Review Report

July 18, 2018

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	Poteligeo Injection 20 mg
Non-proprietary Name	Mogamulizumab (Genetical Recombination) (JAN*)
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	November 30, 2017
Dosage Form/Strength	Solution for injection containing 20 mg of mogamulizumab (genetical recombination) per vial (5 mL)
Application Classification	Prescription drug, (4) Drug with a new indication (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Drug Designation No. 298 of 2013 [*25 yaku*], PSEHB/PED Notification No. 0315-2 dated March 15, 2013, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded the product has efficacy in the treatment of relapsed or refractory cutaneous T-cell 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 indications and dosage and administration, with the following condition.

Indications

CCR4-positive adult T-cell leukemia lymphoma

Relapsed or refractory CCR4-positive peripheral T-cell lymphoma

Relapsed or refractory ~~CCR4-positive~~ cutaneous T-cell lymphoma

(Strikethrough denotes deletion.)

Dosage and Administration

CCR4-positive adult T-cell leukemia lymphoma

The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses.

The usual adult dosage in combination with other antineoplastics is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once every 2 weeks for 8 doses.
Mogamulizumab should be used in combination with other antineoplastics for chemotherapy-naïve patients.

Relapsed or refractory CCR4-positive peripheral T-cell lymphoma
~~Relapsed or refractory CCR4-positive cutaneous T-cell lymphoma~~
The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses.

Relapsed or refractory cutaneous T-cell lymphoma
The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 5 doses and once every 2 weeks for subsequent doses.

(Strikethrough and underline denote deletion and addition, respectively.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

May 24, 2018

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

Product Submitted for Approval

Brand Name	Poteligeo Injection 20 mg
Non-proprietary Name	Mogamulizumab (Genetical Recombination)
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	November 30, 2017
Dosage Form/Strength	Solution for injection containing 20 mg of mogamulizumab (genetical recombination) per vial (5 mL)
Proposed Indications	CCR4-positive adult T-cell leukemia lymphoma Relapsed or refractory CCR4-positive peripheral T-cell lymphoma Relapsed or refractory ~~CCR4-positive~~ cutaneous T-cell lymphoma (Strikethrough denotes deletion.)
Proposed Dosage and Administration	CCR4-positive adult T-cell leukemia lymphoma The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses. The usual adult dosage in combination with other antineoplastics is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once every 2 weeks for 8 doses. Mogamulizumab should be used in combination with other antineoplastics for chemotherapy-naïve patients. Relapsed or refractory CCR4-positive peripheral T-cell lymphoma ~~Relapsed or refractory CCR4-positive cutaneous T-cell lymphoma~~ The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses. <u>Relapsed or refractory cutaneous T-cell lymphoma</u> <u>The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 4 doses in the first 28-day cycle and once every 2 weeks in the subsequent cycles.</u> (Strikethrough and underline denote deletion and addition, respectively.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Overview of product submitted for approval

Mogamulizumab is a humanized anti- CC chemokine receptor 4 (CCR4) monoclonal antibody discovered by Kyowa Hakko Kogyo Co., Ltd. (currently Kyowa Hakko Kirin Co., Ltd.). Mogamulizumab is thought to bind to CCR4, thereby inhibiting tumor growth via its antibody-dependent cellular cytotoxicity (ADCC).

In Japan, mogamulizumab was approved for the indication of "relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma" in March 2012, "relapsed or refractory CCR4-positive peripheral T-cell lymphoma (PTCL)" and "relapsed or refractory CCR4-positive cutaneous T-cell lymphoma (CTCL)" in March 2014, and "CCR4-positive adult T-cell leukemia lymphoma" in December 2014.

1.2 Development history and background

For the clinical development of mogamulizumab for the indication of relapsed or refractory CTCL, the applicant started a global phase III clinical study (Study 010) in December 2012 in patients with relapsed or refractory CTCL.

In the US and EU, in October 2017, data from Study 010 was submitted as the pivotal data for an application for marketing approval of mogamulizumab for the indication of relapsed or refractory CTCL. The applications are currently under review.

As of April 2018, mogamulizumab has not yet approved for the indication of relapsed or refractory CTCL in any country or region.

In Japan, the applicant began to enroll patients in Study 010 in February 2014.

Recently, the results of Study 010 was submitted as the pivotal data with the application for partial change for mogamulizumab to add the indication and the dosage regimen for relapsed or refractory CTCL.

Mogamulizumab was designated as an orphan drug for the proposed indication of treatment of "peripheral T-cell lymphoma and cutaneous T-cell lymphoma" in March 2013 (Drug Designation No. 298 [*25 yaku*]).

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

No data relating to quality was submitted because the current application was filed for a new indication and a new dosage.

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity with FcγR (CTD 4.2.1.1-1)

Binding affinity of mogamulizumab with 2 human Fc γ receptor (FcγR) isoforms was evaluated by using surface plasmon resonance (SPR). The results showed that the dissociation constant (K_D) value (mean ±

standard deviation; n＝3) of mogamulizumab for FcγRIIIa (V158)[1)] and FcγRIIIa (F158)[2)] was 995 ± 65.3 nmol/L and 94.9 ± 1.7 nmol/L, respectively.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the review shown below, PMDA concluded that mogamulizumab may be effective for CCR4-negative CTCL.

3.R.1 Mechanism of action of mogamulizumab

Mogamulizumab exerts inhibitory effects on tumor growth for CTCL determined to be CCR4-negative[3)] by the Poteligeo® Test IHC (Kyowa Medex Co., Ltd.). The applicant provided the following explanation about the mechanism of the inhibitory action of mogamulizumab.

Mogamulizumab is expected to exert its inhibitory effects by inducing mainly the ADCC activity on tumor growth in CTCL judged to be CCR4- negative, as with that judged to be CCR4-positive, in light of the following findings: (1) although the expression of CCR4 on the cell surface of CCR4-negative[3)] tumors is less than detectable levels, the expression level may be sufficient for mogamulizumab to exhibit its ADCC activity; and (2) the ADCC activity of mogamulizumab is suggested to be induced in CCR4-negative tumor cells (*Clin Cancer Res.* 2005;11:2327-36). In addition, mogamulizumab may inhibit the growth of CTCL cells by affecting regulatory T-cells (Tregs), in view of the following findings:

- Tregs express CCR4 (*Oncoimmunology*. 2016;5:e1090075).
- Patients with CTCL treated with mogamulizumab had decreased Treg count in peripheral blood (*Clin Cancer Res.* 2015;21:274-85; *J Clin Oncol.* 2012;30:837-42).
- In mice subcutaneously transplanted with murine malignant tumor-derived cells (e.g., murine colon/rectal cancer-derived MC38 cells) transfected with ovalbumin gene, Treg depletion was induced by *FoxP3* deletion and in turn showed inhibitory effects on tumor growth (*Cancer Res.* 2010;70:7800-9; *Eur J Immunol.* 2010;40:3325-35).

PMDA's view:

PMDA accepted the applicant's explanation generally. However, the contributing role, etc. of Tregs in the inhibitory effects of mogamulizumab on tumor growth remains unclear. Such information can be important for the estimation of the efficacy of mogamulizumab in clinical use, thus investigation should be continued and new findings, when available, should be communicated appropriately to healthcare professionals.

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

New data on non-clinical pharmacokinetics were submitted for the current application. PMDA concluded that there were no discrepancies between the applicant's explanation in the current application and that in the initial application previously reviewed.

[1)] Valine is present at amino acid position 158 in FcγRIIIa.
[2)] Phenylalanine is present at amino acid position 158 in FcγRIIIa.
[3)] CCR4 is judged as negative when CCR4-positive tumor cells account for <10% of the total tumor cells in a cutaneous lesion.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data from mogamulizumab toxicity studies, consisting of a toxicity study and another study (a study on the mechanism of toxicity).

5.1 Repeated-dose toxicity

A 26-week intravenous repeated-dose toxicity study was conducted in cynomolgus monkeys (Table 1). Main findings included low CCR4-positive T-lymphocyte count attributable to the pharmacological action of mogamulizumab. C_{max} and AUC[4)] after administration of mogamulizumab at the no-observed-adverse-effect level (NOAEL) were 79.4 to 83.8 and 90.6 to 115.9 times higher than the clinical exposure[5),] respectively.

Table 1. Repeated-dose toxicity study

Test system	Route	Duration	Dosage (mg/kg/week)	Main findings	NOAEL (mg/kg/week)	Attached data CTD
Male and female cynomolgus monkeys	Intravenous	26 weeks (QW)	0[a)], 2.5, 10, 40	≥2.5: low CCR4-positive T-lymphocyte count	40	4.2.3.2-1

a) 3.68 mmol/L citrate buffer solution containing 0.62% sodium chloride (pH 5.0)

5.2 Other studies

5.2.1 Study on the mechanism of toxicity

An intravenous repeated-dose skin toxicity study was conducted in old cynomolgus monkeys to investigate a possible relationship between skin disorders observed in humans treated with mogamulizumab and the changes in immunological state due to advanced age (Table 2).

Table 2. Study on the mechanism of toxicity

Test system	Study methods	Main findings	Attached data CTD
Female old cynomolgus monkeys	Mogamulizumab 10 mg/kg was intravenously administered QW for 8 weeks. Skin toxicity was assessed during the treatment period and after the 4-week recovery period following completion of the treatment.	Skin erythema was observed but was mild and transient. No clear correlation was indicated between the occurrence of erythema and changes in lymphocyte subset.	Reference data 4.2.3.7.3-1

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the nonclinical toxicity evaluation indicated no new concerns about the clinical use of mogamulizumab.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Assays for mogamulizumab

4) AUC that is twice the value of AUC_{7d} was used to compare exposures in 2 weeks.

5) Estimated by using a population pharmacokinetics (PPK) analysis [see Section 6.2.2]. Mogamulizumab 1 mg/kg was intravenously administered to Japanese patients with CTCL once weekly (QW) in the first 28-day cycle and once every 2 weeks (Q2W) in the subsequent cycles. Steady state C_{max} and $AUC_{0\text{-}\tau}$ after administration were 28.147 μg/mL and 5178.9 mg·h/L, respectively.

