Report on the Deliberation Results

November 4, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lunsumio for Subcutaneous Injection 5 mg Lunsumio for Subcutaneous Injection 45 mg
Non-proprietary Name	Mosunetuzumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 14, 2025

Results of Deliberation

In its meeting held on October 29, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product. The re-examination period is the remainder of the re-examination period for the initial approval of the product (until December 26, 2032). The drug product is classified as a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, prior to marketing, to ensure that the product will be used under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies, in a medical setting where appropriate measures, including management of cytokine release syndrome, are taken, and at a medical institution capable of providing adequate emergency care.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Latest Corrected Version**

Review Report

October 16, 2025
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	Lunsumio for Subcutaneous Injection 5 mg Lunsumio for Subcutaneous Injection 45 mg
Non-proprietary Name	Mosunetuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 14, 2025
Dosage Form/Strength	A solution for subcutaneous injection: each vial contains: 5 mg of mosunetuzumab (genetical recombination) in 0.5 mL; 45 mg of mosunetuzumab (genetical recombination) in 1 mL
Application Classification	Prescription drug, (3) Drugs with a new route of administration
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 follicular lymphoma, 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 product is classified as a biological product. The drug product is classified as a powerful drug.

Indication

Relapsed or refractory follicular lymphoma

Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15.

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** The English translation has been corrected to reflect the corrections listed in the latest errata sheet (dated January 30, 2026) for the Japanese original.

From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, prior to marketing, to ensure that the product will be used under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies, in a medical setting where appropriate measures, including management of cytokine release syndrome, are taken, and at a medical institution capable of providing adequate emergency care.

Latest Corrected Version

Attachment

Review Report (1)

September 11, 2025

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	Lunsumio for Subcutaneous Injection 5 mg Lunsumio for Subcutaneous Injection 45 mg
Non-proprietary Name	Mosunetuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 14, 2025
Dosage Form/Strength	A solution for subcutaneous injection: each vial contains: 5 mg of mosunetuzumab (genetical recombination) in 0.5 mL; 45 mg of mosunetuzumab (genetical recombination) in 1 mL

Proposed Indication

Relapsed or refractory follicular lymphoma

Proposed Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg/dose should be administered on Day 1, followed by 45 mg/dose on Days 8 and 15. From Cycle 2 onward, 45 mg/dose should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information....3
2. Quality and Outline of the Review Conducted by PMDA....3
3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA....4
4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA....4
5. Toxicology and Outline of the Review Conducted by PMDA....4
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA....5
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA....11
8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA....51
9. Overall Evaluation during Preparation of the Review Report (1)....51

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

Mosunetuzumab (genetical recombination) (hereinafter referred to as mosunetuzumab), discovered by Genentech, Inc. in the United States, is a recombinant protein (bispecific antibody) with antigen-binding sites specific for human cluster of differentiation (CD)3 and CD20.

Mosunetuzumab binds to both CD3 expressed on the cell membrane of T cells and CD20 expressed on the cell membrane of B-cell tumors, leading to T-cell dependent cytotoxic activity against CD20-expressing tumor cells, thereby exerting anti-tumor activity.

In Japan, intravenous (IV) formulations of mosunetuzumab (Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg) were approved in December 2024 for the treatment of relapsed or refractory follicular lymphoma.

1.2 Development history, etc.

The objectives of the pharmaceutical development of mosunetuzumab for subcutaneous (SC) administration are twofold (1) slowing the rise in blood concentration compared to IV administration to mitigate acute cytokine release and reduce adverse drug reactions such as cytokine release syndrome (CRS); and (2) shortening the administration time to reduce the burden on patients and healthcare professionals.

Outside Japan, a phase I/II study (Study GO29781) was initiated in September 2015 in patients with relapsed or refractory B-cell tumors by Switzerland-based F. Hoffmann-La Roche Ltd. and Genentech, Inc.

In the US and the EU, applications for approval of the SC formulation of mosunetuzumab were filed in November 2024 based on the results of Study GO29781 as the pivotal study and are currently under review.

As of July 2025, the SC formulation of mosunetuzumab has not been approved in any country or region for the indication of relapsed or refractory follicular lymphoma (FL).

In Japan, the applicant initiated a phase I study (Study JO40295) in March 2018 in patients with relapsed or refractory B-cell non-Hodgkin’s lymphoma (B-NHL).

An application for marketing approval of mosunetuzumab was filed based on data from Studies GO29781 and JO40295 as pivotal studies.

2. Quality and Outline of the Review Conducted by PMDA

The intention of the present application is to obtain approval for a new route of administration, and data relating to quality have been submitted. The 5 mg- and 45 mg- formulations are different from the approved IV

formulations in manufacturing process, etc. associated with [redacted] and the change in concentration . PMDA conducted a quality review and concluded that there were no problems.

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

Although the intention of the present application is to obtain approval for a new route of administration, no new study data on non-clinical pharmacology have been submitted because non-clinical pharmacology was evaluated during the review of the application for the IV formulation.

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

Although the intention of the present application is to obtain approval for a new route of administration, no new study data on non-clinical pharmacokinetics have been submitted because non-clinical pharmacokinetics was evaluated during the review of the application for the IV formulation.

5. Toxicology and Outline of the Review Conducted by PMDA

Although the intention of the present application is to obtain approval for a new route of administration, no new study data on toxicology have been submitted because toxicology was evaluated during the review of the application for the IV formulation.

5.R Outline of the review conducted by PMDA

Based on the discussions in the following sections, PMDA concluded that the applicant's explanation about the toxicity of mosunetuzumab for SC administration is acceptable.

5.R.1 Local toxicity in SC administration

Although local toxicity following repeated SC doses of mosunetuzumab has not been specifically evaluated, the applicant considered safety issues at the administration site to be unlikely in clinical use, based on the following factors:

- A single-dose toxicity study in cynomolgus monkeys, submitted with the initial application for the IV formulation of mosunetuzumab, showed no macroscopic or histopathological changes at the injection site after SC administration of mosunetuzumab to animals in the SC group at 1 mg/kg which is above the maximum clinical dose (at up to 45 mg, 0.9 mg/kg for humans weighing 50 kg) (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).
- Injection site reactions reported in clinical studies following SC administration of mosunetuzumab were limited to Grade 1 or 2 in severity. Although these injection site reactions led to dose interruption in some patients, they resolved following dose interruption, and these patients were able to resume treatment. Therefore, injection site reactions are considered manageable [see Section 7.R.3.3].
- SC doses of mosunetuzumab are administered at intervals of 7 or 21 days. It is considered possible to reduce injection site reactions by including a cautionary statement in the package insert to the effect that repeated injections at the same site should be avoided.

PMDA accepted the applicant's explanation.

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

The SC formulations of mosunetuzumab (F01, F03, and F05) were used to investigate the pharmacokinetics (PK) and other characteristics following subcutaneous administration of mosunetuzumab (Table 1). Formulations F03 and F05 are the proposed commercial formulations.

Table 1. Formulations used in clinical studies

Formulation	Study
F01 (■mg)	Foreign phase I/II study (Study GO29781)
F03 (45 mg)	Foreign phase I/II study (Study GO29781), Japanese phase I study (Study JO40295)
F05 (5 mg)	Foreign phase I/II study (Study GO29781), Japanese phase I study (Study JO40295)

Mosunetuzumab in human serum was determined by enzyme-linked immunosorbent assay (ELISA), with a lower limit of quantitation of 10.0 ng/mL. Anti-mosunetuzumab antibodies in human serum were detected by ELISA.

6.2 Clinical pharmacology

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.5.2-1, Study JO40295, 3L + FL SC cohorts [ongoing since March 2018, data cut-off on March 4, 2024])

An open-label, uncontrolled study was conducted in 5 patients with relapsed or refractory FL to evaluate the safety, tolerability, and other characteristics of the SC administration of mosunetuzumab. Serum mosunetuzumab concentrations were evaluated in all 5 PK-evaluable patients. Mosunetuzumab was administered SC in 21-day cycles: 5 mg on Cycle 1 Day 1, 45 mg on Cycle 1 Day 8 and Day 15, and 45 mg on Day 1 of each subsequent cycle.

Table 2 shows the PK parameters of mosunetuzumab in Cycle 1. The pre-dose serum mosunetuzumab concentrations (mean ± standard deviation) in Cycles 2, 3, and 4 were 7.95 ± 1.91, 5.86 ± 0.33, and 5.60 ± 1.62 μg/mL, respectively.

Table 2. Mosunetuzumab PK parameters

N	C_{max} (μg/mL)	t_{max}* (day)	$AUC_{0\text{-}21d}$ (μg·day/mL)
4	8.64 ± 2.30	18.46 (15.89, 22.95)	78.5 ± 22.7

Mean ± standard deviation; *, median (Min, Max)

No anti-mosunetuzumab antibodies were detected in any of the 5 patients evaluated for anti- mosunetuzumab antibodies following administration of mosunetuzumab.

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I/II study (CTD 5.3.5.2-2, Study GO29781 [ongoing since September 2015, data cut-off on August 27, 2021 (B11 FL RP2D cohort), February 1, 2024 (Groups D and F)]

An open-label, uncontrolled study was conducted in 229 patients with relapsed or refractory B-cell tumors to evaluate the PK and other characteristics of IV or SC administration of mosunetuzumab. Serum mosunetuzumab concentrations were evaluated in PK-evaluable patients (90, 48, and 180 patients in Groups B, D, and F, respectively). The dosing regimens for Groups B, D, and F followed 21-day cycles as shown below [see Table 13 for details].

Group B

B11 recommended Phase II dose (B11 RP2D) cohort:

mosunetuzumab was administered IV, 1 mg (Cycle 1 Day 1), 2 mg (Cycle 1 Day 8), 60 mg (Cycle 1 Day 15), 60 mg (Cycle 2 Day 1), 30 mg (from Cycle 3 onward, Day 1)

Group D

D1 to D6 cohorts: mosunetuzumab 1.6 to 20 mg was administered SC Q3W

Group F

F1 to F3 cohorts: mosunetuzumab was administered SC, 5 mg (Cycle 1 Day 1), 15 or 45 mg (Cycle 1 Day 8), 45 or 90 mg (Cycle 1 Day 15), 45 or 90 mg (Cycle 2 Day 1), 45 mg (from Cycle 3 onward, Day 1)

Pharmacokinetic parameters following SC administration of mosunetuzumab in Cycle 1 are presented in Table 3 and Table 4.

Table 3. PK parameters of mosunetuzumab

Cohort	Dose (mg)	N	C_{max} (µg/mL)	t_{max}* (day)	AUC_{0-21d} (µg·day/mL)
D1	1.6	6	0.0846 ± 0.0438	2.97 (2.85, 13.97)	1.17 ± 0.530
D2	2.4	3	0.0951 ± 0.0324	3.00 (2.98, 13.96)	1.47 ± 0.409
D3	3.6	3	0.166 ± 0.0838	2.94 (2.87, 13.94)	2.80 ± 1.38
D4	7.2	4	0.221 ± 0.148	2.45 (1.97, 13.85)	3.40 ± 2.42
D5	13.5	4	0.565 ± 0.258	2.98 (2.94, 6.87)	8.92 ± 2.84
D6 (Dose-escalation)	20	7	0.963 ± 0.295	3.01 (2.08, 7.15)	14.4 ± 4.52
D6 (Dose-expansion)	20	21	0.967 ± 0.371	6.01 (1.99, 21.77)	12.8 ± 5.56

Mean ± standard deviation; *, median (Min, Max)

Table 4. PK parameters of mosunetuzumab

Cohort	Dose[*1] (mg)	N	C_{max} (μg/mL)	t_{max}[*2] (day)	$AUC_{0\text{-}42d}$ (μg·day/mL)
F1	5/15/45	6	3.52 ± 1.67	20.9 (16.9, 41.9)	154 ± 168[*3]
F2	5/45/45	3	5.45 ± 3.03	16.9 (15.5, 17.0)	106[*4]
F3	5/45/90	3	8.82 ± 2.46	20.9 (17.9, 21.0)	195 ± 48.4
F1 (Dose-expansion)	5/15/45	30	3.16 ± 1.26	17.9 (8.95, 46.0)	75.2 ± 32.1[*5]
F2 RP2D (Dose-expansion)	5/45/45	130	4.64 ± 2.12	20.7 (1.99, 49.9)	113 ± 46.4[*6]

Mean ± standard deviation (individual values for N = 1); *1, Day 1/Day 8/Day 15 and beyond; *2, median (Min, Max); *3, N = 5; *4, N = 1; *5, N = 22; *6, N = 114

Table 5 shows serum mosunetuzumab concentrations before administration of mosunetuzumab in Cycles 3 and 4 in the B11 RP2D cohort (IV, 1/2/60/30 mg[1)]) and in the F2 RP2D cohort (SC, 5/45/45 mg[2)]).

Table 5. Serum mosunetuzumab concentration

Measurement timepoint	B11 RP2D cohort		F2 RP2D cohort	
	N	Concentration (μg/mL)	N	Concentration (μg/mL)
Cycle 3 Day 1, pre-dose	54	2.6 ± 0.9	43	2.9 ± 1.2
Cycle 4 Day 1, pre-dose	57	1.8 ± 0.7	43	2.6 ± 1.1

Mean ± standard deviation

In the F2 RP2D cohort, formulation F01 and the proposed commercial formulations (F03 and F05) were used [see Section 6.1]. Although the composition of F01 differs from that of the proposed commercial formulations, the applicant considers that these differences are unlikely to have an impact on the PK of mosunetuzumab based on the PK parameters observed for each formulation (Table 6).

Table 6. PK parameters of mosunetuzumab

Formulation	N	$C_{max0\text{-}42d}$ (μg/mL)	N	$AUC_{0\text{-}42d}$ (μg·day/mL)
F01	24	4.77 ± 2.20	24	105 ± 49.8
Proposed commercial formulation	67	4.35 ± 1.88	63	115 ± 47.2

Mean ± standard deviation

Anti-mosunetuzumab antibodies were detected in 1 of 216 patients (0.5%) who had evaluable post-treatment immunogenicity data in Groups D and F.

Figure 1 shows the changes in plasma interleukin (IL)-6 concentration over time following administration of mosunetuzumab in the B11 RP2D cohort (IV, 1/2/60 mg[3)]) and F2 RP2D cohort (SC, 5/45/45 mg[2)]).

1) Dose levels on Day 1/ Day 8/ Days 15 and 22/ from Day 43 onward [see Table 13 for details]
2) Dose levels on Day 1/ Day 8/ from Day 15 onward [see Table 13 for details]
3) Dose levels on Day 1/ Day 8/ from Day 15 onward [see Table 13 for details]

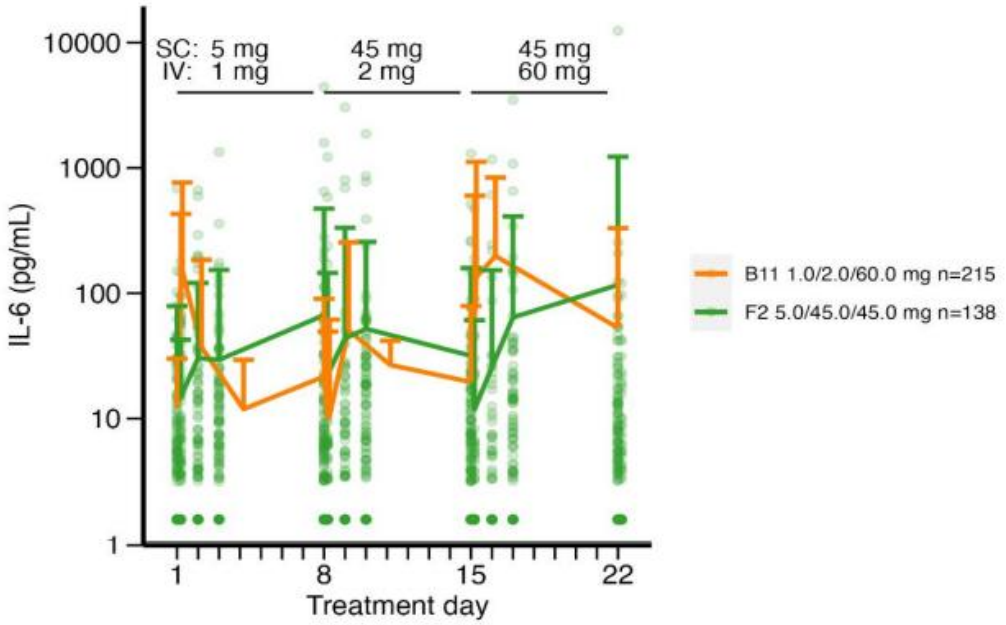


Figure 1. Changes in plasma IL-6 concentrations over time following IV and SC administration of mosunetuzumab

Cytokines such as IL-6 have been reported to down-regulate expression of cytochrome P450 (CYP) (e.g., *Clin Pharmacokinet.* 2010;49:295-310). Therefore, concomitant use of mosunetuzumab with CYP substrates may result in pharmacokinetic drug interactions. Although differences were observed between IV and SC administration in both the time to reach peak IL-6 concentration and the magnitude of IL-6 concentrations, plasma IL-6 concentrations increased at the beginning of mosunetuzumab treatment and at the onset of CRS for both routes of administration. Therefore, as with the IV formulation of mosunetuzumab, caution should be exercised when the mosunetuzumab SC formulation is administered in combination with CYP substrates with a narrow therapeutic range (1) from the start of mosunetuzumab treatment up to pre-dose on Cycle 3 Day 1 and (2) from the onset of CRS and for a certain period thereafter. The applicant explained that cautionary statements to this effect will be included in the package insert.

6.2.2.2 Foreign phase Ib/II (CTD5.3.5.4-1, Study CO41942, randomized stage [ongoing since August 2020, data cut-off on February 1, 2024])

An open-label, uncontrolled study was conducted in 120 patients with FL to evaluate the PK and other characteristics of the SC administration of mosunetuzumab. Serum mosunetuzumab concentrations were evaluated in PK-evaluable patients (39 and 78 patients in the IV and SC groups, respectively). Mosunetuzumab was administered in 21-day cycles according to the dosing regimens shown below. In both groups, lenalidomide hydrate (LEN) 20 mg was administered orally QD from Day 1 through Day 21 in Cycles 2 through 12.

Mosunetuzumab IV group: mosunetuzumab was administered intravenously

1 mg (Cycle 1 Day 1), 2 mg (Cycle 1 Day 8), 30 mg (Cycle 1 Day 15), 30 mg (Cycles 2 through 12, Day 1)

Mosunetuzumab SC group: mosunetuzumab was administered subcutaneously
5 mg (Cycle 1 Day 1), 45 mg (Cycle 1 Day 8), 45 mg (Cycle 1 Day 15), and 45 mg (Cycles 2 through 12, Day 1)

Table 7 shows serum mosunetuzumab concentrations. Following IV or SC administration of mosunetuzumab, cumulative AUC over the first 3 treatment cycles (AUC_{C1-3}, mean ± standard deviation) was 117.7 ± 38.8 µg·day/mL (IV, N = 39) and 205.8 ± 69.0 µg·day/mL (SC, N = 78).

