Report on the Deliberation Results

February 6, 2012
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name] Poteligeo Injection 20 mg

[Non-proprietary name] Mogamulizumab (Genetical Recombination) (JAN*)

[Applicant] Kyowa Hakko Kirin Co., Ltd.

[Date of application] April 26, 2011

[Results of deliberation]
In the meeting held on February 1, 2012, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product with the re-examination period of 10 years, and both the drug substance and the drug product are classified as powerful drugs.

[Conditions for approval]
Since the product has been studied in only a limited number of patients in Japan, the applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of patients treated with this product. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

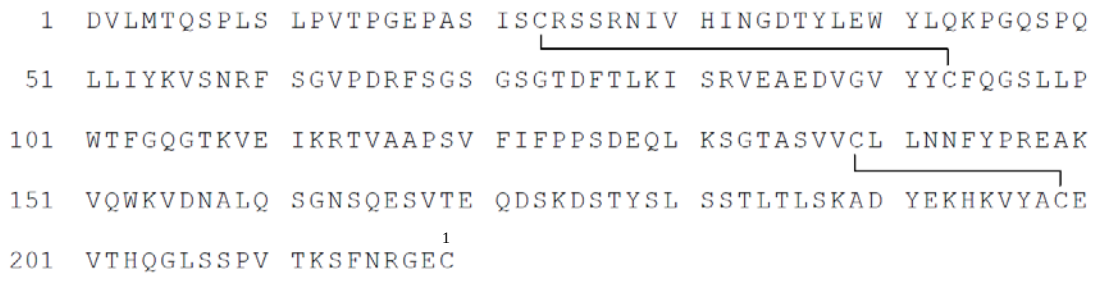
Review Report

January 17, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

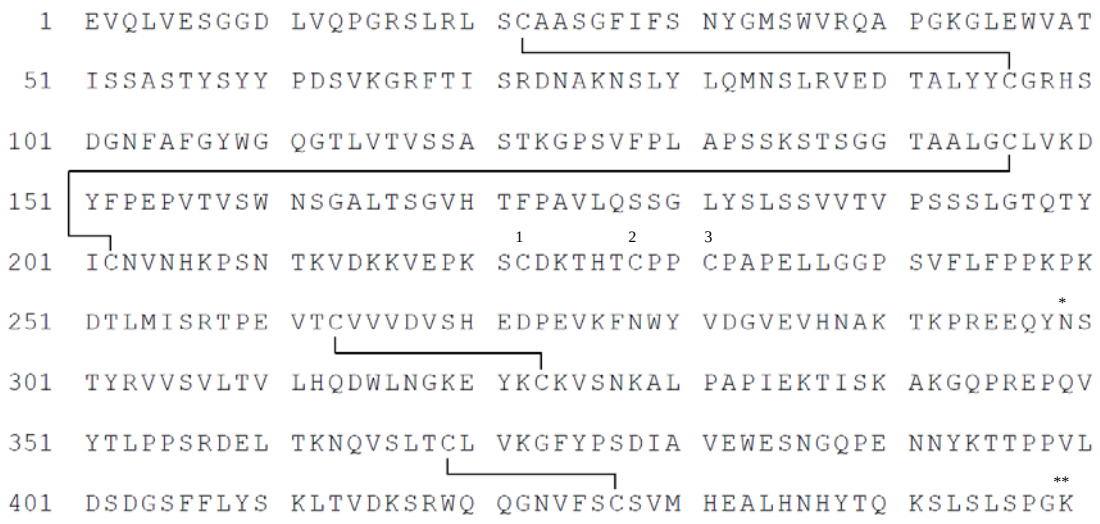
[Brand name]	Poteligeo Injection 20 mg
[Non-proprietary name]	Mogamulizumab (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	April 26, 2011
[Dosage form/Strength]	Injectable solution containing 20 mg Mogamulizumab (Genetical Recombination) per vial
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Amino acid sequence]



Light chain

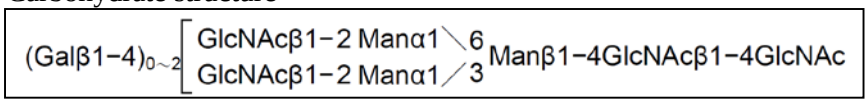
Intramolecular disulfide bonds: solid lines
Intermolecular disulfide bond: 1 (Cys^{219} in light chain – Cys^{222} in heavy chain)



Heavy chain

Intramolecular disulfide bonds: solid lines
Intermolecular disulfide bonds: 1 (Cys^{222} in heavy chain – Cys^{219} in light chain), 2 (Cys^{228} in heavy chain – Cys^{228} in heavy chain), 3 (Cys^{231} in heavy chain – Cys^{231} in heavy chain)
Glycosylation site: * (Asn^{299})
Partial deficiency: ** (Lys^{449})

Carbohydrate structure



Gal: D-Galactose, GlcNAc: D-*N*-acetylglucosamine, Man: D-mannose

Molecular formula: $C_{6520}H_{10072}N_{1736}O_{2020}S_{42}$
Molecular weight: approx. 149,000
Chemical name

Mogamulizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human CC chemokine receptor 4 monoclonal antibody and framework regions and constant regions derived from human IgG1. Mogamulizumab is produced in Chinese hamster ovary cells. Mogamulizumab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chain (γ1- chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 219 amino acid residues each.

[Items warranting special mention] Orphan drug (Notification No. 0811-3 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 11, 2010)

[Reviewing office] Office of New Drug V

Review Results

January 17, 2012

[Brand name]	Poteligeo Injection 20 mg
[Non-proprietary name]	Mogamulizumab (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	April 26, 2011

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma has been demonstrated and its safety is acceptable in view of its observed benefits. The safety concerns such as infusion reaction, skin disorder, infection, and reactivation of hepatitis B virus need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration with the following conditions for approval.

[Indication]	Relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma
[Dosage and administration]	The usual adult dosage is 1 mg/kg of Mogamulizumab (Genetical Recombination) intravenously infused once weekly for 8 doses.
[Conditions for approval]	Since the product has been studied in only a limited number of patients in Japan, a drug use-results survey should be conducted involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of patients treated with this product and, at the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

Review Report (1)

November 22, 2011

I. Product Submitted for Registration

[Brand name]	Poteligeo Injection 20 mg
[Non-proprietary name]	Mogamulizumab (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	April 26, 2011
[Dosage form/Strength]	Injectable solution containing 20 mg Mogamulizumab (Genetical Recombination) per vial
[Proposed indications]	Recurrent/relapsed CCR4-positive adult T-cell leukemia lymphoma
[Proposed dosage and administration]	The usual adult dosage is 1 mg/kg of Mogamulizumab (Genetical Recombination) intravenously infused once weekly for a maximum of 8 doses.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Drug overview

CC-Chemokine receptor 4 (CCR4), one of the chemokine receptors involved in the migration of white blood cells, is a receptor for chemotactic factors macrophage-derived chemokine (MDC or chemokine CCL22) and thymus and activation-regulated chemokine or chemokine CCL17 (hereafter referred to as "TARC"). Normal cells that express the receptor CCR4 include CD4-positive helper T cells type 2 (Th2) producing cytokines such as IL-4, IL-5, and IL-13. CCR4-positive cells are also present among T-cell lymphoma cells. Particularly in patients with adult T-cell leukemia-lymphoma (ATL), a subtype of T-cell lymphoma, CCR4-positive cells are detected at a high frequency. In addition, CCR4 expression is reported as an independent poor prognostic factor of ATL (*Clin Cancer Res* 2003;9:3625-34).

Mogamulizumab (Genetical Recombination) (hereinafter referred to as mogamulizumab) is a humanized anti-CCR4 monoclonal antibody discovered by Kyowa Hakko Kogyo Co., Ltd. (currently Kyowa Hakko Kirin Co., Ltd.). Mogamulizumab is considered to bind with CCR4, suppressing tumor growth by antibody-dependent cellular cytotoxicity (ADCC).