Mogamulizumab in human serum[6)] was quantified by enzyme-linked immunosorbent assay (ELISA) using a peptide with the same amino acid sequence as that for a part of solid-phased CCR4, biotin-labeled anti human immunoglobulin (Ig)-G antibodies, and horseradish peroxidase (HRP)-labeled avidin (with a lower limit of quantitation, 12.5 ng/mL).

6.2 Clinical pharmacology

The pharmacokinetics (PK) of mogamulizumab was evaluated in the monotherapy in patients with cancer.

6.2.1 Global phase III study (CTD 5.3.5.1-1, Study 010 [December 2012 to ongoing (data cutoff date, December 31, 2016)])

An open-label, randomized study was conducted to evaluate the efficacy and safety of mogamulizumab in 372 patients with relapsed or refractory CTCL (308 patients included in the PK analysis). Mogamulizumab 1 mg/kg was administered intravenously over ≥60 minutes QW in the first 28-day cycle and once every 2 weeks (Q2W) in the subsequent cycles, and serum mogamulizumab concentrations were evaluated.

Serum mogamulizumab concentrations are shown in Table 3. Serum mogamulizumab concentrations increased with the repeated doses till Day 1 of Cycle 2 and subsequently remained generally stable till Day 15 of Cycle 3.

Table 3. Serum mogamulizumab concentrations (μg/mL)

Measurement time point			n	Serum mogamulizumab concentrations
Cycle 1	Day 1	Post-dose	241	21.9 ± 6.2
	Day 8	Pre-dose	265	9.3 ± 3.8
	Day 15		260	15.9 ± 6.5
	Day 22		253	20.8 ± 8.2
Cycle 2	Day 1		246	24.5 ± 9.8
	Day 15		216	21.1 ± 9.6
Cycle 3	Day 1		189	19.4 ± 9.3
	Day 15		184	18.5 ± 8.9

Mean ± standard deviation

6.2.2 Population pharmacokinetics analysis

A population pharmacokinetics (PPK) analysis was conducted based on the PK data for mogamulizumab (4,775 time points; 444 patients) obtained from a Japanese phase I study (Study 0761-0501), phase II studies (Studies 0761-002, 0761-003, and 0761- 004), the global phase III study (Study 010), and a foreign phase II study (Study 0761-009). A non-linear mixed effect model was used (the NONMEM software, version 7.3.0). The PK of mogamulizumab was described by a 2-compartment model with linear elimination.

In this analysis, the following candidate covariates for mogamulizumab PK parameters were evaluated: age, body weight, body surface area, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST),

[6)] In the Japanese clinical studies (Studies 0761-0501, 0761-002, 0761-003, and 0761-004), plasma mogamulizumab concentrations were quantified, and the same assays as those for the initial approval were used [see the Review Report for Poteligeo Injection 20 mg, dated January 17, 2012].

total bilirubin, creatinine clearance (CrCL), sex, race, disease (adult T-cell leukemia-lymphoma [ATL] or CTCL), disease subtype (acute type, lymphoma type, or chronic type for ATL; mycosis fungoides [MF] or Sézary syndrome [SS] for CTCL), baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS), renal function,[7)] liver function,[8)] positive or negative for anti-mogamulizumab antibody,[9)] and concomitant use of the mLSG15 regimen. As a result, (1) sex, albumin, AST, and liver function were selected as significant covariates for CL, (2) body surface area for central volume of distribution (V_1), and (3) albumin for peripheral volume of distribution (V_2). According to the applicant, however, these covariates were unlikely to have clinically significant effects on the mogamulizumab PK, in light of the following outcomes from the data available from the global phase III study (Study 010):

- Patients were divided into 4 groups by using the quartile points of albumin, AST, and body surface area, and the efficacy and safety of mogamulizumab were compared among these groups. The comparison showed no clear relationship between the efficacy or safety and these covariates.
- No obvious differences were identified in the efficacy and safety of mogamulizumab between men and women and between patients with and without hepatic function disorders.[8)]

6.2.3 Relationship between the exposure level and the efficacy or safety

A relationship between mogamulizumab exposure levels ($C_{min,1st}$ and $AUC_{(0-\tau),ss}$) and the efficacy or safety of mogamulizumab was evaluated on the basis of data obtained from the global phase III study (Study 010). The $C_{min,1st}$ values were actual measurements,[10)] and $AUC_{(0-\tau),ss}$ values were estimated by the PKK analysis [see Section 6.2.2].

6.2.3.1 Relationship between the exposure level and the efficacy

Patients were divided into 4 groups by using the quartile points of $C_{min,1st}$ and $AUC_{(0-\tau),ss}$ of mogamulizumab ($C_{min,1st}$ of 1.96 to7.33, 7.39 to 9.08, 9.13 to 11.07, and 11.15 to 16.05 mg/L; and $AUC_{(0-\tau),ss}$ of 2,522 to 5,621, 5,630 to 7,392, 7,402 to 10,017, and 10,085 to 16,778 mg·h/L; the same applies hereinafter). The progression-free survival (PFS) in each exposure group was estimated by using the Kaplan-Meier method. No clear relationship was found between the $C_{min,1st}$ or $AUC_{(0-\tau),ss}$ of mogamulizumab and the PFS.

Patients were divided into 4 groups by using the quartile points of $C_{min,1st}$ and $AUC_{(0-\tau),ss}$ of mogamulizumab, and the response rate was compared among the exposure groups. No clear relationship was found between the $C_{min,1st}$ and the response rate, whereas the response rate tended to increase with increasing in $AUC_{(0-\tau),ss}$.

6.2.3.2 Relationship between the exposure level and the safety

Patients were divided into 4 groups by using the quartile points of $C_{min,1st}$ and $AUC_{(0-\tau),ss}$ of mogamulizumab to evaluate a relationship between these values and adverse events most frequently observed in Study 010 (e.g.,

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7) Renal function was classified into 4 stages: normal, CrCL of ≥90 mL/min; mild dysfunction, CrCL of 60 to 89 mL/min; moderate dysfunction, CrCL of 30 to 59 mL/min; and severe dysfunction, CrCL of <30 mL/min.

8) Hepatic function was classified according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria. There were only 3 patients classified as having moderate hepatic dysfunction, they were combined with patients with mild hepatic dysfunction for evaluation. There was no patient classified as having severe hepatic dysfunction.

9) Only data from Studies 0761-009 and 010, which were obtained by the same assay, were evaluated.

10) $C_{min,1st}$ value was estimated by using the PKK analysis [see Section 6.2.2] for patients with missing $C_{min,1st.}$ values.

events classified under “Injury, poisoning and procedural complications,” “Skin and subcutaneous tissue disorders,” “General disorders and administration site conditions,” “Infections and infestations,” or “Gastrointestinal disorders”). No clear relationship was found between the $C_{min,1st}$ or $AUC_{(0-\tau),ss}$ and the occurrence of these adverse events.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of mogamulizumab between Japanese and non-Japanese patients

The applicant’s explanation about differences in the PK of mogamulizumab between Japanese and non-Japanese patients:

Serum mogamulizumab concentrations observed in the Japanese and non-Japanese patients in the global phase III study (Study 010) are shown in Table 4. There were no clear differences between these patient groups, indicating no clear differences in the PK of mogamulizumab identified between Japanese and non-Japanese patients.

Table 4. Serum mogamulizumab concentrations (μg/mL)

Measurement time point			n	Japanese patients	n	Non-Japanese patients
Cycle 1	Day 1	Post-dose	8	20.7 ± 5.3	229	22.0 ± 6.3
	Day 8	Pre-dose	9	8.3 ± 2.7	248	9.4 ± 3.8
	Day 15		9	14.5 ± 5.1	233	16.4 ± 6.5
	Day 22		8	26.8 ± 16.7	228	21.1 ± 7.8
Cycle 2	Day 1		7	24.7 ± 7.3	195	26.2 ± 9.3
	Day 15		7	27.0 ± 23.2	172	22.1 ± 8.7
Cycle 3	Day 1		5	21.4 ± 11.0	136	21.3 ± 9.0
	Day 15		5	16.3 ± 4.1	128	20.1 ± 9.4

Mean ± standard deviation

PMDA’s view:

Limited clinical study data are available for the evaluation of differences in the PK of mogamulizumab between Japanese and non-Japanese patients, precluding rigorous evaluation. Nevertheless, based on the submitted data, PMDA concluded that there are no obvious differences in the PK of mogamulizumab between Japanese and non-Japanese patients.

6.R.2 Effects of anti-mogamulizumab antibodies on the PK of mogamulizumab

The applicant’s explanation about the expression of anti-mogamulizumab antibodies and the effects of anti-mogamulizumab antibodies on the PK of mogamulizumab:

In the global phase III study (Study 010), anti-mogamulizumab antibodies were detected in 15 of 311 (4.8%) of patients from whom samples were collected after the administration of mogamulizumab. No neutralizing antibodies were detected.

The following observations suggest the possibility that mogamulizumab coexisting in the samples might have influenced the measurements of anti-mogamulizumab antibodies, precluding appropriate evaluation. Thus, drawing definite conclusions about the effects of anti-mogamulizumab antibodies on the PK of mogamulizumab is difficult.

- The upper limit of mogamulizumab concentration having no effects on measurements of anti-mogamulizumab antibodies with electrochemical luminescence (ECL) assay used in Study 010 was 16 μg/mL (see the Review Report for Poteligeo Injection 20 mg, dated February 18, 2014).
- The maximum serum mogamulizumab concentration was 58.9 μg/mL at the time of measurement of anti-mogamulizumab antibodies in Study 010.

PMDA's view:
PMDA accepted the applicant's explanation. Nevertheless, data concerning the possible effects of anti-mogamulizumab antibodies on the PK of mogamulizumab should be continuously collected, and new findings should be communicated to healthcare professionals when available.

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

The applicant submitted data from the global phase III study, shown in Table 5, for evaluation of the efficacy and safety of mogamulizumab.