Table 7. Serum mosunetuzumab concentrations (µg/mL)

Measurement timepoint	N	Mosunetuzumab IV	N	Mosunetuzumab SC
Cycle 2 Day 1, pre-treatment	38	1.42 ± 1.03	74	3.47 ± 1.78
Cycle 3 Day 1, pre-treatment	34	0.666 ± 0.355	75	1.48 ± 0.672
Cycle 4 Day 1, pre-treatment	34	0.721 ± 0.523	70	1.37 ± 0.571
Cycle 5 Day 1, pre-treatment	29	1.10 ± 0.770	67	1.91 ± 1.28

Mean ± standard deviation

In the mosunetuzumab SC group, no anti-mosunetuzumab antibodies were detected in 76 patients who had evaluable immunogenicity data following administration of mosunetuzumab.

6.2.3 Population pharmacokinetic analysis

The population pharmacokinetic (PPK) model previously submitted for the application for the IV formulation of mosunetuzumab was updated using data from Groups D and F of Study GO29781.

The PPK analysis was performed using non-linear mixed effect modeling (software, NONMEM version 7.5.0) based on mosunetuzumab PK data from 667 patients (IV, 439 patients, SC, 228 patients; 10,982 timepoints). The PK of mosunetuzumab SC was described by a 2-compartment model with time-dependent total body clearance (CL) and a first-order absorption process.

Body weight, age, sex, race, anti-CD20 antibody concentration, injection site, and drug substance were investigated as covariates for SC-specific PK parameters (ka_1, ka_2, and F). None of these variables were identified as significant covariates for the above PK parameters.

6.2.4 Relationship between exposure and efficacy/safety

6.2.4.1 Exposure-efficacy relationship

In Study GO29781, using data from patients with relapsed or refractory B-cell tumors who received mosunetuzumab 5/45/45 mg SC,[2)] patients were divided into 2 groups based on median mosunetuzumab exposure (e.g., AUC_{0-84d}[4)]). Investigator-assessed complete response (CR) rate and objective response (CR or partial response [PR]) rate were then evaluated in each exposure group. No clear differences in CR or objective response rate were detected between the two exposure groups.

[4)] AUC up to the end of Cycle 4 estimated by the PPK analysis [see Section 6.2.3].

6.2.4.2 Exposure-safety relationship

In Study GO29781, using data from Groups D and F following SC administration of mosunetuzumab, the relationship between mosunetuzumab exposure (maximum receptor occupancy from time equal to 0 to 42 days post-dose [$ROmax_{0\text{-}42d}$][5)]) and the incidence of Grade ≥2 CRS was investigated using a linear logistic regression model. No clear relationships between mosunetuzumab exposure and the incidence of Grade ≥2 CRS were identified.

Based on the results from Groups D and F in Study GO29781, patients were divided into 3 groups[6)] according to the tertiles of mosunetuzumab SC exposure ($AUC_{0\text{-}42d}$), and the relationship between mosunetuzumab exposure and the incidences of Grade ≥3 adverse events, adverse events of any grade, Grade ≥3 neutropenia, and Grade ≥3 infections and infestations were evaluated. No clear relationships between mosunetuzumab exposure and the incidence of any of the above events were identified.

6.2.5 Differences in PK between Japanese and non-Japanese populations

The applicant provided the following explanation regarding potential differences in PK after SC administration of mosunetuzumab between Japanese and non-Japanese populations:

Table 8 summarizes PK parameters following administration of the proposed dosage of mosunetuzumab to Japanese and non-Japanese patients enrolled in the 3L + FL SC cohort (Study JO40295, Japanese phase I study) and the F2 FL RP2D cohort (Study GO29781, foreign phase I/II study). Although exposure tended to be higher in Japanese patients than in non-Japanese patients, the applicant considers that there are no clinically relevant PK differences following SC administration of mosunetuzumab between Japanese and non-Japanese populations for the following reasons.

- No clear relationships were observed between mosunetuzumab exposure and the incidence of Grade ≥3 adverse events, adverse events of any grade, Grade ≥3 neutropenia, or Grade ≥3 infections and infestations [see Section 6.2.4.2].
- No clinically relevant differences were observed between Japanese and non-Japanese patients in the safety profile following SC administration of mosunetuzumab [see Section 7.R.3.1].

Table 8. PK parameters of mosunetuzumab

		N	$C_{max0\text{-}42d}$ (μg/mL)	N	$AUC_{0\text{-}42d}$ (μg·day /mL)
Study JO40295: 3L +FL SC cohort	Japanese patients	4	8.64 ± 2.30	4	224 ± 43.7
Study GO29781: F2 FL RP2D cohort	Non-Japanese patients	91	4.46 ± 1.96	87	112 ± 47.8

Mean ± standard deviation

5) The applicant's explanation: Because CRS is an on-target adverse event associated with mosunetuzumab, the applicant considered that residual rituximab (genetical recombination) (RIT) or obinutuzumab present in serum could compete with mosunetuzumab for CD20 binding, thus affecting the relationship between mosunetuzumab exposure and CRS. Accordingly, instead of using a serum concentration-based index such as AUC, the maximum CD20 receptor occupancy was estimated using serum concentrations of mosunetuzumab, RIT, and obinutuzumab, together with their respective binding affinities for CD20. The relationship between receptor occupancy and the incidence of CRS was then evaluated. The $ROmax_{0\text{-}42d}$ was estimated by PPK analysis based on the changes in serum mosunetuzumab/RIT/obinutuzumab concentrations and the equilibrium dissociation constant for the CD20 receptor.

6) The ranges of $AUC_{0\text{-}42d}$ (μg·day/mL) in the 3 groups were 0.937 to 73.2, 73.2 to 129, and 129 to 314.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology, etc. of SC administration of mosunetuzumab is acceptable.

6.R.1 Differences in mosunetuzumab PK between SC and IV administration of mosunetuzumab

The applicant provided the following explanation regarding the differences in PK between SC and IV administration of mosunetuzumab:

Based on the following results and other data, the PK of mosunetuzumab following SC administration at the proposed dosage regimen is considered to be generally comparable to or higher than that following IV administration at the approved dosage regimen.

- In Study GO29781, regarding the observed mosunetuzumab concentration at pre-dose in Cycle 4 and $AUC_{0\text{-}84d}$ (estimated by PPK model), the co-primary endpoints, the geometric mean ratio (SC/IV) for the observed concentration [90% confidence interval (CI)] was 1.39 [1.20, 1.61], and the geometric mean ratio (SC/IV) for $AUC_{0\text{-}84d}$ was 1.06 [0.92, 1.21]. The lower bounds of both 90% CIs exceeded the non-inferiority margin of 0.80 [see Section 7.1.2.1].
- Figure 2 shows the change in serum mosunetuzumab concentrations over time for IV and SC administration based on the PPK analysis [see Section 6.2.3].

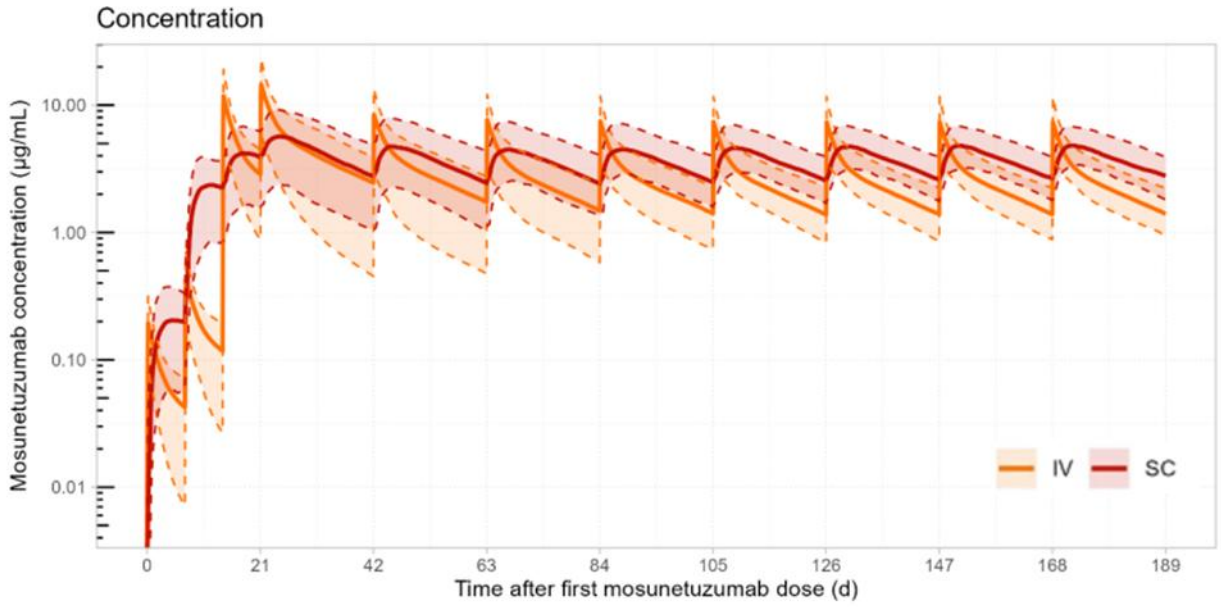


Figure 2. Change in serum mosunetuzumab concentrations over time for IV and SC administration (estimated values)

PMDA accepted the applicant's explanation. The evaluation of the efficacy and safety of SC administration of mosunetuzumab is discussed in Sections "7.R.2 Efficacy" and "7.R.3 Safety," taking into account the differences in PK between IV and SC administration of mosunetuzumab.

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

The applicant submitted the studies listed in Table 9 as evaluation data for efficacy and safety.

Table 9. List of clinical studies on efficacy and safety

Data	Location	Study	Phase	Study population	Number of subjects enrolled	Summary of dosing regimen	Main endpoints
Evaluation	Japan	JO40295	I	Patients with relapsed or refractory B-NHL	Dose-expansion cohort: 19 3L + FL SC cohort: 5 2L + FL SC cohort: 17	Dose-expansion cohort (IV)[*1]: On Cycle 1 Days 1, 8, and 15, 1/2/60 mg[*2] (IV); thereafter, 60 mg on Cycle 2 Day 1; from Cycle 3 onward, 30 mg on Day 1 Q3W (IV) 3L + FL SC cohort (SC)[*1]: On Cycle 1 Days 1, 8, and 15, 5/45/45 mg[*2] (SC); thereafter, from Cycle 2 onward, 45 mg on Day 1 Q3W (SC) 2L + FL SC cohort (SC)[*3]: In combination with LEN[*4], on Cycle 1 Days 1, 8, and 15, 5/45/45 mg[*2] (SC); thereafter, from Cycle 2 onward, 45 mg on Day 1 Q4W (SC)	Efficacy Safety PK
	Foreign	GO29781	I/II	Patients with relapsed or refractory B-cell tumor	Group B Dose-expansion part (B11 RP2D cohort): 218 Group D: 48 Dose-escalation part: 27 Dose-expansion part: 21 Group F: 181 Dose-escalation part:14 Dose-expansion part:167 (F2 FL RP2D cohort: 94)	**Group B (IV)[*1]** Dose-expansion part (B11 RP2D cohort): On Cycle 1 Days 1, 8, and 15, 1/2/60 mg[*2] (IV); thereafter, 60 mg on Cycle 2 Day 1, and from Cycle 3 onward, 30 mg on Day 1 Q3W (IV) **Group D (SC)[*1]** Dose-escalation part: 1.6-20 mg Q3W (SC) Dose-expansion part: 20 mg Q3W (SC) **Group F (SC)[*1]** Dose-escalation part: On Cycle 1 Days 1, 8, and 15, 5/15/45 mg[*2] , 5/45/45 mg[*2], or 5/45/90 mg[*2] (SC); thereafter, the same dose as that of Cycle 1 Day 15 was administered on Cycle 2 Day 1, and from Cycle 3 onward, 45 mg on Day 1 Q3W (SC) Dose-expansion part (including F2 FL RP2D cohort): In Cycle 1 on Days 1, 8, and 15, 5/15/45 mg[*2] or 5/45/45 mg[*2] (SC); thereafter, from Cycle 2 onward, 45 mg on Day 1 Q3W (SC)	Efficacy Safety PK
Reference	Foreign	CO41942	Ib/II	Patients with FL	120 (1) 80 (2) 40	(1) SC group: in combination with LEN[*4], mosunetuzumab 5/45/45 mg[*2] was administered on Cycle 1 Days 1, 8, and 15 (SC); thereafter, from Cycle 2 onward, 45 mg on Day 1 Q4W (SC) (2) IV group: in combination with LEN[*4], mosunetuzumab 1/2/30 mg[*2] was administered on Cycle 1 Days 1, 8, and 15 (IV), from Cycle 2 onward, 30 mg on Day 1 Q4W (IV)	Efficacy Safety PK

*1, Patients who achieved a CR after 8 cycles were to discontinue treatment; patients who had SD or achieved a PR after 8 cycles were to continue treatment up to Cycle 17; *2, dose levels on Days 1/8/15, respectively; *3, treatment was continued up to Cycle 12 unless disease progression occurred or the discontinuation criteria were met; *4, LEN 20 mg was administered orally QD on Days 1 to 21 from Cycle 2 onward.

Table 10 shows the patient population in the clinical studies.

Table 10. Patient populations in clinical studies

Study	Group/part		Cohort		Route of administration	Patient population
JO40295	Dose-expansion part		Dose-expansion		IV	Patients with relapsed or refractory FL[*1] who received ≥2 prior regimens
	—		2L + FL SC		SC[*2]	Patients with relapsed or refractory FL[*1] who received ≥1 prior regimen
			3L + FL SC		SC	Patients with relapsed or refractory FL[*1] who received ≥2 prior regimens
GO29781	Group B	Dose-expansion part	B11 RP2D	B11 FL RP2D	IV	Patients with relapsed or refractory FL[*1] who received ≥2 prior regimens
	Group D	Dose-escalation part	D1-D6		SC	Patients with relapsed or refractory FL (Grade 1-3B), MZL, transformation from low-grade NHL, RS, DLBCL, PMBCL, SLL, or MCL
		Dose-expansion part	D6 (DLBCL/trFL)			Patients with relapsed or refractory DLBCL or trFL who received ≥2 prior regimens
	Group F	Dose-escalation part	F1-F3			Patients with relapsed or refractory FL (Grade 1-3B), MZL, transformation from low-grade NHL, RS, DLBCL, PMBCL, SLL, or MCL
		Dose-expansion part	F1	F1 FL		Patients with relapsed or refractory FL[*1] who received ≥2 prior regimens
				F1 DLBCL/trFL		Patients with relapsed or refractory DLBCL or trFL who received ≥2 prior regimens
			F2 RP2D	F2 FL RP2D		Patients with relapsed or refractory FL[*1] who received ≥2 prior regimens
				F2 DLBCL/trFL RP2D		Patients with relapsed or refractory DLBCL or trFL who received ≥2 prior regimens
CO41942	Non-randomized part		SC group		SC[*2]	Previously untreated patients with FL[*1]
			IV group		IV[*2]	Patients with relapsed or refractory FL[*1] who received ≥1 prior regimen
	Randomized part		SC group		SC[*2]	
			IV group		IV[*2]	

—, not applicable; *1, FL (Grade 1-3A); *2, in combination with LEN

The following sections provide an outline of the clinical studies. Main adverse events other than deaths that occurred in the clinical studies are described in Section "7.3 Adverse events and other findings observed in clinical studies," and pharmacokinetic study results are presented 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 studies

7.1.1.1 Japanese phase I study (CTD 5.3.5.2-1, Study JO40295 [ongoing since March 2018, data cut-off on October 13, 2023 (Dose-expansion cohort), April 4, 2024 (2L + FL SC cohort), and March 4, 2024 (3L + FL SC cohort)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B-NHL[7)] (target sample size, N =19 [dose-expansion cohort], N = 17 [2L + FL SC cohort], and N = 5 [3L + FL SC cohort]) to evaluate the safety, efficacy, and other characteristics of mosunetuzumab monotherapy or

7) Eligible patients for the dose-expansion and 3L + FL SC cohorts were those with relapsed or refractory, CD20-positive, histologically documented FL (Grade 1-3A), who had received ≥2 prior lines of systemic chemotherapy regimens, including an anti-CD20 monoclonal antibody and an alkylating agent. For the 2L + FL SC cohort, eligible patients were those with relapsed or refractory, CD20-positive, histologically documented FL (Grade 1-3A), who had received ≥1 prior line of systemic chemotherapy.

mosunetuzumab/LEN treatment. The study in the dose-expansion, 2L + FL SC, and 3L + FL SC cohorts was conducted at 12, 10, and 7 study sites, respectively.

Table 11 shows the dosing regimens of mosunetuzumab for the dose-expansion, 2L + FL SC, and 3L + FL SC cohorts. In the dose-expansion and 3L + FL SC cohorts, treatment was continued up to Cycle 8 or until disease progression or the discontinuation criteria were met. Patients who achieved a CR at the end of Cycle 8 discontinued treatment. Those who achieved a PR or had stable disease (SD) were to continue treatment up to Cycle 17 unless disease progression occurred or the discontinuation criteria were met. In the 2L + FL SC cohort, treatment was continued up to Cycle 12 unless disease progression occurred or the discontinuation criteria were met. The results for the dose-expansion cohort are not presented here because the data for the cohort had already been evaluated during the review of the application for the IV formulation of mosunetuzumab (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024). Given the intended patient population and dosing regimen for the SC formulation, the present report primarily discusses the results from the 3L + FL SC cohort.

Table 11. Dosing regimens[*1] of mosunetuzumab in Study JO40295

Route	Cohort	Cycle 1			Cycle 2	From Cycle 3 onward	Co-administered
		Day 1	Day 8	Day 15	Day 1	Day 1	
IV	Dose-expansion	1	2	60	60	30	—
SC	3L + FL SC	5	45	45	45	45	—
	2L + FL SC	5	45	45	45	45	LEN[*2]

Dose level (mg); —, not applicable; *1, in the dose-expansion and 3L + FL SC cohorts, the cycle length was 3 weeks (21 days); in the 2L + FL SC cohort, the cycle length was 3 weeks (21 days) for Cycle 1, and 4 weeks (28 days) from Cycle 2 onward; *2, LEN 20 mg was administered orally QD on Days 1 to 21 from Cycle 2 onward.

All 5 subjects enrolled in the 3L + FL SC cohort of the study received mosunetuzumab and were included in the efficacy and safety analysis populations. The efficacy evaluation in this cohort was not based on a statistical hypothesis.

Table 12 shows the independent review facility-assessed CR rate according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68), which was the primary efficacy endpoint for the 3L + FL SC cohort.