1.(2) Development history etc.

A phase I clinical study (Study 0761-0501) commenced in Japan in February 2007 in patients with CCR4-positive ATL or with CCR4-positive peripheral T-cell lymphoma (PTCL) including mycosis fungoides (MF). Subsequently, a phase II study (Study 0761-002) commenced in June 2009 in patients with CCR4-positive ATL. As of November 2011, no development work for [redacted] has been undertaken overseas.

The approval application for mogamulizumab was submitted based on the results of the Japanese Studies 0761-0501 and 0761-002 as the main clinical studies.

The brand name proposed at the time of submission was "Poteligeo for Injection 20 mg" but was changed to "Poteligeo Injection 20 mg" from the point of view of clinical safety.

Mogamulizumab was designated as an orphan drug in August 2010 with the proposed indication for the treatment of “CCR4-positive adult T-cell leukemia lymphoma” (Orphan Drug Designation Number:232 [of 2010]).

2. Data relating to quality

2.A. Summary of the submitted data

2.A.(1) Manufacturing process for the drug substance

2.A.(1).1) Establishment of cell banking system

Hybridoma cells expressing murine anti-human CCR4 monoclonal antibody (KM2160) were prepared by fusing murine myeloma cells with spleen cells isolated from Balb/c mice that had been immunized with a partial peptide of human CCR4. Using the genetic information of the hybridoma cells, the base sequence encoding the variable region of humanized antibody was designed, based on which the amino acid sequence and the base sequence for humanized anti-human CCR4 antibody were designed to have a variable region with the framework region partly replaced by murine antibody to maintain the antigen-binding activity. This base sequence was used to prepare gene fragments each encoding for the variable region of the light chain or the variable region of the heavy chain. These fragments were inserted into a plasmid expressing human IgG1 to prepare a gene expression construct.

The linearized gene expression construct was introduced into Chinese hamster ovary (CHO) cells by [redacted] method, and cell lines were selected by the assessment of the antibody-producing capacity, proliferative capacity, and [redacted] in the medium containing [redacted] and [redacted] ([redacted]). The cell line candidates thus selected were conditioned in a serum-free medium, and subcloned in the serum-free medium to obtain the seed cell line. A master cell bank (MCB) was prepared from the seed cell line and a working cell bank (WCB) was prepared from the MCB. The seed cells, MCB, and WCB were subjected to analysis of glycosylation-related genes.

2.A.(1).2) Characterization and control of cell banks

The MCB, WCB, and cells cultured at the limit of *in vitro* cell age used for production (CAL) were subjected to characterization tests described in the table below, and their genetic stability during the manufacturing period was confirmed. Based on the results of the characterization of the CAL, the maximum population doubling levels used from MCB to immediately before the production culture was determined.

Characterization of cell banks, etc.

Test	MCB	WCB	CAL
Isoenzyme analysis	CHO cell-derived	CHO cell-derived	CHO cell-derived
Restriction enzyme cleavage pattern of inserted DNA	Light chain: ca. [redacted] kb Heavy chain: ca. [redacted] kb	NT	Light chain: ca. [redacted] kb Heavy chain: ca. [redacted] kb
Transcript pattern of inserted DNA	Light chain: around [redacted] kb Heavy chain: around [redacted] kb	NT	Light chain: around [redacted] kb Heavy chain: around [redacted] kb
DNA copy number*[1]	Light chain: [redacted] ± [redacted] copies/cell Heavy chain: [redacted] ± [redacted] copies/cell	NT	Light chain: [redacted] ± [redacted] copies/cell Heavy chain: [redacted] ± [redacted] copies/cell
Base sequence analysis of cDNA	Identical to the expected base sequence	Identical to the expected base sequence	Identical to the expected base sequence
Proliferation in [redacted]-containing medium	Cell proliferation observed.	Cell proliferation observed.	Cell proliferation observed.

NT: Not tested
*1 Mean ± [redacted] standard deviation

In addition, purity tests as shown in the following table were performed. As a result, it was found that, except endogenous retroviruses and retrovirus-like particles commonly observed in rodent-derived cell lines, no adventitious viruses or nonviral infectious substances were detected within the range of the tests performed.

Results of purity tests of cell banks, etc.

Test		MCB	WCB	CAL
Sterility test		Negative	Negative	Negative
Mycoplasma testing (culture method, DNA staining method*1)		Negative	Negative	Negative
Tests for retroviruses and endogenous viruses	Infectivity assay*2	Negative	NT	Negative
	Co-culture test*3	NT	NT	Negative
	Electron microscopy	No viral particles other than retrovirus-like particles were observed.	NT	No viral particles other than retrovirus-like particles were observed.
	Reverse transcriptase activity	Negative	NT	Negative
Tests for non-endogenous or adventitious viruses	*in vitro* viral testing*4	Negative	NT	Negative
	in vivo viral testing*5	Negative	NT	Negative
	Murine antibody production test*6	Negative	NT	NT
	Hamster antibody production test*7	Negative	NT	NT
	In vitro test for porcine virus detection*8	Negative	NT	NT
	In vitro test for bovine virus detection*9	Negative	NT	NT

NT: Not tested
*1 NIH Swiss murine embryonic cells (MCB and WCB), African green monkey kidney-derived cells (CAL)
*2 Mink $MiCl_1$ (S^+L^-) cells
*3 Mink lung cells or human rhabdomyosarcoma cells
*4 Human diploid fibroblasts, African green monkey kidney-derived cells, CHO cells, human kidney-derived cells
*5 Suckling mice, mature mice, guinea pigs, embryonated eggs
*6 Sendai virus, pneumonia virus of mice, mouse hepatitis virus, minute virus of mice, mouse parvovirus, murine encephalomyelitis virus, reovirus type 3, rodent parvovirus, nonstructural protein 1, mouse rotavirus, K virus, ectromelia virus, polyomavirus, mouse adenovirus, lymphocytic choriomeningitis virus, mouse cytomegalovirus, mouse thymic virus, hantaan virus, Prospect Hill virus, lactate dehydrogenase-elevating virus
*7 Sendai virus, simian virus 5, pneumonia virus of mice, minute virus of mice, Kilham rat virus, H-1 virus, rodent parvovirus, nonstructural protein 1, murine encephalomyelitis virus, reovirus type 3, lymphocytic choriomeningitis virus, hantaan virus
*8 Porcine testis-derived cells, bovine turbinate-derived cells, African green monkey kidney-derived cells, fetal African green monkey kidney-derived cells
*9 Bovine testis-derived cells, bovine turbinate-derived cells, African green monkey kidney-derived cells

Cell banks are maintained in the vapor phase of liquid nitrogen separately in multiple facilities. The stability during the storage is to be confirmed by checking the cell viability at least every [redacted] years.

For the regeneration of the MCB, a new cell bank is to be prepared from the seed cell line, the MCB, or the WCB in the same manner as the current MCB, and the newly established MCB is to be qualified by the following tests: isoenzyme analysis, restriction enzyme cleavage pattern of inserted DNA, transcript pattern of inserted DNA, DNA copy number, base sequence analysis of cDNA, analysis of glycosylation-related genes, proliferation in [redacted]-containing medium, sterility test, mycoplasma testing, tests for retroviruses and endogenous viruses (infectivity assay, electron microscopy, reverse transcriptase activity), tests for adventitious viruses (*in vitro*, *in vivo*,

antibody production in mice and hamster, test for porcine viruses, test for bovine viruses).

For the regeneration of the WCB, a new cell bank is to be prepared from the MCB or the WCB in the same manner as the current WCB, and the newly established WCB is to be qualified by the following tests: isoenzyme analysis, base sequence analysis of cDNA, analysis of glycosylation-related genes, proliferation in [redacted]-containing medium, sterility test, mycoplasma testing, and tests for adventitious viruses (*in vitro*, *in vivo*).