Table 5. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Patient population	No. of enrolled patients	Summary of dosage and regimen	Main endpoints
Evaluation	Global	010	III	Patients with relapsed or refractory CTCL	372 (1) 186 (2) 186	(1) Mogamulizumab 1 mg/kg was intravenously administered QW in the first 28-day cycle and Q2W in the subsequent cycles. (2) Vorinostat 400 mg was orally administered QD.	Efficacy Safety PK

The clinical study is summarized below.

Adverse events other than deaths occurring in the clinical study are summarized in Section "7.2 Adverse events observed in clinical studies," and clinical study data for PK are summarized in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study 010 [December 2012 to ongoing (data cutoff date, December 31, 2016)])

An open-label, randomized study was conducted to compare the efficacy and safety of mogamulizumab with those of vorinostat in patients with relapsed or refractory CTCL[11] (target sample size, 317) at 63 sites in 11 countries and regions including Japan.

In the mogamulizumab group, mogamulizumab 1 mg/kg was administered intravenously QW for the first 28-day cycle and Q2W for the subsequent cycles. In the vorinostat group, vorinostat 400 mg was administered orally once daily (QD). In both groups, patients were to continue the treatment until disease progression or any of the discontinuation criteria met.[12] Patients assigned to the vorinostat group were allowed to be switched to

[11] Patients with a histopathological diagnosis of MF or SS with or without CCR4 expression
[12] Treatment could be continued for up to 12 months for patients achieving complete remission (CR) in the overall response evaluation.

mogamulizumab if they were judged by their investigators to have disease progression or experienced intolerable adverse events related to vorinostat at the Week 8 evaluation or later[13] after completing ≥ 2 cycles of vorinostat therapy.

A total of 372 patients who were enrolled and randomized in the study (186 in the mogamulizumab and 186 in the vorinostat group) were included in the intention-to-treat (ITT) population and the efficacy analysis set. In the ITT population, 370 patients who received the study drug (184 in the mogamulizumab and 186 in the vorinostat group) were included in the safety analysis set. Of the 186 patients in the vorinostat group, 136 patients switched to mogamulizumab.

The efficacy primary endpoint was PFS evaluated by the investigators based on the modified criteria for evaluation of anti-tumor response.[14] The PFS results[15] and Kaplan-Meier curves for the PFS are shown in Table 6 and Figure 1, respectively. The superiority of mogamulizumab to vorinostat was demonstrated.

Table 6. Results of PFS analysis (ITT population, judged by investigators, data cutoff date of December 31, 2016)

	Mogamulizumab	Vorinostat
Number of subjects	186	186
Number of death or worsening (%)	110 (59.1)	131 (70.4)
Median [95% CI] (month)	7.70 [5.67, 10.33]	3.10 [2.87, 4.07]
Hazard ratio*1 [95% CI]	0.53 [0.41, 0.69]	
p value (two-sided) *2	<0.0001	

*1 Calculated by using a Cox proportional hazard model with covariates of treatment group, histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and registration region (US, Japan, others).*2 A stratified log-rank test with stratifying factors of histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and registration region (US, Japan, others), with a two-sided significance level of 0.05.

[13] On November 14, 2013, the study protocol was revised to allow patients to switch to mogamulizumab if the disease progressed before Week 8 of the study treatment.

[14] The following amendments were made according to the criteria for evaluation of anti-tumor response (*J Clin Oncol*. 2011;29:2598-607);

(1) Numeric values were specified for the criteria for the surface and tumor swelling of the modified Severity Weighted Assessment Tool (mSWAT) used for evaluation of response in cutaneous lesions.

(2) The criteria for response evaluation for lymph node lesions and visceral lesions were amended as follows: (i) biopsy was not required for the judgment of CR; (ii) the criteria for PD and relapse were more clearly defined; and (iii) unassessable criteria were added.

(3) Patients receiving topical or systemic steroids concomitantly could be assessed to have achieved CR if they met the criteria for achievement of CR in the overall response evaluation.

[15] Initially, the analysis was planned to be performed either when the number of observed events reached 255 or 24 months after the first dose of the study drug in the last randomized patient, whichever came first. However, the collection of events took longer time than expected, and therefore, the analysis was performed when approximately 230 events were observed.

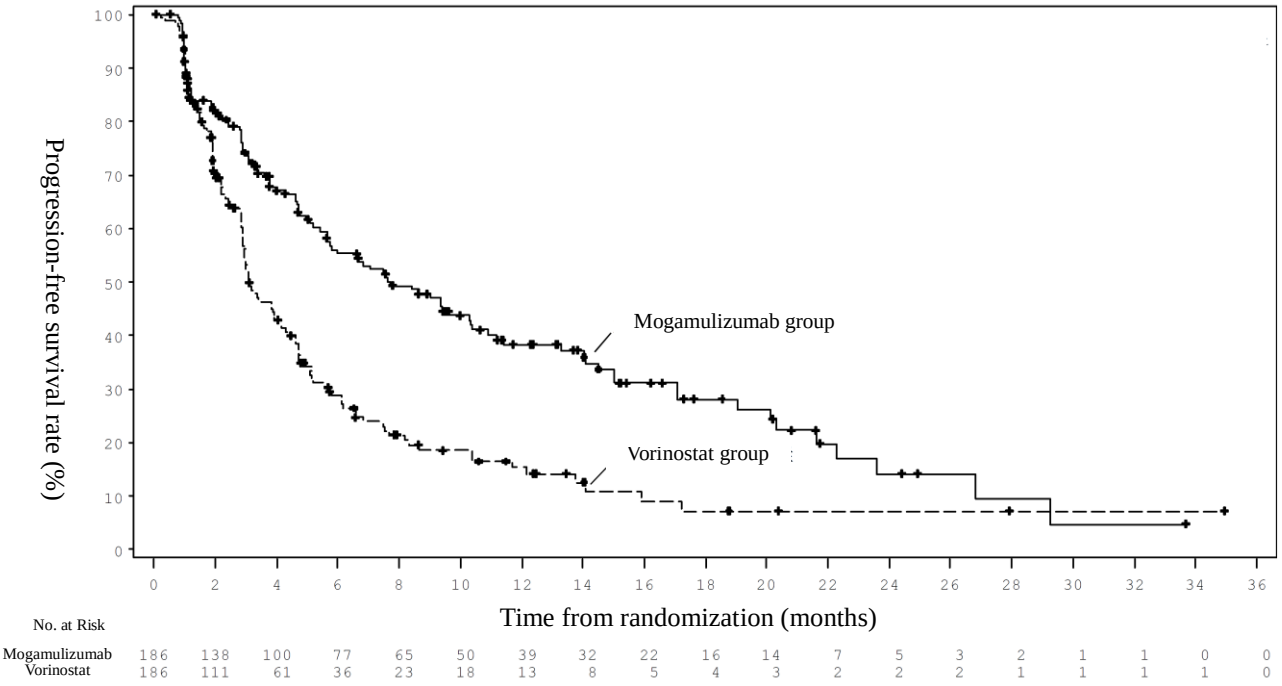

Figure 1. Kaplan-Meier curves for PFS (ITT population, judged by investigators, data cutoff date of December 31, 2016)

The median PFS judged by investigators in patients with relapsed CTCL (62 in the mogamulizumab group and 69 in the vorinostat group) was 6.70 months in the mogamulizumab group and 3.13 months in the vorinostat group (hazard ratio [95% confidence interval (CI)], 0.53 [0.34, 0.84]). The median PFS evaluated by investigators in patients with refractory CTCL (105 in the mogamulizumab group and 99 in the vorinostat group) was 9.00 months in the mogamulizumab group and 3.00 months in the vorinostat group (hazard ratio [95% CI], 0.46 [0.32, 0.65]).

The safety analysis revealed deaths of 3 of 184 patients (1.6%) in the mogamulizumab group and 9 of 186 patients (4.8%) in the vorinostat group during the study drug treatment or within 90 days after completion of the study drug treatment. Causes of the deaths other than disease progression (1 each in the mogamulizumab and vorinostat groups) were pneumonia pneumococcal/polymyositis and sepsis in 1 patient each in the mogamulizumab group; pulmonary embolism in 2 patients, intestinal obstruction/sepsis/septic shock, bronchopneumonia/left ventricular hypertrophy/mycosis fungoides, endocarditis, pneumonia, depressed level of consciousness, and skin disorder in 1 patient each in the vorinostat group. A causal relationship with the study drug was not ruled out for polymyositis and sepsis in 1 patient each in the mogamulizumab group and pulmonary embolism in 2 patients and bronchopneumonia/mycosis fungoides in 1 patient in the vorinostat group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Among the submitted data, PMDA regarded the global phase III study (Study 010), which was conducted in patients with relapsed or refractory CTCL, as the pivotal study for evaluation of the efficacy and safety of mogamulizumab for relapsed or refractory CTCL. Therefore, PMDA decided to mainly evaluate and review

Study 010. Based on the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic principles on Global Clinical Trials – Reference Cases" (Administrative Notice, dated September 5, 2012), PMDA decided to evaluate the efficacy in Japanese patients from the viewpoint of consistency between the entire study population and the Japanese patient subgroup in Study 010.

7.R.2 Efficacy

As a result of its review summarized below, PMDA concluded that the efficacy of mogamulizumab has been demonstrated in patients with relapsed or refractory CTCL.

7.R.2.1 Target patients

Patients with relapsed or refractory CTCL, including CCR4-negative CTCL, were the target population of Study 010. PMDA asked the applicant to explain the rationale for the selection of patients for the study.

The applicant's explanation:
In foreign studies conducted in patients with relapsed or refractory PTCL and CTCL (Studies KW-0761-001 and KW-0761-002), a certain level of response rate (25.0% [2 of 8]) was achieved in patients with CTCL assessed as CCR4 negative (8 of 38),[16)] showing the efficacy of mogamulizumab even in CCR4-negative patients. Based on the results, discussion began on the development of mogamulizumab for CCR4-negative patients. However, the number of patients with relapsed or refractory CTCL including CCR4-negative patients is extremely limited in and outside Japan (*J Dermatol*. 2014;41:3-10), and a clinical study enrolling only CCR4-negative patients was thus infeasible. Therefore, patients with relapsed or refractory CTCL with or without CCR4 expression were specified for the target study population in Study 010 as a confirmatory study.