Table 12. Best overall response and CR rate (Study JO40295, independent review facility-assessed, data cut-off on March 4, 2024)

Best overall response	n (%)
	3L + FL SC cohort N = 5
CR	5 (100)
PR	0
SD	0
PD	0
NE	0
CR rate [95% CI[*]] (%)	100 [47.8, 100]

*, Clopper-Pearson method

In the 2L + FL SC and 3L + FL SC cohorts, there were no deaths from the start of treatment up to 90 days after

the end of treatment, or the start of the next treatment, whichever occurred first.

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase I/II study (CTD 5.3.5.2-2, Study GO29781 [ongoing since September 2015, data cut-off on August 27, 2021 (B11 FL RP2D cohort), February 1, 2024 (Groups D and F)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B-cell tumors[8)] (target sample size, N = 130 to 226 in the dose-escalation part [B-NHL, N = 100-166, CLL, N = 30-60] and N = 290 to 610 in the dose-expansion part [including the F2 RP2D cohort, N = 90[9)]]) to evaluate the efficacy, safety, and other characteristics of mosunetuzumab. The study in Groups D and F was conducted at 37 study sites outside Japan.

Table 13 shows the dosing regimens of mosunetuzumab in 3-week (21-day) cycles for the dose-expansion part of Group B and the dose-escalation and dose-expansion parts of Groups D and F. Treatment was continued for 8 cycles unless disease progression occurred or the discontinuation criteria were met. Patients who achieved a CR after 8 cycles were to discontinue treatment, and patients who achieved a PR or had SD after 8 cycles were to continue treatment up to Cycle 17 unless disease progression occurred or the discontinuation criteria were met. The results for the dose-expansion part in Group B are not presented here because these data had already been evaluated during the review of the application for the IV formulation of mosunetuzumab (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

8) Eligible patients for the F2 FL RP2D cohort were those with relapsed or refractory FL (Grade 1-3A) who had received ≥2 prior lines of systemic chemotherapy regimens, including an anti-CD20 monoclonal antibody and an alkylating agent.

9) Based on the PPK analysis results, the geometric mean ratio (SC/IV) of mosunetuzumab for $AUC_{0\text{-}84d}$ and $C_{trough,\ C3A}$ was estimated to be 1.06 and 1.57, respectively. If the coefficient of variation is 50%, to achieve a power of 80% at a one-sided significance level of 0.05, a sample size of 36 patients would be required to determine non-inferiority at a non-inferiority margin of 0.8. A target sample size of 90 patients was selected because it would provide sufficient statistical power to demonstrate non-inferiority in PK, and allow the CR rate to be estimated with a 95% CI width of no more than ± 11%.

Table 13. Dosing regimens* of mosunetuzumab in Study GO29781

Route	Part	Cohort		Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	From Cycle 3 onward Day 1
IV	Group B Dose-expansion	B11 FL RP2D		1.0	2.0	60	60	30
SC	Group D Dose-escalation	D1-D6		1.6-20	—	—	Same as Cycle 1 Day 1	Same as Cycle 1 Day 1
	Group D Dose-expansion	D6 (DLBCL/trFL)		20	—	—	20	20
	Group F Dose-escalation	F1		5	15	45	45	45
		F2		5	45	45	45	
		F3		5	45	90	90	
	Group F Dose-expansion	F1	F1 FL F1 DLBCL/trFL	5	15	45	45	
		F2 RP2D	F2 FL RP2D F2 DLBCL/trFL RP2D	5	45	45	45	

*, dose level (mg)

All 94 patients who were enrolled in the F2 FL RP2D cohort received mosunetuzumab and were included in the efficacy and safety analysis populations. Dose limiting toxicity (DLT) was evaluated in 27 patients in Group D and 14 patients in Group F.[10)] The PK analysis population comprised 158 patients who received at least 1 dose of the study drug and had at least 1 evaluable concentration measurement post-dose (N = 90 in the B11 FL RP2D cohort and N = 68 in the F2 FL RP2D cohort). Patients with missing blood samples prior to the Cycle 4 dose as well as those meeting other exclusion criteria were removed from the analysis,[11)] and the remaining 109 patients were included in the analysis population for $C_{trough, C3}$ (N = 61 in the B11 FL RP2D cohort and N = 48 in the F2 FL RP2D cohort).

Cycle 1 (21 days) of the dose-escalation part in Group D was defined as the DLT assessment period. Dose limiting toxicity was observed in 1 patient in the D1 (1.6 mg) cohort (Grade 4 neutropenia[12)]); however, the maximum tolerated dose (MTD) was not reached. In Cycle 1 (21 days) of the dose-escalation part in Group F, no DLT was observed, and MTD was likewise not reached.

The co-primary endpoints for the F2 FL RP2D cohort of Study GO29781 were $AUC_{0\text{-}84d}$ and $C_{trough, C3}$. Non-inferiority would be demonstrated if the lower bound of the 90% confidence interval for the geometric mean ratio (F2 FL RP2D/B11 FL RP2D) for both $AUC_{0\text{-}84d}$ and $C_{trough, C3}$ exceeded the non-inferiority margin of 0.8.

[10)] Group D (dose-escalation part) consists of Cohorts D1 (N = 6), D2 and D3 (N = 3 each), D4 and D5 (N = 4 each), and D6 (N = 7). Group F (dose-escalation part) consists of Cohorts F1 (N = 7), F2 (N = 4), and F3 (N = 3).

[11)] (1) Patients with a missing sample prior to the Cycle 4 dose or outside of the sampling window; (2) patients with a dose modification that deviates from the planned dose by >20% in Cycle 2 or 3; (3) patients with a dose delay of >7 days in total in Cycles 2 and 3.

[12)] A male patient aged 7[redacted] years, developed Grade 4 neutropenia on Cycle 1 Day 15, and mosunetuzumab treatment was suspended. The symptoms resolved 9 days after onset. A causal relationship to mosunetuzumab could not be ruled out.

The $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$ for the B11 FL RP2D and F2 FL RP2D cohorts are presented in Table 14 and Table 15, respectively. The lower bound of the 90% confidence interval for the geometric mean ratio exceeded the non-inferiority margin of 0.8 for both endpoints.

Table 14. $AUC_{0\text{-}84d}$ of mosunetuzumab

	B11 FL RP2D cohort	F2 FL RP2D cohort
N	90	68
$AUC_{0\text{-}84d}$ (μg·day/mL)	248.3 (57.8)	262.2 (50.1)
Geometric mean ratio [90% CI]	1.06 [0.92, 1.21]	

Geometric mean (geometric coefficient of variation, %)

Table 15. $C_{trough,\ C3}$ of mosunetuzumab

	B11 FL RP2D cohort	F2 FL RP2D cohort
N	61	48
$C_{trough,\ C3}$ (μg/mL)	1.7 (45.6)	2.4 (52.3)
Geometric mean ratio [90% CI]	1.39 [1.20, 1.61]	

Geometric mean (geometric coefficient of variation, %)

For efficacy data,[13)] the independent review facility-assessed CR rate based on the partially modified[14)] "Revised response criteria for malignant lymphoma" (*J Clin Oncol.* 2007;25:579-86), one of the secondary endpoints for the F2 FL RP2D cohort, is presented in Table 16.

Table 16. Best overall response and CR rate (Study GO29781, independent review facility-assessed, data cut-off on February 1, 2024)

Best overall response	n (%) F2 FL RP2D cohort N = 94
CR	55 (58.5)
PR	15 (16.0)
SD	13 (13.8)
PD	7 (7.4)
NE	0
CR rate [95% CI*] (%)	58.5 [47.9, 68.6]

*, Clopper-Pearson method

Based on the safety data,[13)] deaths reported during and up to 90 days after the end of mosunetuzumab treatment or the start of the next treatment, whichever occurred first, are summarized as follows.

There were no deaths in the dose-escalation part of Group D.

13) The results for the dose-expansion part in Group B (including the B11 FL RP2D cohort) are not presented here because these data had already been evaluated during the review of the application for the IV formulation of mosunetuzumab (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

14) Modifications include clarification of some ambiguous provisions of the "Revised response criteria for malignant lymphoma" (see below) and deletion of criteria for diseases other than FL.
Target lesions are defined as 6 lesions that meet all of the following, and all remaining lesions are to be classified as non-target lesions: 1) bi-dimensionally measurable lesions; 2) lesions from disparate regions of the body; 3) lesions should include mediastinal and retroperitoneal areas; 4) for lesions in the liver or spleen, lesions measuring ≥1 cm in both dimensions; 5) lesions receiving prior radiation therapy within 4 weeks should be excluded; and 6) biopsied lesions do not need to be selected.

In the dose-expansion part of Group D, 6 of 21 subjects (28.6%) died. Five of the 6 subjects died from disease progression, and the remaining 1 subject died of respiratory failure, for which, a causal relationship to mosunetuzumab was ruled out.

In the dose-escalation part of Group F, there were no deaths.

Among the F1 cohorts in the dose-expansion part of Group F, while there were no deaths in the F1 FL cohort, 7 of 22 subjects (31.8%) died in the F1 DLBCL/trFL cohort. Four of the 7 subjects died of disease progression. Other causes of death were COVID-19 pneumonia (2 subjects) and large intestine perforation (1 subject), for which a causal relationship to mosunetuzumab was ruled out.

Among the F2 RP2D cohorts in the dose-expansion part of Group F, 8 of 94 subjects (8.5%) died in the F2 FL RP2D cohort and 8 of 41 subjects (19.5%) died in the F2 DLBCL/trFL cohort. Seven subjects (3 subjects in the F2 FL RP2D cohort and 4 subjects in the F2 DLBCL/trFL cohort) died from disease progression. Other causes of death were COVID-19 pneumonia (2 subjects), COVID-19 (1 subject), general physical health deterioration, and hemophagocytic lymphohistiocytosis (HLH) (1 subject each) in the F2 FL RP2D cohort; and COVID-19 pneumonia (2 subjects), COVID-19 (1 subject), and septic shock (1 subject) in the F2 DLBCL/trFL cohort. Among these, a causal relationship to mosunetuzumab could not be ruled out for COVID-19 pneumonia and HLH (1 subject each) in the F2 FL RP2D cohort and COVID-19 pneumonia (1 subject) in the F2 DLBCL/trFL cohort.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase Ib/II study (CTD 5.3.5.4-1, Study CO41942 [ongoing since August 2020, data cut-off on February 1, 2024])

Deaths reported during and up to Day 90 after the end of mosunetuzumab treatment or the start of the next treatment, whichever occurred first, were as follows: 5 of 78 subjects (6.4%) in the mosunetuzumab SC group and 2 of 39 subjects (5.1%) in the mosunetuzumab IV group. The causes of death were COVID-19 pneumonia, COVID-19, general physical health deterioration, respiratory failure, and pneumonia influenzal (1 subject each) in the mosunetuzumab SC group; and COVID-19 pneumonia (2 subjects) in the mosunetuzumab IV group. Among these, a causal relationship to the study drug could not be ruled out for COVID-19 pneumonia and respiratory failure (1 subject each) in the mosunetuzumab SC group and COVID-19 pneumonia (2 subjects) in the mosunetuzumab IV group.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

Among the evaluation data submitted, PMDA determined that two studies conducted in patients with relapsed or refractory FL, which are the F2 FL RP2D cohort of the foreign phase I/II study (Study GO29781) and the 3L + FL SC cohort of the Japanese phase I study (Study JO40295), constitute the pivotal evidence for

evaluating the efficacy and safety of SC administration of mosunetuzumab. Accordingly, PMDA decided to base its review primarily on these studies.

7.R.2 Efficacy

Based on the following discussions, PMDA concluded that the efficacy of mosunetuzumab SC could be expected to be similar to that of mosunetuzumab IV in patients with relapsed or refractory FL who had received ≥2 prior regimens.

7.R.2.1 Efficacy endpoints and evaluation method

The applicant provided the following explanation regarding the efficacy endpoints established for the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295:

Based on the following factors, the efficacy of mosunetuzumab SC can be estimated by evaluating the non-inferiority of the F2 FL RP2D cohort (SC) relative to the B11 FL RP2D cohort (IV) of Study GO29781 using $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$. Accordingly, $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$ were selected as the co-primary endpoints for the F2 FL RP2D cohort of Study GO29781, and it was decided that non-inferiority would be demonstrated if the lower bound of the 90% confidence interval for the geometric mean ratio (F2 FL RP2D/B11 FL RP2D) exceeds 0.8.

- A certain level of efficacy of the IV administration of mosunetuzumab has been demonstrated in patients with relapsed or refractory FL who had received ≥2 prior regimens (see "Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg," dated November 21, 2024).
- $AUC_{0\text{-}84d}$ is an index that reflects mosunetuzumab exposure, and the results of exposure-response (ER) analysis between $AUC_{0\text{-}84d}$ and CR rate are available.
- $C_{trough,\ C3}$, similar to $AUC_{0\text{-}84d}$, is an index that reflects mosunetuzumab exposure, and measured values are available.
- Based on the ER analysis of $AUC_{0\text{-}84d}$ and the CR rate, when mosunetuzumab is administered at the approved IV dosing regimen, the $AUC_{0\text{-}84d}$ was within the plateau of the ER curve. It was estimated that a 20% decrease in $AUC_{0\text{-}84d}$ would decrease the CR rate by <1%.

It is considered that achieving CR in patients with relapsed or refractory FL who had received ≥2 prior regimens is clinically meaningful because it may lead to improvement in disease-related symptoms such as fever and night sweats (*Ann Oncol.* 2008;19:570-6). Therefore, to evaluate the efficacy of mosunetuzumab SC, the CR rate was selected as a secondary endpoint for the F2 FL RP2D cohort of Study GO29781 and the primary endpoint for the 3L + FL SC cohort of Study JO40295.

PMDA's discussion:

The applicant's justification for the endpoints used in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, as well as the non-inferiority margin set for $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$, was acceptable to a certain extent. However, because neither study prespecified success criteria for the CR rate, it

is difficult to appropriately evaluate the efficacy of mosunetuzumab SC based on the results of these studies. Therefore, it was decided that the efficacy of mosunetuzumab SC should be evaluated comprehensively based not only on the results of $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$ from Study GO29781 but also on the observed CR rates.

7.R.2.2 Efficacy evaluation results

The applicant provided the following explanation regarding the efficacy of mosunetuzumab SC:
Based on the results of $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$, the co-primary endpoints for the F2 FL RP2D cohort of Study GO29781, the non-inferiority of the F2 FL RP2D cohort relative to the B11 FL RP2D cohort with respect to $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$ was demonstrated [see Section 7.1.2.1].

There were no clear differences in the characteristics of patients between the F2 FL RP2D (SC) cohort and the B11 FL RP2D (IV) cohort of Study GO29781 that would affect the interpretation of efficacy.[15)] Therefore, the efficacy of mosunetuzumab SC was investigated by comparing the results obtained with mosunetuzumab SC and those obtained with the approved mosunetuzumab IV.

Table 17 shows the independent review facility-assessed CR rate, a secondary endpoint for the F2 FL RP2D cohort and the independent review facility-assessed CR rate, the primary endpoint for the B11 FL RP2D cohort of Study GO29781 (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024). No clear differences in the CR rate were noted between the 2 cohorts. In both cohorts, the CR rate was evaluated based on the partially modified[14)] "Revised response criteria for malignant lymphoma."

[15)] Both F2 FL RP2D and B11 FL RP2D cohorts enrolled patients with relapsed or refractory FL (Grade 1-3A) who had received ≥2 prior systemic chemotherapy regimens, including an anti-CD20 monoclonal antibody and an alkylating agent. The following factors may affect the CR rate results: (1) presence of large mass lesions ≥6 cm; (2) progression of disease within 24 months of initial therapy (POD24); (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score; (4) number of prior therapies; (5) age; (6) Ann Arbor stage; (7) Follicular Lymphoma International Prognostic Index (FLIPI) score; (8) refractory/non-refractory to anti-CD20 antibody therapy. There were no ≥10% differences between the 2 cohorts in the proportion of patients with large mass lesions ≥6 cm, the proportion of patients with POD24, the proportion of patients with an ECOG PS score of 1, and the proportion of patients with ≥3 prior regimens. In the F2 FL RP2D cohort, the proportion of patients aged ≥65 years, the proportion of patients classified as Ann Arbor stage III or IV, the proportion of patients with a FLIPI score ≥3 were higher by ≥10% compared to the B11 FL RP2D cohort, conversely, the proportion of patients refractory to anti-CD20 antibody therapy was lower by ≥10% compared to the B11 FL RP2D cohort.

Table 17. Best overall response and CR rate (Study GO29781, independent review facility-assessed)

Best overall response	n (%)	
	F2 FL RP2D cohort SC N = 94[*1]	B11 FL RP2D cohort IV N = 90[*2]
CR	55 (58.5)	52 (57.8)
PR	15 (16.0)	19 (21.1)
SD	13 (13.8)	8 (8.9)
PD	7 (7.4)	9 (10.0)
NE	0	0
CR rate [95% CI[*3]] (%)	58.5 [47.9, 68.6]	57.8 [46.9, 68.1]

*1, the number includes 4 patients with missing post-baseline tumor evaluations for whom no response assessment was performed; these patients were classified as non-CR cases; *2, the number includes 2 patients with missing post-baseline tumor evaluations for whom no response assessment was performed; these patients were classified as non-CR cases; *3, Clopper-Pearson method

Figure 3 shows the best percent change from baseline in tumor size (defined as the sum of the products of the two largest perpendicular diameters) of the target lesion.

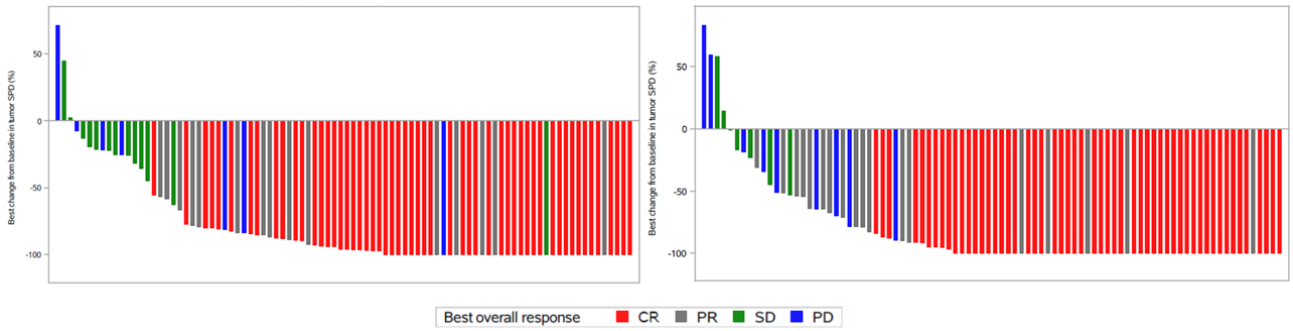


Figure 3. Best percent change from baseline in tumor size (sum of the products of the two largest perpendicular diameters) of the target lesion (Study GO29781, independent review facility-assessed, efficacy analysis population[*1])
(Left, F2 FL RP2D cohort, right, B11 FL RP2D cohort[*2])

*1, Results for the F2 FL RP2D cohort (N = 90; 4 of the 94 enrolled patients were excluded due to missing post-baseline tumor assessments) and the B11 FL RP2D cohort (N = 88; 2 of the 90 enrolled patients were excluded due to missing post-baseline tumor assessments)

*2, The figure corresponds to the left panel of Figure 8 in "Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024."