2.A.(1).3) Manufacturing process

The manufacturing process for the drug substance is as follows.

Manufacturing process		In-process control
Stage 1	WCB thawing, preculture, and expansion culture Steps 1 to 6 Medium: [redacted] medium Equipment: Culturing flask, spinner, and bag Step 7 Medium: [redacted] medium Equipment: [redacted]-L bioreactor Step 8 Medium: [redacted] medium Equipment: [redacted]-L bioreactor	
Stage 2	<u>Full-scale culture process</u> Step 1 (production culture) Medium: [redacted] medium with feed medium [redacted] Equipment: [redacted]-L bioreactor Culture period: [redacted] days Step 2 (cell separation) Equipment: [redacted] and [redacted] (pore size [redacted] μm)	Mycoplasma testing (after step 1) Adventitious virus testing (after step 1)
Stage 3	<u>Purification process 1</u> Equipment: [redacted] chromatography resin	
Stage 4	<u>Viral inactivation process</u> (low pH hold)	
Stage 5	<u>Purification process 2</u> Equipment: [redacted] chromatography resin	[redacted]
Stage 6	Purification process 3 Equipment: [redacted] chromatography resin	
Stage 7	Concentration and buffer exchange process Equipment: [redacted] kDa ultrafiltration membrane	
Stage 8	<u>Membrane filtration for virus removal, concentration adjustment</u> Equipment: [redacted] filter for virus removal (pore size approx. [redacted] nm)	Filter integrity test (after use)
Stage 9	Filtration and filling process Equipment: Filter (pore size [redacted] μm) Container: [redacted] container	

<u>Double-underlined processes</u> indicate critical processes. Since all processes are operated in a consecutive manner, no intermediate products are stored.

Process validation of the manufacturing process for the drug substance was carried out using [redacted] commercial-scale lots. The results showed that each process was controlled appropriately.

The capacity of the purification process to remove impurities was investigated at the commercial scale. Results showed that host cell-derived impurities (host cell-derived DNA and host cell-derived protein [HCP]), cell culture process-related impurities ([redacted], [redacted], [redacted], [redacted] [redacted], [redacted] [redacted], [redacted], [redacted]), purification

process-related impurities (protein A), and product-related impurities (aggregates) were sufficiently removed.

Based on the results of laboratory-scale tests, the maximum number of reuse cycles of the chromatography resins in Stages 3, 5, and 6 was determined.

2.A.(1).4) Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, no raw materials of animal origin except the host cells (CHO cells) are used.

Purity tests for MCB, WCB, and CAL were performed. As a result, neither adventitious viruses nor non-viral infectious substances were detected [see "2.A.(1).2) Characterization and control of cell banks"]. Virus tests were carried out using the culture fluid in the production culture at the commercial scale. As a result, no viruses other than endogenous retroviruses and retrovirus-like particles were detected. Mycoplasma testing and virus testing are conducted on the culture fluid obtained after each production culture.

In order to evaluate the virus clearance capacity of the purification process, virus clearance tests were carried out as shown in the following table. Results showed that all viruses tested were completely removed in the purification process. The resin used in chromatography processes has been confirmed to retain sufficient capacity to remove viruses up to the predetermined maximum number of reuse cycles.

Results of virus clearance study

Purification process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Pseudorabies virus	Reovirus type 3
Step 3: Purification process 1*1 ([redacted] chromatography)	[redacted]	[redacted]	NT	[redacted]
Stage 4; Virus inactivation process*2	[redacted]	NT	[redacted]	NT
Stage 5: Purification process 2*1 ([redacted] chromatography)	[redacted]	[redacted]	[redacted]	[redacted]
Stage 8: Membrane filtration for virus removal*2	[redacted]	[redacted]	[redacted]	[redacted]
Total virus reduction factor	≥ 20.4	≥ 10.7	≥ 17.6	≥ 11.5

NT: Not tested

*1 The test was carried out both with the unused resin and with the resin used to the maximum number of reuse cycles. The lower value obtained is presented here.

*2 Of the results of [redacted] and [redacted] tests, the lower value is presented.

2.A.(1).5) Manufacturing process development (comparability)

During the manufacturing process development of the drug substance, the manufacturing process was changed twice, including the change of the manufacturing site, resulting in the proposed manufacturing process (manufacturing process B).

Summary of changes in manufacturing process

Manufacturing process		Manufacturing process A1	Manufacturing process A2	Manufacturing process B (proposed manufacturing process)
Intended use (except quality-related use)		Nonclinical studies Japanese phase I studies Japanese phase II studies Foreign phase I studies	Nonclinical studies	Nonclinical studies Japanese phase II studies
Stage 1	Medium	• Medium [redacted]: • Medium [redacted]:	• Medium [redacted]: • Medium [redacted]:	• Medium [redacted]: • Medium [redacted]:
	Culture period in each step	[redacted] days ([redacted] days in Step [redacted])	[redacted] or [redacted] days ([redacted] days in Step [redacted])	[redacted] or [redacted] days ([redacted] days in Step [redacted])
	Culture equipment	• Conical flask • Spinner • Cell culture reactor	• Conical flask • Cell culture bag • Cell culture reactor	• Conical flask • Spinner • Cell culture bag • Cell culture reactor
Stage 2	Medium	• Medium [redacted]: • Feed medium [redacted]:	• Medium [redacted]: • Feed medium [redacted]:	• Medium [redacted]: • Feed medium [redacted]:
	Culture scale	[redacted] L	[redacted] L	[redacted] L
Stage 9	Filling container	[redacted] container	[redacted] container	[redacted] container

The comparability between the drug substance produced by manufacturing process A1 and the drug substance produced by manufacturing process A2 and between the drug substance produced by manufacturing process A1 and the drug substance produced by manufacturing process B was investigated (test parameters are shown in the table below). Results demonstrated their comparability.

Tests for comparability in the manufacturing process development for drug substance

Change in manufacturing process	Test parameters
From manufacturing process A1 to A2	Description, pH, purity (SE-HPLC*[1]), biological activity ([redacted] activity), content (UV method*[2]), HCP content, [redacted] content, bacterial endotoxin, microbial limits
From manufacturing process A1 to B	Description, identification (ELISA*[3]), pH, purity (reduced CE-SDS*[4], SE-HPLC*[1], CEX-HPLC*[5]), HIC-HPLC*[6], [redacted] chromatography, biological activity ([redacted] activity), content (UV*[2]), HCP content, DNA content, [redacted] content, monosaccharide composition, glycosylation profile analysis, N-terminal amino acid sequence, peptide mapping, mass spectrometry by ESI-TOF/MS*[7], bacterial endotoxin, microbial limits

*[1] Size exclusion chromatography, *[2] Ultraviolet-visible spectrophotometry, *[3] Enzyme-linked immunosorbent assay, *[4] Capillary SDS gel electrophoresis, *[5] Cation exchange chromatography, *[6] Hydrophobic chromatography, *[7] Electrospray ionization time-of-flight mass spectrometry

2.A.(2) Drug substance

2.A.(2).1) Structure/Composition

The following results were obtained from the characterization of the drug substance.

i) Primary structure

- The amino acid composition determined by the amino acid analysis was identical with the theoretical value estimated from the cDNA base sequence.

- The amino acid sequence determined by N-terminal amino acid sequence analysis by Edman sequencing and by peptide mapping was identical with that estimated from the cDNA base sequence.

- Peptide mapping showed that most of the lysine residue at the C-terminal of the heavy chain is deleted.

ii) Higher-order structure

- Peptide mapping under reducing and non-reducing conditions showed that mogamulizumab has 4 intramolecular disulfide bonds in each heavy chain, 2 intramolecular disulfide bonds in each light chain, 1 disulfide bond between each heavy chain and light chain, and 2 disulfide bonds between heavy chains.

- Far-ultraviolet circular dichroism analysis showed that mogamulizumab has secondary structures with many β-sheets.