PMDA accepted the applicant's explanation, and decided to evaluate the efficacy of mogamulizumab with a focus on the results in the entire study population of Study 010 and to confirm the results in CCR4-negative patients as well.

7.R.2.2 Control group

The applicant's explanation about the rationale for selecting the control group in Study 010:
At the time of planning Study 010 (in 2012), the National Comprehensive Cancer Network Practice (NCCN) Guidelines (v. 2.2011) recommended vorinostat as a therapeutic option for patients eligible for Study 010, and vorinostat was thus selected as the active control in Study 010.

PMDA accepted the applicant's explanation.

7.R.2.3 Efficacy endpoints

The applicant's explanation about the primary efficacy endpoints in Study 010:

[16)] Patients were assessed as CCR4 negative when [redacted].

The primary goal of the treatment of relapsed or refractory CTCL is to relieve symptoms and to delay disease progression. Improvement in PFS is expected to lead to delaying disease progression and is thus considered to be of clinical significance. Accordingly, PFS was selected as the primary efficacy endpoint in Study 010.

PMDA's view:

Because treatment for patients with relapsed or refractory CTCL aims to improve their survival, the appropriate primary endpoint should be overall survival (OS) for the efficacy evaluation. However, the applicant's explanation that improvement in PFS in the patients is of clinical significance is agreeable to some extent. Accordingly, it was decided that the efficacy of mogamulizumab be evaluated with focus on the primary endpoint of PFS based on the modified criteria for evaluation of antitumor response and that OS results be also checked.

7.R.2.4 Results of efficacy evaluation

In Study 010, the superiority of mogamulizumab to vorinostat was validated for the primary endpoint, namely PFS determined by the investigators based on the modified criteria for evaluation of antitumor response [see Section 7.1.1].

A PFS analysis was performed as a sensitivity analysis, in which PFS was judged by an independent review committee (IRC) based on the modified criteria for evaluation of antitumor response. The results are shown in Table 7.

Table 7. Results of PFS analysis (ITT population, judged by IRC, data cutoff date of December 31, 2016)

	Mogamulizumab	Vorinostat
Number of subjects	186	186
Number of death or worsening (%)	110 (59.1)	122 (65.6)
Median [95% CI] (month)	6.70 [5.63, 9.37]	3.83 [3.00, 4.70]
Hazard ratio[*1] [95% CI]	0.64 [0.49, 0.84]	
p value (two-sided) [*2]	0.0007	

*1 Calculated by using a Cox proportional hazard model with covariates including treatment group, histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others). *2 A stratified log-rank test with stratifying factors of histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others).

The results of an analysis of OS, a secondary endpoint, are shown in Table 8 and Figure 2.

Table 8 Results of OS analysis (ITT population, data cutoff date of December 31, 2016)

	Mogamulizumab	Vorinostat
Number of subjects	186	186
Number of death or worsening (%)	40 (21.5)	47 (25.3)
Median [95% CI] (month)	NE [NE, NE]	43.93 [43.57, NE]
Hazard ratio[*1] [95% CI]	0.93 [0.61, 1.43]	
p value (two-sided) [*2]	0.9439	

*1 Calculated by using a Cox proportional hazard model with covariates of treatment group, histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others). *2 A stratified log-rank test with stratifying factors of histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others).

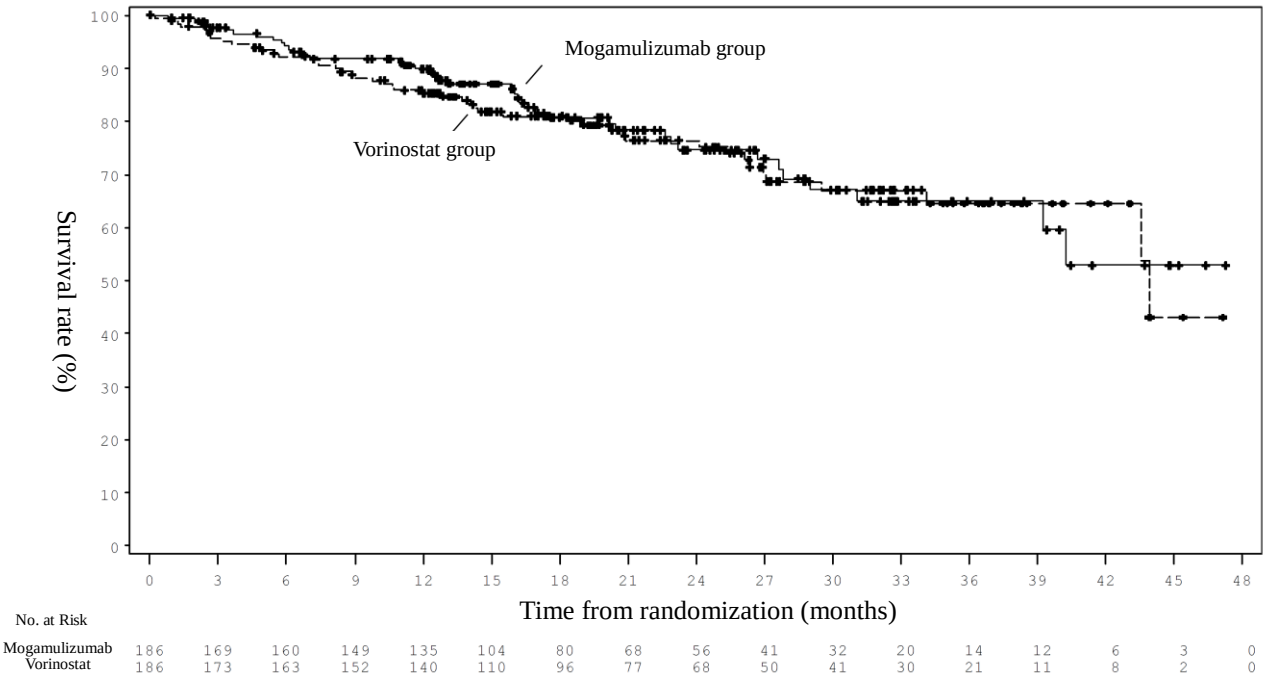

Figure 2. Kaplan-Meier curves for OS (ITT population, data cutoff date of December 31, 2016)

The results of PFS judged by investigators based on the modified criteria for evaluation of antitumor response are shown in Table 9 and Figure 3.

Table 9. Results of PFS analysis in Japanese patient subgroup (ITT population, judged by investigators, data cutoff date of December 31, 2016)

	Mogamulizumab	Vorinostat
Number of subjects	9	6
Number of death or worsening (%)	3 (33.3)	4 (66.7)
Median [95% CI] (month)	11.17 [4.67, NE]	4.95 [1.47, NE]
Hazard ratio[*1] [95% CI]	0.28 [0.05, 1.58]	
p value (two-sided) [*2]	0.1583	

*1 Calculated by using a Cox proportional hazard model with covariates of treatment group, histological type (MF or SS), and TNMB staging classification (IB/II or III/IV). *2 A stratified log-rank test with stratifying factors of histological type (MF or SS) and TNMB staging classification (IB/II or III/IV)

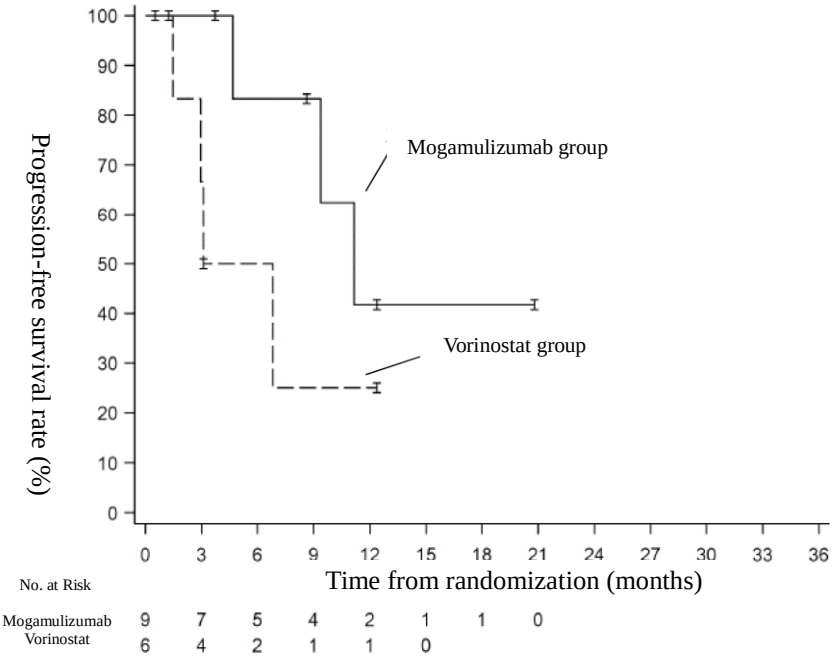

Figure 3. Kaplan-Meier curves at the PFS analysis in Japanese patient subgroup (ITT population, judged by investigators, data cutoff date of December 31, 2016)

The applicant's explanation about the efficacy of mogamulizumab in CCR4-negative patients:

Table 10 are the results of PFS judged by investigators based on the modified criteria for evaluation of antitumor response of patients who were able to undergo CCR4 expression assay[17] in Study 010 shown by CCR4 status[18]. None of patients tested negative for CCR4 achieved a therapeutic response (complete response [CR] or partial remission [PR]) in either the mogamulizumab group or the vorinostat group.