The median duration of the independent review facility-assessed CR (months) [95% CI], a secondary endpoint, was 20.8 [18.8, NE] in the F2 FL RP2D cohort and not estimable (NE) [14.6, NE] in the B11 FL RP2D cohort (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

In the F2 FL RP2D cohort of Study GO29781, no cases of tumor flare, an event that may cause pseudoprogression,[16)] were observed. Based on this finding and other factors, it was considered unlikely that patients assessed as having PD in this cohort were experiencing pseudoprogression.[17)]

[16)] Molecularly targeted drugs that act on the immune system can trigger oedema and inflammation (tumor flare) through infiltration of immune cells and infiltration-associated inflammatory cytokine release, leading to PD-like symptoms (pseudoprogression) such as an increase in tumor lesion size at the beginning of treatment (*Cancer Biol Med.* 2019;16:655-70, *Eur J Nucl Med Mol Imaging.* 2022;49:2447-9). Mosunetuzumab induces T-cell mediated immune activation, which may lead to pseudoprogression; however, currently, the relationship between mosunetuzumab and pseudoprogression is not clear.

[17)] No patients in the 3L + FL SC cohort of Study JO40295 were assessed as having PD.

Regarding the efficacy of mosunetuzumab SC in Japanese patients, Table 18 shows the independent review facility-assessed CR rates based on the Lugano criteria (primary endpoint) in the 3L + FL SC cohort of Study JO40295 and the independent review facility-assessed CR rates based on the partially modified[14] "Revised response criteria for malignant lymphoma" (primary endpoint) in the dose-expansion cohort of Study JO40295 (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024). No clear differences in CR rates between the 2 cohorts were observed.

Table 18. Best overall response and CR rate (Study JO40295, independent review facility-assessed)

Best overall response	n (%)	
	3L + FL SC cohort SC N = 5	Dose-expansion cohort IV N = 19[*1]
CR	5 (100)	13 (68.4)
PR	0	2 (10.5)
SD	0	0
PD	0	2 (10.5)
NE	0	0
CR rate [95% CI[*2]] (%)	100 [47.8, 100.0]	68.4 [43.4, 87.4]

*1, The number includes 2 patients with missing post-baseline tumor evaluations whose responses were not assessed and who were therefore classified as non-CR cases; *2, Clopper-Pearson method

Figure 4 shows the best percent change from baseline in tumor size (sum of the products of the two large perpendicular diameters) of the target lesion.

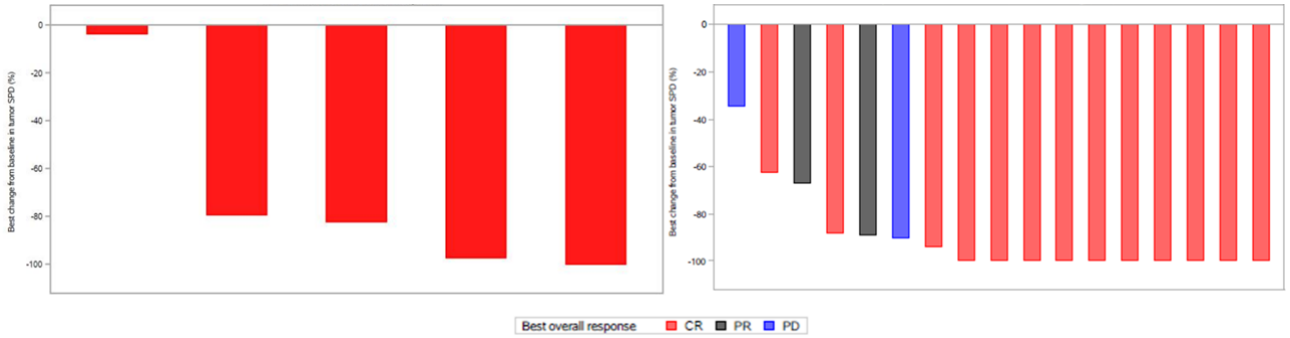


Figure 4. Best percent change from baseline in tumor size (sum of the products of the two large perpendicular diameters) of the target lesion (Study JO40295, independent review facility-assessed, efficacy analysis population[*1])
(Left, 3L + FL SC cohort, right, dose-expansion cohort[*2])

*1, Results for the 3L + FL SC cohort (N = 5) and dose-expansion cohort (N = 17; 2 patients of 19 patients were excluded due to missing post-baseline tumor evaluations, and therefore no response assessment was performed)

*2, The figure corresponds to the right panel of Figure 8 in "Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024."

PMDA's discussion:

Although there are limitations to evaluating the efficacy of mosunetuzumab SC based on the CR rates for the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295 [see Section 7.R.2.1], given the following factors, the efficacy of mosunetuzumab SC in patients with relapsed or refractory FL who had received ≥2 prior regimens is expected to be comparable to that of mosunetuzumab IV.

- $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$, the co-primary endpoints for Study GO29781 met the prespecified non-inferiority criteria [see Section 7.1.2.1].
- The F2 FL RP2D cohort and B11 FL RP2D cohort of Study GO29781 were not randomized, and the studies were conducted at different time periods. Although there are limitations in directly comparing the results of the two cohorts, there was no notable imbalance between patients in the 2 cohorts in terms of known prognostic factors for FL, and no clear difference in CR rates was noted.
- In Study JO40295, the number of Japanese patients treated with mosunetuzumab SC was limited; however, given the following factors, the efficacy of mosunetuzumab SC can also be expected in Japanese patients:
  - There are no clear differences in the diagnosis and treatment approaches to relapsed or refractory FL between Japan and other countries
  - There are no clear differences in the efficacy and safety of mosunetuzumab IV in patients with relapsed or refractory FL between Japanese and non-Japanese populations (see e.g., "Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg," dated November 21, 2024)
  - When mosunetuzumab was administered SC to Japanese patients using the proposed dosing regimen, no trend towards decreased exposure was observed in Japanese patients compared with non-Japanese patients [see Section 6.2.5]

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

On the basis of the discussions presented in the following sections, PMDA considered that adverse events of particular note when administering mosunetuzumab subcutaneously to patients with relapsed or refractory FL are the adverse events of special interest identified during the previous review of the application for the approved intravenous formulation of mosunetuzumab (CRS, neurological events including immune effector cell-associated neurotoxicity syndrome [ICANS], infections, cytopenias, tumor lysis syndrome [TLS], and tumor flare).

Although the use of mosunetuzumab SC requires particular caution with respect to the adverse events described above, PMDA concluded that mosunetuzumab SC is tolerable, provided that appropriate measures, including monitoring of the patient and management of adverse events, are taken by a physician with sufficient knowledge and experience in treating hematopoietic malignancies at a medical institution capable of providing adequate emergency care.

7.R.3.1 Safety profiles and differences in safety between Japanese and non-Japanese populations

The applicant provided the following explanation regarding the safety profiles of mosunetuzumab SC based on the safety data from the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295:

Table 19 summarizes the safety data for mosunetuzumab SC in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295.

Table 19. Summary of safety data for mosunetuzumab SC (Studies GO29781 and JO40295*)

	n (%)	
	GO29781 F2 FL RP2D cohort N = 94	JO40295 3L + FL SC cohort N = 5
All adverse events	93 (98.9)	5 (100)
Grade ≥3 adverse events	48 (51.1)	1 (20.0)
Adverse events leading to death	8 (8.5)	0
Serious adverse events	37 (39.4)	1 (20.0)
Adverse events leading to treatment discontinuation	7 (7.4)	0
Adverse events leading to dose interruption	38 (40.4)	1 (20.0)
Adverse events leading to dose reduction	0	0

*, Data cut-off dates are February 1, 2024 for the F2 FL RP2D cohort of Study GO29781 and March 4, 2024 for the 3L + FL SC cohort of Study JO40295

Table 20 summarizes adverse events with an incidence above the specified thresholds in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295.

Table 20. Adverse events with an incidence above the specified thresholds[*1] following administration of mosunetuzumab SC (Studies GO29781 and JO40295)

PT[*2]	n (%)	
	GO29781 F2 FL RP2D cohort N = 94	JO40295 3L + FL SC cohort N = 5
Adverse events of any grade		
Injection site reaction	57 (60.6)	5 (100)
Fatigue	33 (35.1)	1 (20.0)
CRS	29 (30.9)	1 (20.0)
Diarrhoea	19 (20.2)	0
Blood LDH increased	1 (1.1)	3 (60.0)
Insomnia	14 (14.9)	2 (40.0)
Constipation	13 (13.8)	2 (40.0)
Rash	10 (10.6)	2 (40.0)
Pyrexia	10 (10.6)	2 (40.0)
Dry skin	10 (10.6)	2 (40.0)
Abdominal pain	7 (7.4)	2 (40.0)
Infusion related reaction	0	2 (40.0)
Grade ≥3 adverse events		
Neutropenia	10 (10.6)	0
Neutrophil count decreased	8 (8.5)	0
Anaemia	6 (6.4)	0
Hypophosphataemia	5 (5.3)	0
Adverse events leading to death		
Malignant neoplasm progression	3 (3.2)	0
COVID-19 pneumonia	2 (2.1)	0
Adverse events leading to death for which a causal relationship to mosunetuzumab could not be ruled out		
COVID-19 pneumonia	1 (1.1)	0
Serious adverse events		
CRS	14 (14.9)	0
Serious adverse events for which a causal relationship to mosunetuzumab could not be ruled out		
CRS	14 (14.9)	0
Adverse events leading to mosunetuzumab dose interruption		
COVID-19	12 (12.8)	0
Neutropenia	5 (5.3)	0
Neutrophil count decreased	5 (5.3)	0

*1, Adverse events occurring at ≥20% and in more than 1 patient (adverse events of any grade); adverse events occurring at ≥5% and in more than 1 patient (Grade ≥3 adverse events, serious adverse events, adverse events leading to treatment discontinuation/interruption of mosunetuzumab); adverse events occurring in more than 1 patient (adverse events leading to death); *2, MedDRA ver. 26.1 (Study GO29781) and MedDRA ver. 20.1 (Study JO40295)

The applicant provided the following explanation regarding (1) differences in the safety profiles between mosunetuzumab SC and IV and (2) differences in safety of mosunetuzumab SC between Japanese and non-Japanese populations:

(1) Differences in the safety profiles between mosunetuzumab SC and IV

Table 21 summarizes the safety data of mosunetuzumab from the F2 FL RP2D cohort (SC) and the B11 RP2D cohort (IV) of Study GO29781.

Table 21. Summary of safety data of mosunetuzumab (Study GO29781)

	n (%)	
	F2 FL RP2D cohort SC N = 94	B11 FL RP2D cohort IV N = 90
All adverse events	93 (98.9)	90 (100)
Grade ≥3 adverse events	48 (51.1)	63 (70.0)
Adverse events leading to death	8 (8.5)	2 (2.2)
Serious adverse events	37 (39.4)	42 (46.7)
Adverse events leading to treatment discontinuation	7 (7.4)	4 (4.4)
Adverse events leading to dose interruption	38 (40.4)	33 (36.7)
Adverse events leading to dose reduction	0	5 (5.6)

Table 22 shows adverse events with an incidence ≥10% higher with the SC formulation (Study GO29781, F2 FL RP2D cohort) than with the IV formulation (Study GO29781, B11 FL RP2D cohort). No adverse events leading to death, serious adverse events, Grade ≥3 adverse events, adverse events leading to treatment discontinuation or dose reduction of mosunetuzumab occurred with an incidence ≥10% higher in the F2 FL RP2D cohort than in the B11 FL RP2D cohort.

**Table 22. Adverse events with an incidence ≥10% higher with mosunetuzumab SC than with IV*
(Study GO29781, F2 FL RP2D cohort [SC] and B11 FL RP2D cohort [IV])**

PT (MedDRA ver.26.1)	n (%)	
	F2 FL RP2D cohort SC N = 94	B11 FL RP2D cohort IV N = 90
Adverse events of any grade		
Injection site reaction	57 (60.6)	0
COVID-19	18 (19.1)	3 (3.3)
Adverse events leading to mosunetuzumab dose interruption		
COVID-19	12 (12.8)	2 (2.2)

*, Data cut-off dates are February 1, 2024 for the F2 FL RP2D cohort and August 27, 2021 for the B11 FL RP2D cohort

Table 23 shows adverse events with an incidence ≥10% lower with the SC formulation (Study GO29781, F2 FL RP2D cohort) than with the IV formulation (Study GO29781, B11 FL RP2D cohort). No adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation, dose interruption, or dose reduction of mosunetuzumab occurred with an incidence ≥10% lower in the F2 FL RP2D cohort than in the B11 FL RP2D cohort.

**Table 23. Adverse events with an incidence ≥10% lower with mosunetuzumab SC than with IV*
(Study GO29781, F2 FL RP2D cohort [SC] and B11 FL RP2D cohort [IV])**

PT (MedDRA ver.26.1)	n (%)	
	F2 FL RP2D cohort SC N = 94	B11 FL RP2D cohort IV N = 90
Adverse events of any grade		
CRS	29 (30.9)	41 (45.6)
Headache	16 (17.0)	28 (31.1)
Pyrexia	10 (10.6)	26 (28.9)
Hypophosphataemia	6 (6.4)	24 (26.7)
Pruritus	7 (7.4)	19 (21.1)
Hypokalaemia	6 (6.4)	17 (18.9)
Hypomagnesaemia	1 (1.1)	11 (12.2)
Grade ≥3 adverse events		
Hypophosphataemia	5 (5.3)	15 (16.7)

*, Data cut-off dates are February 1, 2024 for the F2 FL RP2D cohort and August 27, 2021 for the B11 FL RP2D cohort

Table 24 shows adverse events observed in more than 1 patient in the 3L + FL SC cohort (SC) in Study JO40295 with an incidence ≥20% higher in the 3L + FL SC cohort (SC) than in the dose-expansion cohort (IV). No adverse events leading to death, serious adverse events, Grade ≥3 adverse events, adverse events leading to treatment discontinuation, dose interruption, or dose reduction were observed in more than 1 patient in the 3L + FL SC cohort with an incidence ≥20% higher in the 3L + FL SC cohort than in the dose-expansion cohort.

**Table 24. Adverse events with an incidence ≥20% higher with mosunetuzumab SC than with IV*1, 2
(Study JO40295, 3L + FL SC cohort [SC] and dose-expansion cohort [IV])**

PT (MedDRA ver.20.1)	n (%)	
	3L + FL SC cohort SC N = 5	Dose-expansion cohort IV N = 19
Adverse events of any grade		
Injection site reaction	5 (100)	0
Blood LDH increased	3 (60.0)	0
Pyrexia	2 (40.0)	2 (10.5)
Dry skin	2 (40.0)	2 (10.5)
Insomnia	2 (40.0)	2 (10.5)
Abdominal pain	2 (40.0)	0

*1, Adverse events occurring in more than 1 patient in the 3L + FL SC cohort (SC) are listed; *2, data cut-off dates are March 4, 2024 for the 3L + FL SC cohort and October 13, 2023 for the dose-expansion cohort

(2) Differences in safety of mosunetuzumab SC between Japanese and non-Japanese patients

Table 25 shows adverse events observed in more than 1 patient with an incidence ≥10% higher in Japanese patients (3L + FL SC cohort of Study JO40295) than in non-Japanese patients (F2 FL RP2D cohort of Study GO29781). There were no adverse events leading to death, serious adverse events, Grade ≥3 adverse events, adverse events leading to treatment discontinuation, dose interruption, or dose reduction that occurred in more than 1 patient with an incidence ≥10% higher in Japanese patients than in non-Japanese patients.

Table 25. Adverse events with an incidence ≥10% higher in Japanese patients than in non-Japanese patients following mosunetuzumab SC[*1, 2] (Study GO29781 [F2 FL RP2D cohort] and Study JO40295 [3L + FL SC cohort])

PT[*3]	n (%)	
	Japanese population JO40295 (3L + FL SC cohort) N = 5	Non-Japanese population GO29781 (F2 FL RP2D cohort) N = 94
Adverse events of any grade		
Injection site reaction	5 (100)	57 (60.6)
Blood LDH increased	3 (60.0)	1 (1.1)
Insomnia	2 (40.0)	14 (14.9)
Constipation	2 (40.0)	13 (13.8)
Rash	2 (40.0)	10 (10.6)
Pyrexia	2 (40.0)	10 (10.6)
Dry skin	2 (40.0)	10 (10.6)
Abdominal pain	2 (40.0)	7 (7.4)
Infusion related reaction	2 (40.0)	0

*1, Adverse events occurring in more than 1 patient in the Japanese population are listed. *2, The data cut-off dates were February 1, 2024, for the F2 FL RP2D cohort of Study GO29781 and March 4, 2024, for the 3L + FL SC cohort of Study JO40295. *3, MedDRA ver. 26.1 (Study GO29781) and MedDRA ver. 20.1 (Study JO40295)

PMDA's discussion:

Vigilance is required for adverse events that occurred at a higher incidence in the F2 FL RP2D cohort of Study GO29781 and 3L + FL SC cohort of Study JO40295 than in the B11 FL RP2D cohort of Study GO29781 and the dose-expansion cohort of Study JO40295, respectively.

Although the number of Japanese patients evaluated was limited and it is difficult to draw a definitive conclusion regarding differences in safety of mosunetuzumab SC between Japanese and non-Japanese patients, vigilance is warranted for adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients.

Because one of the objectives in developing mosunetuzumab SC was to reduce the incidence and severity of CRS, and because the incidence of injection-site reactions was higher with mosunetuzumab SC than with mosunetuzumab IV, these adverse events are discussed in detail in the following sections.

7.R.3.2 CRS

The following sections summarize the applicant's explanation about mosunetuzumab SC-induced CRS. Unless otherwise specified, this report presents the severity (grade) of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) "cytokine release syndrome" based on the American Society for Transplantation and Cellular Therapy (ASTCT) criteria (*Biol Blood Marrow Transplant.* 2019;25:625-38). In Study GO29781, CRS severity was assessed using the Lee criteria (*Blood.* 2014;124:188-95) and then the ASTCT criteria were used in the retrospective evaluation (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024). Events for which the

severity could not be assessed using the ASTCT criteria were classified as "grade unknown" and were not included in the grade-specific summaries.[18)]

(1) Incidence of CRS in clinical studies

Ten MedDRA PTs[19)] related to CRS were tabulated.