- Near-ultraviolet circular dichroism analysis showed that mogamulizumab has a tertiary structure which holds aromatic amino acids in a fixed steric conformation.

iii) Carbohydrate structure

- Peptide mapping, protein sequencing, and capillary SDS gel electrophoresis (CE-SDS) under reducing conditions showed that an N-linked oligosaccharide is bound to [redacted]% of asparagine residue at position 299 of the heavy chain.

- Glycosylation profile analysis showed that the percentages of each form of the total glycans are as follows: defucosylated biantennary glycans with 0 to 2 galactose residues, approximately [redacted]%; fucosylated biantennary glycans with 0 to 2 galactose residues, approximately [redacted]%; sialylated glycans with 1 or 2 sialic acid residues, approximately [redacted]%; and immature glycans, approximately [redacted]%.

- Analysis of neutral carbohydrates and amino carbohydrates by reverse phase chromatography showed that the content of each carbohydrate per mole of mogamulizumab is as follows: galactose, [redacted] mol; mannose, [redacted] mol; fucose, [redacted] mol; and N-acetylglucosamine, [redacted] mol. Analysis of sialic acid showed that 1 mole of mogamulizumab contains [redacted] mol of N-acetylneuraminic acid and less than the limit of quantitation ([redacted] mol) of N-glycorylneuraminic acid.

iv) Physicochemical properties

a. Molecular weight

- The molecular weight of mogamulizumab determined by electrospray ionization time-of-flight mass spectrometry (ESI-TOF/MS) was mostly identical with the theoretical molecular weight.

b. Electrophoresis

- Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under non-reducing conditions showed a major band of the monomer between [redacted] kDa and [redacted] kDa. SDS-PAGE under reducing conditions showed a major band of the heavy chain between [redacted] kDa and [redacted] kDa, and a major band of the light chain between [redacted] kDa and [redacted] kDa.

- CE-SDS under non-reducing conditions showed the main peak. CE-SDS under reducing conditions showed, in addition to the light chain and the heavy chain, the peaks of non-glycosylated heavy chain (approx. [redacted]%), molecular species smaller than the light chain (approx. [redacted]%), molecular species migrating between the light chain peak and the non-glycosylated heavy chain peak (approx. [redacted]%), and molecular species larger than the heavy chain (approx. [redacted]%).

- Isoelectric focusing showed [redacted] bands with the isoelectric point (pI) ranging from [redacted] to [redacted] and a major band near pI [redacted].

c. Liquid chromatography

- Size exclusion liquid chromatography (SE-HPLC) showed, in addition to the main peak of the monomer, a peak of aggregates mainly derived from [redacted] (approx. [redacted]%) and a peak of a truncated form (approx. [redacted]%). SE-HPLC of a sample that had been stored under stress conditions ([redacted]°C, [redacted] months) showed 2 peaks of truncated forms, one of which was mogamulizumab lacking Fab region, and the other was Fab fragment.

- Cation exchange chromatography (CEX-HPLC) showed, in addition to the main peak (approx. [redacted]%), a peak in the acidic region (approx. [redacted]%) and a peak in the alkaline region (approx. [redacted]%). Each peak fraction was assayed for biological activity ([redacted] activity) using [redacted] cell line ([redacted] cells) and [redacted] ([redacted]) cell line ([redacted] cells). Results did not show any clear difference among the peak fractions. In addition, SE-HPLC, [redacted] chromatography, peptide mapping, and glycosylation profile analysis showed that the main peak was the monomer lacking the C-terminal lysine residue in the heavy chain; that the peak in the acidic region had a higher content of sialoglycosylated forms, [redacted], glycated mogamulizumab (glycated form), and Glycosylated Form A, compared with the main peak; and that the peak in the alkaline region had a higher content of molecular species with C-terminal lysine residue in the heavy chain, molecular species with amidated C-terminal proline residue in the heavy chain, [redacted], [redacted], [redacted], and [redacted], compared with the main peak.

- Hydrophobic chromatography (HIC-HPLC) after [redacted] digestion showed a peak due to Fab fragment, a main Fc peak due to Fc fragment (devoid of C-terminal lysine residue), and a pre-Fc peak due to Fc fragment with C-terminal lysine residue, Fc fragment of oxidized molecular species (oxidized form), etc.

d. Others

- The drug substance had an ultraviolet absorption spectrum with peak characteristic of protein (maximum absorption wavelength, minimum absorption wavelength).

- Extinction coefficient $E^{0.1\%}_{1cm}$ (280 nm) was approximately [redacted].

v) Biological properties [see "3.(i) Summary of pharmacology studies"]

- Enzyme-linked immunosorbent assay (ELISA) showed that mogamulizumab bound to human CCR4 peptide (hereafter referred to as "antigenic peptide") in a concentration-dependent manner. Binding affinity of the antigenic peptide with mogamulizumab (4 lots) was investigated by surface plasmon resonance (SPR). Results showed that the binding rate constant of the antigenic peptide with mogamulizumab was [redacted], [redacted], [redacted], and [redacted] × 10[redacted] $(mol/L)^{-1} \cdot s^{-1}$ (mean of 2 measurements for each lot).

- Flow cytometry (FCM) showed that the binding of mogamulizumab to human lymphocytes expressing human CCR4 was inhibited by the antigenic peptide in a concentration-dependent manner. Specific binding of mogamulizumab to human peripheral lymphocytes was observed mainly in CD4-positive fraction. No specific binding of mogamulizumab to peripheral monocytes or granulocytes was observed.

- ELISA of Fc receptor binding showed that mogamulizumab was bound to FcγRIIIa in a concentration-dependent manner.

- Mogamulizumab induced ADCC activity in a concentration-dependent manner. ADCC activity was investigated using 7 different types of human CCR4-positive cell lines as the target cells and peripheral blood mononuclear cells derived from healthy adults as the effector cells. Results showed that ADCC activity by mogamulizumab reached the

maximum level at 0.1 to 100 μg/mL.

vi) Product-related substances

Based on the examination of the biological activity ([redacted] activity) and the pharmacokinetics (PK), the oxidized form was regarded as the product-related substance.

2.A.(2).2) Impurities

i) Process-related impurities

Host cell-derived DNA, HCP, [redacted], and [redacted] were regarded as process-related impurities. It has been confirmed that all process-related impurities were completely removed during the purification process [see "2.A.(1).3) Manufacturing process"].

ii) Product-related impurities

Based on the biological activity ([redacted] activity), aggregates, truncated forms, Glycosylated Form A, and non-glycosylated forms were handled as product-related impurities. Aggregates and truncated forms are controlled by purity (SE-HPLC) that is included in the specifications for the drug substance and the drug product. Glycosylated Form A and non-glycosylated forms are controlled by purity (CE-SDS under reduced conditions) that is included in the specifications for the drug substance and the drug product.

2.A.(2).3) Drug substance specifications

The proposed specifications for the drug substance are description, identification (ELISA), pH, purity (CE-SDS under reducing conditions, CEX-HPLC, SE-HPLC), bacterial endotoxin, biological activity ([redacted] activity), glycosylation profile, and content (ultraviolet-visible spectrophotometry [UV method]).

2.A.(2).4) Stability of the drug substance

Stability tests of the drug substance manufactured at the commercial scale were performed under the conditions shown in the table below.

Outline of the stability tests of drug substance

	Storage conditions	Test period	Test parameters
Long-term testing (3 lots)	−70 ± 10°C, in a dark place	18 months*1	• Description • Identification (ELISA) • pH • Purity (CE-SDS under reducing conditions, SE-HPLC, CEX-HPLC) • HIC-HPLC • Biological activity ([redacted] activity) • Content (UV method) • Bacterial endotoxin (kinetic colorimetry)*2 • Microbial limits*2
Storage stability testing 1 (3 lots)	[redacted] ± [redacted]°C, in a dark place	[redacted] months	
Storage stability testing 2 (3 lots)	[redacted] ± [redacted]°C, in a dark place	[redacted] months	
Stress testing (1 lot)	[redacted] ± [redacted]°C, in a dark place	[redacted] months	
Photostability testing (1 lot)	2 to 8°C with and without light protection		
	Total illuminance 1.2 × 10^6 lx·h, Total near UV radiant energy 200W·h/m^2		

*1 Stability test ongoing for up to [redacted] months.
*2 Performed in the long-term storage test only.