Table 10. Results of PFS analysis in CCR4-positive and -negative patients (ITT population, judged by investigators, data cutoff date of December 31, 2016)

	CCR4-positive		CCR4-negative	
	Mogamulizumab	Vorinostat	Mogamulizumab	Vorinostat
Number of subjects	134	146	6	4
Number of death or worsening (%)	76 (56.7)	101 (69.2)	3 (50.0)	4 (100)
Median [95% CI] (month)	9.40 [5.77, 14.03]	3.13 [2.87, 4.63]	3.77 [0.93, 3.77]	1.67 [0.77, 2.87]
Hazard ratio*1 [95% CI]	0.51 [0.37, 0.70]		0.07 [0.00, 1.03]	
p value (two-sided) *2	<0.0001		0.1966	

*1 Calculated by using a Cox proportional hazard model with covariates of treatment group, histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others). *2 A stratified log-rank test with stratifying factors of histological type (MF or SS), TNMB staging classification (IB/II or III/IV), and region enrolled (US, Japan, others).

A post-hoc CCR4 assay with the Poteligeo® Test IHC (Kyowa Medex Co., Ltd.), a companion diagnostic approved in Japan, was performed on the samples collected in Study 010. In patients tested negative for CCR4 (9 in the mogamulizumab group and 4 in the vorinostat group),[3] the hazard ratio [95% CI] of PFS judged by investigators based on the modified criteria for evaluation of antitumor response in the mogamulizumab group

[17] In Study 010, patients were eligible irrespective of CCR4 expression. However, CCR4 expression assays were performed in 311 of 372 patients to investigate a possible relationship between CCR4 expression and the efficacy of mogamulizumab, and 290 of the 311 patients were evaluable for CCR4 expression.

[18] [redacted].

relative to that in the vorinostat group was 0.09 [0.01, 1.16], and a therapeutic response (documented CR or PR) judged by investigators based on the criteria for evaluation of antitumor response was achieved in 2 patients (22.2%) in the mogamulizumab group and none in the vorinostat group.

Based on the above, despite the limited size of the subgroup of patients judged to be CCR4 negative in Study 010, mogamulizumab is expected to be effective even in CTCL patients tested negative for CCR4 because 1) PFS tended to improve in the mogamulizumab group as compared with the vorinostat group in the subgroup of patients tested CCR4-negative, as with the entire study population; and 2) a certain number of patients in the subgroup of patients tested CCR4-negative by the Poteligeo® Test IHC had a therapeutic response to mogamulizumab.

PMDA's view:
The efficacy of mogamulizumab has been demonstrated in patients with relapsed or refractory CTCL, given the following:

- The superiority of mogamulizumab to vorinostat in PFS judged by investigators based on the modified criteria for evaluation of antitumor response, the primary endpoint of Study 010, was shown, and clinically significant improvement in PFS with mogamulizumab was demonstrated.
- Mogamulizumab did not tend to reduce OS obviously, the secondary efficacy endpoint of Study 010, as compared with the vorinostat.
- Despite the limited number of Japanese patients in Study 010, there was no clear difference in the results of PFS between the Japanese subgroup and the entire study population.
- In the subgroup of CCR4-negative patients enrolled in Study 010, despite its limited number, PFS tended to improve in the mogamulizumab group as compared with the vorinostat group. In addition, a certain number of patients in the subgroup had a therapeutic response to mogamulizumab. These findings suggest that mogamulizumab is expected to have efficacy in CTCL patients tested CCR4 negative as well.

7.R.3 Safety [see Section "7.2 Adverse events observed in clinical studies" for adverse events]

As a result of its review shown below, PMDA has concluded that treatment with mogamulizumab in patients with relapsed or refractory CTCL requires particular attention to the adverse events that were previously identified and warned against at the review for the approved indication. They are namely, hematotoxicity (bone marrow depression), infusion reactions, infections/immune system disorders, skin disorders, tumor lysis syndrome (TLS), hepatic dysfunction, cardiac dysfunction, interstitial lung diseases (ILDs), and hyperglycemia (see Review Report for Poteligeo Injection 20 mg dated January 17, 2012, Review Report for Poteligeo Injection 20 mg dated February 18, 2014, and Review Report for Poteligeo Injection 20 mg dated November 18, 2014). PMDA has concluded that caution should be given against these adverse events during the use of mogamulizumab for patients with relapsed or refractory CTCL, as practiced for the approved indication.

In addition, PMDA has concluded that mogamulizumab, although the above adverse events are subject to caution, is tolerable in patients with relapsed or refractory CTCL when appropriate measures, such as monitoring and management of adverse events and discontinuation/interruption of mogamulizumab, are taken

by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

7.R.3.1 Safety profiles of mogamulizumab

The applicant's explanation about the safety profile of mogamulizumab:

The safety of mogamulizumab during the randomized treatment period in Study 010[19)] is summarized in Table 11.

Table 11. Safety (Study 010, the randomized treatment period)

	Number of subjects (%)	
	Mogamulizumab N = 184	Vorinostat N = 186
All adverse events	179 (97.3)	185 (99.5)
Adverse events Grade ≥3	78 (42.4)	85 (45.7)
Adverse events resulting in death	3 (1.6)	9 (4.8)
Serious adverse events	69 (37.5)	46 (24.7)
Adverse events leading to treatment discontinuation	35 (19.0)	43 (23.1)
Adverse events leading to treatment interruption	77 (41.8)	45 (24.2)

The following adverse events occurred in the mogamulizumab group at an incidence higher by ≥5 percent points than in the vorinostat group during the randomization treatment period in Study 010: infusion related reaction (61 patients [33.2%] in the mogamulizumab group, 1 patient [0.5%] in the vorinostat group); drug eruption (44 [23.9%] in the mogamulizumab group, 1 [0.5%] in the vorinostat group); pyrexia (32 [17.4%] in the mogamulizumab group, 11 [5.9%] in the vorinostat group); weight increased (14 [7.6%] in the mogamulizumab group, 2 [1.1%] in the vorinostat group); and upper respiratory tract infection (19 [10.3%] in the mogamulizumab group, 9 [4.8%] in the vorinostat group). An adverse event occurring in the mogamulizumab group at an incidence higher by ≥5 percent points than in the vorinostat group and leading to treatment discontinuation was drug eruption (13 [7.1%] in the mogamulizumab group, none in the vorinostat group). Adverse events occurring in the mogamulizumab group at an incidence higher by ≥5 percent points than in the vorinostat group and led to treatment interruption were drug eruption (13 [7.1%] in the mogamulizumab group, none in the vorinostat group) and infusion related reaction (12 [6.5%] in the mogamulizumab group, none in the vorinostat group). There was no Grade ≥3 adverse event occurring in the mogamulizumab group at an incidence higher by ≥5 percent points than in the vorinostat group. No distinct difference in the safety profile was found between the patients in the mogamulizumab group and 136 patients in the vorinostat group who switched to mogamulizumab.

Table 12 summarizes the safety of mogamulizumab in patients positive and negative for CCR4[18)] in the subgroup of patients who underwent CCR expression assay in Study 010. Although the comparison of the safety between these patient groups is inadequate due to the small size of CCR4-negative patients, no obvious difference was identified in the safety profile of mogamulizumab between patients positive and negative for CCR4.

19) The period in which the first allocated study drug was administered in individual treatment groups.

Table 12. Safety in patients positive and negative for CCR4 (Study 010, the randomized treatment period)

	Number of subjects (%)			
	Mogamulizumab		Vorinostat	
	CCR4-positive N = 132	CCR4-negative N = 6	CCR4-positive N = 146	CCR4-negative N = 4
All adverse events	129 (97.7)	6 (100)	145 (99.3)	4 (100)
Adverse events Grade ≥3	57 (43.2)	3 (50.0)	68 (46.6)	1 (25.0)
Adverse events resulting in death	2 (1.5)	0	8 (5.5)	0
Serious adverse events	49 (37.1)	2 (33.3)	36 (24.7)	0
Adverse events leading to treatment discontinuation	28 (21.2)	1 (16.7)	37 (25.3)	1 (25.0)
Adverse events leading to treatment interruption	56 (42.4)	3 (50.0)	35 (24.0)	0

The applicant's explanation about differences in the safety of mogamulizumab between Japanese and non-Japanese patients:

Table 13 summarizes the safety of mogamulizumab in the Japanese and non-Japanese patients during the randomized treatment period in Study 010.

Table 13. Differences in safety between Japanese and non-Japanese patients (Study 010, the randomized treatment period)

	Number of subjects (%)			
	Japanese patients		Non-Japanese patients	
	Mogamulizumab N = 9	Vorinostat N = 6	Mogamulizumab N = 175	Vorinostat N = 180
All adverse events	9 (100)	6 (100)	170 (97.1)	179 (99.4)
Adverse events Grade ≥3	3 (33.3)	2 (33.3)	75 (42.9)	83 (46.1)
Adverse events resulting death	0	0	3 (1.7)	9 (5.0)
Serious adverse events	3 (33.3)	0	66 (37.7)	46 (25.6)
Adverse events leading to treatment discontinuation	2 (22.2)	1 (16.7)	33 (18.9)	42 (23.3)
Adverse events leading to treatment interruption	6 (66.7)	1 (16.7)	71 (40.6)	44 (24.4)

Adverse events occurring in Japanese patients at an incidence higher by ≥15 percent points than in non-Japanese patients in the mogamulizumab group during the randomization treatment period in Study 010 were pyrexia (4 Japanese [44.4%], 28 non-Japanese [16.0%]), dermatitis contact (2 Japanese [22.2%], 3 non-Japanese [1.7%]), and viral upper respiratory tract infection (2 Japanese [22.2%], 9 non-Japanese [5.1%]). An adverse event leading to treatment interruption occurring in Japanese patients at an incidence higher by ≥15 percent points than in non-Japanese patients was infusion related reaction (3 Japanese [33.3%], 9 non-Japanese [5.1%]). There were no ≥Grade 3 serious adverse events, or those leading to treatment discontinuation occurring in Japanese patients at an incidence higher by ≥15 percent points than in non-Japanese patients.

