thereafter	Safety PK
		13983	Ib	Patients with newly diagnosed MM who were noneligible for ASCT	17	Cycles 1-12: Isatuximab was used in combination with CBd.[19)] Cycle 1: Isatuximab 10 or 20 mg/kg intravenously on Days 1, 8, 15, 22, and 29 of a 42-day cycle. Cycles 2-12: Isatuximab 10 or 20 mg/kg intravenously Q2W in 28-day cycles. Cycle 13 and subsequent cycles: Isatuximab 10 or 20 mg/kg intravenously Q4W in combination with DEX[20)] in 28-day cycles	Safety PK
		10893	I/II	Patients with relapsed or refractory CD38-positive hematological malignancies or MM	Phase I: 89 Phase II Stage 1: 97 Stage 2: 93 (1) 30 (2) 63	Phase I: Isatuximab 0.0001-20 mg/kg intravenously Q2W or Isatuximab 10 or 20 mg/kg intravenously QW in 14-day cycles Phase II Stage 1: Treatment was administered in 28-day cycles. Isatuximab 3 or 10 mg/kg intravenously Q2W, Isatuximab 10 mg/kg intravenously Q2W in the first and second cycles and Q4W thereafter, or Isatuximab 20 mg/kg intravenously QW in the first cycle and Q2W thereafter Phase II Stage 2: Treatment was administered in 28-day cycles. Isatuximab 20 mg/kg intravenously QW in the first cycle and Q2W thereafter, (1) with or (2) without DEX[21)]	Efficacy Safety PK

[18)] Lenalidomide 25 mg was to be administered orally QD on Days 1-21 of each 28-day cycle and DEX 40 mg was to be administered orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle.

[19)] Cycle 1 was 42 days, and subsequent cycles were 28 days. Isatuximab was used in combination with cyclophosphamide, bortezomib, and DEX. Cyclophosphamide 300 mg/m^2 orally on Days 1, 8, 22, and 29 of Cycle 1 and on Days 1, 8, and 15 of Cycles 2-12, bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and on Days 1, 8, 15, and 22 of Cycles 2-12, and DEX 20 mg intravenously or orally on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32 of Cycle 1 and on Days 1, 2, 8, 9, 15, 16, 22, and 23 (on Days 1, 8, 15, and 22 for patients aged ≥75 years) of Cycles 2-12.

[20)] DEX 20 mg intravenously or orally on Day 1 of each 28-day cycle

[21)] DEX 40 mg (20 mg for patients aged >75 years) orally or intravenously on Days 1, 8, 15, and 22 of each cycle

The clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies." PK data are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I/II study (CTD 5.3.3.2-7, Study 14095 [ongoing since September 2016 (data cutoff date of July 31, 2018)])

An open-label, uncontrolled study was conducted at 13 sites in Japan to evaluate the efficacy, safety, and PK of isatuximab in patients with relapsed or refractory MM (target sample size, 6-12 subjects in Phase I and approximately 30 subjects in Phase II).

Treatment was to be administered in 28-day cycles. Isatuximab 10 or 20 mg/kg in Phase I or isatuximab 20 mg/kg in Phase II was to be administered intravenously QW in the first cycle and Q2W thereafter. Treatment was to be continued until disease progression or a criterion for treatment discontinuation was met.

All of 36 subjects enrolled in the study (3 in the 10 mg/kg cohort and 5 in the 20 mg/kg cohort in Phase I, 28 in Phase II) received isatuximab and were included in the efficacy and safety analyses. In Phase I, 7 subjects excluding 1 subject in the 20 mg/kg cohort who received isatuximab and then discontinued due to adverse events[22)] were evaluated for dose limiting toxicity (DLT).[23)]

No DLTs were observed during the DLT evaluation period, i.e. Cycle 1 of Phase I.

Regarding efficacy, the overall response rate based on the independent response committee (IRC) assessment using the International Myeloma Working Group (IMWG) criteria (*J Clin Oncol*. 2014;32:587-600) [95% CI] in patients treated with isatuximab 20 mg/kg was 36.4% [20.4, 54.9] (12 of 33 patients).

Regarding safety, 1 of 36 subjects (2.8%) (1 subject in the 20 mg/kg cohort of Phase I) died during the isatuximab treatment period or within 30 days after the last dose of isatuximab, and the cause of death was disease progression.

22) Isatuximab was discontinued due to the occurrence of diplegia and neurogenic bladder after the second dose of isatuximab. As a causal relationship to isatuximab was denied for both adverse events, these events were not recorded as DLTs.
23) Patients who received 4 doses of study drug in the first cycle and patients who discontinued study drug due to DLT before completion of Cycle 1 were evaluated for DLT.

7.1.2 Global study

7.1.2.1 Global phase III study (CTD 5.3.5.1-1, Study 14335 [ongoing since January 2017 (data cutoff date of November 22, 2018[24])])

An open-label, randomized study was conducted at 102 sites in 24 countries or regions including Japan to evaluate the efficacy and safety of isatuximab/Pd compared with Pd in patients with relapsed or refractory MM[25] (target sample size, 300 subjects).

Treatment was to be administered in 28-day cycles. In the isatuximab/Pd group, isatuximab 10 mg/kg was to be administered intravenously QW in the first cycle and Q2W thereafter, in combination with Pd.[11] In the Pd group, Pd[11] was to be administered. In both the isatuximab/Pd and Pd groups, treatment was to be continued until disease progression or a criterion for treatment discontinuation was met.

Three hundred seven subjects who were enrolled in the study and randomized (154 in the isatuximab/Pd group, 153 in the Pd group) were included in the intent-to-treat (ITT) population, which was used as the efficacy analysis population (including 9 Japanese patients in the isatuximab/Pd group and 4 Japanese patients in the Pd group). Among the ITT population, 301 subjects who received study drug (152 in the isatuximab/Pd group, 149 in the Pd group) were included in the safety population (including 9 Japanese patients in the isatuximab/Pd group and 4 Japanese patients in the Pd group).

The primary endpoint for the study was PFS based on the IRC assessment using the IMWG criteria (*Lancet Oncol*. 2016;17:e328-46). The PFS analysis was planned to be performed when 162 PFS events had been observed.

Regarding efficacy, the PFS results based on the IRC assessment using the IMWG criteria and the Kaplan-Meier curves are shown in Table 25 and Figure 1, respectively.

Table 25. Results of final analysis of PFS (ITT population, IRC assessment, data cutoff date of October 11, 2018)

	Isatuximab/Pd	Pd
N	154	153
No. of deaths or progressive disease events (%)	73 (47.4)	89 (58.2)
Median [95% CI] (months)	11.5 [8.9, 13.9]	6.5 [4.5, 8.3]
Hazard ratio*1 [95% CI]	0.60 [0.44, 0.81]	
P-value (one-sided)*2	0.001	

*1, Calculated using a stratified Cox proportional hazards model, with the stratification factors of age (<75 versus ≥75 years) and the number of previous lines of therapy (2 or 3 versus ≥4); *2, Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), One-sided significance level of 0.025

[24] The data cutoff date for efficacy analyses was October 11, 2018.

[25] Patients who had received ≥2 prior lines of therapy including lenalidomide and a PI and had progressed on or within 60 days of completion of the last therapy were eligible for enrollment in the study.

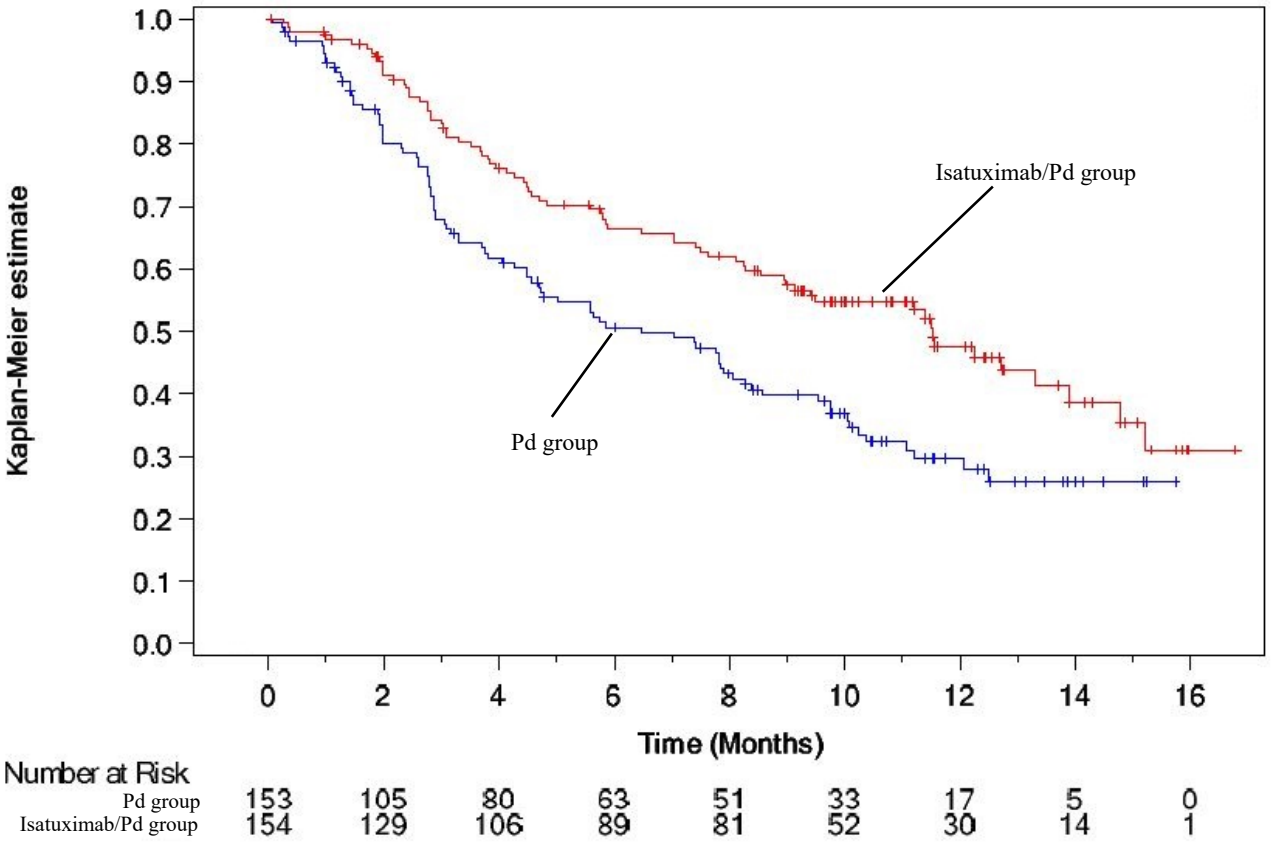

Figure 1. Kaplan-Meier curves of PFS at final analysis time
(ITT population, IRC assessment, data cutoff date of October 11, 2018)

In patients with relapsed and refractory disease[26] (122 in the isatuximab/Pd group, 110 in the Pd group), the median PFS based on the IRC assessment was 11.5 months in the isatuximab/Pd group and 6.5 months in the Pd group (hazard ratio [95% CI], 0.66 [0.46, 0.93]). In patients with refractory disease[27] (32 in the isatuximab/Pd group, 43 in the Pd group), the median PFS based on the IRC assessment was not estimable (NE) in the isatuximab/Pd group and 5.6 months in the Pd group (hazard ratio [95% CI], 0.42 [0.21, 0.87]).

Regarding safety, 11 of 152 subjects (7.2%) in the isatuximab/Pd group and 13 of 149 subjects (8.7%) in the Pd group died during the study treatment period or within 30 days after the last dose of study treatment. The causes of deaths other than disease progression (5 in the isatuximab/Pd group, 2 in the Pd group) were death (2 subjects); and hepatic enzyme increased; pneumonia influenzal; hepatic failure and multiple organ dysfunction syndrome; and sepsis (1 subject each) in the isatuximab/Pd group and septic shock (2 subjects); and pneumonia; intracranial haemorrhage; cauda equina syndrome; acute kidney injury; sepsis; death; sudden death; urinary tract infection; and renal failure (1 subject each) in the Pd group. A causal relationship to study drug could not be ruled out for sepsis (1 subject) in the isatuximab/Pd group and pneumonia; and urinary tract

[26] Patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment (progressed on or within 60 days after end of the previous therapy)
[27] Patients who were refractory to all previous lines of treatment (progressed on or within 60 days after end of the previous therapy) but had achieved at least a minimal response (MR) in one previous line

infection (1 subject each) in the Pd group (No Japanese patients had an adverse event leading to death in either group).

7.1.3 Foreign clinical study

7.1.3.1 Foreign phase Ib study (CTD 5.3.3.2-4, CTD 5.3.3.2-5, Study 14079 [ongoing since May 2015 (data cutoff date of February 26, 2019)])

An open-label, uncontrolled study was conducted at 6 sites overseas for Part A and at 12 sites overseas for Part B to evaluate the safety, PK, etc. of isatuximab/Pd in patients with relapsed or refractory MM (target sample size, 36-42 subjects in Part A, 40 subjects in Part B).

Treatment was to be administered in 28-day cycles. Isatuximab 5, 10, or 20 mg/kg in Part A or isatuximab 10 mg/kg in Part B was to be administered intravenously QW in the first cycle and Q2W thereafter, in combination with Pd.[11)]

Among 108 subjects enrolled in the study (54 in Part A, 54 in Part B), 92 subjects who received isatuximab (45 in Part A [23 in the dose escalation cohort and 22 in the dose expansion cohort], 47 in Part B) were included in the safety population. Among the dose escalation cohort in Part A, 18 subjects (6 each in the 5 mg/kg, 10 mg/kg, and 20 mg/kg groups) excluding 2 subjects in the 5 mg/kg group and 3 subjects in the 10 mg/kg group[28)] were evaluated for DLT.

During the DLT evaluation period, i.e. Cycle 1 in the dose escalation cohort of Part A, DLTs were observed in 1 of 6 subjects in the 5 mg/kg group (Grade 4 neutropenia), 1 of 6 subjects in the 10 mg/kg group (Grade 4 neutropenic infection), and 1 of 6 subjects in the 20 mg/kg group (Grade 3 confusional state), but the maximum tolerated dose (MTD) was not reached.

Regarding safety, 11 of 92 subjects (12.0%) (5 subjects [1 in the 5 mg/kg group and 4 in the 10 mg/kg group] in Part A, 6 subjects in Part B) died during the study treatment period or within 30 days after the last dose of study treatment. The causes of deaths other than disease progression (5 subjects) (3 subjects [1 in the 5 mg/kg group and 2 in the 10 mg/kg group) in Part A, 2 subjects in Part B) were malignant neoplasm progression; and intestinal perforation (1 subject each) (both in the 10 mg/kg group of Part A) and sepsis; sepsis and rectal haemorrhage; myocardial infarction; and sudden death (1 subject each) (all in Part B) (the 10 mg/kg group), and a causal relationship to study drug was denied for all those events.