The long-term testing and the storage stability testing 1 did not detect significant changes in any of the test parameters.

The storage stability testing 2 showed a decrease in the sum of the peaks of the heavy chain and the light chain in CE-SDS under reducing conditions, decrease in the main peak in SE-HPLC, increase in [redacted] peak and decrease in the main peak in CEX-HPLC, decrease in the main Fc peak

in HIC-HPLC, and decrease in [redacted] activity.

The stress testing showed deterioration of the drug substance with the same test parameters as those in the storage stability testing 2.

The photostability testing showed deterioration of the light-irradiated sample with the same parameters as in those in the storage stability testing 2, except the decrease in [redacted] activity. In contrast, no significant changes were observed in the light-protected sample for any of the test parameters.

Based on the above results, a shelf life of 18 months has been proposed for the drug substance when stored in a teflon container at −70°C.

2.A.(3) Drug product

2.A.(3).1) Formulation development

The product (Poteligeo Injection 20 mg) is an injectable solution containing 20 mg of mogamulizumab in each vial (5 mL). It contains 112.5 mg glycine as [redacted], [redacted] mg citric acid hydrate as [redacted], 1 mg polysorbate 80 as [redacted], and appropriate amounts of pH adjusters (hydrochloric acid and sodium hydroxide) and water for injection. The product is supplied in a colorless glass vial with a butyl rubber stopper used as the container closure system. Cartons are used for the secondary packaging.

2.A.(3).2) Drug product formulation process

The manufacturing process for the drug product is as follows.

	Manufacturing process	In-process control
First step	Dissolution of drug substance, mixing and stirring, pH adjustment, volume adjustment	pH, protein concentration
Second step	Sterile filtration	
	Equipment: [redacted] filter (pore size [redacted] μm)	Filter integrity test (after use)
Third step	Filling, stoppering, clamping	Filling mass, seal performance
Fourth step	Packaging	
Fifth step	Product inspection, storage	

Double-underlined processes indicate critical processes.

Process validation for the formulation process was conducted using 3 lots manufactured at the commercial scale. Results showed that each manufacturing process was controlled appropriately.

2.A.(3).3) Manufacturing process development (comparability)

During the pharmaceutical development, the manufacturing process, the composition of the drug product, or the manufacturing site was not changed. Thus, the formulation used in clinical studies, the formulation used in specification development, and the formulation used in stability tests were all produced by the same manufacturing process, and also these formulations were the same as the to-be-marketed formulation.

2.A.(3).4) Drug product specifications

The proposed specifications for the drug product include description, identification (ELISA), pH, purity (CE-SDS under reducing conditions, SE-HPLC, CEX-HPLC), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, biological activity ([redacted] activity), and content (UV method).

2.A.(3).5) Stability of drug product

Stability testing of the drug product manufactured at the commercial scale was performed under the conditions shown in the table below.

Outline of stability tests of drug product

	Storage conditions	Test period	Test parameters
Long-term testing (3 lots)	5 ± 3°C Ambient humidity, in a dark place	18 months*1	• Description • Identification (ELISA) • pH • Purity (CE-SDS under reducing conditions, SE-HPLC, CEX-HPLC) • Biological activity (activity) • Content (UV method) • Osmotic ratio*2 • HIC-HPLC • Bacterial endotoxin (gelation method)*3 • Bacterial endotoxin (kinetic colorimetry)*2 • Extractable volume*2 • Foreign insoluble matter • Insoluble particulate matter • Sterility*2
Accelerated testing (3 lots)	25 ± 2°C 60 ± 5°C, RH, in a dark place	months	
Stress testing (1 lot)	± °C ± %, RH, in a dark place	months	
Photostability testing (1 lot)	5 ± 3°C Ambient humidity Primary package and secondary package (carton containing the primary package) Total illuminance 1.2×10^6 lx·h, Total near UV radiant energy 200 W·h/m^2		

*1 Stability test ongoing for up to months.
*2 Performed in the long-term storage testing and the accelerated testing only.
*3 Performed in the long-term storage testing only.

The long-term testing did not show significant changes in any of the test parameters.

The accelerated testing showed a decrease in the sum of the peaks of the heavy chain and the light chain in CE-SDS under reducing conditions, decrease in the main peak in SE-HPLC, increase in peak and decrease in the main peak in CEX-HPLC, and decrease in the main Fc peak in HIC-HPLC.

The stress testing showed a decrease in activity, in addition to the deterioration observed in the same test parameters as those observed in the accelerated testing.

In the photostability testing, the product in the primary package (filled in glass vial) showed deterioration in the same test parameters as those observed in the accelerated testing, whereas the product in the secondary package (carton containing the primary package) did not show significant changes in any of the test parameters.

Based on the above results, a shelf life of 18 months has been proposed for the drug product when stored at 2°C to 8°C with light protection.

2.A.(4) Reference material

The reference material is prepared according to the manufacturing process of the drug substance, filled in portions into , and stored at or below °C. Only the in-house primary reference material is established; no working reference material is established. The reference material is confirmed to be stable for months at the moment.

The control parameters for the reference material include description, identification (ELISA), pH, purity (CE-SDS under reducing conditions, CEX-HPLC, SE-HPLC), biological activity (activity), glycosylation profile, content (UV method), peptide mapping, , , , and .

2.B. Outline of the review by PMDA

Based on the submitted data and on the main results of the following reviews, PMDA has

concluded that the quality of the drug substance and the drug product is adequately controlled. However, since no detailed study has been performed to elucidate the relationship between the structural characteristics of mogamulizumab and the biological activity, it is desirable to conduct further studies to elucidate the relationship.

2.B.(1) Binding characteristics to Fc receptor

The applicant explained that, during the development phase of mogamulizumab, a cell line highly expressing defucosylated IgG1 was selected in the process of cell bank preparation, using the binding capacity to [redacted] as the index. Also, characterization of mogamulizumab has shown that the fucose content of mogamulizumab is lower than that reported for IgG in published literature, that the main carbohydrate structure in the Fc region of mogamulizumab is defucosylated form, and that mogamulizumab binds FcγRIIIa in a concentration-dependent manner.

In view of the above results of the characterization as well as in light of the reports that (i) defucosylated IgG1 has an enhanced binding affinity with FcγRIIIa compared with fucosylated IgG1 (e.g., *J Mol Biol* 2004;336:1239-49) and that (ii) defucosylated IgG1 has an enhanced ADCC activity compared with fucosylated IgG1 (e.g., *Cancer Res* 2004;64:2127-33), PMDA asked the applicant to explain the results of studies on the binding affinity of mogamulizumab with each class of Fc receptor and to explain the relationship between the fucose content of mogamulizumab and ADCC activity.

The applicant responded as follows:

The binding of defucosylated IgG1 to each class of Fc receptor and the relationship between the binding capacity to each class of Fc receptor and ADCC activity have been investigated using antigens different from CCR4 (*Clin Cancer Res* 2004;10:6248-55), but no such study has been performed on mogamulizumab. In response to PMDA's instruction, an additional study was performed on the binding affinity of mogamulizumab with Fc receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, neonatal Fc receptor [FcRn]) by SPR. The results showed that the binding constant of mogamulizumab with FcγRI or FcRn was not significantly different from that of IgG1 reported in published literature albeit not by direct comparison (binding constant for FcγRI $(mol/L)^{-1}$, [redacted] × 10[redacted] (mogamulizumab)/[redacted] × 10[redacted] (value for IgG1 reported in literature [*Blood* 2009;113:3716-25]); binding constant for FcRn $(mol/L)^{-1}$, [redacted] × 10[redacted] (mogamulizumab)/[redacted] × 10[redacted] (calculated from the dissociation constant for IgG1 reported in literature [*Drug Metab Dispos* 2007;35:86-94])), whereas the binding constant of mogamulizumab with FcγRIIIa tended to be higher than that of IgG1 with FcγRIIIa reported in the literature (binding constant for FcγRIIIa $(mol/L)^{-1}$, [redacted] × 10[redacted] (mogamulizumab)/[redacted] × 10[redacted] (value for IgG1 reported in literature [*Blood* 2009;113:3716-25])). The binding constant of mogamulizumab with FcγRIIa and FcγRIIb could not be calculated because of the low binding affinity. The relationship between the fucose content of mogamulizumab and ADCC activity has not been investigated.