PMDA's view:

Attention should be paid to adverse events occurring in the mogamulizumab group at a higher incidence than in the vorinostat group in Study 010. Although the small number of Japanese patients evaluated precludes a clear conclusion on the differences in the safety of mogamulizumab between Japanese and non-Japanese patients with relapsed or refractory CTCL, attention should be paid to adverse events which occurred more frequently in Japanese patients than in non-Japanese patients. However, these are the known adverse events of

mogamulizumab, mogamulizumab is tolerable in patients with relapsed or refractory CTCL when appropriate measures, such as monitoring and management of adverse events and interruption of mogamulizumab, etc., are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

7.R.4 Clinical positioning and indications

In the current application for partial changes, the approved indication of mogamulizumab, "relapsed or refractory CCR4-positive cutaneous T-cell lymphoma" was to be revised to "relapsed or refractory cutaneous T-cell lymphoma." The applicant proposed that the descriptions in the "Precautions for Indications" section of the current package insert to the effect that "Patients should undergo a CCR4 antigen test by flow cytometry (FCM) or immunohistochemistry (IHC), and mogamulizumab should be used for patients with relapsed or refractory CCR4-positive CTCL" and the word "CCR4-positive" be deleted.

As a result of its review shown below and in the "7.R.2 Efficacy" and "7.R.3 Safety" sections, PMDA has concluded that the "Indications" and "Precautions for Indications" sections of the package insert should be described as per the applicant's proposal.

7.R.4.1 Clinical positioning and indications of mogamulizumab

The clinical practice guidelines and major textbooks on clinical oncology and hematology in Japan explain mogamulizumab used for the treatment of relapsed or refractory CTCL as follows:

Clinical practice guidelines

- Japan Society of Clinical Oncology: Clinical Practice Guidelines for Cutaneous Malignancy (Appendix): In a Japanese phase II study conducted in patients with relapsed or refractory CCR4-positive PTCL or CTCL, 8 patients with CTCL received mogamulizumab. Of these, 3 patients were assessed to have PR, while 4 patients were assessed to have stable disease (SD) and 1 patient progressive disease (PD). The most frequent nonhematological toxicity included pyrexia (30%) and skin disorders (51%).

Textbooks

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Wolters Kluwer. 2014, USA): In a phase II study conducted in patients with relapsed or refractory CTCL, the response rate was 37% (MF, 29%; SS, 47%). Phase II clinical studies enrolling patients with CTCL, PTCL, and ATL are ongoing.

The applicant's explanation about the clinical positioning and indications of mogamulizumab for relapsed or refractory CTCL:

Study 010 was conducted in patients with relapsed or refractory CTCL with or without CCR4 expression and demonstrated the clinical benefit of mogamulizumab [see Sections 7.R.2 and 7.R.3]. Therefore, mogamulizumab is considered a therapeutic option for patients with relapsed or refractory CTCL, irrespective of CCR4 expression.

Accordingly, patients with relapsed or refractory CTC are not required to undergo a CCR4 expression test before treated with mogamulizumab. The "Precautions for Indications" section of the current package insert notes that patients should undergo a test for CCR4 antigen before receiving mogamulizumab, and only those who are confirmed to be CCR4 positive should be treated with mogamulizumab. This description should be deleted. Furthermore, and the word "CCR4-positive" should be deleted from the indication definition to be modified to "relapsed or refractory cutaneous T-cell lymphoma."

PMDA accepted the applicant's explanation.

7.R.4.2 Histological type

The applicant's explanation about the efficacy and safety of mogamulizumab by histological type in Study 010:

Study 010 was conducted in patients with MF and SS, histological types accounting for approx. 60% of CTCL (*Blood*. 2005; 105: 3768-85). Results of the subgroup analyses of efficacy and safety by histological type are shown in Tables 14 and 15, showing no clear differences in the efficacy or safety of mogamulizumab between each histological type subgroup and the entire study population.

Table 14. Results of PFS analysis by histological type (ITT population, judged by investigators, data cutoff date of December 31, 2016)

	MF patients		SS patients	
	Mogamulizumab	Vorinostat	Mogamulizumab	Vorinostat
Number of subjects	105	99	81	87
Number of death or worsening (%)	66	69	44	62
Median [95% CI] (month)	5.40 [3.97, 7.57]	3.10 [2.87, 4.70]	13.30 [7.70, 17.07]	3.13 [2.83, 3.87]
Hazard ratio*1 [95% CI]	0.72 [0.51, 1.01]		0.32 [0.21, 0.49]	
p value (two-sided) *2	0.0675		＜0.0001	

*1 Calculated by using a stratified Cox proportional hazard model with stratifying factors TNMB staging classification (IB/II or III/IV) and region enrolled (US, Japan, others). *2 A stratified log-rank test (Staging [the same stratifying factor as that used in the Cox proportional hazard model])

Table 15. Outline of safety by histological type (Study 010, during the randomized treatment period)

	Number of subjects (%)			
	MF patients		SS patients	
	Mogamulizumab N = 105	Vorinostat N = 99	Mogamulizumab N = 79	Vorinostat N = 87
All adverse events	100 (95.2)	98 (99.0)	79 (100)	87 (100)
Adverse events Grade ≥3	42 (40.0)	42 (42.4)	36 (45.6)	43 (49.4)
Adverse events resulting in death	1 (1.0)	7 (7.1)	2 (2.5)	2 (2.3)
Serious adverse events	33 (31.4)	23 (23.2)	36 (45.6)	23 (26.4)
Adverse events leading to treatment discontinuation	19 (18.1)	20 (20.2)	16 (20.3)	23 (26.4)
Adverse events leading to treatment interruption	33 (31.4)	24 (24.2)	44 (55.7)	21 (24.1)

PMDA asked the applicant to explain the treatment with mogamulizumab in patients with CTCL with a histological type other than MF or SS, who were not included in Study 010.

The applicant's answer:

There is no clinical trial data to confirm the efficacy and safety of mogamulizumab in patients with CTCL with a histological type other than MF or SS because only patients with a histological type of MF or SS were enrolled in Study 010. However, mogamulizumab is expected to be clinically beneficial even in patients with relapsed or refractory CTCL with a histological type other than MF or SS, in light of the following findings:

- In patients with CTCL (7 MF patients and 1 patient with primary cutaneous CD30-positive T-cell lymphoproliferative disorder) enrolled in a Japanese phase II study conducted in patients with relapsed or refractory CCR4-positive PTCL or CTCL (Study 004), the patient with primary cutaneous CD30-possitive T-cell lymphoproliferative disorder achieved PR. Based on data including the above in this study, mogamulizumab was approved for the indication of "relapsed or refractory CCR4-positive cutaneous T-cell lymphoma" regardless of the CTCL histological types (see the Review Report for Poteligeo Injection 20 mg, dated February 18, 2014).

Accordingly, the indication of mogamulizumab was defined as "relapsed or refractory cutaneous T-cell lymphoma." In the package insert, as practiced for the approved indication of relapsed or refractory CCR4-positive CTCL, the histopathological types of patients enrolled in Study 010 were mentioned in the "Clinical Studies" section. Further, in the "Precautions for Indications" section, a cautionary note was given to the effect that physicians should become acquainted with information in the "Clinical Studies" section to have good knowledge of the histopathological types of patients enrolled in the clinical studies and thoroughly understand the efficacy and safety of mogamulizumab so that eligible patients are appropriately selected.

PMDA's view:

Since only patients with relapsed or refractory CTCL with a histological type of MF or SS were enrolled in Study 010, it is difficult to draw a definite conclusion on the efficacy of mogamulizumab in patients with CTCL with a histological type other than MF or SS. In light of the following, however, limiting the CTCL histological types in the indication is less than necessary, as with the approved indications, as long as the histological types of patients with CTCL enrolled in Study 010 are communicated via the "Clinical Studies" section and a cautionary note is added in the "Precautions for Indications" of the package insert as per the applicant's proposal.

- Patients with CTCL is extremely limited in number, and conducting clinical studies to evaluate the efficacy of mogamulizumab by histological type is difficult.
- For patients with CTCL, there is no available therapy that is expected to improve OS, or no standard therapies established for individual histological types in [see Section 7.R.4.1].

7.R.5 Dosage and administration

The proposed dosage regimen of mogamulizumab is "The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 4 doses in the first 28-day cycle and once every 2 weeks for the subsequent cycles." The proposed statements in the "Precautions for Dosage and Administration" section follow those in the current package insert referring to CCR4-positive CTCL, with the word "CCR4-positive" deleted.

As a result of its review shown below, and in the sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA has concluded that the description of the dosage regimen of mogamulizumab be modified as follows and that notes in the "Precautions for Dosage and Administration" section be described as per the applicant's proposal.

Dosage and Administration:
The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 5 doses and once every 2 weeks for subsequent doses.

7.R.5.1 Dosage regimen of mogamulizumab

The applicant's explanation about the rationale for selecting the dosage regimen:
Based on the data from Study 004, the dosage regimen for the approved indication of relapsed or refractory CCR4-positive PTCL or CTCL is specified as "The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses" (see the Review Report for Poteligeo Injection 20 mg, dated February 18, 2014). Meanwhile, the dosage regimen for Study 010 was specified as "1 mg/kg of mogamulizumab intravenously infused once weekly for 4 doses in the first 28-day cycle and once every 2 weeks for the subsequent cycles." This dosage regimen was determined based on foreign clinical studies (Studies KW-0761-001 and KW-0761-002) conducted in patients with relapsed or refractory PTCL or CTCL with a certain level of response rate (36.8% [14 of 38] of patients with CTCL), which was confirmed to have no significant safety issues.

Based on the data from Study 010 that demonstrated the clinical benefit of mogamulizumab [see Sections 7.R.2 and 7.R.3], etc., the dosage regimen of mogamulizumab was changed to that used in Study 010 from the approved one.

PMDA's view:
The applicant's explanation is generally acceptable. Nonetheless, the description in the "Dosage and Administration" section of the package insert should be modified as follows.

Dosage and administration:
The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 5 doses and once every 2 weeks for subsequent doses.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
Post-marketing surveillance is underway targeting patients with relapsed or refractory CCR4-positive PTCL or CTCL to evaluate the efficacy of mogamulizumab in post-marketing use. The surveillance is designed with the following specification.