Table 26 and Table 27 show the incidence of CRS events in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295. In either cohort, there were no CRS events leading to treatment discontinuation or dose reduction of mosunetuzumab occurring in more than 1 patient.

Table 26. Incidence of CRS events occurring in either cohort (Studies GO29781 and JO40295)

PT*	n (%)			
	GO29781 (F2 FL RP2D cohort) N = 94		JO40295 (3L + FL SC cohort) N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS	30 (31.9)	3 (3.2)	1 (20.0)	0
CRS	29 (30.9)	2 (2.1)	1 (20.0)	0
HLH	1 (1.1)	1 (1.1)	0	0
Capillary leak syndrome	1 (1.1)	0	0	0

*, MedDRA ver.26.1 (Study GO29781) and MedDRA ver.20.1 (Study JO40295)

Table 27. Incidence of serious CRS events, etc.*1 (Studies GO29781 and JO40295)

PT*2	n (%)	
	GO29781 (F2 FL RP2D cohort) N = 94	JO40295 (3L + FL SC cohort) N = 5
CRS events leading to death		
HLH	1 (1.1)	0
CRS events leading to death for which a causal relationship to mosunetuzumab could not be ruled out		
HLH	1 (1.1)	0
Serious CRS events		
CRS	14 (14.9)	0
HLH	1 (1.1)	0
Serious CRS events for which a causal relationship to mosunetuzumab could not be ruled out		
CRS	14 (14.9)	0
HLH	1 (1.1)	0
CRS events leading to dose interruption		
CRS	2 (2.1)	0

*1, Total events included in the analysis; *2, MedDRA ver.26.1 (Study GO29781) and MedDRA ver.20.1 (Study JO40295)

18) Grades as per the ASTCT-consensus grading were reported as unknown for the following CRS cases: in 1 patient, the adverse events of chills, pain, and headache were reported as CRS events; however, signs and symptoms encoded as pyrexia, high fever, or elevation of body temperature were not recorded; severity of CRS could not be evaluated using the ASTCT-consensus grading in 2 patients.

19) Preferred terms "cytokine release syndrome," "cytokine storm," "shock," "macrophage activation," "haemophagocytic lymphohistiocytosis," "histiocytosis haematophagic," "capillary leak syndrome," "capillary permeability increased," "cytokine abnormal," and "cytokine test." No MedDRA PT corresponds to "haemophagocytic lymphohistiocytosis" in MedDRA ver.20.1, and no MedDRA PT corresponds to "histiocytosis haematophagic" in MedDRA ver. 26.1.

Time to initial onset of CRS from the start of mosunetuzumab treatment (median [range]) was 2 days [1-20] for the F2 FL RP2D cohort of Study GO29781 and 10 days[20] for the 3L + FL SC cohort of Study JO40295.

Table 28 summarizes the incidence of CRS by timing of mosunetuzumab administration in the F2 FL RP2D cohort of Study GO29781.

Table 28. Incidence of CRS events by timing of mosunetuzumab administration (Study GO29781, F2 FL RP2D cohort)

	Patients developed CRS/patients received mosunetuzumab (%)			
	Cycle 1			From Cycle 2 onward
	Day 1 (5 mg)	Day 8 (45 mg)	Day 15 (45 mg)	Day 1 (45 mg)
All Grades	18/94 (19.1)	13/94 (13.8)	3/94 (3.2)	0
Grade 1	15/94 (16.0)	8/94 (8.5)	0	0
Grade 2	3/94 (3.2)	5/94 (5.3)	0	0
Grade 3	0	0	2/94 (2.1)	0
Grade 4	0	0	0	0
Grade 5	0	0	1/94 (1.1)	0

In the 3L + FL SC cohort of Study JO40295, CRS occurred in 1 of 5 patients (Grade 1) and this patient developed CRS on Cycle 1 Day 8 (45 mg).

Table 29 presents the time from administration to the onset of CRS among patients who experienced CRS following the first dose of 5 mg (Cycle 1 Day 1) or the first dose of 45 mg (Cycle 1 Day 8) in the F2 FL RP2D cohort of Study GO29781.

Table 29. Time from administration to the onset of CRS[*1] among patients who experienced CRS (Study GO29781, F2 FL RP2D cohort)

N[*2]	Time from first dose of 5 mg to the onset of CRS, n (%)			
	≤24 hours	24-48 hours	48-72 hours	≥72 hours
20	11 (55.0)	7 (35.0)	1 (5.0)	1 (5.0)
N[*3]	Time from first dose of 45 mg to the onset of CRS, n (%)			
	≤24 hours	24-48 hours	48-72 hours	≥72 hours
13	0	5 (38.5)	3 (23.1)	5 (38.5)

*1, If a patient experienced more than one event of CRS, the first occurrence of the CRS was included in the analysis; *2, the number of patients who developed CRS following administration of the first 5-mg dose; *3, the number of patients who developed CRS following administration of the first 45-mg dose.

In the 3L + FL SC cohort of Study JO40295, 1 patient developed CRS, with a time to onset of 24 to 48 hours.

Table 30 summarizes the details of patients who developed Grade ≥2 serious CRS events following treatment with mosunetuzumab in cohorts[21] treated with mosunetuzumab SC in Study GO29781. In the 3L + FL SC cohort of Study JO40295, no patients developed Grade ≥2 serious CRS events.

[20] In the 3L+FL SC cohort of Study JO40295, only 1 CRS-related event occurred in 1 patient.

[21] Group D (dose-escalation part and dose-expansion part) and Group F (dose-escalation part: F1, F2, and F3 cohorts; dose-expansion part: F1 3L FL, F1 DLBCL/trFL, F2 FL RP2D, and F2 DLBCL/trFL cohorts).

Table 30. List of patients who developed Grade ≥2 serious CRS events (Study GO29781, data cut-off on February 1, 2024)

Part/cohort	Age	Sex	PT	Max. Grade	Causal relationship	Onset[*1]	Duration (days)	Mosunetuzumab dosing change	Pharmacotherapy performed[*6]	Outcome
F2 FL RP2D cohort	7[redacted]	M	CRS	2	Related	1/9	5	No	Other symptomatic therapy	Resolved
	5[redacted]	M	CRS[*2]	3	Related	1/17	6	No	TCZ Other symptomatic therapy	Resolved
	6[redacted]	F	CRS	2	Related	1/2	1	No	TCZ Other symptomatic therapy	Resolved
	4[redacted]	F	CRS	2	Related	1/10	2	No	Other symptomatic therapy	Resolved
	6[redacted]	F	CRS	2	Related	1/11	4	No	TCZ Other symptomatic therapy	Resolved
	4[redacted]	M	HLH[*3]	5[*4]	Related	1/20	—	Discontinuation	Corticosteroid Other symptomatic therapy	Death
	7[redacted]	F	CRS	2	Related	1/5	2	No	Corticosteroid TCZ Other symptomatic therapy	Resolved
Dose-escalation D cohort	5[redacted]	F	CRS	2	Related	1/1	3	No	Other symptomatic therapy	Resolved
Dose-escalation F1 cohort	7[redacted]	F	CRS	2	Related	1/17	3	No	TCZ Other symptomatic therapy	Resolved
Dose-expansion F1 DLBCL/trFL cohort	7[redacted]	F	CRS	2	Related	1/2	3	No	TCZ Other symptomatic therapy	Resolved
	7[redacted]	M	CRS	2	Related	1/46[*5]	6	No	TCZ Other symptomatic therapy	Resolved
Dose-expansion F2 DLBCL/trFL cohort	7[redacted]	M	CRS	2	Related	1/2	2	No	Other symptomatic therapy	Resolved

—, not applicable; *1, the cycle/day in the cycle on which the patient developed CRS; *2, this patient developed pyrexia and tachycardia 1 day after administration of mosunetuzumab on Cycle 1 Day 15. On Day 17, the patient was diagnosed as having CRS and treated with TCZ, oxygen therapy, vasopressors, etc.;*3, this was classified as a CRS-related event. Five days after administration of mosunetuzumab on Cycle 1 Day 15, digestive symptoms, AST increased, blood bilirubin increased, and other events were noted. On Day 25, the patient was diagnosed as having HLH (CTCAE ver. 4.0 Grade 2) and received corticosteroids and other therapy; however, the patient died on Day 28; *4, CTCAE ver. 4.0; *5, on Day 20, the dose was interrupted due to COVID-19 (Grade 2) and on Day 44, the patient received mosunetuzumab 45 mg; *6, other symptomatic therapies included oxygen therapy, infusion, and vasopressors.

Table 31 shows clinical symptoms observed at the onset of CRS.

Table 31. Incidence[*1] of clinical symptoms and abnormal laboratory test results occurring in ≥10% of subjects at the time of CRS (Studies GO29781 and JO40295)

	n (%)	
	GO29781 (F2 FL RP2D cohort) N = 28[*2]	JO40295 (3L + FL SC cohort) N = 1
CRS		
Pyrexia	27 (96.4)	1 (100)
Hypoxia	6 (21.4)	0
Hypotension	6 (21.4)	0
Tachycardia	4 (14.3)	0
Chills	3 (10.7)	0
Headache	3 (10.7)	0

*1, The incidence of each clinical symptom and abnormal laboratory result was calculated using the number of patients experiencing CRS as the denominator; *2, in 1 patient, the adverse events of chills, pain, and headache were reported as CRS; however, because no signs and symptoms encoded as pyrexia, high fever, or elevation of body temperature were recorded, this patient was not included in the CRS tabulation. Therefore, this patient was excluded, and the remaining 28 patients were included.

(2) Premedication for CRS

The following rules regarding premedication for CRS were specified in the protocols for the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295.

- In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, in Cycle 1, corticosteroid (dexamethasone [DEX] 20 mg or methylprednisolone [mPSL] 80 mg IV or orally) was administered on the day of mosunetuzumab administration. From Cycle 2 onward, corticosteroid prophylaxis was optional; however, for patients who had developed CRS during previous administration with mosunetuzumab, corticosteroid prophylaxis was mandatory for subsequent doses until no additional CRS events were observed. The timing of corticosteroid premedication was not specified.
- Premedication with an antipyretic (acetaminophen or paracetamol), antihistamine (e.g., diphenhydramine hydrochloride) was optional. For the 3L + FL SC cohort of Study JO40295, the protocol specified that premedication should be administered 1 hour before administration of mosunetuzumab, whereas for the F2 FL RP2D cohort of Study GO29781, the timing of premedication was not specified.

(3) Treatment under inpatient conditions

The protocols for the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295 did not require treatment with mosunetuzumab SC under inpatient conditions. Among the 29 patients who developed CRS in the F2 FL RP2D cohort of Study GO29781, 15 patients[22)] required hospitalization or prolongation of hospitalization due to CRS following mosunetuzumab SC administration. In the 3L + FL SC cohort of Study JO40295, the single patient who developed CRS did not require hospitalization or prolongation of hospitalization. Case report forms were collected only for patients who were hospitalized due to CRS in the

22) There were 13 patients who developed Grade 1 or 2 CRS, 1 patient who developed Grade 3 CRS, and 1 patient who developed Grade 5 (CTCAE) HLH. This group comprised 9 patients (10 events) who developed CRS and were hospitalized, and 6 patients (6 events) with prolonged existing hospitalization. During hospitalization, 10 events required therapeutic drugs (corticosteroids, TCZ, or vasopressor) or oxygen therapy. Eight patients (8 events) required inpatient treatment after the first dose of 5 mg (hospitalization due to CRS: 5 patients [5 events], prolonged hospitalization: 3 patients [3 events]); 6 patients (6 events) required inpatient treatment after the first dose of 45 mg (hospitalization due to CRS: 4 patients [4 events], prolonged existing hospitalization: 2 patients [2 events]); and 2 patients (2 events) required inpatient treatment at or after the second dose of 45-mg dose (hospitalization due to CRS: 1 patient [1 event], prolonged existing hospitalization: 1 patient [1 event]).

F2 FL RP2D cohort of Study GO29781, and for patients who were hospitalized due to serious adverse events in the 3L + FL SC cohort of Study JO40295. Consequently, it was unknown whether the remaining 14 patients in the F2 FL RP2D cohort of Study GO29781 and 1 patient in the 3L + FL SC cohort of Study JO40295 had already been hospitalized before the onset of CRS or whether inpatient management was considered unnecessary despite the onset of CRS.

Based on the above circumstances, the applicant explained the management of CRS after administration of mosunetuzumab SC to patients with relapsed or refractory FL as follows.

Based on the results of clinical studies in which measures such as prophylactic premedication for CRS and CRS management guidance[23)] were implemented, mosunetuzumab SC was shown to be well tolerated. Accordingly, the applicant plans to include cautionary statements and information on CRS management, consistent with those used in the clinical studies, in the package insert and educational materials.

With respect to the need for inpatient management, although the package insert for mosunetuzumab IV formulation advises inpatient monitoring for 48 hours following the first dose of 60 mg, the applicant considered that, in light of the points described below, there is little need to include a specific recommendation for hospitalization during mosunetuzumab SC administration and for a certain period thereafter. Instead, it is more appropriate to advise that the need for hospitalization should be evaluated based on the patient's clinical condition.

- In Study GO29781, the incidence of CRS events tended to be lower in patients treated with mosunetuzumab SC than in those treated with mosunetuzumab IV [see Section 7.R.3.1]. Even on Cycle 1 Day 1, when the incidence of CRS was highest with mosunetuzumab SC treatment, the incidence was 19.1%.
- In the F2 FL RP2D cohort of Study GO29781, appropriate inpatient management was implemented when CRS occurred in patients managed in the outpatient setting, demonstrating that CRS was manageable.[24)]
- In treatment with mosunetuzumab SC, as with mosunetuzumab IV, institutional requirements will be established to ensure that mosunetuzumab SC will be used under an appropriate system that allows patients to contact the facility on a 24-hour basis and enables prompt hospital admission, diagnostic testing, and other necessary measures when required.

PMDA's discussion:

Cytokine release syndrome is a characteristic phenomenon likely associated with mosunetuzumab's mechanism of action. In the F2 FL RP2D cohort of Study GO29781 and 3L + FL SC cohort of Study JO40295,

23) In Study GO29781, the guidance for the management of CRS used in the F2 FL RP2D cohort was the same as that used in the B11 FL RP2D cohort, and in Study JO40295, the guidance for the management of CRS used in the 3L + FL SC cohort was the same as that used in the dose-expansion cohort (see Table 39 in Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

24) Among 15 patients (16 events) who required hospitalization due to CRS, CRS management was conducted under inpatient conditions for 6 events, whereas CRS developed under outpatient conditions and resulted in hospitalization in 10 events.

CRS associated with mosunetuzumab SC occurred at a certain frequency. In addition, because serious CRS events including deaths were also reported in multiple patients, vigilance is required for the occurrence of CRS when mosunetuzumab is administered subcutaneously. Therefore, in addition to the clinical study findings on the incidence of CRS, information on prophylaxis for CRS and specific management procedures when CRS occurs should be appropriately provided to healthcare professionals in clinical settings using the package insert and educational materials.

Furthermore, appropriate cautionary statements should be included in the package insert and other documents to ensure that mosunetuzumab SC is administered at a medical institution capable of providing adequate emergency care and under the supervision of a physician with sufficient knowledge and experience in the systemic management of critical conditions such as hematopoietic malignancies and CRS.

In addition, with respect to inpatient management during mosunetuzumab SC administration, considering the factors listed below, PMDA considers it appropriate to require hospitalization for at least 48 hours following administration of mosunetuzumab SC 5 mg on Cycle 1 Day 1.

- Since CRS is a condition that may rapidly become severe over time, immediate therapeutic intervention is required upon onset.
- Although the incidence of CRS in clinical studies tended to be lower in patients treated with mosunetuzumab SC than in those treated with mosunetuzumab IV, serious CRS was still observed at a certain frequency.
- The incidence of CRS tended to be highest on Cycle 1 Day 1 (5 mg). Among patients who developed CRS, the time from administration to the onset of CRS was generally within 48 hours [see Table 28 and Table 29].

Furthermore, given that CRS has been observed following doses administered after Day 1 in Cycle 1, the need for inpatient management should also be carefully evaluated, based on the patient's condition, not only on Cycle 1 Day 1 but also at subsequent administrations during Cycle 1. Therefore, PMDA concluded that cautionary statements to this effect should be included in the package insert and other documents

7.R.3.3 Injection site reactions

The applicant's explanation about the incidence of injection site reactions associated with mosunetuzumab SC: Events classified as PTs corresponding to MedDRA high level term (HLT) "injection site reactions" were captured.

Table 32 shows the incidence of injection site reactions in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295.

Table 32. Incidence of injection site reactions[*1] occurring in ≥5% of patients in either cohort (Studies GO29781 and JO40295)

PT[*2]	n (%)			
	GO29781 (F2 FL RP2D cohort) N = 94		JO40295 (3L + FL SC cohort) N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Injection site reactions	65 (69.1)	0	5 (100)	0
Injection site reaction	57 (60.6)	0	5 (100)	0
Injection site erythema	9 (9.6)	0	0	0
Injection site rash	5 (5.3)	0	0	0

*1, Total events included in the analysis; *2, MedDRA ver.26.1 (Study GO29781) and MedDRA ver.20.1 (Study JO40295)

There were no injection site reactions leading to death, serious injection site reactions, Grade ≥3 injection site reactions, injection site reactions leading to treatment discontinuation or dose reduction of mosunetuzumab in either cohort. Injection site reactions led to dose interruption of mosunetuzumab in 2 patients (2.1%, injection site reaction) in the F2 FL RP2D cohort of Study GO29781. No injection site reactions led to dose interruption of mosunetuzumab in the 3L + FL SC cohort of Study JO40295.

As for the incidence of injection site reactions in cohorts other than the F2 FL RP2D cohort, to which mosunetuzumab SC was administered in Study GO29781, a serious injection site reaction occurred in 1 subject (4.5%, injection site reaction) in the DLBCL/trFL cohort of Study GO29781, and a causal relationship to mosunetuzumab could not be ruled out. With the exception of the above cohort, no serious injection site reactions occurred.

PMDA's discussion:
While the number of patients who developed serious injection site reactions for which a causal relationship to mosunetuzumab SC could not be ruled out was small, given that the incidence in clinical studies was high, it was concluded that information on the incidence of injection site reactions in clinical studies should be provided to healthcare professionals through the package insert and other documents.

7.R.4 Clinical positioning and indication

The proposed indication of mosunetuzumab was specified as "relapsed or refractory follicular lymphoma." The applicant explained that the "Precautions Concerning Indication" section would be established as shown below:

- Mosunetuzumab SC should be administered to patients who relapsed after or failed to respond to at least 2 prior lines of standard-of-care regimens, including an anti-CD20 monoclonal antibody.
- Mosunetuzumab SC should be administered to patients diagnosed as having Grade 1 to 3A FL by a pathologist with sufficient experience.