PMDA accepts the results of the additional study on the binding affinity of mogamulizumab with each class of Fc receptor. However, since the results were not obtained by direct comparison with highly fucosylated IgG1 with the identical amino acid sequence, and since the relationship between the fucose content of mogamulizumab and ADCC activity has not been studied, PMDA considers that it is unclear whether or not the enhancement of ADCC activity in defucosylated IgG1 as reported in published literature is achieved with mogamulizumab as well.

2.B.(2) Specifications

PMDA required the applicant take the following measures on the specifications.

1) The applicant should include, as an identification test, peptide mapping that is highly specific to the target substance and allows direct confirmation of the consistency of the primary structure.

2) Since only a limited number of lots have so far been manufactured at the commercial scale, it is practically impossible to conclude, based on the submitted test results, that HCP is consistently controllable. Until sufficient manufacturing experience is gained, the applicant should control the residual HCP by in-process control test or a purity test included in the specifications.
3) The major carbohydrate structure of mogamulizumab is defucosylated form; mogamulizumab has been developed aiming at obtaining defucosylated IgG1. There are reports suggesting the relationship between fucose content and ADCC activity in monoclonal antibodies of IgG1 class. Therefore, the applicant should include in the specifications the fucose content or the relative abundance of defucosylated forms and fucosylated forms in the total glycans.
4) The range of the acceptance criteria for biological activity is too wide to ensure the consistency in quality attributes. Therefore, the applicant should re-examine the specification range based on the results of the analytical procedure validation and lot analysis, and also by examining the method of data processing at the time of measurement.

The applicant responded to the above instructions as follows:
1) In addition to ELISA, peptide mapping will be included in the specifications as an identification test.
2) HCP content will be included in the specifications as a purity test to control the remaining HCP.
3) Regarding glycosylation profile, the relative abundance of major defucosylated forms in the total glycans and the limit value for fucosylated glycans will be included in the specifications.
4) The acceptance criteria for biological activity will be changed. At the same time, the acceptance criteria for biological activity of the drug product will also be changed.

PMDA accepted the response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A. Summary of submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Tumor growth-suppressing effect

***in vitro*:**

i) ADCC activity against human ATL-derived cell lines and against HTLV-1-infected human T cell line (Studies d-[redacted]-318, [redacted]-001, d-[redacted]-186)

The expression level of CCR4 protein in human ATL-derived cell lines (TL-Om1, ATN-1, ATL102, HUT102) and in an HTLV-1-infected human T cell line (MT-2) was investigated by FCM. Based on the ratio of the mean fluorescence intensity (MFI) of cells treated with mogamulizumab to the MFI of cells treated with the isotype control (human IgG1), the applicant concluded that TL-Om1, ATN-1, ATL102, and MT-2 were “CCR4-positive” and HUT102 was “CCR4-negative” (see the table below).

Also, ADCC activity (relative to cytotoxic activity of 1% Nonidet P-40, etc.; the same applies to all studies on ADCC activity.) of mogamulizumab (0.0001-100 μg/mL) against TL-Om1, ATN-1, ATL102, HUT102, and MT-2 (target cells [T]) was investigated by chromium 51 (^{51}Cr) release assay using peripheral blood mononuclear cells (PBMC) of healthy adults as the effector cells (E) (E:T = 25:1). The ADCC activity induced by mogamulizumab (10 μg/mL) was as shown in the following table.

CCR4 protein expression in tumor cell lines and ADCC activity induced by mogamulizumab (E:T = 25:1)

	Tumor cell line	MFI ratio*1	CCR4 protein	ADCC activity (%)*2	
				Without mogamulizumab	With mogamulizumab*3
Human ATL-derived cell lines	TL-Om1	1.5	Positive	1 ± 2	54 ± 7
	ATN-1	3.1		14 ± 5	59 ± 2
	ATL102	2.5		14 ± 5	54 ± 2
	HUT102	1.0	Negative	6 ± 5	19 ± 5
HTLV-1-infected human T cell line	MT-2	9.8	Positive	17 ± 5	53 ± 2

*1 MFI of cells treated with mogamulizumab/MFI of cell treated with isotype control
*2 Mean ± standard deviation (SD) (n = 3)
*3 Treated with 10 μg/mL mogamulizumab

The applicant explained that the above results suggest that (i) mogamulizumab induces ADCC activity of the effector cells against human ATL-derived cell lines and an HTLV-1-infected human T cell line and that (ii) the mogamulizumab-induced ADCC activity is more potent against "CCR4-positive" cell lines than against "CCR4-negative" cell lines.

ii) ADCC activity against tumor cells derived from ATL patients (Study [redacted]-002)

ADCC activity of mogamulizumab (0.1-10 μg/mL) against CD3 positive cells (target cells [T]) isolated from PBMC of 10 ATL patients was investigated by ^{51}Cr release assay using CD3-negative cells isolated from PBMC of healthy adults as the effector cells (E) (under allogneic conditions) (E:T = 50:1). Since it is reported that immune function is suppressed in ATL patients (*Oncogene* 2005;24:6047-57), ADCC activity was also investigated using CD3-negative cells of the same patients as the effector cells (E) (under autologous conditions) (E:T = 50:1). The ADCC activity induced by mogamulizumab (10 μg/mL) was as shown in the following table.

Mogamulizumab-induced ADCC activity against tumor cells derived from ATL patients (E:T = 50:1)

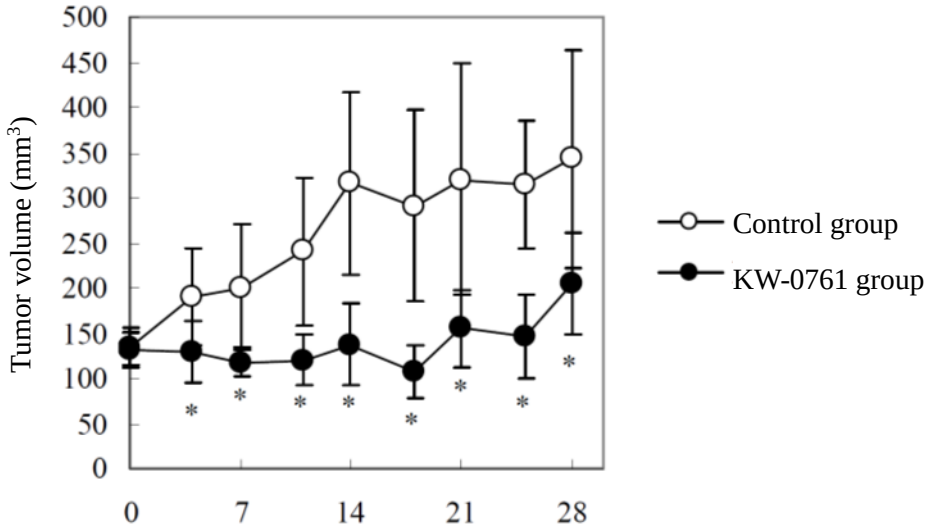
Sample No.	Target cells		Effector cells	ADCC activity (%)*1	
	Rate of CCR4-positive ATL cells (%)	CCR4 positive rate in ATL cells (%)	CD16 positive rate (%)	Without mogamulizumab	With mogamulizumab*2
			Upper row, autologous; lower row, allogenic		
IM-1	83	94	16	-4 ± 1	30 ± 7
			28	-5 ± 1	45 ± 1
IM-2	95	99	16	0 ± 1	49 ± 1
			28	-1 ± 2	65 ± 12
IM-3	26	83	19	-18 ± 9	22 ± 8
			31	-22 ± 9	83 ± 12
IM-5	53	92	22	1 ± 4	14 ± 4
			27	0 ± 2	48 ± 7
IM-6	51	94	37	5 ± 2	60 ± 6
			33	4 ± 1	79 ± 4
IM-7	72	93	51	-3 ± 2	52 ± 2
			23	0 ± 16	93 ± 4
IM-8	43	91	25	-6 ± 5	48 ± 4
			23	8 ± 28	85 ± 16
IM-9	88	98	12	-1 ± 2	17 ± 3
			28	-4 ± 0	59 ± 1
IM-10	49	97	15	1 ± 3	31 ± 4
			23	0 ± 1	93 ± 3
IM-11	92	97	8	-5 ± 1	-6 ± 2
			26	2 ± 8	63 ± 8
IM-12*3	94	99	35	4 ± 3	64 ± 8
			26	2 ± 2	82 ± 6
IM-13*4	56	99	21	-1 ± 4	45 ± 2
			26	3 ± 13	105 ± 6