[28)] Among subjects in the 5 mg/kg group, 1 subject who could not complete Cycle 1 due to an infusion reaction and 1 subject who required dose modification of study drug for a non-DLT reason were excluded from DLT evaluation. Among subjects in the 10 mg/kg group, 3 subjects waiting for the dose expansion phase to open were enrolled in the dose escalation cohort, but excluded from DLT evaluation. No DLTs were observed in these 3 subjects.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase I study (CTD 5.3.3.2-6, Study 14154 Part A [ongoing since October 2015 (data cutoff date of July 21, 2017)])

An open-label, uncontrolled study was conducted at 6 sites overseas to evaluate the safety, PK, etc. of isatuximab in patients with relapsed or refractory MM (target sample size, 15-18 subjects).

All of 26 subjects enrolled in the study received isatuximab and were included in the safety population.

In this study, there were no deaths during the study treatment period or within 30 days after the last dose of study treatment.

7.2.1.2 Foreign phase Ib study (CTD 5.3.3.2-1, Study 11863 [ongoing since February 2013 (data cutoff date of May 26, 2016)])

An open-label, uncontrolled study was conducted at 5 sites overseas to evaluate the safety, PK, etc., of isatuximab/lenalidomide and dexamethasone (Ld) in patients with relapsed or refractory MM (target sample size, 60 subjects).

All of 57 subjects enrolled in the study received study drug and were included in the safety population.

In this study, there were 5 deaths during the study treatment period or within 30 days after the last dose of study treatment. The causes of deaths other than disease progression (3 subjects) were procedural haemorrhage; and bacterial sepsis (1 subject each), and a causal relationship to study drug was denied for both cases.

7.2.1.3 Foreign phase Ib study (CTD 5.3.3.2-2, Study 13983 [ongoing since September 2015 (data cutoff date of September 22, 2017)])

An open-label, uncontrolled study was conducted at 5 sites overseas to evaluate the safety, PK, etc. of isatuximab/cyclophosphamide, bortezomib, and dexamethasone (CBd) in patients with newly diagnosed MM who were non-eligible for autologous stem cell transplantation (ASCT) (target sample size, 15-18 subjects).

All of 17 subjects enrolled in the study received study drug and were included in the safety population.

In this study, 1 death occurred during the study treatment period or within 30 days after the last dose of study treatment. The cause of death was sudden death, and its causal relationship to study drug was denied.

7.2.1.4 Foreign phase I/II study (CTD 5.3.3.2-3, CTD 5.3.5.1-2, CTD 5.3.5.1-3, Study 10893 [ongoing since June 2010 (data cutoff date of November 15, 2017)])

An open-label study was conducted in patients with relapsed or refractory CD38-positive hematological malignancies or MM (target sample size, 85 subjects in Phase I [patients with CD38-positive hematological malignancies], 256 subjects in Phase II [patients with MM] [96 in Stage 1, 160 in Stage 2]) at

13 sites overseas for Phase I, at 17 sites overseas for Phase II Stage 1, and at 35 sites overseas for Phase II Stage 2. The study consisted of Phase I to evaluate the safety and PK of single-agent isatuximab, Phase II Stage 1 to evaluate the efficacy and safety of single-agent isatuximab, and Phase II Stage 2 to evaluate the efficacy and safety of isatuximab as a single agent or in combination with DEX.

All of 279 subjects enrolled in the study (89 in Phase I, 97 in Phase II Stage 1, 93 in Phase II Stage 2) received isatuximab and were included in the safety population.

There were 15 deaths during the study treatment period or within 30 days after the last dose of study treatment (1 subject in Phase I, 8 subjects in Phase II Stage 1, 6 subjects in Phase II Stage 2 [1 in the isatuximab/DEX group, 5 in the single agent isatuximab group]). The causes of deaths other than disease progression (7 subjects) (5 in Phase II Stage 1, 2 in Phase II Stage 2) were acute kidney injury; cerebral haemorrhage; sudden death; atrial fibrillation; general physical condition decreased; ischaemic stroke; bone pain[29)]; and multiple organ dysfunction syndrome (1 subject each), and a causal relationship to study drug was denied for all those events.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal study to evaluate the efficacy and safety of isatuximab/Pd is a global phase III study in patients with relapsed or refractory MM (Study 14335). PMDA decided to focus its efficacy review on this study. PMDA decided to evaluate its efficacy in Japanese patients in terms of the consistency of the results between the overall population and the Japanese subgroup in Study 14335, based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD Administrative Notice dated September 5, 2012), etc.

7.R.2 Efficacy

As a result of the following reviews, PMDA concluded that the efficacy of isatuximab/Pd was demonstrated in patients with relapsed or refractory MM.

7.R.2.1 Control group

The applicant's explanation about the basis for choosing a control group for Study 14335:

At the time of planning Study 14335 in 2016, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma (v.3.2016) (NCCN guidelines) recommended Pd for the treatment of patients with relapsed or refractory MM (the patient population of Study 14335) based on the results from a foreign clinical study (*Lancet Oncol*. 2013;14:1055-66). Thus, the Pd group was chosen as a control group for Study 14335.

29) The patient died due to disease progression associated with Grade 5 bone pain, but the investigator reported that the cause of death was bone pain.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint

The applicant's explanation about the reason for selecting PFS as the primary endpoint for Study 14335:
MM is a refractory disease with recurring relapses that is difficult to cure with existing therapies, and the improvement of clinical symptoms, delay of disease progression, etc., are expected in patients with prolonged PFS (*Leukemia*. 2006;20:1467-73) etc. Thus, PFS was selected as the primary endpoint for Study 14335.

PMDA's discussion:
The applicant's explanation is largely understandable. However, given that patients with relapsed or refractory MM receive treatment, hoping that it will prolong their survival, the results of overall survival (OS) are also important. Thus, PMDA decided to conduct its efficacy review, focusing on the primary endpoint of PFS based on the IRC assessment using the IMWG criteria, and assess OS as well.

7.R.2.3 Results of efficacy evaluation

Study 14335 demonstrated the superiority of isatuximab/Pd over Pd in the primary endpoint of PFS based on the IRC assessment using the IMWG criteria [see Section 7.1.2.1].

The results of a sensitivity analysis of PFS based on the investigator assessment using the IMWG criteria are shown in Table 26.

Table 26. Results of final analysis of PFS (ITT population, investigator assessment, data cutoff date of October 11, 2018)

	Investigator assessment	
	Isatuximab/Pd	Pd
N	154	153
No. of deaths or progressive disease events (%)	76 (49.4)	96 (62.7)
Median [95% CI] (months)	11.1 [7.5, 14.8]	6.5 [4.5, 7.9]
Hazard ratio*1 [95% CI]	0.60 [0.44, 0.82]	
P-value (one-sided)*2	0.0009	

*1, Calculated using a stratified Cox proportional hazards model, with the stratification factors of age (<75 versus ≥75 years) and the number of previous lines of therapy (2 or 3 versus ≥4); *2, Stratified log-rank test [the same stratification factors as the Cox proportional hazards model])

In Study 14335, if there was a statistically significant difference in the primary endpoint, the hypothesis testing of the secondary efficacy endpoints was planned to be conducted in a sequential, hierarchical manner: (1) the overall response rate based on the IRC assessment and (2) OS. The above analysis (1) showed a statistically significant difference, but the analysis (2) did not.[30)]

The results of the interim analysis of the secondary endpoint of OS (data cutoff date of October 11, 2018) and the Kaplan-Meier curves are shown in Table 27 and Figure 2, respectively.

30) One-sided significance level for OS at the time of PFS analysis was set to 0.0008 using the Lan-DeMets O'Brien-Fleming α spending function.

Table 27. Results of interim analysis of OS (ITT population, data cutoff date of October 11, 2018)

	Isatuximab/Pd	Pd
N	154	153
No. of deaths (%)	43 (27.9)	56 (36.6)
Median [95% CI] (months)	NE [NE, NE]	NE [13.9, NE]
Hazard ratio*1 [95% CI]	0.69 [0.46, 1.02]	
P-value (one-sided)*2	0.0631	

*1, Calculated using a stratified Cox proportional hazards model adjusted for age (<75 versus ≥75 years) and the number of previous lines of therapy (2 or 3 versus ≥4); *2, Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), One-sided significance level of 0.0008

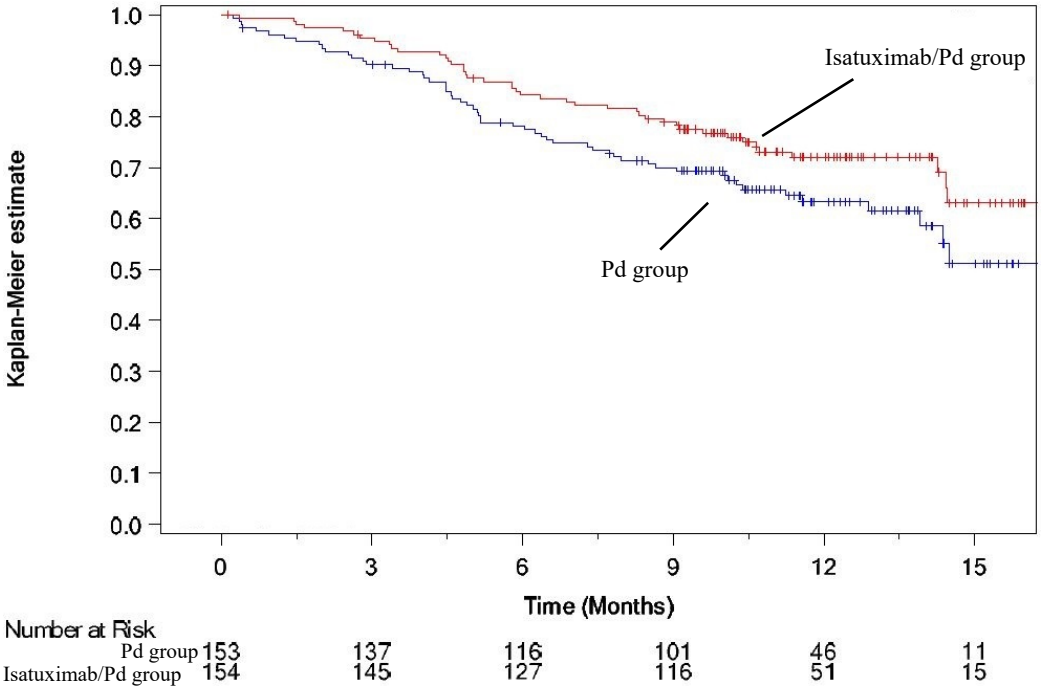

Figure 2. Kaplan-Meier curves of OS at interim analysis time (ITT population, data cutoff date of October 11, 2018)

The results of PFS based on the IRC assessment using the IMWG criteria and the Kaplan-Meier curves in the Japanese subgroup of Study 14335 are shown in Table 28 and Figure 3, respectively.

Table 28. Results of final analysis of PFS in Japanese subgroup (ITT population, IRC assessment, data cutoff date of October 11, 2018)

	Isatuximab/Pd	Pd
N	9	4
No. of deaths or progressive disease events (%)	3 (33.3)	1 (25.0)
Median [95% CI] (months)	NE [5.8, NE]	NE [7.8, NE]
Hazard ratio* [95% CI]	1.2 [0.13, 11.8]	

* Calculated using an unstratified Cox proportional hazards model.

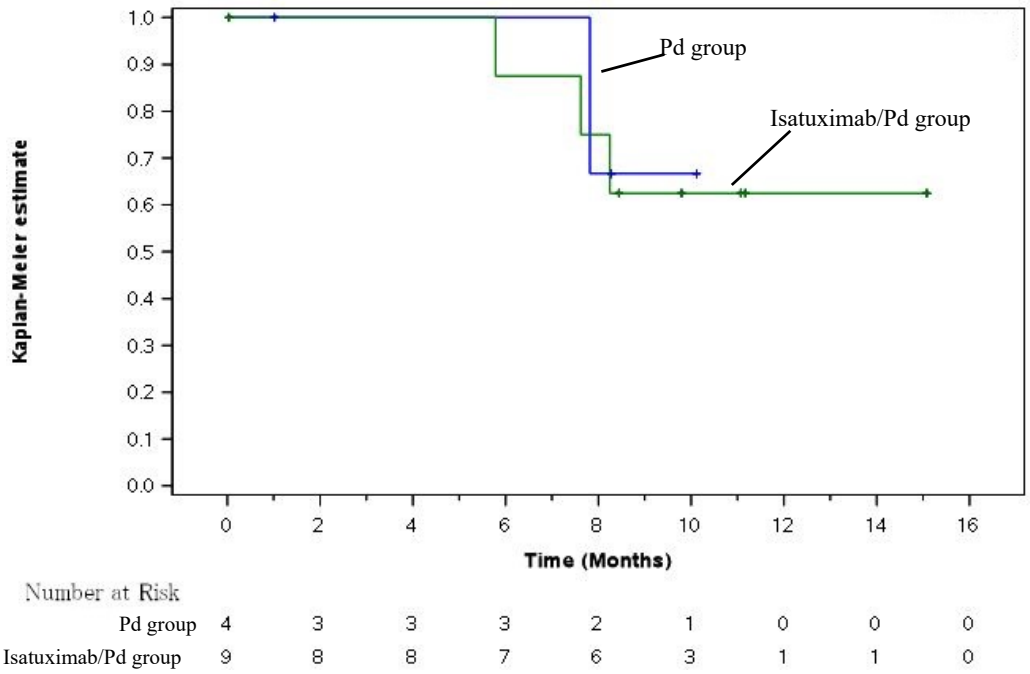

Figure 3. Kaplan-Meier curves of PFS at final analysis time in Japanese subgroup (ITT population, IRC assessment, data cutoff date of October 11, 2018)

The applicant's explanation about the efficacy of isatuximab in Japanese patients:

Since the results of PFS based on the IRC assessment using the IMWG criteria (the primary endpoint for Study 14335) in the overall population tended to differ from those in the Japanese subgroup, the possible influence of imbalances in prognostic factors for MM was examined, but this influence was limited. Given that (1) the number of Japanese patients in Study 14335 was limited and that (2) the number of patients in the Pd group was smaller than that in the isatuximab/Pd group in the Japanese subgroup, etc., there are limitations to evaluating the efficacy of isatuximab in Japanese patients, based on these results. However, considering that the overall response rate in the isatuximab/Pd group in the Japanese subgroup (6 of 9 subjects [66.7%]) was similar to that in the overall population (93 of 154 subjects [60.4%]) in Study 14335, etc., the efficacy of isatuximab/Pd is expected in Japanese patients with relapsed or refractory MM.

PMDA's discussion:

Given the following points etc., the efficacy of isatuximab/Pd in the patient population of Study 14335 was demonstrated.

- Study 14335 demonstrated the superiority of isatuximab/Pd over Pd in the primary endpoint of PFS based on the IRC assessment using the IMWG criteria, and the prolonged PFS achieved is considered clinically meaningful.
- The interim analysis of OS (the secondary endpoint for Study 14335) showed no trend towards shorter OS in the isatuximab/Pd group compared to the Pd group.
- Although the number of Japanese patients in Study 14335 was limited, and there are limitations to evaluating the efficacy of isatuximab/Pd in Japanese patients, taking account of the above explanation by the applicant and the following points etc., the efficacy of isatuximab/Pd is expected also in Japanese patients.