- Key survey items: infusion reaction, skin disorders (e.g., various types of rash, pruritus, hyperhidrosis, dermatitis, eczema, and erythema), infections and immune disorders associated with hematotoxicity

(including reactivation of hepatitis B virus, fulminant hepatitis and cytomegalovirus (CMV) infection, and worsening/recurrence of autoimmune diseases), TLS, and ILD

- Target sample size: 150 patients
- Observation period: 31 weeks

Data from Study 010 suggest no new safety concerns in treating relapsed or refractory CTCL at the higher dosage than the approved dosage. However, results from the above post-marketing surveillance have not been available, and the safety information of mogamulizumab in Japanese patients with CTCL remains limited. Therefore, the post-marketing surveillance will be continued targeting patients with relapsed or refractory CTCL including those who are CCR4-negative, without changing the key survey items, target sample size, or observation period.

PMDA accepted the applicant's explanation.

7.2 Adverse events observed in clinical studies

Deaths reported in the clinical studies in the submitted data package for the safety evaluation are described in Section "7.1 Evaluation Data." Other main adverse events are described below.

7.2.1 Global phase III study (Study 010)

Adverse events occurred during the randomized treatment period in 179 of 184 patients (97.3%) in the mogamulizumab group and 185 of 186 patients (99.5%) in the vorinostat group. Adverse events for which a causal relationship with the study drug could not be ruled out occurred in 156 of 184 patients (84.8%) in the mogamulizumab group and 178 of 186 patients (95.7%) in the vorinostat group. Adverse events with an incidence of ≥20% in either group are shown in Table 16.

Table 16. Adverse events with an incidence of ≥20% in either group (the randomized treatment period)

SOC PT (MedDRA/J ver.20.0)	Number of subjects (%)			
	Mogamulizumab N = 184		Vorinostat N = 186	
	All grades	≥Grade 3	All grades	≥Grade 3
All adverse events	179 (97.3)	78 (42.4)	185 (99.5)	85 (45.7)
Blood and lymphatic system disorders				
Thrombocytopenia	21 (11.4)	0	57 (30.6)	13 (7.0)
Gastrointestinal disorders				
Diarrhoea	43 (23.4)	1 (0.5)	115 (61.8)	9 (4.8)
Nausea	28 (15.2)	1 (0.5)	79 (42.5)	3 (1.6)
General disorders and administration site conditions				
Fatigue	43 (23.4)	3 (1.6)	70 (37.6)	11 (5.9)
Injury, poisoning and procedural complications				
Infusion related reaction	61 (33.2)	3 (1.6)	1 (0.5)	0
Investigations				
Blood creatinine increased	6 (3.3)	0	53 (28.5)	0
Metabolism and nutrition disorders				
Decreased appetite	14 (7.6)	2 (1.1)	46 (24.7)	2 (1.1)
Nervous system disorders				
Dysgeusia	6 (3.3)	0	54 (29.0)	1 (0.5)
Skin and subcutaneous tissue disorders				
Drug eruption	44 (23.9)	8 (4.3)	1 (0.5)	0

Serious adverse events occurred in 69 of 184 patients (37.5%) in the mogamulizumab group and 46 of 186 patients (24.7%) in the vorinostat group. The serious adverse events occurring in ≥2 patients in the mogamulizumab group are pyrexia (8 patients; 4.3%), cellulitis (5; 2.7%), disease progression, pneumonia (4 each; 2.2%), sepsis, infusion related reaction, hypercalcaemia (3 each; 1.6%), bacteraemia, bronchitis, herpes simplex, osteomyelitis, fall, ALT increased, AST increased, arthralgia, acute kidney injury, respiratory failure, drug eruption, and embolism (2 each; 1.1%). The serious adverse events occurring in ≥2 patients in the vorinostat group are cellulitis, pulmonary embolism (6 each; 3.2%), sepsis (5; 2.7%), thrombocytopenia, pneumonia, skin infection (3 each; 1.6%), neutropenia, asthenia, and upper respiratory tract infection (2 each; 1.1%). A causal relationship with the study drug was not ruled out for, in the mogamulizumab group, pyrexia, pneumonia (4 patients each), cellulitis, infusion related reaction (3 each), sepsis, ALT increased, AST increased, respiratory failure, drug eruption (2 each), bronchitis, osteomyelitis, and arthralgia (1 each), and in the vorinostat group, pulmonary embolism (5), thrombocytopenia (3), asthenia (2), cellulitis, sepsis, pneumonia, skin infection, and neutropenia (1 each).

Adverse events leading to the discontinuation of the study drug occurred in 35 of 184 patients (19.0%) in the mogamulizumab group and 43 of 186 patients (23.1%) in the vorinostat group. The adverse events leading to discontinuation in ≥2 patients in each group are, in the mogamulizumab group, drug eruption (13 patients; 7.1%), disease progression (3; 1.6%), skin infection, and acute kidney injury (2 each; 1.1%); and in the vorinostat group, fatigue (8; 4.3%), thrombocytopenia, diarrhoea (5 each; 2.7%), nausea, weight decreased, pulmonary embolism (4 each; 2.2%), vomiting, asthenia (3 each; 1.6%), decreased appetite, muscular weakness, myalgia, dysgeusia, and deep vein thrombosis (2 each; 1.1%). A causal relationship with the study drug was

not ruled out for, in the mogamulizumab group, drug eruption (13 patients) and acute kidney injury (1); and in the vorinostat group, fatigue (8), diarrhoea (5), thrombocytopenia, nausea, weight decreased, pulmonary embolism (4 each), vomiting, asthenia (3 each), decreased appetite, muscular weakness, myalgia, dysgeusia and deep vein thrombosis (2 each).

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

Compliance assessment is now underway, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

Compliance assessment is now underway, and the results and PMDA's conclusion will be reported in the 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 product has efficacy in the treatment of relapsed or refractory CTCL and that the product has acceptable safety in view of its benefits. The product offers a new therapeutic option for relapsed or refractory CTCL and has clinical significance. PMDA considers that further discussion is necessary for the efficacy and indications, etc.

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

Review Report (2)

July 17, 2018

Product Submitted for Approval

Brand Name	Poteligeo Injection 20 mg
Non-proprietary Name	Mogamulizumab (Genetical Recombination)
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	November 30, 2017

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

1.1 Efficacy

As a result of it review described in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has concluded that the efficacy of mogamulizumab has been demonstrated in patients with relapsed or refractory CTCL by significant improvement in the primary endpoint, that is, PFS judged by investigators based on the modified criteria for evaluation of antitumor response, in the mogamulizumab group as compared with the control vorinostat group in the global phase III study in patients with relapsed or refractory CTCL (Study 010).

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

1.2 Safety

As a result of its review in the "7.R.3 Safety" section of the Review Report (1), PMDA has concluded that the adverse events that require vigilance during the treatment with mogamulizumab are hematotoxicity (bone marrow depression), infusion reactions, infections/immune system disorders, skin disorders, TLS, hepatic function disorders, cardiac dysfunction, ILD, and hyperglycemia. All these events were also identified during the review for the approved indications as subject to caution.

In addition, PMDA has concluded that mogamulizumab, despite the need for vigilance against these adverse events in its use, is tolerable when the adverse events are monitored and managed, and appropriate measures such as discontinuation/interruption of mogamulizumab are taken by physicians with adequate knowledge and

experience in the treatment of hematopoietic malignancy.

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

1.3 Clinical positioning and indications

As a result of its review described in the section "7.R.4 Clinical positioning and indications" of the Review Report (1), PMDA has concluded that mogamulizumab should be indicated for the treatment of "relapsed or refractory cutaneous T-cell lymphoma" as proposed, after deleting the phrases stating that "Patients should be tested for CCR4 antigen by flow cytometry (FCM) or immunohistochemistry (IHC), and mogamulizumab should be used for patients with relapsed or refractory CCR4-positive CTCL" and the word "CCR4-positive" from the statements in the section of the current package insert.

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

Based on the above, PMDA instructed the applicant that the "Indications" and "Precautions for Indications" sections of the package insert should be defined as mentioned above. The applicant answered that they would follow the instruction.

1.4 Dosage and administration

As a result of its review described in the section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the statements in the "Precautions for Dosage and Administration" section should be described as proposed by the applicant, and that the "Dosage and Administration" section should be described as follows:

Dosage and Administration

The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 5 doses and once every 2 weeks for subsequent doses.

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

Based on the above, PMDA instructed the applicant that the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package insert be described as above. The applicant answered that they would follow the instruction.

1.5 Risk management plan (draft)

Post-marketing surveillance is underway according to the specification below in patients with relapsed or refractory CCR4-positive peripheral T-cell lymphoma or CTCL, and results have yet to be available. The safety information of mogamulizumab in Japanese patients with CTCL remains limited. Given these, the applicant plans to continue with the post-marketing surveillance on CTCL targeting patients with relapsed or refractory

CTCL newly including those who are CCR4-negative, without changing the key survey items, target sample size, or the observation period.

- Key survey items: infusion reaction, skin disorder (e.g., various types of rash, pruritus, hyperhidrosis, dermatitis, eczema, and erythema) infections and immune disorders associated with hematotoxicity (including hepatitis B virus reactivation, fulminant hepatitis and CMV infection, and worsening/recurrence of autoimmune diseases), TLS, and ILD.
- Target sample size: 150 patients
- Observation period: 31 weeks

As a result of its review in the "7.R.6 Post-marketing investigations" section of the Review Report (1), PMDA has concluded that the applicant's explanation on the implementation of the above-mentioned post-marketing surveillance is acceptable and that it is appropriate to continue with the surveillance according to the applicant's plan.