*1 Mean ± SD (n = 3)
*2 Treated with 10 μg/mL mogamulizumab
*3 Derived from the same sample as that of IM-2
*4 Derived from the same sample as that of IM-10

The applicant explained as follows:
The above results suggest that mogamulizumab may induce ADCC activity against CCR4-positive ATL cells under autologous conditions, albeit less potent compared with the activity induced under allogeneic conditions. Sample IM-11 failed to show the induction of ADCC activity under autologous conditions due to the low percentage of CD16 (FcγRIII)-positive cells in the effector cells.

***in vivo*:**
i) Tumor growth-suppressing effect against human ATL-derived cell line (Study d-[redacted]-333)
The tumor growth-suppressing effect of mogamulizumab was investigated in severe combined immunodeficient (SCID) mice subcutaneously-implanted with human ATL-derived CCR4-positive TL-Om1 cell line. Starting 21 days post-implantation (Day 0), mogamulizumab (20 mg/kg) was intravenously administered once weekly for a total of 4 doses, and tumor volume was calculated (see Figure below).

Tumor growth-suppressing effect (TL-Om1 cell line)



n = 10, mean ± SD, *: $P < 0.05$ against control (vehicle) group (Wilcoxon rank sum test)
[Note by PMDA: Mogamulizumab is described as "KW-0761" in the figure.]

Based on the above results showing a statistically significant tumor growth suppression in the mogamulizumab group compared with the control (vehicle) group, the applicant explained that the tumor growth-suppressing effect of mogamulizumab against human ATL-derived CCR4-positive TL-Om1 cell line has been demonstrated.

3.(i).A.(1).2) Mechanism of action
i) Binding affinity
a. Binding affinity to CCR4 peptide (Study d-[redacted]-405)
The binding affinity of mogamulizumab (4 lots) to human CCR4 peptide (antigenic peptide with

the amino acid sequence comprising positions [redacted] to [redacted] from the [redacted] terminus of mogamulizumab) was investigated by SPR. The binding rate constant of each lot of mogamulizumab was [redacted], [redacted], [redacted], and [redacted] × 10[redacted] $(mol/L)^{-1} \cdot s^{-1}$ (mean results of 2 experiments for each lot). Dissociation rate constant was not able to be calculated due to the slow rate of dissociation.

b. Binding to peripheral white blood cells (Study [redacted]-055)

Binding of mogamulizumab to peripheral white blood cells of humans, cynomolgus monkeys, dogs, rats, and mice was investigated by FCM using biotin-labeled mogamulizumab. Mogamulizumab bound to lymphocytes (mainly CD4-positive cells) of humans and cynomolgus monkeys but not to cells of other animal species tested. Mogamulizumab did not bind to monocytes or granulocytes of any animal species tested.

ii) ADCC activity against CCR4-positive cell lines

The applicant explained that the results of the following *in vitro* and *in vivo* studies suggest that (i) mogamulizumab suppresses the growth of CCR4-positive malignant tumor cells via ADCC activity and that (ii) the extent of ADCC activity induced by mogamulizumab depends on the level of CCR4-protein expressed on the cell membrane.

***in vitro*:**

a. ADCC activity against CCR4 gene-introduced cell lines with different CCR4 protein expression levels (Study d-[redacted]-319)

The expression level of CCR4 protein in murine thymoma-derived EL-4 cell line (not expressing human CCR4 protein) and in human CCR4 gene-introduced EL-4 cell line was investigated by FCM. The ratio of MFI of cells treated with mogamulizumab to that of cells treated with the isotype control (human IgG) was as shown in the table below.

Mogamulizumab (10 μg/mL)-induced ADCC activity against EL-4, [redacted], [redacted], [redacted], and [redacted] was investigated by ^{51}Cr release assay using PBMC of healthy adults as the effector cells (E:T = 25:1). Mogamulizumab (10 μg/mL)-induced ADCC activity was as shown in the following table.

CCR4 protein expression level in CCR4 gene-introduced cell lines and ADCC activity induced by mogamulizumab (E:T = 25:1)

	MFI ratio*1	ADCC activity (%)*2	
		Without mogamulizumab	With mogamulizumab*3
EL-4	0.8	1.3 ± 0.9	2.2 ± 0.3
[redacted]	1.0	-0.2 ± 0.7	11.7 ± 0.8
[redacted]	1.1	0.9 ± 1.3	20.6 ± 1.4
[redacted]	2.5	0.6 ± 1.5	50.7 ± 0.3
[redacted]	4.7	0.2 ± 0.5	58.4 ± 4.3

*1 MFI of cells treated with mogamulizumab/MFI of cells treated with isotype control
*2 Mean ± SD (n = 3)
*3 Treated with 10 μg/mL mogamulizumab

b. ADCC activity against CCR4-positive cell line derived from malignant tumor of human T cells (Studies d-[redacted]-318, d-[redacted]-182, d-[redacted]-185, d-[redacted]-189)

Expression level of CCR4 protein in human cutaneous T-cell lymphoma (CTCL)-derived cell lines (HH, HuT78) and in a human T-cell acute lymphoblastic leukemia (T-ALL)-derived cell line (CCRF-CEM) was investigated by FCM. Based on the ratio of MFI of cells treated with mogamulizumab to that of cells treated with the isotype control (human IgG1), the applicant concluded that HH, HuT78, and CCRF-CEM were "CCR4-positive."

Mogamulizumab (0.0001-100 μg/mL)-induced ADCC activity against HH, HuT78, and CCRF-CEM was investigated by ^{51}Cr release assay using PBMC of healthy adults as the effector cells

(E:T = 25:1). The ADCC activity induced by mogamulizumab (10 μg/mL) was as shown in the following table.