- In Phase I of Study 14095 in Japanese patients with relapsed or refractory MM, a certain overall response rate (2 of 3 subjects [66.7%]) was achieved with single-agent isatuximab 10 mg/kg.
- There are no clear differences in the diagnosis of and treatment paradigms for MM or the PK of isatuximab between Japanese and non-Japanese populations [see Section 6.2.7].

7.R.3 Safety (for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies")

As a result of the following reviews, PMDA concluded that adverse events that require particular attention following administration of isatuximab are infusion reactions, myelosuppression, infections, cardiac disorders, second primary malignancies, tumor lysis syndrome (TLS), and hemolysis. Attention should be paid to the possible occurrence of these adverse events during treatment with isatuximab.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with isatuximab, isatuximab is tolerable as long as physicians with adequate knowledge of and experience in the treatment of hematological malignancies take appropriate measures, e.g. monitoring for and management of adverse events. However, as there is very limited clinical experience with isatuximab in Japanese patients, it is necessary to collect further safety information after marketing [see Section 7.R.7].

7.R.3.1 Safety profile of isatuximab and differences in safety between Japanese and non-Japanese populations

The applicant's explanation about the safety profile of isatuximab based on safety information from Study 14335:

Safety data from Study 14335 are summarized in Table 29.

Table 29. Summary of safety data (Study 14335)

	n (%)					
	Overall population		Japanese subgroup		Non-Japanese subgroup	
	Isatuximab/Pd	Pd	Isatuximab/Pd	Pd	Isatuximab/Pd	Pd
	N = 152	N = 149	N = 9	N = 4	N = 143	N = 145
All adverse events	151 (99.3)	146 (98.0)	9 (100)	4 (100)	142 (99.3)	142 (97.9)
Grade ≥3 adverse events	132 (86.8)	105 (70.5)	8 (88.9)	4 (100)	124 (86.7)	101 (69.7)
Adverse events leading to death	11 (7.2)	13 (8.7)	0	0	11 (7.7)	13 (9.0)
Serious adverse events	94 (61.8)	80 (53.7)	4 (44.4)	0	90 (62.9)	80 (55.2)
Adverse events leading to treatment discontinuation*1	24 (15.8)	21 (14.1)	2 (22.2)	0	22 (15.4)	21 (14.5)
Adverse events leading to dose interruption or reduction[31)*2]	132 (86.8)	96 (64.4)	9 (100)	4 (100)	123 (86.0)	92 (63.4)

*1, Discontinuation of isatuximab, pomalidomide, or DEX

*2, (1) Dose interruption of isatuximab, pomalidomide, or DEX, or (2) Dose reduction of pomalidomide or DEX

In Study 14335, adverse events reported at a ≥10% higher incidence in the isatuximab/Pd group than in the Pd group were neutropenia (71 subjects [46.7%] in the isatuximab/Pd group, 50 subjects [33.6%] in the Pd group), infusion related reaction (56 subjects [36.8%], 2 subjects [1.3%][32)]), upper respiratory tract infection (43

31) As "adverse events leading to dose interruption or reduction" were defined as adverse events leading to dose reduction or interruption of study drug in Study 14335, those events were counted as adverse events leading to dose interruption or reduction.

32) Infusion related reactions observed in 2 subjects in the Pd group were reported by the investigator as adverse events related to subsequent anti-myeloma treatment (daratumumab).

subjects [28.3%], 26 subjects [17.4%]), and bronchitis (36 subjects [23.7%], 13 subjects [8.7%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the isatuximab/Pd group than in the Pd group were neutropenia (70 subjects [46.1%], 48 subjects [32.2%]) and febrile neutropenia (18 subjects [11.8%], 3 subjects [2.0%]). Adverse events leading to death reported at a higher incidence in the isatuximab/Pd group than in the Pd group and reported by more than 1 subject were disease progression (5 subjects [3.3%], 2 subjects [1.3%]) and death (2 subjects [1.3%], 1 subject [0.7%]). Serious adverse events reported at a ≥2% higher incidence in the isatuximab/Pd group than in the Pd group were febrile neutropenia (10 subjects [6.6%], 3 subjects [2.0%]), urinary tract infection (6 subjects [3.9%], 2 subjects [1.3%]), infusion related reaction (6 subjects [3.9%], 1 subject [0.7%]), neutropenia (5 subjects [3.3%], 2 subjects [1.3%]), viral pneumonia (3 subjects [2.0%], 0 subjects), squamous cell carcinoma of skin (3 subjects [2.0%], 0 subjects), hyperglycaemia (3 subjects [2.0%], 0 subjects), and traumatic fracture (3 subjects [2.0%], 0 subjects). Adverse events leading to dose interruption or reduction of study drug[31)] reported at a ≥5% higher incidence in the isatuximab/Pd group than in the Pd group were neutropenia (69 subjects [45.4%], 46 subjects [30.9%]), pneumonia (25 subjects [16.4%], 14 subjects [9.4%]), upper respiratory tract infection (21 subjects [13.8%], 13 subjects [8.7%]), febrile neutropenia (16 subjects [10.5%], 2 subjects [1.3%]), and bronchitis (16 subjects [10.5%], 0 subjects). There were no adverse events leading to study drug discontinuation reported at a ≥5% higher incidence in the isatuximab/Pd group than in the Pd group.

The applicant's explanation about differences in safety between Japanese and non-Japanese populations:
In the isatuximab/Pd group of Study 14335, adverse events reported at a ≥15% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutropenia (7 subjects [77.8%] in the Japanese subgroup, 64 subjects [44.8%] in the non-Japanese subgroup), nasopharyngitis (4 subjects [44.4%], 10 subjects [7.0%]), upper respiratory tract inflammation (3 subjects [33.3%], 0 subjects), stomatitis (2 subjects [22.2%], 8 subjects [5.6%]), pruritus (2 subjects [22.2%], 3 subjects [2.1%]), and pharyngitis (2 subjects [22.2%], 1 subject [0.7%]). Grade ≥3 adverse events reported at a ≥15% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutropenia (7 subjects [77.8%], 63 subjects [44.1%]). Serious adverse events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup and reported by more than 1 subject were pneumonia (2 subjects [22.2%], 21 subjects [14.7%]). Adverse events leading to dose interruption or reduction of study drug[31)] reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup and reported by more than 1 subject were neutropenia (7 subjects [77.8%], 62 subjects [43.4%]) and pneumonia (2 subjects [22.2%], 23 subjects [16.1%]). There were no adverse events leading to death reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup or adverse events leading to study drug discontinuation reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup and reported by more than 1 subject.

PMDA's discussion:
Attention should be paid to the possible occurrence of specific adverse events that were reported at a higher incidence in the isatuximab/Pd group than in the Pd group in Study 14335, and it is necessary to appropriately provide information on the incidences of these events to healthcare professionals in clinical practice, using the package insert etc.

Since the number of Japanese patients enrolled in Study 14335 was limited, it is difficult to draw a definitive conclusion on differences in the safety of isatuximab between Japanese and non-Japanese populations. Meanwhile, given that some adverse events were reported at a higher incidence in Japanese patients than in non-Japanese patients, it is necessary to appropriately provide information on the incidences of specific adverse events in Japanese patients to healthcare professionals in clinical practice. As isatuximab safety information from Japanese patients is limited, it is necessary to collect post-marketing information and appropriately provide any new finding to healthcare professionals in clinical practice.

In the following sections, based mainly on the safety results from Study 14335, PMDA conducted its safety review, focusing on serious adverse events for which a causal relationship to study drug could not be ruled out observed in the isatuximab/Pd group of Study 14335, serious adverse events reported at a higher incidence in the isatuximab/Pd group than in the Pd group, specific events listed as clinically significant adverse reactions in the package insert for daratumumab, which has a similar mechanism of action to isatuximab, etc.

7.R.3.2 Infusion reactions

(1) Incidence and time to onset

The applicant's explanation about the incidence of infusion reactions associated with isatuximab infusions:

As infusion reaction-related adverse events, 141 MedDRA PTs (MedDRA/J ver.21.0)[33)] were counted if (i) they were considered by the investigator to be infusion reactions associated with isatuximab infusions or their associated symptoms, or (ii) they were not considered by the investigator to be infusion reactions associated with isatuximab infusions or their associated symptoms, but occurred from the day of the start of isatuximab infusion to the following day.[34)]

The incidence of infusion reactions in Study 14335 is shown in Table 30.

[33)] abdominal distension, abdominal pain, abdominal pain upper, acute coronary syndrome, acute kidney injury, acute psychosis, acute pulmonary oedema, agitation, anosmia, arthralgia, asthenia, atrial fibrillation, back pain, bone pain, bradycardia, bronchospasm, bronchostenosis, bursitis, chest discomfort, chills, choking, confusional state, cough, cytokine release syndrome, decreased appetite, delirium, depressed level of consciousness, dermatitis, diarrhoea, discomfort, disturbance in attention, dizziness, drug hypersensitivity, dry eye, dry skin, taste abnormality, dyskinesia, dyspepsia, dysphagia, dysphonia, dyspnoea, enterocolitis, erythema, eye pain, eye pruritus, eyelid oedema, face oedema, fatigue, feeling hot, feeling jittery, flushing, gait disturbance, gastrointestinal pain, generalised erythema, gingival discomfort, gingival pain, groin pain, headache, hiccups, hot flush, hyperglycaemia, hyperhidrosis, hypertension, hypoaesthesia, hyposmia, hypotension, hypoxia, inflammation, influenza like illness, infusion related reaction, insomnia, irritability, joint swelling, lacrimation increased, lethargy, malaise, mania, memory impairment, mood altered, mood swings, muscle spasms, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, nasal congestion, nasal obstruction, nausea, neck pain, non-cardiac chest pain, ocular hyperaemia, oedema, oedema peripheral, oropharyngeal discomfort, oropharyngeal pain, oxygen saturation decreased, pain, pain in extremity, pain in jaw, palpitations, paraesthesia, pelvic pain, peripheral coldness, peripheral swelling, pruritus, pruritus generalised, psychomotor hyperactivity, pyrexia, rash, rash maculo-papular, respiratory rate increased, respiratory symptom, restlessness, rhinitis, rhinorrhoea, seizure, sinus bradycardia, sinus congestion, sinus tachycardia, somnolence, stridor, syncope, tachycardia, tachypnoea, throat irritation, throat tightness, tremor, ventricular arrhythmia, ventricular extrasystoles, vertigo, vision blurred, visual impairment, vomiting, wheezing, angina pectoris, chest pain, drug intolerance, musculoskeletal discomfort, respiratory tract congestion

[34)] In the Pd group, adverse events occurring from Days 1, 8, 15, and 22 of Cycle 1 and Days 1 and 15 in subsequent cycles to their following days were counted.

Table 30. Infusion reactions reported by ≥5% of subjects in either group (Study 14335)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction	110 (72.4)	18 (11.8)	77 (51.7)	9 (6.0)
Infusion related reaction	56 (36.8)	4 (2.6)	0	0
Dyspnoea	34 (22.4)	3 (2.0)	5 (3.4)	0
Nausea	17 (11.2)	0	4 (2.7)	0
Cough	14 (9.2)	0	4 (2.7)	0
Fatigue	13 (8.6)	2 (1.3)	16 (10.7)	0
Asthenia	13 (8.6)	3 (2.0)	12 (8.1)	1 (0.7)
Back pain	12 (7.9)	0	10 (6.7)	1 (0.7)
Pyrexia	11 (7.2)	1 (0.7)	3 (2.0)	0
Hypertension	9 (5.9)	4 (2.6)	4 (2.7)	3 (2.0)
Tremor	8 (5.3)	2 (1.3)	2 (1.3)	0
Oedema peripheral	8 (5.3)	1 (0.7)	4 (2.7)	0
Diarrhoea	8 (5.3)	0	6 (4.0)	1 (0.7)
Muscle spasms	8 (5.3)	0	4 (2.7)	0
Chills	8 (5.3)	0	0	0
Insomnia	7 (4.6)	0	9 (6.0)	0

Serious infusion reactions occurred in 9 subjects (5.9%) in the isatuximab/Pd group (infusion related reaction [6 subjects]; and hyperglycaemia; acute psychosis; confusional state; bone pain; and acute kidney injury [1 subject each] [some subjects had more than 1 event]) and 5 subjects (3.4%) in the Pd group (acute kidney injury [2 subjects]; and syncope; hypertension; diarrhoea; and back pain [1 subject each] [some subjects had more than 1 event]), and a causal relationship to study drug could not be ruled out for infusion related reaction (6 subjects); and acute psychosis; and confusional state (1 subject each) in the isatuximab/Pd group. Infusion reactions leading to study drug discontinuation occurred in 6 subjects (3.9%) in the isatuximab/Pd group. Infusion reactions leading to dose interruption or reduction of study drug occurred in 27 subjects (17.8%) in the isatuximab/Pd group and 18 subjects (12.1%) in the Pd group. There were no infusion reactions leading to death.

Besides the above infusion reaction-related adverse events counted, the incidence of anaphylactic reactions[35)] associated with isatuximab infusions was assessed.

In Study 14335, no anaphylactic reactions were reported.

In clinical studies other than Study 14335 (including clinical studies using dosing regimens other than that used in Study 14335), anaphylactic reactions occurred in 3 subjects (5.3%) in Study 11863 and 1 subject (1.0%) in Study 10893 Phase II Stage 1, and a causal relationship to isatuximab could not be ruled out for all those events.

35) MedDRA PT (MedDRA/J ver.21.0) "anaphylactic reaction" was counted.

The applicant's explanation about the time of occurrence of infusion reactions associated with isatuximab infusions:

The incidence of infusion reactions by treatment cycle in Study 14335 is shown in Table 31. The median time from the start of infusion to the onset of infusion related reaction[36] (range) was 55 minutes (10-190 minutes).

Table 31. Incidence of infusion reactions by treatment cycle (Study 14335)

Treatment cycle (Number of cycles)	N	n (%)		
		All Grades	Grade ≥3	First onset (All Grades)
1	152	87 (57.2)	12 (7.9)	87 (57.2)
2	143	20 (14.0)	1 (0.7)	6 (4.2)
3	135	23 (17.0)	2 (1.5)	5 (3.7)
4	123	15 (12.2)	1 (0.8)	3 (2.4)
5	112	21 (18.8)	2 (1.8)	1 (0.9)
6	108	7 (6.5)	0	2 (1.9)
7-	99	40 (40.4)	4 (4.0)	6 (6.1)

(2) Infusion rates

The applicant's explanation about the infusion rates of isatuximab in Study 14335:

In Study 14335, the infusion rate of isatuximab was increased incrementally as shown in Table 32, in the absence of infusion reactions within a specified period of time.

Table 32. Infusion rates of isatuximab (Study 14335)

Time after start of infusion	Infusion rate (mg/hour)					
	0-60 minutes after start of infusion	60-90 minutes after start of infusion	90-120 minutes after start of infusion	120-150 minutes after start of infusion	150-180 minutes after start of infusion	≥180 minutes after start of infusion
First infusion	175	225	275	325	375	400
Second and subsequent infusions	175	275	375	400		

The following provision was included in Study 14335:

If an infusion reaction occurs during the isatuximab infusion, administration adjustments should be made as follows.

- Grade 2: Interrupt isatuximab infusion until improvement to Grade ≤1, and then isatuximab infusion may be resumed at 87.5 mg/hour. If symptoms do not recur, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Grade ≥3: Permanently discontinue isatuximab therapy, and do not readminister isatuximab.