Based on the evaluations described in Sections "7.R.2 Efficacy" and "7.R.3 Safety," as well as the considerations outlined below, PMDA concluded that the indication and the "Precautions Concerning Indication" section should be established as proposed in the application.

7.R.4.1 Clinical positioning of mosunetuzumab

In the established clinical practice guidelines[25] and textbooks on hematology and clinical oncology[26] published in and outside Japan, no descriptions regarding SC administration of mosunetuzumab for the treatment of relapsed or refractory FL were found.

The applicant provided the following explanation regarding the clinical positioning of mosunetuzumab SC in patients with relapsed or refractory FL as well as its differentiation from the IV formulation:
Based on the results from the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, both of which were conducted in patients with relapsed or refractory FL who had received ≥2 prior regimens, the efficacy of mosunetuzumab SC can be expected to be comparable to that of mosunetuzumab IV. In addition, the incidence of CRS, a characteristic adverse event associated with mosunetuzumab, tended to be lower with SC administration than with IV administration [see Sections 7.R.2.2 and 7.R.3.2]. Moreover, whereas IV administration requires a prolonged infusion time, SC administration can be completed in a short period, thereby reducing the burden on patients and healthcare professionals. Therefore, for these reasons, mosunetuzumab SC in patients with relapsed or refractory FL is considered to represent a new treatment option as an alternative to mosunetuzumab IV. Conversely, taking into account issues such as injection site reactions [see Section 7.R.3.3] associated with SC administration, there is still a medical need for IV administration. Regarding selection between mosunetuzumab SC and other antineoplastic agents (other than mosunetuzumab IV formulation), currently, no clinical study data comparing the clinical utility of mosunetuzumab SC with that of approved antineoplastic agents are available. Therefore, it is assumed that appropriate treatment will be selected in clinical practice taking into account the efficacy and safety of each therapy as well as the condition of individual patients. However, given that patients' access to tisagenlecleucel, a chimeric antigen receptor T-cell (CAR-T) therapy, is limited by challenges such as manufacturing lead time and related processes, and the limited number of medical institutions that can provide the therapy, it is expected that mosunetuzumab SC can serve as a treatment option for patients with relapsed or refractory FL who face challenges accessing CAR-T therapy at specialized medical institutions.

PMDA's discussion:
The applicant's explanation of the clinical positioning of mosunetuzumab SC is acceptable.

The applicant's explanation regarding the selection of mosunetuzumab SC over mosunetuzumab IV formulation is reasonable. Regarding selection between mosunetuzumab SC and other antineoplastic agents (other than mosunetuzumab IV formulation), no clinical study data comparing the clinical utility of mosunetuzumab SC with that of approved antineoplastic agents or regenerative medical products are available. Therefore, it is difficult to draw a definitive conclusion, and such decisions should be made appropriately in

[25] Practical Guidelines for Hematological Malignancies 3.1 edition (2024) (the Japanese Society of Hematology); NCCN Guidelines (v.2.2025); ESMO Guidelines (*Ann Oncol.* 2021;32:298-308); and US NCI-PDQ (dated June 13, 2025)
[26] Textbook of Hematology, Revised 4th Edition. (the Japanese Society of Hematology, 2023); Clinical Oncology Update-Essentials for Medical Oncologists, Revised 7th Edition (Japanese Society of Medical Oncology, 2024); Williams Hematology, 10th Edition (McGraw Hill Education, 2021, USA); Wintrobe's Clinical Hematology, 15th Edition (Wolters Kluwer, 2023, USA); and Principles & Practice of Oncology, 12th Edition (Wolters Kluwer, 2023, USA)

clinical practice taking into account the efficacy and safety of each therapy, as well as the condition of individual patients.

7.R.4.2 Indication and intended patient population

The applicant's explanation regarding the indication for mosunetuzumab SC and the intended patient population:

Based on the clinical utility demonstrated in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, both of which were conducted in patients with relapsed or refractory FL who had received ≥2 prior regimens, including an anti-CD20 monoclonal antibody, the applicant considers that administration of mosunetuzumab SC can be recommended for such patients. Since in both studies patients with Grade 1 to 3A FL were eligible, the proposed indication for mosunetuzumab SC was specified as "relapsed or refractory follicular lymphoma," and the following cautionary statements were included in the "Precautions Concerning Indication" section:

Precautions Concerning Indication

- Treatment with mosunetuzumab SC should be limited to patients who relapsed after or failed to respond to at least 2 prior lines of standard-of-care regimens, including an anti-CD20 monoclonal antibody.
- Mosunetuzumab SC should be administered to patients diagnosed as having Grade 1 to 3A FL by a pathologist with sufficient experience.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration for mosunetuzumab SC and proposed statements in the "Precautions Concerning Dosage and Administration" were specified as follows:

Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg/dose should be administered on Day 1, followed by 45 mg/dose on Days 8 and 15. From Cycle 2 onward, 45 mg/dose should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Precautions Concerning Dosage and Administration

- Mosunetuzumab SC should be administered to well-hydrated patients to prevent treatment-related TLS.
- Treatment-related CRS may occur. For patients receiving mosunetuzumab SC, corticosteroid should be administered prior to dosing on Days 1, 8, and 15 of Cycle 1. From Cycle 2 onward, patients who developed CRS following the previous dose should continue to receive corticosteroid premedication until CRS no longer occurs. Regardless of cycle, antihistamine and antipyretic premedications should be administered as necessary, prior to dosing.

- If any of the following adverse drug reactions occur following administration of mosunetuzumab SC, consider interrupting treatment based on the symptoms, severity, and other clinical factors, in accordance with the guidance below.

Adverse drug reaction	Severity[Note)]	Actions
CRS	Grade 1	Confirm that symptoms have resolved before administering the next dose.
	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours. The next dose should be 5 mg and consideration should be given to administering it under inpatient management.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
ICANS	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. If Grade 3 symptoms persist for >7 days, consider discontinuing treatment with mosunetuzumab SC.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Decreased platelets	<50,000/mm^3	Consider withholding treatment until platelet count recovers to ≥50,000/mm^3.
Decreased neutrophils	<1,000/mm^3	Consider withholding treatment until neutrophil count recovers to ≥1,000/mm^3.

Note) Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

- The following guidance on resuming mosunetuzumab SC after dose delays should be followed to prevent CRS.

Last dosing day/dose administered		Time since last dose administered[Note 1)]	Action for next dosing
Cycle 1	Day 1 5 mg	>2 weeks	Restart administration from Cycle 1 Day 1: 5 mg/dose on Day 1, 45 mg/dose on Day 8.[Note2)] Thereafter, 45 mg/dose on Day 1 of each subsequent cycle.
	Day 8 45 mg	≥6 weeks	Restart administration from Cycle 1 Day 8: 5 mg/dose on Day 8, 45 mg/dose on Day 15.[Note2)] Thereafter, 45 mg/dose on Day 1 of each subsequent cycle.
	Day 15 45 mg	≥6 weeks	Restart administration from Cycle 2 Day 1: 5 mg/dose on Day 1, 45 mg/dose on Day 8.[Note2)] Thereafter, 45 mg/dose on Day 1 of each subsequent cycle.
Cycle 2 onward 45 mg		≥6 weeks	Restart administration at 5 mg/dose on Day 1, 45 mg/dose on Day 8.[Note2)] Thereafter, 45 mg/dose on Day 1 of each subsequent cycle.

Note 1) If the interval since the previous dose is shorter than indicated above, resume treatment at the originally planned dosage.
Note 2) Administer corticosteroid premedication prior to treatment with mosunetuzumab SC.

- The efficacy and safety of mosunetuzumab SC in combination with other antineoplastic agents have not been established.

Based on the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that the "Dosage and administration" and "Precautions concerning dosage and administration" sections should be established as shown below.

Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15. From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Precautions Concerning Dosage and Administration

- Mosunetuzumab SC should be administered to well-hydrated patients to prevent treatment-related TLS.
- Treatment-related CRS may occur. For patients receiving mosunetuzumab SC, corticosteroid should be administered prior to dosing on Days 1, 8, and 15 of Cycle 1. From Cycle 2 onward, patients who developed CRS following the previous dose should continue to receive corticosteroid premedication until CRS no longer occurs. Regardless of cycle, antihistamine and antipyretic premedications should be administered as necessary, prior to dosing.
- If any of the following adverse drug reactions occur following administration of mosunetuzumab SC, consider interrupting treatment based on the symptoms, severity, and other clinical factors, in accordance with the guidance below.

Adverse drug reaction	Severity[Note)]	Actions
CRS	Grade 1	Confirm that symptoms have resolved before administering the next dose.
	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. The next dose should be 5 mg and consideration should be given to administering it under inpatient management.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
ICANS	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. If Grade 3 symptoms persist for >7 days, consider discontinuing treatment with mosunetuzumab SC.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Decreased platelets	<50,000/mm^3	Consider withholding treatment until platelet count recovers to ≥50,000/mm^3.
Decreased neutrophils	<1,000/mm^3	Consider withholding treatment until neutrophil count recovers to ≥1,000/mm^3.

Note) Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

- The following guidance on resuming mosunetuzumab SC after dose interruption should be followed to prevent CRS.

Last dosing day/dose administered		Time since the last dose administered[Note 1)]	Action for next dose (s)
Cycle 1	Day 1 5 mg	>2 weeks	Restart administration from Cycle 1 Day 1: 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day 15.[Notes2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 8 45 mg	≥6 weeks	Restart administration from Cycle 1 Day 8: 5 mg on Day 8, 45 mg on Day 15. [Note2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 15 45 mg	≥6 weeks	Restart administration from Cycle 2 Day 1: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] From Cycle 3 onward, 45 mg on Day 1 of each subsequent cycle.
Cycle 2 onward 45 mg		≥6 weeks	Restart administration: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] Thereafter, administer 45 mg on Day 1 of each subsequent cycle.

Note 1) If the interval since the previous dose is shorter than indicated above, resume treatment at the originally planned dose.
Note 2) Administer corticosteroid premedication prior to treatment with mosunetuzumab SC.
Note 3) Do not administer on Day 15 of the first cycle after resuming treatment.

- The efficacy and safety of mosunetuzumab SC in combination with other antineoplastic agents have not been established.

7.R.5.1 Dosing regimen for mosunetuzumab SC

The applicant provided the following rationale for the dosing regimen of mosunetuzumab SC:

Based on the factors presented below, the following proposed dosing regimen was established for the F2 FL RP2D cohort of Study GO29781: "mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15. From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles."

- Rationales for the selection of dosage and step-up dosing
  - Because the C_{max} following a 5 mg SC dose of mosunetuzumab was estimated to be comparable to the C_{max} following a 1 mg IV dose in Group B of Study GO29781, the applicant considered 5 mg to be an appropriate starting dose for SC administration.
  - In the dose-escalation part of Group F for Study GO29781, a 2-step escalation regimen (F1 cohort: in Cycle 1, 5 mg on Day 1, 15 mg on Day 8, and 45 mg on Day 15) and a 1-step escalation regimen (F2 cohort: in Cycle 1, 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day 15) were evaluated. No clear differences in the safety profiles were identified between the step-up dosing regimens.[27)] Based on the results and other data, the 1-step escalation regimen was considered appropriate.
  - The time course of blood mosunetuzumab concentrations in the F2 cohort (SC) of the Group F dose-escalation part in Study GO29781 (in Cycle 1, 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day 15; from Cycle 2 onward, 45 mg on Day 1 of each subsequent cycle) was similar to that in the B11 FL RP2D cohort (IV) of Study GO29781 (in Cycle 1, 1 mg on Day 1, 2 mg on Day 8, and 60 mg on

[27)] The incidence of adverse events was 100% (39 of 39 subjects) in the F1 cohort and 98.6% (137 of 139 subjects) in the F2 cohort. The incidence of serious adverse events was 51.3% in the F1 cohort and 38.1% in the F2 cohort; the incidence of Grade ≥3 adverse events was 61.5% in the F1 cohort and 56.8% in the F2 cohort; the incidence of adverse events leading to discontinuation of mosunetuzumab SC was 7.7% in the F1 cohort and 8.6% in the F2 cohort; the incidence of CRS was 38.5% in the F1 cohort (Grade 1, 25.6% and Grade 2, 12.8%) and 25.9% in the F2 cohort (Grade 1, 17.3%, Grade 2, 7.2%, and Grade 3, 1.4%).

Day 15; in Cycle 2, 60 mg on Day 1; from Cycle 3 onward, 30 mg on Day 1 of each subsequent cycle) [see Figure 2 in Section 6.R.1].

- Rationale for the selection of treatment cycles
  - In the development of the mosunetuzumab SC formulation, the applicant applied a rationale similar to that used for mosunetuzumab IV administration to determine the number of treatment cycles, taking into account the treatment duration of existing therapies for FL and the need to minimize the risks of chronic toxicity and cumulative toxicity. Accordingly, an 8-cycle (21 days per cycle) treatment regimen was selected, with discontinuation of treatment at the end of Cycle 8 in patients who achieved a CR, and continuation of treatment for up to 17 cycles in patients with PR or SD (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

Under the above conditions, the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC of Study JO40295 were conducted and the clinical utility of mosunetuzumab SC was demonstrated [see Sections 7.R.2 and 7.R.3]. Based on these findings and other data, the proposed dosing regimen for mosunetuzumab SC was selected based on the dosing regimens used in both cohorts.

In the F2 FL RP2D cohort of Study GO29781, among the 41 patients who achieved a CR at the end of Cycle 8 and discontinued treatment, maintenance of CR was confirmed in 24 patients.[28)] In the F2 FL RP2D cohort of Study GO29781, among the 13 patients who continued treatment beyond Cycle 9, 6 completed treatment up to Cycle 17, and 3 of these 6 patients achieved a response. In the 3L + FL SC cohort of Study JO40295, all patients achieved a CR at the end of Cycle 8, and no patients continued treatment up to Cycle 17).

Currently, as no clinical study data are available regarding the efficacy and safety of mosunetuzumab when administered in combination with other antineoplastic agents, such combination use is not recommended. Accordingly, a statement to the effect that the efficacy and safety of mosunetuzumab in combination with other antineoplastic agents have not been established was included in the "Precautions Concerning Dosage and Administration" section.

PMDA's discussion:
The applicant's explanation was acceptable. PMDA concluded that the dosage and administration of mosunetuzumab SC should be specified as follows:

Dosage and Administration
For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15. From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be

[28)] The median observation period after completion of Cycle 8 was 12.21 months in patients who achieved a CR. The efficacy results at the final evaluation timepoint (clinical data cut-off on February 1, 2024) were CR in 24 patients, PR in 6 patients, and PD in 11 patients.

discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

7.R.5.2 Prophylactic measures for mosunetuzumab SC

The applicant provided the following explanation regarding prophylactic measures to prevent CRS and TLS during administration of mosunetuzumab SC:

In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, premedication for CRS was implemented as a prophylactic measure [see Section 7.R.3.2]. Therefore, specific information on premedication for CRS consistent with the clinical study protocol will be provided through the package insert and other documents. In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, as with mosunetuzumab IV, protocols specified that patients should be rehydrated with approximately 2 to 3 L/day of fluids 24 to 48 hours prior to administration of the first mosunetuzumab dose as prophylaxis for TLS. When administering mosunetuzumab SC, it is also important to ensure adequate hydration; therefore, a statement to the effect that mosunetuzumab SC should be administered to well-hydrated patients was included in the "Precautions Concerning Dosage and Administration" section of the package insert.

PMDA's discussion:

The applicant's explanation of premedication for CRS and adequate hydration as prophylaxis for TLS was acceptable. It was concluded that the wording of the statements regarding prophylactic measures for CRS and TLS in the "Precautions Concerning Dosage and Administration" section should be adopted as proposed, as shown below:

Precautions Concerning Dosage and Administration

- Mosunetuzumab SC should be administered to well-hydrated patients to prevent treatment-related TLS.
- Treatment-related CRS may occur. For patients receiving mosunetuzumab SC, corticosteroid should be administered prior to dosing on Days 1, 8, and 15 of Cycle 1. From Cycle 2 onward, patients who developed CRS following the previous dose should continue to receive corticosteroid premedication until CRS no longer occurs. Regardless of cycle, antihistamine and antipyretic premedications may be administered as necessary, prior to dosing.

7.R.5.3 Dose modification and dosing regimen for resuming treatment with mosunetuzumab SC after dose interruption

The applicant provided the following explanation regarding the dose modification criteria and dosing regimen upon resumption of treatment with mosunetuzumab SC after dose interruption:

(1) Dose modification criteria

In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, criteria for dose interruption, reduction, and treatment discontinuation in response to adverse events were established. As adherence to these criteria allowed mosunetuzumab SC to be well-tolerated, the applicant specified the dose modification criteria in the "Precautions Concerning Dosage and Administration" section based on the clinical study protocols, with the following modifications.

- In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, the protocols specified that, for initial Grade 3 CRS (first onset), the next dose should be 5 mg if CRS occurred following a 5-mg dose, and 20 mg if CRS occurred following a 45-mg dose. Because the number of Grade 3 CRS cases following administration of mosunetuzumab SC was extremely limited and supporting data to justify dose reduction to 20 mg were insufficient, the package insert uniformly specifies a next dose of 5 mg following initial onset of Grade 3 CRS.
- In the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, no discontinuation criteria were specified in the protocol for recurrence of Grade 3 ICANS. In the clinical studies, ICANS-related events occurred in 8 patients[29)] following administration of mosunetuzumab SC. All these events were classified as non-serious Grade 1 events. However, given that Grade 3 ICANS occurred when mosunetuzumab IV was administered, the applicant considered it appropriate to adopt the same criteria used for mosunetuzumab IV administration, namely, discontinuation of treatment upon recurrence of Grade 3 ICANS.
- In the clinical studies, criteria for dose interruption, reduction, and treatment discontinuation were established for anaemia, infection, tumour flare, TLS, injection site reaction, skin disorder, hepatic dysfunction, and gastrointestinal disorder. However, in both the F2 FL RP2D cohort of Study GO29781 and 3L + FL SC cohort of Study JO40295, the incidence of serious events, events leading to treatment discontinuation, or events requiring dose modification was low and all events were manageable.[30)] Therefore, while information on the incidence of these adverse events should be included in the package insert and other documents to raise awareness, it is unnecessary to include dose interruption, reduction, and treatment discontinuation criteria for each event in the package insert.

(2) Dosing regimen for resuming therapy after dose interruption

Because CRS may recur when a certain period elapses between two doses of mosunetuzumab (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024), criteria were established in the F2 FL RP2D cohort of Study GO29781 to mitigate the risk of CRS upon resuming treatment:

(i) If the dosing interval from Day 1 to Day 8 of Cycle 1 is delayed by >2 weeks, dosing should be resumed from Cycle 1 Day 1: administer 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day15.

[29)] Lethargy (3 subjects), confusional state (2 subjects), memory impairment (1 subject), amnesia (1 subject), and dysphonia (1 subject). Among these cases, a causal relationship to mosunetuzumab SC could not be ruled out for lethargy (2 subjects) and memory impairment (1 subject).