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

In view of the discussion above, PMDA has concluded that the safety and efficacy specifications listed in Table 17 should be included in the current draft risk management plan for Poteligeo and that the applicant should conduct additional pharmacovigilance activities, survey/study on efficacy, and risk minimization activities listed in Tables 18 and 19.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Skin disorders • Infusion reaction • TLS • Bone marrow depression • Infections and immune disorders (including reactivation of hepatitis B virus, fulminant hepatitis, and CMV infection) • Hepatic function disorders • ILD • Hyperglycemia	• Worsening of autoimmune diseases • Cardiac dysfunction • Increased occurrence of serious acute graft-versus-host-disease (GVHD) after hematopoietic stem cell transplantation (HSCT) in patients receiving Poteligeo before HSCT.	• Use of Poteligeo in patients status post HSCT
Efficacy specification		
• Efficacy in routine clinical practice		

There are no amendments in the current application for partial change.

Table 18. Summary of additional pharmacovigilance activities, survey/study on efficacy, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Survey/study on efficacy	Additional risk minimization activities
• A specified drug use-results survey in patients with relapsed or refractory CCR4-positive ATL. • <u>A specified drug use-results survey in patients with relapsed or refractory CCR4-positive PTCL and relapsed or refractory CTCL.</u> • A specified drug use-results survey in chemotherapy-naïve patients with CCR4-positive ATL.	• A specified drug use-results survey in patients with relapsed or refractory CCR4-positive ATL. • <u>A specified drug use-results survey in patients with relapsed or refractory CCR4-positive PTCL and relapsed or refractory CTCL.</u> • A specified drug use-results survey in chemotherapy-naïve patients with CCR4-positive ATL.	• <u>Preparation and provision of materials for healthcare professionals (Guidelines for proper use)</u>

Underline denotes planned additional activities for the indication and dosage regimen.

Table 19. Outline of post-marketing surveillance (draft)

Objective	To evaluate the safety and other relevant factors of mogamulizumab in routine clinical practice.
Survey method	Central registration
Population	Patients with relapsed or refractory CCR4-positive PTCL or relapsed or refractory CTCL
Observation period	31 weeks
Planned sample size	150 patients
Main survey items	Key survey items: infusion reaction, skin disorders (e.g., various types of rash, pruritus, hyperhidrosis, dermatitis, eczema, and erythema), infections and immune disorders associated with hematotoxicity (including hepatitis B virus reactivation, fulminant hepatitis and CMV infection, and worsening/recurrence of autoimmune diseases), TLS, and ILD. Other: Responsiveness to pretreatment provided immediately before the administration of mogamulizumab, histopathological types, safety in re-administration, information on stem cell transplantation (SCT) (implementation of SCT before or after administration of mogamulizumab, occurrence of complications such as GVHD), laboratory data (including blood biochemistry examinations such as blood glucose), etc.

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA recognized that, in general, the studies were conducted in compliance with GCP, and thus concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following matter at some study sites and the sponsor (the clinical trial in-country representative), although which had no significant impact on the overall assessment of the studies. The matter was notified to the heads of relevant sites and the sponsor (the clinical trial in-country representative) to request improvement.

Findings requiring improvement

Trial sites and the sponsor (the clinical trial in-country representative)

- Misdescription in the contract on the conduct of the clinical studies

3. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration modified as presented below, with the following condition. The approval however is granted on the premise that necessary cautions are given in the package insert and information about the proper use of the product is provided appropriately to the post-marketing setting, and that the product is used appropriately under the supervision of physicians with adequate knowledge and experience in the

treatment of hematopoietic malignancy at medical institutions with adequate capability for emergency response. The re-examination period for the current application is the remainder of re-examination period for the partial change approval as of March 2014 (until March 16, 2024).

Indications (Strikethrough denotes deletions)

CCR4-positive adult T-cell leukemia lymphoma

Relapsed or refractory CCR4-positive peripheral T-cell lymphoma

Relapsed or refractory ~~CCR4 positive~~ cutaneous T-cell lymphoma

Dosage and administration (Strikethrough and underline denote deletions and additions, respectively.)

CCR4-positive adult T-cell leukemia lymphoma

The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses.

The usual adult dosage in combination with other antineoplastics is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once every 2 weeks for 8 doses.

Mogamulizumab should be used in combination with other antineoplastics for chemotherapy-naïve patients.

Relapsed or refractory CCR4-positive peripheral T-cell lymphoma

~~Relapsed or refractory CCR4-positive cutaneous T-cell lymphoma~~

The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 8 doses.

Relapsed or refractory cutaneous T-cell lymphoma

The usual adult dosage is 1 mg/kg of mogamulizumab (genetical recombination) intravenously infused once weekly for 5 doses and once every 2 weeks for subsequent doses.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warning (no change)

1. Mogamulizumab should be administered only to patients for whom the treatment is deemed eligible, under the supervision of physicians with adequate knowledge and experience in treatment of hematopoietic organ tumor at medical institutions with adequate facilities for the treatment of emergencies. Prior to the start of the treatment, the efficacy and the risk should be explained in detail to the patient or his/her family and informed consent should be obtained.
2. Severe skin disorders with systemic symptoms such as toxic epidermal necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) were reported. The treatment with Mogamulizumab should be started in cooperation with dermatologists. The treatment should be administered with following cautions in mind:
   (1) Severe skin disorders were reported not only during treatment with Mogamulizumab but also several

weeks after the completion of the treatment. Close vigilance is required.

(2) Treat skin disorders at an early stage appropriately with adrenocortical hormone preparations, antiallergics, or antihistamines. Discontinue Mogamulizumab if a severe skin disorder develops, and administer appropriate treatment.

Contraindications (no change)

Patients with a history of hypersensitivity to Mogamulizumab or any of the excipients.

Precautions for Indications (Strikethrough and underline denote deletions and additions, respectively.)

1. The disease to be treated with mogamulizumab should be diagnosed by a physician or a clinical center well experienced in pathological diagnosis.
2. For patients with CCR4-positive adult T-cell leukemia lymphoma (ATL), relapsed or refractory CCR4-positive peripheral T-cell lymphoma (PTCL), patients should be tested for CCR4 antigen by immunohistochemical staining, and only those who are confirmed to be CCR4-antigen positive should be treated with Mogamulizumab.
3. For patients with CCR4-positive ~~adult T-cell leukemia lymphoma (~~ATL~~)~~, physicians should thoroughly understand the disease type and presence/absence of poor prognostic factors in patients enrolled in clinical studies by reading the description in the "Clinical Studies" section and become fully aware of the efficacy and safety of Mogamulizumab before selecting patients to be treated with the drug.
4. For patients with relapsed or refractory CCR4-positive ~~peripheral T-cell lymphoma (~~PTCL~~)~~ or relapsed or refractory cutaneous T-cell lymphoma (CTCL), physicians should should thoroughly understand the histopathological types in patients enrolled in clinical studies by reading the "Clinical Studies" section and become fully aware of the efficacy and safety of Mogamulizumab before selecting patients to be treated with the drug.

Precautions for Dosage and Administration (Strikethrough and underline denote deletions and additions, respectively.)

1. Chemotherapy-naive patients with CCR4-positive ATL

(1) The efficacy and safety of Mogamulizumab monotherapy have not been established.

(2) Physicians should thoroughly understand information provided in the "Clinical Studies" section before choosing chemotherapy including Mogamulizumab.

(3) Physicians should carefully read the package insert of anticancer drugs to be used concomitantly.

2. Patients with relapsed or refractory CCR4-positive ATL~~,~~ or PTCL or relapsed or refractory CTCL

The efficacy and safety of concomitant use of Mogamulizumabg with other anticancer drugs have not been established.

3. Infusion reactions (e.g., pyrexia, chills, tachycardia) may occur after Mogamulizumab administration. Prior treatment with an anti-histamic drug antipyretic analgesic agent, or adrenocortical hormone preparation should be performed 30 minutes before Mogamulizumab administration to alleviate these symptoms.
4. Patients should be carefully monitored. If infusion reaction is noticed, treatment discontinuation or

administration at a reduced infusion rate should be considered immediately. When resuming the treatment, Mogamulizumab should be carefully administered at a reduced infusion rate as necessary. If, after the resumption of administration, an infusion reaction has occurred again, administration should be discontinued, and retreatment should not be performed.

5. Method for the preparation of the injection solution and the duration of infusion:

Take out the necessary amount of Mogamulizumab solution using a syringe, add 200 to 250 mL of saline, and infuse the solution over 2 hours.

List of Abbreviations

ADCC	antibody dependent cell mediated cytotoxicity
ALT	alanine aminotransferase
AMP regimen	combination therapy with doxorubicin hydrochloride, ranimustine, and prednisolone
Application for partial change	Application for partial changes in approved product information
AST	aspartate aminotransferase
ATL	adult T-cell leukemia-lymphoma
$AUC_{(0-\tau),ss}$	area under the serum concentration-time curve over the dosing interval at steady state
CCR4	CC chemokine receptor 4
CI	confidence interval
$C_{min,1st}$	minimum serum concentration after first dose
CMV	cytomegalovirus
CR	complete response
CrCL	creatinine clearance
CTCL	cutaneous T-cell lymphoma
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
Fc	fragment crystallizable
FcγR	Fc γ receptor
Foxp3	forkhead box P3
GVHD	graft versus host disease
HRP	horseradish peroxidase
Ig	immunoglobulin
ILD	interstitial lung disease
ITT	intent-to-treat
IRC	independent review committee
K_D	dissociation constant
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Mycosis fungoides
mLSG15 regimen	combination therapy with VCAP regimen, AMP regimen, VECP regimen, cytarabine, methotrexate, and prednisolone
mSWAT	modified Severity Weighted Assessment Tool
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluable
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial remission
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma

QD	quaque die
QW	quaque 1 week
Q2W	quaque 2 weeks
SCT	stem cell transplantation
SD	stable disease
SOC	system organ class
SPR	surface plasmon resonance
SS	Sézary syndrome
Study 004	Study 0761-004
Study 010	Study 0761-010
TLS	tumor lysis syndrome
Treg	regulatory T cells
V_1	central volume of distribution
V_2	peripheral volume of distribution
VCAP regimen	combination therapy with vincristine sulfate, cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone
VECP regimen	combination therapy with vindesine sulfate, etoposide, carboplatin, and prednisolone