(3) Premedications

The applicant's explanation about premedications prior to isatuximab infusion in Study 14335:

In Study 14335, the following premeditations were to be administered 15 to 60 minutes prior to isatuximab infusion: (i) DEX 40 mg (20 mg for patients aged >75 years) orally or intravenously (DEX as part of the

[36] Among infusion reaction-related adverse events, the time from the start of infusion to event onset was assessed based on events that were considered by the investigator to be infusion reactions or their associated symptoms and defined "infusion related reactions." Although the time to the onset of "infusion related reaction" was not collected, as isatuximab infusion was interrupted upon onset of the event, the time from the start of isatuximab infusion to infusion interruption was calculated.

backbone treatment), (ii) acetaminophen 650 to 1,000 mg orally, (iii) ranitidine 50 mg or equivalent, iv) diphenhydramine 25 to 50 mg or equivalent antihistamines intravenously.

The protocol was amended in May 2017. As a result, patients who did not have infusion reactions with first 4 administrations of isatuximab could have the premedication requirement reconsidered at the investigator's discretion.[37)]

Study 14335 was conducted according to the above (2) (3), and the study demonstrated the tolerability of isatuximab. Thus, the infusion rates of isatuximab, the management of infusion reactions, and the premedication requirement in Study 14335 will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert [see Section 7.R.6]. Given that (i) most patients received a dilution volume of 250 mL[38)] in Study 14335 and that (ii) infusion rates in mg/hour for isatuximab administration are converted to infusion pump flow rates in mL/hour, etc., in order to simplify the isatuximab administration procedures and reduce the risk of medication errors etc., the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert will advise the following: Dilute to a final volume of 250 mL; and the calculation procedure for converting infusion rates in mg/hour to mL/hour.

PMDA's discussion:
In Study 14335 that required premedication, infusion reaction-related adverse events occurred frequently in the isatuximab/Pd group, and serious infusion reactions and infusion reactions leading to study drug discontinuation were also reported. Taking account of these findings etc., attention should be paid to the possible occurrence of infusion reactions during the infusion of isatuximab. As serious anaphylactic reactions for which a causal relationship to isatuximab could not be ruled out also occurred in clinical studies, attention should be paid to the possible occurrence of this event as well.

While infusion reactions occurred most frequently during the first infusion, there were also patients who had their first infusion reaction at subsequent infusions or who developed more than one episode of infusion reaction. Thus, it is necessary to appropriately provide information on the aforementioned profile and incidence of infusion reactions in clinical studies, etc., using the package insert etc.

The infusion rates of isatuximab, the management of infusion reactions, and the premedication requirement in Study 14335 should be appropriately included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert, etc. [see Section 7.R.6]. However, the following information should be disseminated using the information materials etc.: (1) the names of specific premedication agents and the provision of premedication for patients who did not have infusion reactions with first 4 administrations of isatuximab, and (2) the calculation procedure for conversion of infusion rates.

[37)] In the isatuximab/Pd group of Study 14335, 5 of 22 subjects (22.7%) who did not receive one of the premedication agents, after first 4 administrations of isatuximab, experienced infusion reactions, which were all Grade 1 or 2.
[38)] In Study 14335, the formulation was to be diluted to achieve an isatuximab concentration of 0.8-5.3 mg/mL, and 149 of 152 subjects in the isatuximab/Pd group received a dilution volume of 250 mL.

7.R.3.3 Myelosuppression

The applicant's explanation about the incidence of myelosuppression associated with isatuximab:

As myelosuppression-related adverse events, PTs in the MedDRA SMQ "haematopoietic cytopenias (broad)" were counted.

The incidence of myelosuppression in Study 14335 is shown in Table 33.

Table 33. Incidence of myelosuppression (Study 14335)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	88 (57.9)	88 (57.9)	63 (42.3)	60 (40.3)
Neutropenia	71 (46.7)	70 (46.1)	50 (33.6)	48 (32.2)
Thrombocytopenia	19 (12.5)	18 (11.8)	18 (12.1)	18 (12.1)
Febrile neutropenia	18 (11.8)	18 (11.8)	3 (2.0)	3 (2.0)
Anaemia	6 (3.9)	5 (3.3)	2 (1.3)	1 (0.7)
Pancytopenia	1 (0.7)	1 (0.7)	2 (1.3)	2 (1.3)
Neutrophil count decreased	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
Myelodysplastic syndrome	1 (0.7)	1 (0.7)	0	0
Leukopenia	0	0	1 (0.7)	1 (0.7)

In Study 14335, serious myelosuppression occurred in 19 subjects (12.5%) in the isatuximab/Pd group (febrile neutropenia [10 subjects]; neutropenia [5 subjects]; anaemia; and thrombocytopenia [3 subjects each]; and myelodysplastic syndrome; and pancytopenia [1 subject each] [some subjects had more than 1 event]) and 8 subjects (5.4%) in the Pd group (febrile neutropenia [3 subjects]; neutropenia [2 subjects]; and anaemia; thrombocytopenia; and pancytopenia [1 subject each]), and a causal relationship to study drug could not be ruled out for febrile neutropenia (10 subjects); neutropenia; and thrombocytopenia (3 subjects each); anaemia (2 subjects); and pancytopenia (1 subject) in the isatuximab/Pd group and febrile neutropenia (3 subjects); neutropenia (2 subjects); and pancytopenia; and thrombocytopenia (1 subject each) in the Pd group. Myelosuppression leading to study drug discontinuation occurred in 3 subjects (2.0%) in the isatuximab/Pd group and 7 subjects (4.7%) in the Pd group. Myelosuppression leading to dose interruption or reduction of study drug occurred in 84 subjects (55.3%) in the isatuximab/Pd group and 54 subjects (36.2%) in the Pd group. There was no myelosuppression leading to death.

PMDA's discussion:

In Study 14335, Grade ≥3 myelosuppression occurred more frequently in the isatuximab/Pd group than in the Pd group, and multiple cases of serious myelosuppression for which a causal relationship to study drug could not be ruled out were reported. Given these findings etc., attention should be paid to the possible occurrence of myelosuppression during treatment with isatuximab. Thus, it is necessary to appropriately provide information on the incidence of myelosuppression in clinical studies to healthcare professionals in clinical practice, and the package insert etc. should appropriately advise healthcare professionals in clinical practice to perform hematological test periodically during treatment with isatuximab and take measures such as dose interruption/reduction of isatuximab and the combination drugs if abnormalities are observed.

7.R.3.4 Infections

The applicant's explanation about the incidence of infections associated with isatuximab:
As infection-related adverse events, PTs in the MedDRA SOC "infections and infestations" were counted.

The incidence of infections in Study 14335 is shown in Table 34.

Table 34. Infections reported by ≥5% of subjects in either group (Study 14335)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections	123 (80.9)	65 (42.8)	96 (64.4)	45 (30.2)
Upper respiratory tract infection	43 (28.3)	5 (3.3)	26 (17.4)	1 (0.7)
Bronchitis	36 (23.7)	5 (3.3)	13 (8.7)	1 (0.7)
Pneumonia	31 (20.4)	25 (16.4)	26 (17.4)	23 (15.4)
Urinary tract infection	15 (9.9)	7 (4.6)	14 (9.4)	2 (1.3)
Nasopharyngitis	14 (9.2)	0	7 (4.7)	0
Influenza	9 (5.9)	4 (2.6)	8 (5.4)	1 (0.7)
Lower respiratory tract infection	8 (5.3)	5 (3.3)	8 (5.4)	4 (2.7)

In Study 14335, infections leading to death occurred in 2 subjects (1.3%) in the isatuximab/Pd group (influenzal pneumonia; and sepsis [1 subject each]) and 5 subjects (3.4%) in the Pd group (septic shock [2 subjects]; and pneumonia; sepsis; and urinary tract infection [1 subject each]), and a causal relationship to study drug could not be ruled out for sepsis (1 subject) in the isatuximab/Pd group and pneumonia; and urinary tract infection (1 subject each) in the Pd group. Serious infections occurred in 60 subjects (39.5%) in the isatuximab/Pd group (those reported by ≥3 subjects were pneumonia [23 subjects]; urinary tract infection [6 subjects]; lower respiratory tract infection; and sepsis [4 subjects each]; and bronchitis; influenza; lung infection; pneumocystis jirovecii pneumonia; and viral pneumonia [3 subjects each] [some subjects had more than 1 event]) and 46 subjects (30.9%) in the Pd group (those reported by ≥3 subjects were pneumonia [23 subjects]; pneumocystis jirovecii pneumonia [4 subjects]; and lower respiratory tract infection; lung infection; and septic shock [3 subjects each] [some subjects had more than 1 event]), and a causal relationship to study drug could not be ruled out for those events reported by 29 subjects in the isatuximab/Pd group (pneumonia [15 subjects]; pneumocystis jirovecii pneumonia; urinary tract infection; and sepsis [2 subjects each]; and atypical pneumonia; pneumococcal pneumonia; influenza; upper respiratory tract infection; respiratory tract infection; lung infection; orchitis; herpes zoster disseminated; bacterial pneumonia; pneumonia haemophilus; bronchitis; and lower respiratory tract infection [1 subject each]) and those events reported by 14 subjects in the Pd group (pneumonia [8 subjects]; respiratory tract infection; and urinary tract infection [2 subjects each]; and influenzal pneumonia; lung infection; diverticulitis; septic shock; and candida pneumonia [1 subject each]). Infections leading to study drug discontinuation occurred in 4 subjects (2.6%) in the isatuximab/Pd group and 8 subjects (5.4%) in the Pd group. Infections leading to dose interruption or reduction of study drug occurred in 75 subjects (49.3%) in the isatuximab/Pd group and 42 subjects (28.2%) in the Pd group.

PMDA's discussion:
In Study 14335, Grade ≥3 infections occurred more frequently in the isatuximab/Pd group than in the Pd group, and multiple cases of serious adverse events for which a causal relationship to study drug could not be ruled out, including fatal cases, were reported. Given these findings etc., attention should be paid to the possible occurrence of infections during treatment with isatuximab. Thus, it is necessary to appropriately provide information on the incidence of infections in clinical studies to healthcare professionals in clinical practice, using the package insert etc.

PMDA is currently making inquiries to the applicant about the provision and implementation of prophylaxis against opportunistic infections (including virus reactivation) and HBV infection, and the incidences of opportunistic infections and HBV infection, etc. in Study 14335. The responses to these inquiries will be reported in the Review Report (2).

7.R.3.5 Cardiac disorders

The applicant's explanation about the incidence of cardiac disorders:
As cardiac disorder-related events, PTs in the MedDRA SOC "cardiac disorders" were counted.

The incidence of cardiac disorders in Study 14335 is shown in Table 35.

Table 35. Cardiac disorders reported by ≥2 subjects in either group (Study 14335)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders	22 (14.5)	7 (4.6)	6 (4.0)	3 (2.0)
Atrial fibrillation	7 (4.6)	3 (2.0)	3 (2.0)	1 (0.7)
Angina pectoris	2 (1.3)	0	1 (0.7)	1 (0.7)
Sinus bradycardia	2 (1.3)	0	1 (0.7)	0
Ventricular arrhythmia	2 (1.3)	0	0	0

In Study 14335, serious cardiac disorders occurred in 6 subjects (3.9%) in the isatuximab/Pd group (atrial fibrillation [3 subjects]; and acute coronary syndrome; unstable angina; and supraventricular arrhythmia [1 subject each]) and 3 subjects (2.0%) in the Pd group (atrial fibrillation; angina pectoris; and cardiac failure [1 subject each]), and a causal relationship to study drug could not be ruled out for 1 case of atrial fibrillation in the Pd group. Cardiac disorders leading to dose interruption or reduction occurred in 4 subjects (2.6%) in the isatuximab/Pd group and 1 subject (0.7%) in the Pd group. There were no cardiac disorders leading to death or study drug discontinuation.

The applicant's explanation about the relationship between isatuximab and the occurrence of cardiac disorders, based on the incidence of cardiac disorders in the above clinical study:
In Study 14335, the incidence of cardiac disorders tended to be higher in the isatuximab/Pd group than in the Pd group. However, taking account of the following points etc., it is difficult at present to draw a definitive conclusion on the relationship between isatuximab and the occurrence of cardiac disorders.

- Given that isatuximab specific binding was not detected in the heart tissue in a tissue cross-reactivity study of isatuximab with normal human tissues [see Section 5.7.1] etc., the effect of isatuximab on the heart was not suggested, from the viewpoint of the mechanism of action of isatuximab.
- There was no clear relationship between plasma isatuximab concentrations and ΔQTcF [see Section 6.2.3].
- In Study 14335,[39] there were no clear differences in the proportion of patients with an ECG that was normal at baseline and abnormal during study treatment, as assessed by the investigator, between the isatuximab/Pd group (20 of 91 subjects [22.0%]) and the Pd group (26 of 102 subjects [25.5%]).

PMDA's discussion:
Given the above explanation by the applicant, and taking also into account that a causal relationship to study drug was denied for all serious cardiac disorders observed in the isatuximab/Pd group of Study 14335, etc., it is difficult at present to draw a definitive conclusion on the relationship between isatuximab and the occurrence of cardiac disorders. Thus, it is necessary to collect post-marketing information on the incidence of cardiac disorders and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.3.6 Second primary malignancies

The applicant's explanation about second primary malignancies associated with isatuximab:
As second primary malignancy-related events, all PTs excluding "plasma cell leukaemia," "plasma cell leukaemia in remission," "Epstein Barr virus positive mucocutaneous ulcer," "microsatellite instability cancer," "Good syndrome," and "minimal residual disease" in the MedDRA SMQ "malignant or unspecified tumours" and PTs in the MedDRA SMQ "myelodysplastic syndrome (narrow)" were counted.

The incidence of second primary malignancies in Study 14335 is shown in Table 36.

Table 36. Incidence of second primary malignancies (Study 14335)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Second primary malignancies	6 (3.9)	4 (2.6)	1 (0.7)	0
Squamous cell carcinoma of skin	4 (2.6)	2 (1.3)	1 (0.7)	0
Breast angiosarcoma	1 (0.7)	1 (0.7)	0	0
Myelodysplastic syndrome	1 (0.7)	1 (0.7)	0	0

In Study 14335, serious second primary malignancies occurred in 4 subjects (2.6%) in the isatuximab/Pd group (squamous cell carcinoma of skin [3 subjects]; and myelodysplastic syndrome [1 subject]), and a causal relationship to study drug could not be ruled out for 2 cases of squamous cell carcinoma of skin. Second primary malignancy leading to study drug discontinuation occurred in 1 subject (0.7%) in the isatuximab/Pd group (myelodysplastic syndrome [1 subject]), and its causal relationship to study drug was denied. Second primary malignancy leading to dose interruption or reduction of study drug occurred in 1 subject (0.7%) in the

[39] In Study 14335, a 12-lead ECG was to be performed at screening, at Cycle 2 Day 1, and at the end of treatment, and if clinically indicated.

isatuximab/Pd group (breast angiosarcoma [1 subject]), and its causal relationship to study drug was denied. There were no second primary malignancies leading to death.