[30)] The incidence of the following events in the F2 FL RP2D cohort of Study GO29781, hereinafter referred to as (1) (N = 94), and that in the 3L + FL SC cohort of Study JO40295, hereinafter referred to as (2) (N = 5):

- Infections: serious infections (1) 18.1% (n = 17) and (2) 20.0% (n = 1); infections leading to treatment discontinuation (1) 5.3% (n = 4) and (2) 0%; infections leading to dose interruption or reduction (1) 20.2% (n = 19) and (2) 0%
- Hepatic dysfunction: serious hepatic dysfunction (1) 1.1% (n = 1) and (2) 0%; hepatic dysfunction leading to treatment discontinuation (1) 0% and (2) 0%; hepatic dysfunction leading to dose interruption or reduction (1) 2.1% (n = 2) and (2) 0%
- Gastrointestinal disorder: serious gastrointestinal disorder (1) 1.1% (n = 1) and (2) 0%; gastrointestinal disorder leading to treatment discontinuation (1) 0% and (2) 0%; gastrointestinal disorder leading to dose interruption or reduction (1) 1.1% (n = 1) and (2) 0%
- Anaemia, injection site reaction, skin disorder, tumour flare, and TLS: there were no serious events, events leading to treatment discontinuation, dose interruption, or dose reduction in either of the cohorts (1) and (2).

(ii) If, on or after Cycle 1 Day 8, dosing is delayed by ≥6 weeks from the previous dose, treatment should be resumed using a step-up dosing regimen, as described below:

- If the previous dose was on Cycle 1 Day 8, resume treatment from Cycle 1 Day 8: administer 5 mg on Day 8, followed by 45 mg 7 days later for the Cycle 1 Day 15 dose.
- If the previous dose was on Cycle 1 Day 15 or on/after Cycle 2 Day 1, in the next cycle, administer 5 mg on Day 1 and 45 mg on Day 8; the 45-mg dose on Day 15 should be omitted.[31)]

In the F2 FL RP2D cohort of Study GO29781, which was conducted under the above criteria, none of the 10 patients who resumed treatment after a delay of ≥6 weeks from the previous dose on or after Cycle 1 Day 8 experienced CRS at the time of resumption. No patients experienced a delay of >2 weeks between Cycle 1 Day 1 and Day 8. Although the dosing regimen for resuming treatment in the 3L + FL SC cohort of Study JO40295 was different from that in the F2 FL RP2D cohort of Study GO29781,[32)] the exposure at steady state prior to treatment interruption was comparable to the exposure expected after resuming treatment according to the step-up dosing method described in (ii) above. Based on this, it was considered feasible to adopt provisions consistent with those used in the F2 FL RP2D cohort of Study GO29781.

Based on the above, the method for resuming treatment with mosunetuzumab SC following dose interruption specified in the protocol for the F2 FL RP2D cohort of Study GO29781 should be specified in the "Precautions Concerning Dosage and Administration" section.

PMDA's discussion:
The applicant's explanation is acceptable. PMDA concluded that it is appropriate to establish the dose modification criteria for treatment with mosunetuzumab SC, as well as the dosing regimen for resumption after dose interruption, as specified below.

Precautions Concerning Dosage and Administration

- If any of the following adverse drug reactions occur following administration of mosunetuzumab SC, consider interrupting treatment based on the symptoms, severity, and other clinical factors in accordance with the guidance below.

[31)] From the standpoint of steady-state exposure before dose interruption, it was decided not to administer 45 mg on Day 15 after resuming treatment following ≥6 weeks of dose interruption (Protocol version 16).
[32)] In the 3L + FL SC cohort of Study JO40295, if the dose is delayed by >6 weeks, the Day 15 dose of 45 mg was to be administered after resuming treatment. Under the protocol provision, 1 patient received 45 mg on Day 15 after resuming treatment following a delay of >6 weeks. No CRS was observed in this patient.

Adverse drug reaction	Severity[Note)]	Actions
CRS	Grade 1	Confirm that symptoms have resolved before administering the next dose.
	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. The next dose should be 5 mg and consideration should be given to administering it under inpatient management
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
ICANS	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. If Grade 3 symptoms persist for >7 days, consider discontinuing treatment with mosunetuzumab SC.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Decreased platelets	<50,000/mm^3	Consider withholding treatment until platelet count recovers to ≥50,000/mm^3.
Decreased neutrophils	<1,000/mm^3	Consider withholding treatment until neutrophil count recovers to ≥1,000/mm^3.

Note) Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

- The following guidance on resuming mosunetuzumab SC after dose delays should be followed to prevent CRS.

Last dosing day/dose administered		Time since the last dose administered[Note 1)]	Action for next dose (s)
Cycle 1	Day 1 5 mg	>2 weeks	Restart administration from Cycle 1 Day 1: 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day 15.[Notes2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 8 45 mg	≥6 weeks	Restart administration from Cycle 1 Day 8: 5 mg on Day 8, 45 mg on Day 15. [Note2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 15 45 mg	≥6 weeks	Restart administration from Cycle 2 Day 1: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] From Cycle 3 onward, 45 mg on Day 1 of each subsequent cycle.
Cycle 2 onward 45 mg		≥6 weeks	Restart administration: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] Thereafter, administer 45 mg on Day 1 of each subsequent cycle.

Note 1) If the interval since the previous dose is shorter than indicated above, resume treatment at the originally planned dose.
Note 2) Administer corticosteroid premedication prior to treatment with mosunetuzumab SC.
Note 3) Do not administer on Day 15 of the first cycle after resuming treatment.

7.R.5.4 Switching between mosunetuzumab SC and IV

The applicant provided the following explanation regarding switching between SC and IV mosunetuzumab:
In Study GO29781, 1 patient[33)] switched from SC to IV administration. No patients switched from IV to SC administration in Study GO29781 nor were there any patients who switched between SC and IV administration in Study JO40295. Because the bioequivalence of the mosunetuzumab SC and IV formulations has not been

[33)] This patient, a female aged 5[redacted] years, received mosunetuzumab SC 45 mg on Cycle 1 Day 8 and developed an injection site reaction (Grade 2) on Day 10. Treatment with mosunetuzumab SC 45 mg was continued thereafter. However, due to recurrent injection site reactions (Grade 2 on Day 17, Grade 1 on Day 25, and Grade 2 on Day 65), treatment was switched to mosunetuzumab IV 30 mg on Day 127 and was continued for a total of 17 cycles. PK analysis showed that trough concentrations before and after switching were comparable.

demonstrated, and information on the safety and PK associated with switching between SC and IV administration is limited, the applicant considers that switching between SC and IV mosunetuzumab is not recommended. However, since the incidence of adverse events reported with mosunetuzumab SC differs from that with mosunetuzumab IV, depending on the patient's condition, there may be cases where switching between SC and IV administration is necessary as a treatment option. Switching is considered acceptable only when clinically indicated. Therefore, healthcare professionals will be advised to closely monitor the patient's condition when switching between SC and IV mosunetuzumab; supporting data on switching between SC and IV from the clinical studies will also be provided.

PMDA's discussion:
The applicant's explanation is acceptable. PMDA also determined that when new information becomes available regarding safety in patients who undergo switching between SC and IV mosunetuzumab, such information should be appropriately provided to healthcare professionals in clinical practice.

7.R.6 Measures to prevent mix-ups and medication errors between the mosunetuzumab SC and IV formulations

The applicant provided details of the measures to prevent formulation mix-ups and medication errors that may occur in clinical practice where both the mosunetuzumab SC and IV formulations are used concurrently:
Although the drug solution concentrations differ (1 mg/1 mL IV formulation and 45 mg/1 mL SC formulation), each vial contains the same volume of solution. There is potential for both SC and IV formulations to be present in the same area in clinical practice, which may lead to medication errors due to mix-ups between the SC and IV formulations at the time of prescribing or dispensing.

Accordingly, the applicant plans to implement the following measures to prevent mix-ups between the SC and IV formulations.

- Distinct packaging and vial color systems will be used to distinguish between strengths and between routes of administration. The route of administration and dose level will be displayed in large font to enhance differentiation.
- Educational materials for healthcare professionals on preventing formulation mix-ups will be developed and distributed, including specific information on the appearance of the formulations described above, to increase awareness of proper product use.

PMDA's discussion:
The applicant's explanation is generally acceptable. However, it was also concluded that besides providing information through educational materials, the package insert should also include cautionary statements regarding the risk of mix-ups between the SC and IV formulations.

7.R.7 Risk management plan (draft)

The risk management plan (RMP)[34)] has been published based on the previous review for the approved IV formulation of mosunetuzumab.

In view of the discussions presented in Section "7.R.3 Safety," PMDA concluded that there is no need to change the safety and efficacy specifications in the currently published RMP[34)] for the present application.

7.R.8 Post-marketing investigations

For the reasons stated below, the applicant considers that it is not necessary at this time to conduct post-marketing surveillance immediately upon approval of the present application to evaluate the safety and other characteristics associated with switching the route of administration of mosunetuzumab in patients with relapsed or refractory FL. The applicant plans to collect safety data through routine pharmacovigilance activities and early post-marketing phase vigilance.

- Apart from injection site reactions, no new safety concerns have been identified associated with mosunetuzumab SC. The profiles of injection site reactions have already been clarified to some extent in previous clinical studies [see Section 7.R.3].
- The ongoing specified use-results survey[35)] for mosunetuzumab IV formulation, conducted to clarify the patient characteristics and risk factors associated with CRS development in patients with relapsed or refractory FL, is expected to complete enrollment of the planned number of cases.

PMDA accepted the applicant's explanation.

7.3 Adverse events and other findings observed in clinical studies

Among the clinical study results submitted for safety evaluation, deaths are discussed in Sections "7.1 Evaluation data" and "7.2 Reference data." The main adverse events other than death are described in the following sections. The results for the dose-expansion cohort of Study JO40295 and the dose-expansion part of Group B for Study GO29781 are omitted here because these data had already been evaluated during the previous review of the application for the IV formulation of mosunetuzumab (see Review Report of Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg, dated November 21, 2024).

7.3.1 Japanese phase I study (Study JO40295)

7.3.1.1 2L + FL SC cohort

Adverse events occurred in all 17 subjects. Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out also occurred in all these subjects. Adverse events occurring in ≥20% of subjects were injection site reaction (15 subjects, 88.2%), rash (10 subjects, 58.8%), CRS (8 subjects, 47.1%),

34) Risk management plan for Lunsumio for Intravenous Infusion 1 mg, Lunsumio for Intravenous Infusion 30 mg (submitted on April 1, 2025).
35) A specified use-results survey (target sample size: 120 patients) has been conducted. As of June 9, 2025, contracting procedures had been completed for 49 patients.

neutropenia (7 subjects, 41.2%), neutrophil count decreased (6 subjects, 35.3%), white blood cell count decreased (5 subjects, 29.4%), leukopenia (5 subjects, 29.4%), and ALT increased (4 subjects, 23.5%).

Serious adverse events occurred in 5 of 17 subjects (29.4%). The only serious adverse event reported in more than 1 subject was rash (2 subjects, 11.8%), for which a causal relationship to mosunetuzumab SC was ruled out.

No adverse events led to treatment discontinuation of mosunetuzumab SC.

7.3.1.2 3L + FL SC cohort

Adverse events occurred in all 5 subjects. Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out also occurred in all these subjects. Adverse events occurring in ≥30% of subjects were injection site reaction (5 subjects, 100%); blood LDH increased (3 subjects, 60.0%); pyrexia, rash, dry skin, abdominal pain, constipation, infusion related reaction, and insomnia (2 subjects each, 40.0%).

Serious adverse events occurred in 1 of 5 subjects (20.0%). There were no serious adverse events that occurred in more than 1 subject.

No adverse events led to treatment discontinuation of mosunetuzumab SC.

7.3.2 Foreign phase I/II study (Study GO29781)

7.3.2.1 Dose-escalation part of Group D

Adverse events occurred in 26 of 27 subjects (96.3%). Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out occurred in 20 of 27 subjects (74.1%). Adverse events occurring in ≥10% of subjects were injection site reaction (10 subjects, 37.0%); CRS (9 subjects, 33.3%); neutropenia (7 subjects, 25.9%); fatigue and headache (6 subjects each, 22.2%); constipation, cough, and hypokalaemia (5 subjects each, 18.5%); abdominal pain, pruritus, hypophosphataemia, and hypertension (4 subjects each, 14.8%); pyrexia, diarrhoea, nausea, sinusitis, arthralgia, neutrophil count decreased, and anaemia (3 subjects each, 11.1%).

Serious adverse events occurred in 4 of 27 subjects (14.8%). There were no serious adverse events that occurred in more than 1 subject.

Adverse events led to treatment discontinuation of mosunetuzumab SC in 1 of 27 subjects (3.7%).

7.3.2.2 Dose-expansion part of Group D

Adverse events occurred in 20 of 21 subjects (95.2%). Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out occurred in 19 of 21 subjects (90.5%). Adverse events occurring in ≥10% of subjects were injection site reaction (17 subjects, 81.0%); fatigue (8 subjects, 38.1%); CRS (7 subjects,

33.3%); malignant neoplasm progression (5 subjects, 23.8%); constipation, blood creatinine increased, and hypotension (4 subjects each, 14.3%); pyrexia, diarrhoea, headache, neutropenia, dyspnoea, and hypokalaemia (3 subjects each, 14.3%).

Serious adverse events occurred in 12 of 21 subjects (57.1%). Serious adverse events occurring in more than 1 subject were malignant neoplasm progression (5 subjects, 23.8%); CRS, diarrhoea, and tumour flare (2 subjects each, 9.5%). Among these events, a causal relationship to mosunetuzumab SC could not be ruled out for CRS and tumour flare (2 subjects each).

Adverse events leading to treatment discontinuation of mosunetuzumab SC occurred in 1 of 21 subjects (4.8%).

7.3.2.3 Dose-escalation part of Group F

Adverse events occurred in all subjects (7, 4, and 3 subjects in the F1, F2, and F3 cohorts, respectively). Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out occurred in 6 of 7 subjects (85.7%), 1 of 4 subjects (25.0%), and 3 of 3 subjects (100%) in the F1, F2, and F3 cohorts, respectively. Adverse events occurring in ≥2 subjects in each cohort were injection site reaction (3 subjects, 42.9%); fatigue, rash, erythema, and CRS (2 subjects each, 28.6%) in the F1 cohort; pyrexia, neutropenia, and anaemia (2 subjects each, 50.0%) in the F2 cohort; and injection site reaction (3 subjects, 100%); pyrexia, rash, and hypophosphataemia (2 subjects each, 66.7%) in the F3 cohort.

Serious adverse events occurred in 3 of 7 subjects (42.9%), 1 of 4 subjects (25.0%), and 2 of 3 subjects (66.7%) in the F1, F2, and F3 cohorts, respectively. None of these serious adverse events occurred in more than 1 subject.

No adverse events led to treatment discontinuation of mosunetuzumab SC.

7.3.2.4 Dose-expansion part of Group F

7.3.2.4.1 F1 cohort

Adverse events occurred in all subjects (22 and 10 subjects in the DLBCL/trFL and FL cohorts, respectively). Adverse events for which a causal relationship to mosunetuzumab SC could not be ruled out occurred in 20 of 22 subjects (90.9%) in the DLBCL/trFL cohort and 9 of 10 subjects (90.0%) in the FL cohort. Adverse events occurring in ≥20% of subjects were injection site reaction (14 subjects, 63.6%), CRS (9 subjects, 40.9%), pyrexia (7 subjects, 31.8%), neutrophil count decreased (5 subjects, 22.7%) in the DLBCL/trFL cohort; and injection site reaction (7 subjects, 70.0%), fatigue (5 subjects, 50.0%), CRS (4 subjects, 40.0%), headache (3 subjects, 30.0%); chills, diarrhoea, abdominal pain, upper respiratory tract infection, pneumonia, dry skin, myalgia, dizziness, hypoaesthesia, dyspnoea, rhinorrhoea, and hypokalaemia (2 subjects each, 20.0%) in the FL cohort.

Serious adverse events occurred in 15 of 22 subjects (68.2%) in the DLBCL/trFL cohort and 2 of 10 subjects (20.0%) in the FL cohort. Serious adverse events occurring in more than 1 subject were CRS (6 subjects, 27.3%), malignant neoplasm progression (4 subjects, 18.2%), COVID-19 (2 subjects, 9.1%) in the DLBCL/trFL cohort and pneumonia (2 subjects, 20.0%) in the FL cohort. Among these events, those for which a causal relationship to mosunetuzumab SC could not be ruled out were CRS (6 subjects, 27.3%) in the DLBCL/trFL cohort and pneumonia (1 subject, 10.0%) in the FL cohort.

Adverse events led to treatment discontinuation of mosunetuzumab SC in 3 of 22 subjects (13.6%) in the DLBCL/trFL cohort (none in the FL cohort). Adverse events leading to treatment discontinuation of mosunetuzumab SC in more than 1 subject were COVID-19 (2 subjects, 9.1%) in the DLBCL/trFL cohort, and a causal relationship to mosunetuzumab SC was ruled out in all cases.

7.3.2.4.2 F2 RP2D cohort

Adverse events occurred in 40 of 41 subjects (97.6%) in the DLBCL/trFL cohort and 93 of 94 subjects (98.9%) in the FL cohort (F2 FL RP2D cohort). Among these events, a causal relationship to mosunetuzumab SC could not be ruled out in 37 of 41 subjects (90.2%) in the DLBCL/trFL cohort and 86 of 94 subjects (91.5%) in the FL cohort. Adverse events occurring in ≥10% of subjects were injection site reaction (28 subjects, 68.3%); fatigue and CRS (9 subjects each, 22.0%); constipation, rash, headache, and insomnia (8 subjects each, 19.5%); pyrexia, COVID-19, back pain, neutropenia, anaemia, and cough (6 subjects each, 14.6%); and diarrhoea (5 subjects, 12.2%) in the DLBCL/trFL cohort. In the FL cohort, injection site reaction (57 subjects, 60.6%), fatigue (33 subjects, 35.1%), CRS (29 subjects, 30.9%), diarrhoea (19 subjects, 20.2%), COVID-19 (18 subjects, 19.1%), headache (16 subjects, 17.0%), insomnia (14 subjects, 14.9%); nausea, constipation, and neutropenia (13 subjects each, 13.8%); arthralgia and anaemia (12 subjects each, 12.8%); back pain and cough (11 subjects each, 11.7%); chills, pyrexia, oedema peripheral, rash, rash maculo-papular, and dry skin (10 subjects each, 10.6%) were reported.