PMDA's discussion:
In Study 14335, (1) the number of reported cases of second primary malignancies was limited and (2) there was no consistent trend in the type or time to onset of second primary malignancies. Given these findings etc., it is difficult to draw a definitive conclusion on the relationship between isatuximab and the development of second primary malignancies, based on the currently available information. However, given that (1) the incidence of a specific second primary malignancy for which a causal relationship to study drug could not be ruled out tended to be higher in the isatuximab/Pd group than in the Pd group and (2) multiple cases of serious second primary malignancies were reported, etc., in Study 14335, it is necessary to provide information on the incidence of second primary malignancies in clinical studies, using the package insert etc., and collect post-marketing information on the incidence of second primary malignancies.

7.R.3.7 TLS

The applicant's explanation about the incidence of TLS associated with isatuximab:
As TLS-related adverse events, MedDRA PT (MedDRA/J ver.21.0) "tumour lysis syndrome" was counted.

In Study 14335, TLS occurred in 1 subject (0.7%) in the isatuximab/Pd group. This event was Grade ≥3 and serious TLS, and its causal relationship to study drug could not be ruled out. There was no TLS leading to death, study drug discontinuation, or dose interruption or reduction of study drug.

In clinical studies other than Study 14335 (including clinical studies using dosing regimens other than that used in Study 14335), TLS occurred in 1 subject (1.1%) in Study 10893 Phase I and 1 subject (2.2%) in Study 14079 Part A, and a causal relationship to isatuximab could not be ruled out for 1 case in Study 10893.

PMDA's discussion:
Given that the number of reported cases of TLS in Japanese and foreign clinical studies was limited, and that TLS observed in the isatuximab/Pd group of Study 14335 may have been related to the combination drugs, etc., it is difficult to draw a definitive conclusion on the relationship between isatuximab and the occurrence of TLS, based on the currently available information. However, considering that serious TLS for which a causal relationship to isatuximab could not be ruled out was reported in clinical studies etc., it is necessary to provide information on the incidence of TLS in clinical studies, using the package insert etc., and collect post-marketing information on the incidence of this event.

7.R.3.8 Hemolysis

The applicant's explanation about the incidence of hemolysis:
As hemolysis-related adverse events, PTs in the MedDRA SMQ (MedDRA/J ver.21.0) "haemolytic disorders (broad)" were counted.

In the clinical studies submitted, hemolysis occurred in 1 subject (Grade 1, non-serious hemolysis) in the isatuximab/Pd group and 1 subject (Grade 2, non-serious transfusion reaction) in the Pd group in Study 14335, and a causal relationship to study drug was denied for both events.

PMDA's discussion:
It is difficult to draw a definitive conclusion on the relationship between isatuximab and hemolysis, based on the incidence of hemolysis in clinical studies. However, given that isatuximab is an antibody drug that binds to a specific extracellular epitope of CD38, etc., the possibility that isatuximab induces hemolysis by binding to CD38 expressed on red blood cells cannot be ruled out. Thus, it is necessary to appropriately provide information on the hemolysis potential of isatuximab to healthcare professionals in clinical practice, using information materials etc., and collect post-marketing information on the incidence of this event.

7.R.4 Laboratory test interference by isatuximab

(1) Impact on response assessment
Isatuximab is an IgGκ monoclonal antibody that can be detected on both serum protein electrophoresis and immunofixation assays used to monitor serum M-protein.

The applicant's explanation about isatuximab interference with serum M-protein detection and its impact on the assessment of best overall response, and the need for a warning/precaution about this interference:
To evaluate whether isatuximab had interfered with serum M-protein quantification, 22 very good partial response (VGPR) patients (based on the IRC assessment) in whom the criteria for complete response (CR) were met except for residual immunofixation positivity in Study 14335 were identified. Serum samples from these patients were tested by mass spectrometry. After separation of isatuximab signal from the myeloma M-protein signal, in 11 out of the 22 patients, there was no residual myeloma M-protein detectable at the sensitivity level of the immunofixation test (25 mg/dL).

The above results indicated that isatuximab interferes with serum protein electrophoresis and immunofixation assays used to monitor M-protein, which can impact the accuracy of the determination of CR. Thus, the package insert etc. will appropriately advise healthcare professionals in clinical practice about this interference.

(2) Interference with the indirect Coombs test and its effects on blood transfusions
Isatuximab binds to CD38 weakly expressed on red blood cells and may result in a false positive indirect Coombs test. This may mask the detection of irregular antibodies in patients treated with isatuximab.

The applicant's explanation about the incidences of adverse events related to isatuximab interference with the indirect Coombs test and its effects on blood transfusions, and solutions to the interference problem:
As adverse events related to interference with the indirect Coombs test and its effects on blood transfusions, MedDRA PTs (MedDRA/J ver.21.0) "Coombs indirect test," "Coombs indirect test positive," "crossmatch incompatible," "laboratory test interference," "Coombs test," and "Coombs test positive" were counted.

In all clinical studies submitted, no adverse events related to interference with the indirect Coombs test and its effects on blood transfusions were reported. In the isatuximab/Pd group of Study 14335, 67 subjects had a positive indirect Coombs test[40] during the treatment period, of whom 20 received a red blood cell (RBC) transfusion. No haemolysis was reported post-RBC transfusion in these patients [see Section 7.R.3.8].

As a mitigation method for interference with the indirect Coombs test, it has been reported that daratumumab (another anti-CD38 antibody) interference with the indirect Coombs test can be resolved by using dithiothreitol (DTT)-treated RBCs to prevent daratumumab binding to CD38 on RBCs (*Transfusion*. 2015;55:1545-54). Also as with isatuximab, an investigation using sera from 14 healthy adult subjects demonstrated that isatuximab interference with the indirect Coombs test can be resolved using DTT-treated RBCs. DTT denatures the Kell antigen, and Kell antibodies would be missed when screening for irregular antibodies. If the sample is treated with DTT when screening for irregular antibodies, Kell-negative units should be supplied.

Isatuximab interference with the indirect Coombs test is important information for blood transfusions for patients during and after treatment with isatuximab, and if exposure to isatuximab is not shared, there may be the risk of blood transfusion delays etc. Thus, it is necessary to advise healthcare professionals including blood transfusion laboratory personnel in clinical practice, patients, and laboratories that provide pre-transfusion testing about isatuximab interference with the indirect Coombs test and the need for pre-transfusion testing prior to starting treatment with isatuximab, using the package insert, information materials, etc.

PMDA accepted the applicant's explanation.

7.R.5 Clinical positioning and indication

The proposed indication for isatuximab is "relapsed or refractory multiple myeloma." The following statements are included in the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert (A precautionary statement about the use of isatuximab in patients who have received 1 prior therapy has been added after regulatory submission).

- Isatuximab should be used to treat patients previously treated with at least a proteasome inhibitor (PI) and lenalidomide.
- Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab. Especially for patients who have received 1 prior therapy, alternative treatments should also be considered carefully prior to the use of isatuximab.

As a result of its reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following considerations, PMDA concluded as follows: The following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the proposed indication of "relapsed or refractory multiple myeloma" is appropriate.

[40] Among 67 subjects with a positive indirect Coombs test during the treatment period, 47 were negative and 20 were missing at screening.

- Isatuximab should be used to treat patients who have failed or relapsed following at least 2 standard of care treatments.
- Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab.

7.R.5.1 Clinical positioning of isatuximab

There is no mention of isatuximab for the treatment of relapsed or refractory MM in the Japanese and foreign clinical practice guidelines[41)] or the major textbooks of hematology and clinical oncology.[42)]

The applicant's explanation about the clinical positioning of isatuximab:
The Japanese and foreign clinical practice guidelines list immunomodulatory drugs such as lenalidomide, PIs such as bortezomib, carfilzomib, and ixazomib citrate, antibody drugs such as daratumumab and elotuzumab, etc., as treatment options for relapsed or refractory MM (NCCN guidelines [v.2.2020], etc.). However, in many of the clinical studies that evaluated the clinical usefulness of the combinations of these agents, (1) patients previously untreated with lenalidomide or a PI, or (2) patients who are sensitive to prior treatment with lenalidomide or a PI[43)] were eligible for enrollment. On the other hand, at present, the clinical usefulness of Pd and elotuzumab/Pd has been demonstrated in clinical studies in patients with relapsed or refractory MM who have received ≥2 prior regimens including lenalidomide and a PI and have failed treatment with lenalidomide and a PI,[44)] i.e. the patient population of Study 14335, and these patients have limited treatment options.

MM patients eligible for enrollment in Study 14335 had to meet all of the following previous treatment criteria. The results of PFS by the number of prior lines of therapy in this study are shown in Table 37.

- ≥2 prior lines of therapy including lenalidomide and a PI given alone or in combination
- Failure to treatment with lenalidomide and a PI[44)]
- Refractory to the last line of treatment (progressive disease [PD] had occurred while on or within 60 days from the end of the treatment)
- Not refractory to anti-CD38 antibody treatment

41) NCCN guidelines (v.2.2020), and Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 2nd edition, Japanese Society of Hematology ed.
42) Williams Hematology, 9th Edition (The McGraw-Hill Company. Inc, 2016, USA), Wintrobe's Clinical Hematology 14th edition (Wolters Kluwer. 2019, USA)
43) Patients who have not progressed on treatment with lenalidomide or a PI within a specified period of time, etc.
44) Failure to treatment with lenalidomide and a PI was defined by any of the following: (1) refractory to lenalidomide or a PI, (2) In case of previous response ≥PR to lenalidomide and/or a PI, patient had progressed within 6 months, or (3) intolerant to lenalidomide or a PI

Table 37. Results of PFS analysis by number of prior lines of therapy (ITT population, IRC assessment, data cutoff date of October 11, 2018)

No. of prior lines of therapy	Isatuximab/Pd		Pd		Hazard ratio [95% CI]
	N	Median PFS [95% CI] (months)	N	Median PFS [95% CI] (months)	
Any	154	11.5 [8.9, 13.9]	153	6.5 [4.5, 8.3]	0.60 [0.44, 0.81]
2	45	12.3 [8.9, NE]	45	7.8 [3.8, 12.1]	0.55 [0.30, 1.03]
3	52	13.3 [7.4, NE]	58	7.8 [4.5, 11.1]	0.62 [0.37, 1.06]
≥4	57	8.5 [4.7, 14.8]	50	4.3 [2.6, 8.6]	0.56 [0.34, 0.92]

The above indicated that, in the setting of treatment of relapsed or refractory MM, (1) the results of Study 14335 demonstrated the superior clinical usefulness of isatuximab/Pd over Pd in patients with relapsed or refractory MM who had received ≥2 prior regimens including lenalidomide and a PI [see Sections 7.R.2 and 7.R.3], and (2) a clinical study that evaluated the clinical usefulness of elotuzumab/Pd was just exploratory (see "Empliciti for I.V. infusion 300 mg and 400 mg Review Report as of October 15, 2019"). Given these findings etc., isatuximab/Pd is positioned as standard of care treatment for these patients.

PMDA's discussion:
Although the results of Study 14335 in patients with relapsed or refractory MM who had received ≥2 prior regimens including lenalidomide and a PI confirmed prolonged PFS in the isatuximab/Pd group compared with the Pd group, given that (1) prolonged OS has not been demonstrated at present, and that (2) there are no data from a clinical study that evaluated the clinical usefulness of isatuximab/Pd compared with elotuzumab/Pd, etc., isatuximab/Pd is positioned as a treatment option for these patients.

7.R.5.2 Target population and indication for isatuximab

The applicant's explanation about the target population and indication for isatuximab:
On the basis of the results from Study 14335 [see Sections 7.R.2 and 7.R.3], isatuximab/Pd is recommended in this study population.

Among patients with relapsed or refractory MM who are not eligible for Study 14335, isatuximab/Pd is not recommended in (1) those previously untreated with lenalidomide and a PI or (2) those who are expected to respond to treatment with lenalidomide and a PI, because there are no data from a clinical study that evaluated the efficacy and safety of isatuximab/Pd in these patients. On the other hand, given the following points etc., patients with relapsed or refractory MM who have received 1 prior regimen and are not expected to respond to treatment with lenalidomide and a PI can be treated with isatuximab/Pd.

- Although bortezomib in combination with Ld is recommended in patients with previously untreated MM (NCCN guidelines [v2.2020] etc.), and it is envisaged that some previously untreated patients will receive the combination of lenalidomide and a PI, there is currently no treatment whose clinical usefulness has been confirmed in the above patients.
- Study 14335 demonstrated the clinical usefulness of isatuximab/Pd in patients with relapsed or refractory MM previously treated with lenalidomide and a PI [see Sections 7.R.2 and 7.R.3].

However, given that Study 14335 enrolled patients who had received ≥2 prior regimens, prior to the use of isatuximab/Pd, alternative treatments should also be considered carefully for patients with relapsed or refractory MM who have received 1 prior regimen and are not expected to respond to treatment with lenalidomide and a PI, in order to select appropriate patients.

From the above, the following statements have been included in the PRECAUTIONS CONCERNING INDICATION section, and then the indication of "relapsed or refractory multiple myeloma" has been proposed.

- Isatuximab should be used to treat patients previously treated with at least a PI and lenalidomide.
- Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab. Especially for patients who have received 1 prior therapy, alternative treatments should also be considered carefully prior to the use of isatuximab.

PMDA's discussion:
Given that the clinical usefulness of isatuximab/Pd in patients with relapsed or refractory MM who are not eligible for Study 14335 is unknown at present, etc., isatuximab/Pd is recommended in the patient population of Study 14335, i.e. patients with relapsed or refractory MM who have received ≥2 prior regimens including lenalidomide and a PI. In addition to the above considerations and taking also into account that isatuximab will be used by physicians with adequate knowledge of and experience in the treatment of hematological malignancies, etc., the proposed indication of "relapsed or refractory multiple myeloma" is appropriate, provided that prior therapies etc. of patients enrolled in Study 14335 are mentioned in the CLINICAL STUDIES section of the package insert and that the following statements are included in the PRECAUTIONS CONCERNING INDICATION section.

Precautions Concerning Indication

- Isatuximab should be used to treat patients who have failed or relapsed following at least 2 standard of care treatments.
- Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab.

7.R.6 Dosage and administration

The proposed dosage and administration statement is "Isatuximab in combination with pomalidomide and dexamethasone; The usual adult dose is 10 mg/kg (body weight) of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. The administration schedule must be followed. If a planned dose of isatuximab is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval." In the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert, the statement regarding the infusion rates of

isatuximab has been modified based on Study 14335 after regulatory submission, and the following statements are included.

Precautions Concerning Dosage and Administration

- The efficacy and safety of isatuximab monotherapy have not been established.
- Anti-neoplastic drugs etc. for combination with isatuximab should be used by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.
- The efficacy and safety of isatuximab in combination with anti-neoplastic drugs other than pomalidomide and DEX have not been established.
- Use of premedication with corticosteroids, antipyretic analgesics, antihistamines, etc., to reduce the risk and severity of infusion reactions
- Dilution and infusion rates of isatuximab
- Management of infusion reactions
- Guidelines for interruption and resumption of isatuximab administration for neutropenia

As a result of its review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following review, PMDA concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

Dosage and Administration

Isatuximab in combination with pomalidomide and dexamethasone

The usual adult dose is 10 mg/kg of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period.