Serious adverse events occurred in 15 of 41 subjects (36.6%) in the DLBCL/trFL cohort and 37 of 94 subjects (39.4%) in the FL cohort. In the DLBCL/trFL cohort, serious adverse events occurring in more than 1 subject were COVID-19 pneumonia and malignant neoplasm progression (4 subjects each, 9.8%); CRS (3 subjects, 7.3%); COVID-19 (2 subjects, 2.1%). In the FL cohort, CRS (14 subjects, 14.9%); COVID-19 pneumonia (4 subjects, 4.3%); malignant neoplasm progression (3 subjects, 3.2%); COVID-19, cytomegalovirus (CMV) infection reactivation, device related infection, hyperglycaemia, general physical health deterioration, sepsis, pyrexia, febrile neutropenia (2 subjects each, 2.1%) were reported. Among these events, those for which a causal relationship to mosunetuzumab SC could not be ruled out were CRS (3 subjects) and COVID-19 pneumonia (1 subject) in the DLBCL/trFL cohort, and CRS (14 subjects), COVID-19 pneumonia, device related infection, sepsis, and febrile neutropenia (1 subject each) in the FL cohort.

Adverse events leading to treatment discontinuation of mosunetuzumab SC occurred in 5 of 41 subjects (12.2%) in the DLBCL/trFL cohort, and 7 of 94 subjects (7.4%) in the FL cohort. Adverse events leading to

treatment discontinuation of mosunetuzumab SC in more than 1 subject were COVID-19 pneumonia (2 subjects in the DLBCL/trFL cohort and 3 subjects in the FL cohort). Among these events, a causal relationship to mosunetuzumab SC could not be ruled out for COVID-19 pneumonia (1 subject each in both cohorts).

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 inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that the efficacy of mosunetuzumab SC for relapsed or refractory FL is expected to be comparable to that of the IV formulation, and its safety is considered acceptable in view of its benefits. The drug product is classified as a powerful drug. Mosunetuzumab SC is clinically meaningful as a treatment option for patients with relapsed or refractory FL. PMDA considers that several issues including efficacy, safety, and post-marketing investigations require further evaluation.

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

Review Report (2)

October 15, 2025

Product Submitted for Approval

Brand Name	Lunsumio for Subcutaneous Injection 5 mg Lunsumio for Subcutaneous Injection 45 mg
Non-proprietary Name	Mosunetuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	March 14, 2025

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

In view of the discussions presented in Section "7.R.2 Efficacy" in Review Report (1), PMDA concluded that mosunetuzumab SC can be expected to demonstrate efficacy in patients with relapsed or refractory FL comparable to that of the IV formulation, based on the results obtained in the F2 FL RP2D cohort of Study GO29781 and the 3L + FL SC cohort of Study JO40295, as summarized below.

- The $AUC_{0\text{-}84d}$ and $C_{trough,\ C3}$, the co-primary endpoints for Study GO29781, met the prespecified non-inferiority criteria.
- In the F2 FL RP2D cohort and B11 FL RP2D cohort of Study GO29781, there was no notable imbalance between patients in the 2 cohorts in terms of known prognostic factors associated with outcomes in FL, and no clear difference in CR rates was noted.
- In Study JO40295, although the number of Japanese patients treated with mosunetuzumab SC was limited, no clear differences in CR rates were noted between the 3L + FL SC cohort and the dose-expansion cohort.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

In view of the discussions presented in Section "7.R.3 Safety" in Review Report (1), PMDA considered that

adverse events of particular note when administering mosunetuzumab subcutaneously to patients with relapsed or refractory FL are the adverse events of special interest identified during the previous review of the intravenous formulation (CRS, neurological events including ICANS, infections, cytopenias, TLS, and tumour flare). PMDA concluded that patients should be able to tolerate mosunetuzumab SC, provided that appropriate measures, including monitoring of the patient and management of adverse events, are taken by a physician with sufficient knowledge and experience in treating hematopoietic malignancies at a medical institution capable of providing adequate emergency care.

Regarding CRS, based on the discussion in Section "7.R.3.2 CRS" in Review Report (1), PMDA considers that the following issues should be addressed:

- In addition to the clinical study findings on the incidence of CRS, information on prophylaxis for CRS and specific management procedures when CRS occurs should be appropriately provided to healthcare professionals in clinical settings using the package insert and educational materials.
- Appropriate cautionary statements should be included in the package insert and other documents to ensure that mosunetuzumab SC is administered at a medical institution capable of providing adequate emergency care and under the supervision of a physician with sufficient knowledge and experience in the systemic management of critical conditions such as hematopoietic malignancies and CRS.
- Patients should be hospitalized for at least 48 hours after administration of the first dose. For other doses, the need for inpatient treatment should be carefully evaluated based on the patient's condition.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indication

In view of the discussions presented in Section "7.R.4 Clinical positioning and indication" of Review Report (1), PMDA concluded that the indication for mosunetuzumab SC and the statements in the "Precautions Concerning Indication" section should be as proposed below.

Indication

Relapsed or refractory follicular lymphoma

Precautions Concerning Indication

- Mosunetuzumab SC should be administered to patients who relapsed after or failed to respond to at least 2 prior lines of standard-of-care regimens including an anti-CD20 monoclonal antibody.
- Mosunetuzumab SC should be administered to patients diagnosed as having Grade 1 to 3A FL by a pathologist with sufficient experience.

At the Expert Discussion, the expert advisors supported PMDA's conclusion shown above.

1.4 Dosage and administration

In view of the discussions presented in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration of mosunetuzumab SC and the statements in the "Precautions Concerning Dosage and Administration" section should be as follows.

Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15. From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Precautions Concerning Dosage and Administration

- Mosunetuzumab SC should be administered to well-hydrated patients to prevent treatment-related TLS.
- Treatment-related CRS may occur. For patients receiving mosunetuzumab SC, corticosteroid should be administered prior to dosing on Days 1, 8, and 15 of Cycle 1. From Cycle 2 onward, patients who developed CRS following the previous dose should continue to receive corticosteroid premedication until CRS no longer occurs. Regardless of cycle, antihistamine and antipyretic premedications should be administered as necessary, prior to dosing.
- If any of the following adverse drug reactions occur following administration of mosunetuzumab SC, consider interrupting treatment based on the symptoms, severity, and other clinical factors, in accordance with the guidance below.

Adverse drug reaction	Severity[Note)]	Actions
CRS	Grade 1	Confirm that symptoms have resolved before administering the next dose.
	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. The next dose should be 5 mg and consideration should be given to administering it under inpatient management.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
ICANS	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. If Grade 3 symptoms persist for >7 days, consider discontinuing treatment with mosunetuzumab SC.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Decreased platelets	<50,000/mm^3	Consider withholding treatment until platelet count recovers to ≥50,000/mm^3.
Decreased neutrophils	<1,000/mm^3	Consider withholding treatment until neutrophil count recovers to ≥1,000/mm^3.

Note) Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

- The following guidance on resuming mosunetuzumab SC after dose interruption should be followed to prevent CRS.

Last dosing day/dose administered		Time since last dose administered[Note1)]	Action for next dosing
Cycle 1	Day 1 5 mg	>2 weeks	Restart administration from Cycle 1 Day 1: 5 mg on Day 1, 45 mg on Day 8, and 45 mg on Day 15.[Notes2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 8 45 mg	≥6 weeks	Restart administration from Cycle 1 Day 8: 5 mg on Day 8, 45 mg on Day 15. [Note2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 15 45 mg	≥6 weeks	Restart administration from Cycle 2 Day 1: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] From Cycle 3 onward, 45 mg on Day 1 of each subsequent cycle.
Cycle 2 onward 45 mg		≥6 weeks	Restart administration: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] Thereafter, administer 45 mg on Day 1 of each subsequent cycle.

Note 1) If the interval since the previous dose is shorter than indicated above, resume treatment at the originally planned dosage.
Note 2) Administer corticosteroid premedication prior to treatment with mosunetuzumab SC.
Note 3) Do not administer on Day 15 of the first cycle after resuming treatment.

- The efficacy and safety of mosunetuzumab SC in combination with other antineoplastic agents have not been established.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

Based on the above, PMDA instructed the applicant to establish the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as shown above. The applicant agreed with the instruction.

1.5 Measures to prevent mix-ups and medication errors between mosunetuzumab SC and IV formulations

In view of the discussions presented in Section "7.R.6 Measures to prevent mix-ups and medication errors between the mosunetuzumab SC and IV formulations" in Review Report (1), PMDA concluded that it is appropriate to include a cautionary statement in the package insert regarding such mix-ups between the SC and IV formulations in addition to the measures planned by the applicant to prevent such mix-ups, as shown below.

- Distinct packaging and vial color systems will be used for each strength and route of administration. The route of administration and dose will be displayed in large font to enhance differentiation.
- Educational materials for healthcare professionals on preventing formulation mix-ups will be developed and distributed, including information on the appearance of the formulations described above, together with precautions regarding proper use.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above, and the following comments were made by the expert advisors.

- In addition to developing educational materials, information on the risk of mix-ups between the SC and IV formulations needs to be provided to healthcare professionals at the time of the first delivery of the product and other appropriate opportunities.

- A framework should be established to ensure the prompt collection of information and the implementation of preventive measures in the event of a medication administration error.

Based on the above, PMDA instructed the applicant not only to include a cautionary statement in the package insert regarding the risk of mix-ups between the SC and IV formulations, but also to appropriately implement measures for providing information to healthcare professionals to raise awareness of such risks, and to establish a framework for collecting and disseminating information related to medication errors. The applicant responded that it would comply with these instructions.

1.6 Risk Management Plan (draft) and post-marketing investigations

In view of the discussions presented in Section "7.R.7 Risk management plan (draft)" in Review Report (1), PMDA concluded that there is no need to change the safety and efficacy specifications in the currently published RMP (Table 33) for the RMP (draft) of mosunetuzumab SC.

Table 33. Safety and efficacy specifications in the RMP (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• CRS • Neurological events (including ICANS) • Infections • Tumour flare • TLS • Cytopenias	None	None
Efficacy specification		
None		

No new changes for the present application

In view of the discussions presented in Section "7.R.8 Post-marketing investigations" in Review Report (1), PMDA concluded that it is not necessary at this time for the applicant to conduct post-marketing surveillance immediately upon approval of the present application to evaluate the safety and other characteristics associated with switching the route of administration of mosunetuzumab in patients with relapsed or refractory FL. The collection of safety data through routine pharmacovigilance activities and early post-marketing phase vigilance is considered sufficient.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

In view of the discussion above, PMDA has concluded that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 34 as part of the RMP (draft) for mosunetuzumab SC.

Table 34. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the RMP (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance (IV formulation) • Early post-marketing phase vigilance (SC formulation) • Use-results survey in patients with relapsed or refractory FL (IV formulation)	None	• Provision of information gathered during early post-marketing phase vigilance (IV formulation) • Provision of information gathered during early post-marketing phase vigilance (SC formulation) • Preparation and provision of educational materials for healthcare professionals Preparation and provision of educational materials for patients • Establish the conditions for use

Underline: planned activities for the new route of administration to be added

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

2.1 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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

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

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

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication, dosage and administration, with the following approval conditions, provided that after the product launch, cautionary statements are included in the package insert to highlight the risks, and information on proper use is adequately disseminated, and that mosunetuzumab SC will be used in compliance with the recommended conditions of use at a medical institution capable of providing adequate emergency care under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (December 26, 2032).

Indication

Relapsed or refractory follicular lymphoma

Dosage and Administration

For adults, mosunetuzumab (genetical recombination) should be administered subcutaneously in 21-day cycles. In Cycle 1, 5 mg should be administered on Day 1, followed by 45 mg on Days 8 and 15. From Cycle 2 onward, 45 mg should be administered on Day 1 for up to 8 cycles. At the end of Cycle 8, treatment should be discontinued in patients who have achieved a complete response, whereas patients with stable disease or a partial response should continue treatment for up to a total of 17 cycles.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, prior to marketing, to ensure that the product will be used under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies, in a medical setting where appropriate measures, including management of cytokine release syndrome, are taken, and at a medical institution capable of providing adequate emergency care.

Warnings

1. Mosunetuzumab SC should be administered only to patients who are considered eligible for its use under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies at a medical institution capable of providing adequate emergency care. Prior to the start of therapy, the efficacy and risks associated with mosunetuzumab SC should be thoroughly explained to the patient or his/her family members and consent must be obtained.
2. Severe cytokine release syndrome can occur. Hemophagocytic lymphohistiocytosis can occur, and cases resulting in death have been reported. At the beginning of treatment, in particular, mosunetuzumab SC should be administered under inpatient management or in another suitable medical setting. Prophylactic measures, including premedication for cytokine release syndrome, should be taken. The patient should be closely monitored. If any abnormality occurs, appropriate action should be taken in accordance with the guidance materials, including the Cytokine Release Syndrome Management Guidance, provided by the Marketing Authorization Holder.
3. Severe neurologic events (including immune effector cell-associated neurotoxicity syndrome) can occur. The patient should be closely monitored. If any abnormality occurs, appropriate action should be taken in accordance with the guidance materials, including the Management Guidance for Immune Effector Cell-associated Neurotoxicity Syndrome, provided by the Marketing Authorization Holder.

Contraindication

Patients with a history of hypersensitivity to any component of this product

Precautions Concerning Indication

1. Mosunetuzumab SC should be administered to patients who relapsed after or failed to respond to at least 2 prior lines of standard-of-care regimens, including an anti-CD20 monoclonal antibody.

2. Mosunetuzumab SC should be administered to patients diagnosed as having Grade 1 to 3A follicular lymphoma by a pathologist with sufficient experience.

Precautions Concerning Dosage and Administration

1. Mosunetuzumab SC should be administered to well-hydrated patients to prevent treatment-related tumor lysis syndrome.
2. Treatment-related cytokine release syndrome may occur. For patients receiving mosunetuzumab SC, corticosteroid should be administered prior to dosing on Days 1, 8, and 15 of Cycle 1. From Cycle 2 onward, patients who developed cytokine release syndrome following the previous dose should continue to receive corticosteroid premedication until cytokine release syndrome no longer occurs. Regardless of cycle, antihistamine and antipyretic premedications should be administered as necessary, prior to dosing.
3. If any of the following adverse drug reactions occur following administration of mosunetuzumab SC, consider interrupting treatment based on the symptoms, severity, and other clinical factors in accordance with the guidance below.

Adverse drug reaction	Severity[Note)]	Actions
Cytokine release syndrome	Grade 1	Confirm that symptoms have resolved before administering the next dose.
	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. The next dose should be 5 mg and consideration should be given to administering it under inpatient management.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Immune effector cell-associated neurotoxicity syndrome	Grade 2	Confirm that symptoms have resolved for ≥72 hours before administering the next dose.
	Grade 3	Confirm that symptoms have resolved for ≥72 hours before administering the next dose. If Grade 3 symptoms persist for >7 days, consider discontinuing treatment with mosunetuzumab SC.
	Grade 3 (recurrence)	Discontinue treatment with mosunetuzumab SC.
	Grade 4	
Decreased platelets	<50,000/mm^3	Consider withholding treatment until platelet count recovers to ≥50,000/mm^3.
Decreased neutrophils	<1,000/mm^3	Consider withholding treatment until neutrophil count recovers to ≥1,000/mm^3.

Note) Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading.

4. The following dosing instructions for resuming mosunetuzumab SC after dose interruption should be followed to prevent cytokine release syndrome.

Last dosing day/dose administered		Time since last dose administered[Note1)]	Action for next dosing
Cycle 1	Day 1 5 mg	>2 weeks	Restart administration from Cycle 1 Day 1: 5 mg on Day 1, 45 mg on Day 8 and 45 mg on Day 15.[Notes2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 8 45 mg	≥6 weeks	Restart administration from Cycle 1 Day 8: 5 mg on Day 8, 45 mg on Day 15. [Note2)] From Cycle 2 onward, administer 45 mg on Day 1 of each subsequent cycle.
	Day 15 45 mg	≥6 weeks	Restart administration from Cycle 2 Day 1: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] From Cycle 3 onward, 45 mg on Day 1 of each subsequent cycle.
Cycle 2 onward 45 mg		≥6 weeks	Restart administration: 5 mg on Day 1, 45 mg on Day 8.[Notes2),3)] Thereafter, administer 45 mg on Day 1 of each subsequent cycle.

Note 1) If the interval since the previous dose is shorter than indicated above, resume treatment at the originally planned dosage.
Note 2) Administer corticosteroid premedication prior to treatment with mosunetuzumab SC.
Note 3) Do not administer on Day 15 of the first cycle after restarting treatment.

5. The efficacy and safety of mosunetuzumab SC in combination with other antineoplastic agents have not been established.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
Application	application for marketing approval
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under concentration-time curve
$AUC_{0\text{-}21d}$	AUC from time zero to 21 days
$AUC_{0\text{-}42d}$	AUC from time zero to 42 days
$AUC_{0\text{-}84d}$	AUC from time zero to 84 days
$AUC_{C1\text{-}3}$	cumulative AUC over the first 3 treatment cycles
B-NHL	B-cell non-Hodgkin lymphoma
CAR-T	chimeric antigen receptor T-cell
CD	cluster of differentiation
CI	confidence interval
CL	total body clearance
C_{max}	maximum concentration
$C_{max0\text{-}42d}$	maximum concentration from 0 to 42 days
CMV	cytomegalovirus
COVID-19	corona virus infectious disease emerged in 2019
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough,\ C3}$	serum trough concentration at steady state, approximated by Cycle 3
CYP	cytochrome P450
DEX	dexamethasone
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
HLH	hemophagocytic lymphohistiocytosis
HLT	high level term
ICANS	immune effector cell-associated neurotoxicity syndrome
IL	interleukin
IV	intravenous
LDH	lactate dehydrogenase
LEN	lenalidomide hydrate
Lunsumio	mosunetuzumab subcutaneous formulation
MedDRA	Medical Dictionary for Regulatory Activities
Mosunetuzumab	mosunetuzumab (genetical recombination)
Mosunetuzumab ／LEN	mosunetuzumab in combination with lenalidomide hydrate
mPSL	methylprednisolone
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-cell Lymphomas

NCI-PDQ	National Cancer Institute - Physician Data Query
NE	not estimable
NHL	non-Hodgkin’s lymphoma
PD	progressive disease
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
POD24	progression of disease within 24 months of initial therapy
PPK	population pharmacokinetics
PR	partial response
Practical Guidelines for Hematological Malignancies	Practical Guidelines for Hematological Malignancies 3.1 edition (2024) (the Japanese Society of Hematology)
PS	performance status
PT	preferred term
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
RIT	rituximab (genetical recombination)
RMP	risk management plan
$ROmax_{0\text{-}42d}$	maximum receptor occupancy from time equal to 0 to 42 days post-dose
RP2D	recommended Phase II dose
RS	Richter’s syndrome
SC	subcutaneous
SD	stable disease
SLL	small lymphocytic lymphoma
TCZ	tocilizumab (genetical recombination)
TLS	tumor lysis syndrome
t_{max}	time to reach maximum concentration
Tr FL	transformed follicular lymphoma