Precautions Concerning Dosage and Administration

- The efficacy and safety of isatuximab monotherapy have not been established.
- Anti-neoplastic drugs for combination with isatuximab should be used by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.
- The efficacy and safety of isatuximab in combination with anti-neoplastic drugs other than pomalidomide and DEX have not been established.
- To reduce the risk and severity of infusion reactions associated with isatuximab infusions, patients should be premedicated with DEX as part of the backbone treatment, antihistamines, H_2 antagonists, and antipyretic analgesics 15 to 60 minutes prior to starting an isatuximab infusion.
- The appropriate volume of Sarclisa concentrate should be withdrawn and diluted in the 250 mL infusion bag with saline or 5% glucose solution, and the first infusion should be initiated at 175 mg/hour. In the absence of infusion reactions, the infusion rate may be increased incrementally to a maximum of 400 mg/hour as shown below, while monitoring the patient's condition.

Infusion rates of isatuximab

Time after start of infusion	Infusion rate (mg/hour)	
	First infusion	Second and subsequent infusions
0-60 minutes after start of infusion	175	175
60-90 minutes after start of infusion	225	275
90-120 minutes after start of infusion	275	375
120-150 minutes after start of infusion	325	400
150-180 minutes after start of infusion	375	
≥180 minutes after start of infusion	400	

- If patients experience infusion reactions, appropriate measures, e.g. infusion interruption and discontinuation of isatuximab, and adjustment of the infusion rate, should be taken, as shown below.
  - Grade 2*: Interrupt isatuximab infusion until improvement to Grade ≤1*, and then isatuximab infusion may be resumed at 87.5 mg/hour. If symptoms do not recur, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
  - Grade ≥3*: Permanently discontinue isatuximab therapy, and do not readminister isatuximab.
- In case of Grade 3 or 4* neutropenia, delay the isatuximab dose until neutrophil count recovery to ≥1000/mm^3.

*: Severity grade based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03

7.R.6.1 Dosage and administration of isatuximab

The applicant's explanation about dosage and administration of isatuximab:

On the basis of the following study results, isatuximab 10 mg/kg in combination with Pd, QW for the first cycle, followed by Q2W for the subsequent cycles, was chosen for Study 14335.

- A pooled efficacy analysis of single-agent studies in patients with newly diagnosed, or relapsed or refractory MM (Study 10893 Phase I and Phase II Stage 1, Study 14154) was performed. There were no clear differences in the overall response rate[45)] between isatuximab 10 mg/kg QW for the first cycle followed by Q2W for the subsequent cycles and isatuximab 20 mg/kg QW for the first cycle followed by Q2W for the subsequent cycles (Each treatment cycle consisted of a 28-day period). The safety results from these studies demonstrated the tolerability of both dosing regimens.
- The results from Part A of Study 14079 with isatuximab/Pd in patients with relapsed or refractory MM showed no clear differences in the efficacy or tolerability of isatuximab in combination with Pd between isatuximab 10 mg/kg QW for the first cycle followed by Q2W for the subsequent cycles and isatuximab 20 mg/kg QW for the first cycle followed by Q2W for the subsequent cycles (Each treatment cycle consisted of a 28-day period).

Since Study 14335 with the above dosing regimen demonstrated the clinical usefulness of isatuximab/Pd in patients with relapsed or refractory MM [see Sections 7.R.2 and 7.R.3], the proposed dosing regimen of isatuximab was selected based on this study.

45) The overall response rates with isatuximab 10 and 20 mg/kg were 24.3% and 22.6%, respectively.

PMDA's discussion:
PMDA largely accepted the applicant's explanation, and concluded that the proposed dosage and administration statement should be modified as shown below. Given that isatuximab will be used by physicians with adequate knowledge of and experience in the treatment of hematological malignancies, etc., "treatment is repeated until disease progression or unacceptable toxicity" and action to take following a missed dose in the proposed DOSAGE AND ADMINISTRATION section are unnecessary.

Dosage and Administration
Isatuximab in combination with pomalidomide and dexamethasone
The usual adult dose is 10 mg/kg of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period.

7.R.6.2 Isatuximab dose modifications
The applicant's explanation about isatuximab dose modifications:
Study 14335 was conducted according to the guidelines for interruption, resumption, and discontinuation of isatuximab treatment, and the study demonstrated the tolerability of isatuximab. In Study 14335, isatuximab dose reductions were not permitted.

From the above, a revised version of these guidelines used in Study 14335 is included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert. However, the guidelines for interruption, resumption, and discontinuation of isatuximab treatment for adverse events other than infusion reactions [see Section 7.R.3.2] and neutropenia used in Study 14335 are not included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, for the following reasons etc.

- Thrombocytopenia
  In Study 14335, considering that thrombocytopenia associated with pomalidomide may be enhanced by isatuximab, in case of Grade 3 or 4 thrombocytopenia, isatuximab treatment was to be interrupted until platelet count recovery to ≥50,000/mm^3. However, as there was no trend towards clear differences in the incidence of thrombocytopenia between the isatuximab/Pd and Pd groups in Study 14335 [see Section 7.R.3.3] etc., the isatuximab treatment interruption guideline for thrombocytopenia was considered unnecessary.
- Non-hematological toxicities other than infusion reactions (Grade 4 deep vein thromboembolism/pulmonary embolism, Grade ≥2 hypersensitivity, Grade ≥3 gastrointestinal disorders, etc.)
  In Study 14335, for more stringent guidelines, in case of these events, isatuximab treatment was to be interrupted until resolution of symptoms. However, given that these guidelines do not provide special management of these events, and that isatuximab will be used by physicians with adequate knowledge of and experience in the treatment of hematological malignancies, etc., the isatuximab treatment interruption guidelines for these events were considered unnecessary.

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, it is necessary to appropriately communicate the above information included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section and the dose modification guidelines including dose modifications of pomalidomide and dexamethasone in Study 14335 to healthcare professionals in clinical practice, using information materials etc.

7.R.6.3 Isatuximab monotherapy and anti-neoplastic drugs for combination with isatuximab

The applicant's explanation about isatuximab monotherapy and isatuximab in combination with anti-neoplastic drugs other than Pd:
Since there are no data from a clinical study that demonstrated the clinical usefulness of isatuximab monotherapy or isatuximab in combination with anti-neoplastic drugs other than Pd in patients with relapsed or refractory MM, these therapies are not recommended. Thus, the following statements will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- The efficacy and safety of isatuximab monotherapy have not been established.
- The efficacy and safety of isatuximab in combination with anti-neoplastic drugs other than pomalidomide and DEX have not been established.

PMDA accepted the applicant's explanation.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:
Because the number of cases of TLS reported in Japanese and foreign clinical studies is limited, etc., the applicant has included TLS in the safety specification for the surveillance, and is planning to conduct a post-marketing database survey to determine the incidence of TLS following administration of isatuximab/Pd in clinical practice.

PMDA's discussion:
Since the safety information from Japanese patients treated with isatuximab is very limited, etc., it is necessary to conduct a post-marketing survey covering all patients treated with isatuximab over a specified period of time in order to collect safety information in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals in clinical practice as soon as possible.

Taking account of considerations in Section "7.R.3 Safety," the safety specification for the surveillance should include infusion reactions, myelosuppression, infections, and cardiac disorders among the events that require particular attention during treatment with isatuximab, because these events occurred at a certain frequency in clinical studies.

The planned sample size and observation period need to be determined, taking account of the incidences etc. of the above events that should be included in the safety specification for the surveillance.

7.3 Adverse events etc. observed in clinical studies

Among clinical study data submitted for safety evaluation, deaths are described in Sections "7.1 Evaluation data" and "7.2 Reference data." The main adverse events other than deaths are described below.

7.3.1 Japanese phase I/II study (Study 14095)

Adverse events occurred in (1) 3 of 3 subjects (100%) in the 10 mg/kg cohort of Phase I, (2) 4 of 5 subjects (80.0%) in the 20 mg/kg cohort of Phase I, and (3) 25 of 28 subjects (89.3%) in Phase II, and those for which a causal relationship to isatuximab could not be ruled out occurred in (1) 2 of 3 subjects (66.7%), (2) 1 of 5 subjects (20.0%), and (3) 18 of 28 subjects (64.3%). Adverse events reported by ≥40% of subjects in each part were (1) nasopharyngitis; and infusion related reaction (2 subjects each [66.7%]), (2) vomiting (2 subjects [40.0%]), and (3) infusion related reaction (12 subjects [42.9%]).

Serious adverse events occurred in (1) 1 of 3 subjects (33.3%), (2) 1 of 5 subjects (20.0%), and (3) 7 of 28 subjects (25.0%), which were (1) pneumonia; and deep vein thrombosis (1 subject each [33.3%]) (1 subject had more than 1 event), (2) diplegia; neurogenic bladder; and disease progression (1 subject each [20.0%]) (1 subject had more than 1 event), and (3) pneumonia (2 subjects [7.1%]); and intervertebral discitis; lung infection; disseminated intravascular coagulation; seizure; thrombotic cerebral infarction; ileus; synovial cyst; and non-cardiac chest pain (1 subject each [3.6%]) (some subjects had more than 1 event). A causal relationship to isatuximab could not be ruled out for (1) pneumonia (1 subject) and (3) pneumonia (2 subjects [7.1%]) [(2) none].

Adverse events leading to isatuximab discontinuation occurred in (2) 1 of 5 subjects (20.0%) and (3) 2 of 28 subjects (7.1%) [(1) none], which were (2) diplegia; and neurogenic bladder (1 subject each [20.0%]) (1 subject had more than 1 event) and (3) intervertebral discitis; pneumonia; disseminated intravascular coagulation; and thrombotic cerebral infarction (1 subject each [3.6%]) (1 subject had more than 1 event). A causal relationship to isatuximab could not be ruled out for (3) pneumonia (1 subject).

7.3.2 Global phase III study (Study 14335)

Adverse events occurred in 151 of 152 subjects (99.3%) in the isatuximab/Pd group and 146 of 149 subjects (98.0%) in the Pd group, and those for which a causal relationship to study drug could not be ruled out occurred in 138 of 152 subjects (90.8%) in the isatuximab/Pd group and 119 of 149 subjects (79.9%) in the Pd group. Adverse events reported by ≥10% of subjects in either group are shown in Table 38.

Table 38. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA/J ver.21.0)	n (%)			
	Isatuximab/Pd N = 152		Pd N = 149	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	151 (99.3)	132 (86.8)	146 (98.0)	105 (70.5)
Infections and infestations				
Upper respiratory tract infection	43 (28.3)	5 (3.3)	26 (17.4)	1 (0.7)
Bronchitis	36 (23.7)	5 (3.3)	13 (8.7)	1 (0.7)
Pneumonia	31 (20.4)	25 (16.4)	26 (17.4)	23 (15.4)
Gastrointestinal disorders				
Diarrhoea	39 (25.7)	3 (2.0)	29 (19.5)	1 (0.7)
Constipation	24 (15.8)	0	26 (17.4)	0
Nausea	23 (15.1)	0	14 (9.4)	0
Vomiting	18 (11.8)	2 (1.3)	5 (3.4)	0
General disorders and administration site conditions				
Fatigue	26 (17.1)	6 (3.9)	32 (21.5)	0
Asthenia	23 (15.1)	5 (3.3)	27 (18.1)	4 (2.7)
Pyrexia	22 (14.5)	2 (1.3)	21 (14.1)	2 (1.3)
Peripheral oedema	20 (13.2)	1 (0.7)	16 (10.7)	0
Musculoskeletal and connective tissue disorders				
Back pain	25 (16.4)	3 (2.0)	22 (14.8)	2 (1.3)
Arthralgia	16 (10.5)	4 (2.6)	13 (8.7)	1 (0.7)
Muscle spasms	14 (9.2)	0	15 (10.1)	0
Blood and lymphatic system disorders				
Neutropenia	71 (46.7)	70 (46.1)	50 (33.6)	48 (32.2)
Thrombocytopenia	19 (12.5)	18 (11.8)	18 (12.1)	18 (12.1)
Febrile neutropenia	18 (11.8)	18 (11.8)	3 (2.0)	3 (2.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	23 (15.1)	6 (3.9)	15 (10.1)	2 (1.3)
Injury, poisoning and procedural complications				
Infusion related reaction	56 (36.8)	4 (2.6)	2 (1.3)	0

Serious adverse events occurred in 94 of 152 subjects (61.8%) in the isatuximab/Pd group and 80 of 149 subjects (53.7%) in the Pd group. Those reported by ≥2% of subjects in each group were pneumonia (23 subjects [15.1%]); febrile neutropenia (10 subjects [6.6%]); disease progression (7 subjects [4.6%]); urinary tract infection; and infusion related reaction (6 subjects each [3.9%]); neutropenia; pathological fracture; and acute kidney injury (5 subjects each [3.3%]); lower respiratory tract infection; sepsis; syncope; dyspnoea; and arthralgia (4 subjects each [2.6%]); and bronchitis; influenza; lung infection; pneumocystis jirovecii pneumonia; viral pneumonia; squamous cell carcinoma of skin; anaemia; thrombocytopenia; hyperglycaemia; atrial fibrillation; pulmonary embolism; pyrexia; and traumatic fracture (3 subjects each [2.0%]) in the isatuximab/Pd group and pneumonia (23 subjects [15.4%]); disease progression (7 subjects [4.7%]); acute kidney injury (6 subjects [4.0%]); pneumocystis jirovecii pneumonia (4 subjects [2.7%]); and lower respiratory tract infection; lung infection; septic shock; febrile neutropenia; hypercalcaemia; pathological fracture; and renal failure (3 subjects each [2.0%]) in the Pd group. A causal relationship to study drug could not be ruled out for pneumonia (15 subjects); febrile neutropenia (10 subjects); infusion related reaction (6 subjects); neutropenia; thrombocytopenia; and pulmonary embolism (3 subjects each); pneumocystis jirovecii pneumonia; sepsis; urinary tract infection; squamous cell carcinoma of skin; anaemia; and pyrexia (2 subjects each); and bronchitis; influenza; lower respiratory tract infection; lung infection; hyperglycaemia; syncope; dyspnoea; arthralgia; and traumatic fracture (1 subject each) (some subjects had more than 1 event) in the

isatuximab/Pd group and pneumonia (8 subjects); febrile neutropenia (3 subjects); and lung infection; and septic shock (1 subject each) in the Pd group.

Adverse events leading to study drug discontinuation occurred in 24 of 152 subjects (15.8%) in the isatuximab/Pd group and 21 of 149 subjects (14.1%) in the Pd group. Those reported by ≥2 subjects in each group were infusion related reaction (4 subjects [2.6%]); and death; and fatigue (2 subjects each [1.3%]) in the isatuximab/Pd group and thrombocytopenia (7 subjects [4.7%]); pneumonia (3 subjects [2.0%]); and septic shock; and neutropenia (2 subjects each [1.3%]) in the Pd group. A causal relationship to study drug could not be ruled out for infusion related reaction (4 subjects); and fatigue (2 subjects) in the isatuximab/Pd group and thrombocytopenia (6 subjects); neutropenia (2 subjects); and pneumonia (1 subject) in the Pd group.

7.3.3 Foreign phase Ib study (Study 14079)

Adverse events occurred in (1) 8 of 8 subjects (100%) in the 5 mg/kg group of Part A, (2) 31 of 31 subjects (100%) in the 10 mg/kg group of Part A, (3) 6 of 6 subjects (100%) in the 20 mg/kg group of Part A, and (4) 46 of 47 subjects (97.9%) in Part B, and those for which a causal relationship to study drug could not be ruled out occurred in (1) (2) (3) all subjects and (4) 45 of 47 subjects (95.7%). Adverse events reported by ≥30% of subjects in each part were (1) neutropenia (6 subjects [75.0%]); dyspnoea; and fatigue (5 subjects each [62.5%]); upper respiratory tract infection; headache; dizziness; constipation; muscle spasms; and infusion related reaction (4 subjects each [50.0%]); and sinus tachycardia; cough; vomiting; rash; pruritus generalised; and arthralgia (3 subjects each [37.5%]), (2) neutropenia (20 subjects [64.5%]); fatigue (18 subjects [58.1%]); infusion related reaction (14 subjects [45.2%]); upper respiratory tract infection (12 subjects [38.7%]); insomnia; dyspnoea; and diarrhoea (11 subjects each [35.5%]); and constipation (10 subjects [32.3%]), (3) fatigue (5 subjects [83.3%]); neutropenia (4 subjects [66.7%]); upper respiratory tract infection; diarrhoea; nausea; and pyrexia (3 subjects each [50.0%]); and pneumonia; nasopharyngitis; thrombocytopenia; headache; dizziness; peripheral sensory neuropathy; dyspnoea; cough; productive cough; constipation; and contusion (2 subjects each [33.3%]), and (4) fatigue (26 subjects [55.3%]); infusion related reaction (19 subjects [40.4%]); and upper respiratory tract infection; and neutropenia (18 subjects each [38.3%]).

Serious adverse events occurred in (1) 5 of 8 subjects (62.5%), (2) 17 of 31 subjects (54.8%), (3) 4 of 6 subjects (66.7%), and (4) 23 of 47 subjects (48.9%). Those reported by ≥2 subjects in each part were (1) neutropenia; and traumatic fracture (2 subjects each [25.0%]), (2) pneumonia (7 subjects [22.6%]); neutropenia; and disease progression (3 subjects each [9.7%]); and respiratory syncytial virus infection; and mental status changes (2 subjects each [6.5%]), and (4) pneumonia; and atrial fibrillation (3 subjects each [6.4%]); and sepsis; neutropenia; dehydration; spinal cord compression; transient ischaemic attack; disease progression; and traumatic fracture (2 subjects each [4.3%]) [(3) none]. A causal relationship to study drug could not be ruled out for (1) neutropenia (2 subjects), (2) pneumonia (4 subjects); neutropenia (3 subjects); and respiratory syncytial virus infection (2 subjects), and (4) pneumonia; and neutropenia (2 subjects each); and transient ischaemic attack; and atrial fibrillation (1 subject each).

Adverse events leading to study drug discontinuation occurred in (2) 3 of 31 subjects (9.7%) and (4) 5 of 47 subjects (10.6%) [(1)(3) none], which were (2) intestinal perforation; weight increased; and infusion related reaction (1 subject each [3.2%]) and (4) sepsis (2 subjects [4.3%]); and anxiety; tremor; acute myocardial infarction; flushing; gait disturbance; and sudden death (1 subject each [2.1%]) (some subjects had more than 1 event). A causal relationship to study drug could not be ruled out for (2) weight increased; and infusion related reaction (1 subject each) and (4) anxiety; tremor; flushing; and gait disturbance (1 subject each) (some subjects had more than 1 event).

7.3.4 Foreign phase I study (Study 14154)

Adverse events occurred in 25 of 26 subjects (96.2%), and those for which a causal relationship to isatuximab could not be ruled out occurred in 20 of 26 subjects (76.9%). Adverse events reported by ≥20% of subjects were infusion related reaction (18 subjects [69.2%]); nausea; and fatigue (11 subjects each [42.3%]); headache (10 subjects [38.5%]); cough; and back pain (8 subjects each [30.8%]); diarrhoea (7 subjects [26.9%]); and anaemia (6 subjects [23.1%]).

Serious adverse events occurred in 6 of 26 subjects (23.1%), which were pneumonia (3 subjects [11.5%]); and bronchitis; enteritis; ileus; and pyrexia (1 subject each [3.8%]) (some subjects had more than 1 event). A causal relationship to isatuximab could not be ruled out for pneumonia; and pyrexia (1 subject each).

There were no adverse events leading to isatuximab discontinuation.

7.3.5 Foreign phase Ib study (Study 13983)

Adverse events occurred in 17 of 17 subjects (100%), and those for which a causal relationship to study drug could not be ruled out occurred in 16 of 17 subjects (94.1%). Adverse events reported by ≥30% of subjects were back pain; and infusion related reaction (8 subjects each [47.1%]); peripheral sensory neuropathy; and diarrhoea (7 subjects each [41.2%]); and cough; nausea; and peripheral oedema (6 subjects each [35.3%]).

There were no serious adverse events or adverse events leading to study drug discontinuation reported by ≥2 subjects.

7.3.6 Foreign phase Ib study (Study 11863)

Adverse events occurred in 57 of 57 subjects (100%), and those for which a causal relationship to study drug could not be ruled out also occurred in all subjects. Adverse events reported by ≥20% of subjects were infusion related reaction (32 subjects [56.1%]); diarrhoea (30 subjects [52.6%]); fatigue (28 subjects [49.1%]); upper respiratory tract infection (23 subjects [40.4%]); nausea (20 subjects [35.1%]); insomnia; and pyrexia (18 subjects each [31.6%]); dyspnoea (16 subjects [28.1%]); anaemia; and cough (15 subjects each [26.3%]); headache; vomiting; and muscle spasms (13 subjects each [22.8%]); and neutropenia; hypokalaemia; and nasal congestion (12 subjects each [21.1%]).

Serious adverse events occurred in 32 of 57 subjects (56.1%). Those reported by ≥2 subjects were pneumonia (5 subjects [8.8%]); pyrexia (4 subjects [7.0%]); lung infection; febrile neutropenia; anaphylactic reaction; disease progression; fatigue; and infusion related reaction (3 subjects each [5.3%]); and hypotension; and dyspnoea (2 subjects each [3.5%]). A causal relationship to study drug could not be ruled out for anaphylactic reaction; pyrexia; and infusion related reaction (3 subjects each); pneumonia; lung infection; febrile neutropenia; and hypotension (2 subjects each); and fatigue; and dyspnoea (1 subject each).

Adverse events leading to study drug discontinuation occurred in 14 of 57 subjects (24.6%). Those reported by ≥2 subjects were infusion related reaction (5 subjects [8.8%]); anaphylactic reaction (3 subjects [5.3%]); and insomnia; flushing; bronchospasm; dyspnoea; face oedema; and fatigue (2 subjects each [3.5%]), and a causal relationship to study drug could not be ruled out for all those events.

7.3.7 Foreign phase I/II study (Study 10893)

7.3.7.1 Phase I

Adverse events occurred in 88 of 89 subjects (98.9%), and those for which a causal relationship to study drug could not be ruled out occurred in 65 of 89 subjects (73.0%). Adverse events reported by ≥20% of subjects were infusion related reaction (44 subjects [49.4%]); fatigue (33 subjects [37.1%]); nausea (29 subjects [32.6%]); anaemia (25 subjects [28.1%]); upper respiratory tract infection; and cough (20 subjects each [22.5%]); and diarrhoea; and back pain (18 subjects each [20.2%]).

Serious adverse events occurred in 36 of 89 subjects (40.4%). Those reported by ≥2 subjects were pneumonia (6 subjects [6.7%]); sepsis; and anaemia (3 subjects each [3.4%]); and pneumocystis jirovecii pneumonia; hypercalcaemia; back pain; bone pain; and acute kidney injury (2 subjects each [2.2%]). A causal relationship to study drug could not be ruled out for pneumonia (4 subjects).

Adverse events leading to study drug discontinuation occurred in 4 of 89 subjects (4.5%), which were infusion related reaction (2 subjects [2.2%]); and acute coronary syndrome; hypertensive crisis; apnoea; bone pain; and acute kidney injury (1 subject each [1.1%]) (some subjects had more than 1 event). A causal relationship to study drug could not be ruled out for infusion related reaction (2 subjects); and hypertensive crisis; and apnoea (1 subject each).

7.3.7.2 Phase II

Adverse events occurred in (1) 96 of 97 subjects (99.0%) in Stage 1, (2) 50 of 63 subjects (79.4%) in the single-agent isatuximab group of Stage 2, and (3) 24 of 30 subjects (80.0%) in the isatuximab/DEX group of Stage 2, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 67 of 97 subjects (69.1%), (2) 36 of 63 subjects (57.1%), and (3) 17 of 30 subjects (56.7%). Adverse events reported by ≥20% of subjects in each stage were (1) infusion related reaction (52 subjects [53.6%]); nausea (33 subjects [34.0%]); fatigue (31 subjects [32.0%]); upper respiratory tract infection (28 subjects [28.9%]); anaemia (27 subjects [27.8%]); cough; and diarrhoea (26 subjects each [26.8%]); headache (23 subjects [23.7%]); and dyspnoea (22

subjects [22.7%]), (2) infusion related reaction (26 subjects [41.3%]), and (3) infusion related reaction (13 subjects [43.3%]).

Serious adverse events occurred in (1) 43 of 97 subjects (44.3%), (2) 18 of 63 subjects (28.6%), and (3) 6 of 30 subjects (20.0%). Those reported by ≥2 subjects in each stage were (1) pneumonia (7 subjects [7.2%]); disease progression (6 subjects [6.2%]); sepsis (5 subjects [5.2%]); acute kidney injury (4 subjects [4.1%]); upper respiratory tract infection; and pathological fracture (3 subjects each [3.1%]); and hyperviscosity syndrome; dehydration; pleural effusion; back pain; and asthenia (2 subjects each [2.1%]), (2) anaemia; disease progression; and infusion related reaction (3 subjects each [4.8%]); and pneumonia; bone pain; and acute kidney injury (2 subjects each [3.2%]) [(3) none]. A causal relationship to study drug could not be ruled out for (2) infusion related reaction (3 subjects); and anaemia; and bone pain (1 subject each).

Adverse events leading to study drug discontinuation occurred in (1) 5 of 97 subjects (5.2%), (2) 5 of 63 subjects (7.9%), and (3) 4 of 30 subjects (13.3%). Those reported by ≥2 subjects in each stage were (1) infusion related reaction (2 subjects [2.1%]) and (2) infusion related reaction (3 subjects [4.8%]); and bronchospasm (2 subjects [3.2%]) [(3) none]. A causal relationship to study drug could not be ruled out for (1) infusion related reaction (2 subjects) and (2) infusion related reaction (3 subjects); and bronchospasm (2 subjects).

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

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

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

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

The new drug application data (CTD 5.3.3.2-7, CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that isatuximab has efficacy in the treatment of relapsed or refractory MM, and that isatuximab has acceptable safety in view of its benefits. Isatuximab is a drug with a new active ingredient. Upon binding to CD38 expressed on the surface of MM cells, isatuximab is thought to induce anti-tumor activity through ADCC, ADCP, and CDC and by induction of apoptosis, etc.

Isatuximab is clinically meaningful because it offers a new treatment option for patients with relapsed or refractory MM. PMDA considers that the clinical positioning of isatuximab, post-marketing investigations, etc. need to be further discussed.

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

Review Report (2)

May 7, 2020

Product Submitted for Approval

Brand Name	Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion
Non-proprietary Name	Isatuximab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	August 23, 2019

List of Abbreviations

See Appendix.

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

As a result of its review in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that the efficacy of isatuximab was demonstrated in patients with relapsed or refractory MM since the global phase III study (Study 14335) demonstrated the superiority of isatuximab/Pd over Pd in the primary endpoint of PFS based on the IRC assessment using the IMWG criteria, etc.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

As a result of its review in Section "7.R.3 Safety" in the Review Report (1), PMDA concluded that adverse events that require particular attention following administration of isatuximab/Pd are infusion reactions, myelosuppression, infections, cardiac disorders, second primary malignancies, TLS, and hemolysis.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with isatuximab, isatuximab is tolerable as long as physicians with adequate knowledge of and experience in the treatment of hematological malignancies take appropriate measures, e.g. monitoring for and management of adverse events.

During the preparation of the Review Report (1), PMDA was making inquiries to the applicant about (1) the implementation of screening and monitoring for opportunistic infections (including virus reactivation) and HBV infection, and (2) the incidences of opportunistic infections and HBV infection and the implementation of prophylaxis in Study 14335.

The applicant's responses to the above inquiries:
(1) HIV-positive patients and patients with active hepatitis viral infection were to be excluded from enrollment in Study 14335. The provision of screening and monitoring for HBV infection was not included in the study.
(2) The provision of the prophylaxis against opportunistic infections and HBV infection was not included in Study 14335. The incidences of opportunistic infections and HBV infection and the implementation of prophylaxis in the study are described below. MedDRA PTs (MedDRA/J ver.21.0) listed in Table 39 were counted as different types of infection-related events.

- Four of 152 patients (2.6%) in the isatuximab/Pd group and 6 of 149 patients (4.0%) in the Pd group received anti-HBV prophylaxis. No HBV infections were reported in either group.
- Seventy-one of 152 patients (46.7%) in the isatuximab/Pd group and 64 of 149 patients (43.0%) in the Pd group received anti-cytomegalovirus (CMV) prophylaxis. Among patients who received anti-CMV prophylaxis, CMV infection occurred in 1 of the 71 patients (1.4%) (cytomegalovirus gastritis [1 patient]) in the isatuximab/Pd group and 1 of the 64 patients (1.6%) (cytomegalovirus gastrointestinal infection [1 patient]) in the Pd group. Among patients who did not receive anti-CMV prophylaxis, CMV infection occurred in 1 of the 81 patients (1.2%) (cytomegalovirus infection [1 patient]) in the isatuximab/Pd group. Grade ≥3 or serious CMV infection was not reported.
- Seventy-one of 152 patients (46.7%) in the isatuximab/Pd group and 68 of 149 patients (45.6%) in the Pd group received anti-pneumocystis jirovecii prophylaxis. Among patients who received anti-pneumocystis jirovecii prophylaxis, pneumocystis jirovecii infection occurred in 1 of the 71 patients (1.4%) (pneumocystis jirovecii pneumonia [1 patient]) in the isatuximab/Pd group. Among patients who did not receive anti-pneumocystis jirovecii prophylaxis, pneumocystis jirovecii infection occurred in 2 of the 81 patients (2.5%) (pneumocystis jirovecii pneumonia [2 patients]) in the isatuximab/Pd group and 4 of the 81 patients (4.9%) (pneumocystis jirovecii pneumonia [4 patients]) in the Pd group. All of the reported cases of pneumocystis jirovecii infection were Grade ≥3, serious events.
- One hundred four of 152 patients (68.4%) in the isatuximab/Pd group and 103 of 149 patients (69.1%) in the Pd group received anti-herpes virus (excluding CMV) prophylaxis. Among patients who received anti-herpes virus prophylaxis, herpes virus (excluding CMV) infection occurred in 3 of the 104 patients (2.9%) (oral herpes [2 patients]; and herpes zoster [1 patient]) in the isatuximab/Pd group and 1 of the 103 patients (1.0%) (oral herpes [1 patient]) in the Pd group. Among patients who did not receive anti-herpes virus prophylaxis, herpes virus (excluding CMV) infection occurred in 12 of the 48 patients (25.0%) (oral herpes [5 patients]; herpes zoster [4 patients]; herpes simplex [2 patients]; varicella [1 patient]; and herpes zoster disseminated [1 patient] [some patients had more than 1 event]) in the isatuximab/Pd group and 3 of the 46 patients (6.5%) (oral herpes [2 patients]; and herpes zoster [1 patient]) in the Pd group. Grade ≥3 herpes virus (excluding CMV) infection occurred in 1 patient in the isatuximab/Pd group who did not receive

prophylaxis (2.1%) (herpes zoster disseminated [1 patient][46]) (none in the Pd group, regardless of the use of prophylaxis).

Table 39. MedDRA PTs counted as events of different types of infections

Infection	MedDRA PT
HBV infection	acute hepatitis B, chronic hepatitis B, congenital hepatitis B infection, HBV-DNA polymerase increased, hepatitis B, hepatitis B DNA assay positive, hepatitis B DNA decreased, hepatitis B DNA increased, hepatitis B antibody abnormal, hepatitis B antibody positive, hepatitis B antigen positive, hepatitis B core antibody positive, hepatitis B core antigen positive, hepatitis B e antibody positive, hepatitis B e antigen positive, hepatitis B surface antibody positive, hepatitis B surface antigen positive, hepatitis B virus test positive, perinatal HBV infection
CMV infection	congenital cytomegalovirus infection, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus duodenitis, cytomegalovirus enteritis, cytomegalovirus enterocolitis, cytomegalovirus gastritis, cytomegalovirus gastroenteritis, cytomegalovirus gastrointestinal infection, cytomegalovirus gastrointestinal ulcer, cytomegalovirus hepatitis, cytomegalovirus infection, cytomegalovirus mononucleosis, cytomegalovirus mucocutaneous ulcer, cytomegalovirus myelomeningoradiculitis, cytomegalovirus myocarditis, cytomegalovirus nephritis, cytomegalovirus oesophagitis, cytomegalovirus pancreatitis, cytomegalovirus pericarditis, cytomegalovirus syndrome, cytomegalovirus test positive, cytomegalovirus urinary tract infection, cytomegalovirus viraemia, disseminated cytomegaloviral infection, cytomegalovirus encephalitis, cytomegaloviral pneumonia
Pneumocystis jirovecii infection	pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia
Herpes virus (excluding CMV) infection	herpes colitis, congenital herpes simplex infection, congenital varicella infection, disseminated varicella zoster vaccine virus infection, eczema herpeticum, exanthema subitum, herpes gastritis, genital herpes, genital herpes simplex, genital herpes zoster, haemorrhagic varicella syndrome, herpes dermatitis, herpes oesophagitis, herpes ophthalmic, herpes pharyngitis, herpes sepsis, herpes simplex, herpes simplex cervicitis, herpes simplex colitis, herpes simplex encephalitis, herpes simplex gastritis, herpes simplex hepatitis, herpes simplex meningitis, herpes simplex meningoencephalitis, herpes simplex meningomyelitis, herpes simplex necrotising retinopathy, herpes simplex oesophagitis, herpes simplex otitis externa, herpes simplex pharyngitis, herpes simplex pneumonia, herpes simplex sepsis, herpes simplex test positive, herpes simplex viraemia, neonatal herpes simplex virus conjunctivitis, herpes simplex visceral, herpes virus infection, herpes virus test abnormal, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, neurological herpes zoster infection, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, human herpes virus 6 serology positive, human herpes virus 8 test positive, human herpesvirus 6 infection, human herpesvirus 7 infection, human herpesvirus 8 infection, lower respiratory tract herpes infection, herpes meningitis, neonatal herpes simplex meningoencephalitis, herpetic meningoencephalitis, herpes meningomyelitis, nasal herpes, necrotising herpetic retinopathy, neonatal mucocutaneous herpes simplex, ophthalmic herpes simplex, ophthalmic herpes zoster, oral herpes, herpes viral pneumonia, herpes proctitis, varicella, varicella keratitis, varicella post vaccine, varicella virus test positive, varicella zoster gastritis, varicella zoster oesophagitis, varicella zoster pneumonia, varicella zoster virus infection

PMDA's discussion:

Although the provision of the prophylaxis against opportunistic infections was not included in Study 14335, given that the prophylaxis against opportunistic infections was implemented to some extent, and taking account of the incidences of opportunistic infections and HBV infection in the above Study 14335, etc., it is necessary to appropriately provide information on the specific safety measures against infections implemented in Study 14335, etc., to healthcare professionals in clinical practice, using information materials etc.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

[46] Grade 3 serious adverse event

1.3 Clinical positioning and indication

As a result of its review in Section "7.R.5 Clinical positioning and indication" in the Review Report (1), PMDA concluded that the proposed indication of "relapsed or refractory multiple myeloma" is appropriate, provided that prior therapies etc. of patients enrolled in Study 14335 are mentioned in the CLINICAL STUDIES section of the package insert and that the following statements are included in the PRECAUTIONS CONCERNING INDICATION section.

Precautions Concerning Indication

- Isatuximab should be used to treat patients who have failed or relapsed following at least 2 standard of care treatments.
- Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

From the above, PMDA instructed the applicant to amend the PRECAUTIONS CONCERNING INDICATION section accordingly. The applicant agreed.

1.4 Dosage and administration

As a result of its review in Section "7.R.6 Dosage and administration" in the Review Report (1), PMDA concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

Dosage and Administration

Isatuximab in combination with pomalidomide and dexamethasone

The usual adult dose is 10 mg/kg of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period.

Precautions Concerning Dosage and Administration

- The efficacy and safety of isatuximab monotherapy have not been established.
- Anti-neoplastic drugs for combination with isatuximab should be used by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.
- The efficacy and safety of isatuximab in combination with anti-neoplastic drugs other than pomalidomide and DEX have not been established.
- To reduce the risk and severity of infusion reactions associated with isatuximab infusions, patients should be premedicated with DEX as part of the backbone treatment, antihistamines, H_2 antagonists, and antipyretic analgesics 15 to 60 minutes prior to starting an isatuximab infusion.
- The appropriate volume of Sarclisa concentrate should be withdrawn and diluted in the 250 mL infusion

bag with saline or 5% glucose solution, and the first infusion should be initiated at 175 mg/hour. In the absence of infusion reactions, the infusion rate may be increased incrementally to a maximum of 400 mg/hour as shown below, while monitoring the patient's condition.

Infusion rates of isatuximab

Time after start of infusion	Infusion rate (mg/hour)	
	First infusion	Second and subsequent infusions
0-60 minutes after start of infusion	175	175
60-90 minutes after start of infusion	225	275
90-120 minutes after start of infusion	275	375
120-150 minutes after start of infusion	325	400
150-180 minutes after start of infusion	375	
≥180 minutes after start of infusion	400	

- If patients experience infusion reactions, appropriate measures, e.g. infusion interruption and discontinuation of isatuximab, and adjustment of the infusion rate, should be taken, as shown below.
  - Grade 2*: Interrupt isatuximab infusion until improvement to Grade ≤1*, and then isatuximab infusion may be resumed at 87.5 mg/hour. If symptoms do not recur, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
  - Grade ≥3*: Permanently discontinue isatuximab therapy, and do not readminister isatuximab.
- In case of Grade 3 or 4* neutropenia, delay the isatuximab dose until neutrophil count recovery to ≥1000/mm^3.

*: Severity grade based on NCI-CTCAE v4.03

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

From the above, PMDA instructed the applicant to amend the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections accordingly. The applicant agreed.

1.5 Risk management plan (draft)

The applicant has included TLS in the safety specification for the surveillance, and is planning to conduct a post-marketing database survey to determine the incidence of TLS following administration of isatuximab/Pd in clinical practice.

As a result of its review in Section "7.R.7 Post-marketing investigations" in the Review Report (1), PMDA concluded that it is necessary to conduct a post-marketing survey covering all patients treated with isatuximab over a specified period of time in order to collect safety information in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals in clinical practice as soon as possible.

PMDA's conclusion on the surveillance plan:

- The safety specification for the surveillance should include infusion reactions, myelosuppression, infections, and cardiac disorders.

- The planned sample size and observation period need to be determined, taking account of the incidences etc. of the events that are included in the safety specification for the surveillance in clinical studies.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

In light of the above, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:
- A use-results survey covering all patients treated with isatuximab will be conducted.
- The safety specification for the surveillance includes infusion reactions, myelosuppression, infections, and cardiac disorders.
- Taking account of the incidences etc. of the events that are included in the safety specification for the surveillance in clinical studies, the planned sample size is 100 patients and the observation period is 1 year.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for isatuximab should include the safety specification presented in Table 40, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 41 and Table 42.

Table 40. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Interference with the indirect Coombs test • Infusion reactions • Myelosuppression • Infections	• Cardiac disorders • Second primary malignancies • TLS • Hemolysis	None
Efficacy specification		
None		

Table 41. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study (an extension study of 14335)	None	• Disseminate data gathered during early post-marketing phase vigilance • Develop information materials to be distributed to healthcare professionals (prescribing physicians etc., blood transfusion division) • Develop information materials to be distributed to patients.

Table 42. Outline of use-results survey (draft)

Objective	To assess the safety etc. of isatuximab in clinical practice after marketing.
Survey method	All-case surveillance
Population	All patients treated with isatuximab
Observation period	1 year
Planned sample size	100 patients
Main survey items	Safety specification: infusion reactions, myelosuppression, infections, and cardiac disorders Other main survey items: patient characteristics (sex, age, disease stage, complications, prior therapies, etc.), the use of isatuximab, concomitant medications, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in the treatment of hematological malignancies at medical institutions that can provide adequate emergency medical care. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

Isatuximab in combination with pomalidomide and dexamethasone

The usual adult dose is 10 mg/kg of Isatuximab (Genetical Recombination) administered as an intravenous infusion weekly (Days 1, 8, 15, and 22) in the first cycle and every 2 weeks (Days 1 and 15) thereafter. Each treatment cycle consists of a 28-day period.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Warnings

Isatuximab should be administered only to patients appropriate for isatuximab therapy, under the supervision of physicians with adequate knowledge of and experience in the treatment of hematological malignancies at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

Contraindication

Patients with a history of hypersensitivity to any of the components of the product

Precautions Concerning Indication

1. Isatuximab should be used to treat patients who have failed or relapsed following at least 2 standard of care treatments.
2. Appropriate patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of isatuximab.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of isatuximab monotherapy have not been established.
2. Anti-neoplastic drugs for combination with isatuximab should be used by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.
3. The efficacy and safety of isatuximab in combination with anti-neoplastic drugs other than pomalidomide and dexamethasone have not been established.
4. To reduce the risk and severity of infusion reactions associated with isatuximab infusions, patients should be premedicated with dexamethasone as part of the backbone treatment, antihistamines, H_2 antagonists, and antipyretic analgesics 15 to 60 minutes prior to starting an isatuximab infusion.
5. The appropriate volume of Sarclisa concentrate should be withdrawn and diluted in the 250 mL infusion bag with saline or 5% glucose solution, and the first infusion should be initiated at 175 mg/hour. In the absence of infusion reactions, the infusion rate may be increased incrementally to a maximum of 400 mg/hour as shown below, while monitoring the patient's condition.

Infusion rates of isatuximab

Time after start of infusion	Infusion rate (mg/hour)	
	First infusion	Second and subsequent infusions
0-60 minutes after start of infusion	175	175
60-90 minutes after start of infusion	225	275
90-120 minutes after start of infusion	275	375
120-150 minutes after start of infusion	325	400
150-180 minutes after start of infusion	375	
≥180 minutes after start of infusion	400	

6. If patients experience infusion reactions, appropriate measures, e.g. infusion interruption and discontinuation of isatuximab, and adjustment of the infusion rate, should be taken, as shown below.
   - Grade 2*: Interrupt isatuximab infusion until improvement to Grade ≤1*, and then isatuximab infusion may be resumed at 87.5 mg/hour. If symptoms do not recur, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
   - Grade ≥3*: Permanently discontinue isatuximab therapy, and do not readminister isatuximab.
7. In case of Grade 3 or 4* neutropenia, delay the isatuximab dose until neutrophil count recovery to ≥1000/mm^3.

*: Severity grade based on NCI-CTCAE v4.03

Appendix

List of Abbreviations

ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ALT	alanine aminotransferase
application	marketing application
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
cADPR	cyclic adenosine diphosphate ribose
CAL	cells at the limit of *in vitro* cell age
CBd	the combination of cyclophosphamide, bortezomib, and DEX
CD	cluster of differentiation
Recombinant CD38-Fc fusion protein	a recombinant protein generated by fusing human CD38 to the Fc domain of murine IgG2a
CDC	complement dependent cytotoxicity
CE-SDS	capillary electrophoresis-sodium dodecyl sulfate
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
CMV	Cytomegalovirus
CR	complete response
CrCL	creatinine clearance
cyclophosphamide	Cyclophosphamide Monohydrate
daratumumab	Daratumumab (Genetical Recombination)
DEX	Dexamethasone
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
[redacted]	[redacted]
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
elotuzumab	Elotuzumab (Genetical Recombination)
elotuzumab/Pd	the combination of elotuzumab and Pd
Fc	fragment, crystallizable
FcγR	Fc gamma receptor
HBV	hepatitis B virus
HCP	host cell protein
HIV	human immunodeficiency virus
HRP	horseradish peroxidase
icIEF	imaged capillary isoelectric focusing
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
IMWG criteria	The response criteria developed by IMWG
isatuximab	Isatuximab (Genetical Recombination)
isatuximab/CBd	the combination of isatuximab and CBd
isatuximab/DEX	the combination of isatuximab and DEX
isatuximab/Ld	the combination of isatuximab and Ld
isatuximab/Pd	the combination of isatuximab and Pd
isatuximab/pomalidomide	the combination of isatuximab and pomalidomide
ISS	international staging system
ITT	intent-to-treat

KCL	time to decrease 50% of the linear clearance
Ld	the combination of lenalidomide and DEX
LDH	lactate dehydrogenase
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
[redacted]	[redacted]
MTD	maximum tolerated dose
MVM	minute virus of mice
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
NE	not estimable
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
Pd	the combination of pomalidomide and DEX
PFS	progression-free survival
PI	proteasome inhibitor
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
QbD	quality by design
QD	quaque die
QW	quaque 1 week
Q2W	quaque 2 weeks
Q4W	quaque 4 weeks
SEC	size exclusion liquid chromatography
SMQ	standard MedDRA queries
SOC	system organ class
Study 10893	Study TED10893
Study 11863	Study TCD11863
Study 13983	Study TCD13983
Study 14079	Study TCD14079
Study 14095	Study TED14095
Study 14154	Study TED14154
Study 14335	Study EFC14335
T-ALL	T-cell acute lymphoblastic leukemia
TLS	tumor lysis syndrome
VGPR	very good partial response
WCB	working cell bank