Mogamulizumab-induced ADCC activity against CCR4-positive cell line derived from malignant tumor of human T cells (E:T = 25:1)

	MFI ratio*1	CCR4 protein	ADCC activity (%)*2	
			Without mogamulizumab	With mogamulizumab*3
HH	3.1	Positive	5 ± 7	73 ± 4
HuT78	1.3		11 ± 3	73 ± 6
CCRF-CEM	1.3		11 ± 4	63 ± 11

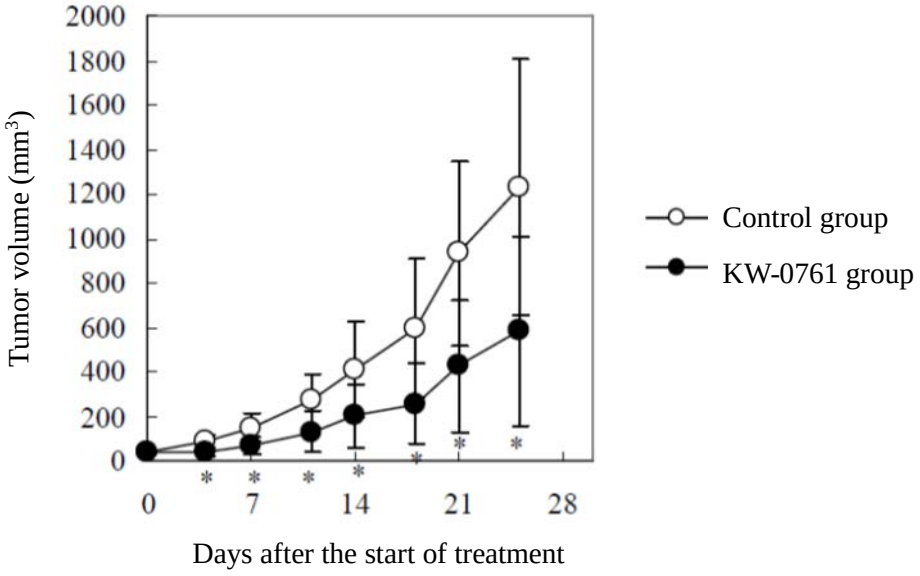
*1 MFI of cell treated with mogamulizumab/MFI of cells treated with isotype control
*2 Mean ± SD (n = 3)
*3 Treated with 10 μg/mL mogamulizumab

***in vivo*:**

Tumor growth-suppressing effect against CCR4-positive cell line derived from malignant tumor of human T cells (Study d-[redacted]-334)

The tumor growth-suppressing effect of mogamulizumab was investigated in SCID mice subcutaneously-implanted with CCR4-positive HH cell line. Starting 6 days post-implantation (Day 0), mogamulizumab (20 mg/kg) was intravenously administered once weekly for a total of 4 doses, and tumor volume was calculated (see Figure below).

Tumor growth-suppressing effect of mogamulizumab (HH cell line)



n = 10, mean ± SD, *: $P < 0.05$ against control (vehicle) group (Wilcoxon rank sum test)
[Note by PMDA: Mogamulizumab is described as "KW-0761" in the figure.]

iii) Effect on CCR4-positive cells in the peripheral blood of cynomolgus monkeys (Studies d-[redacted]-360, [redacted]-01)

Mogamulizumab (0.0001-100 μg/mL)-induced ADCC activity against HH cell line was investigated by ^{51}Cr release assay using PBMC of 3 cynomolgus monkeys as the effector cells. As a result, ADCC activity was induced by mogamulizumab in PBMC of all animals tested. Therefore, the effect of a single-dose intravenous administration of mogamulizumab (0.0000725-1 mg/kg) on the number of CCR4-positive/CD4-positive cells in the peripheral blood was investigated by FCM using cynomolgus monkeys. Administration of mogamulizumab at 0.01 mg/kg or higher dose caused a decrease in the number of CCR4-positive CD4 cells in the peripheral blood.

Based on these results, the applicant explained that mogamulizumab is expected to decrease the number of CCR4-positive cells *in vivo* as well.

iv) Others

a. Effect on the binding of CCR4 ligand (TARC) (Study d-[redacted]-348)

The effect of mogamulizumab on the binding of CCR4 with its ligand TARC was investigated using CCR4-positive [redacted] cell line. Mogamulizumab (0.01-2375 μg/mL) did not affect the binding of ^{125}I-labeled TARC ([^{125}I]-TARC) to the [redacted] cell line.

The applicant explained that mogamulizumab did not affect the binding of CCR4 with the ligand, which suggests that the drug does not interfere with the CCR4-mediated signal transduction system.

b. Effect on the expression level of CCR4 protein on cell membrane (Study d-[redacted]-316)

The effect of mogamulizumab on the expression level of CCR4 protein on cell membrane was investigated by FCM using CCR4-positive [redacted] cell line. Cells were preincubated in the presence of 50 μg/mL mogamulizumab for 60 minutes on ice, followed by incubation at 37°C. The expression level of CCR4 protein relative to that before the start of incubation was 96.9% at 5 minutes after the start of incubation, 87.4% after 15 minutes, 85.3% after 30 minutes, and 81.3% after 60 minutes.

The applicant explained that the above results suggest that mogamulizumab only has a small effect on the expression level of CCR4 protein on the cell membrane.

c. Complement-dependent cytotoxicity (CDC) (Study d-[redacted]-317)

The effect of mogamulizumab on CDC activity was investigated by ^{51}Cr release assay using TL-Om1 and HH cell lines. Mogamulizumab (0.0001-100 μg/mL) did not show CDC activity when human serum was used as the complement.

Since it is reported that CDC activity is suppressed by complement regulatory factors such as CD55 and CD59 (*Blood* 2001;98:3383-9), CDC activity was investigated in the presence of neutralizing antibodies against CD55 and CD59 as well. As a result, mogamulizumab (100 μg/mL) did not show any CDC activity.

The applicant explained that these results suggest that mogamulizumab does not induce CDC activity.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effect on platelets

It is reported that CCR4 protein is expressed on human platelets and that CCR4 ligands, MDC and TARC, induce platelet aggregation (*Blood* 2000;96:4046-54, *Blood* 2001;97:937-45, *Thromb Res* 2001;101:279-89). Therefore, the effects of mogamulizumab on platelets and on their function were investigated.

Based on the results of the studies shown in i) to iii) below, the applicant explained that mogamulizumab is unlikely to affect platelets or their function.

i) Binding of mogamulizumab to platelets (Studies d-[redacted]-107, d-[redacted]-309)

Binding of mogamulizumab (6.8-8.0 μg/mL) and other anti-human CCR4 antibodies ([redacted] antibody) (7.1-8.3 μg/mL) to human platelets was investigated by FCM. [redacted] antibody bound to platelets, whereas mogamulizumab did not. Also, mogamulizumab did not bind to platelets of humans or cynomolgus monkeys even at higher concentrations (0.2-500 μg/mL).

ii) Effect on platelet aggregation (Studies d-[redacted]-310, r-[redacted]-300)
The effect of mogamulizumab (0.2-2000 μg/mL) on platelet aggregation induced by adenosine diphosphate (ADP) or collagen was investigated using platelet-rich plasma (PRP) of humans and cynomolgus monkeys. Results showed that mogamulizumab did not affect platelet aggregation.

The effect of mogamulizumab or [redacted] antibody (both 100 μg/mL) on platelet aggregation that is induced by the combination of TARC and a low concentration of ADP was investigated using human PRP. Neither of the antibodies had any effect.

iii) Effect on platelet count (Study d-[redacted]-054)
The effect of mogamulizumab (10 or 100 μg/mL) on platelet count was investigated using human whole blood. As a result, mogamulizumab had no effect on platelet count. This study also investigated the effect of mogamulizumab on the percentage of CCR4-positive lymphocytes among CD4-positive cells in the whole blood of humans. Results showed that mogamulizumab caused a decrease in the percentage.

3.(i).A.(2).2) Effect on cytokine release (Study [redacted]-023)
Since mogamulizumab is a monoclonal antibody that acts on T cells, it may affect cytokine release from T cells. Therefore, the effect of mogamulizumab (1-10,000 ng/mL) on the release of tumor necrosis factor (TNF)-α and interferon (IFN)-γ was investigated by ELISA using the whole blood of humans (6 samples). [redacted] (anti-[redacted] antibody, [redacted] ng/mL) was used as a low-activity positive control, and [redacted] (anti-[redacted] antibody, [redacted] ng/mL) as a high-activity positive control.

TNF-α was detected in all samples in the presence of the positive controls, whereas the cytokine was not detected in any of the samples in the presence of mogamulizumab.

IFN-γ was detected in all samples in the presence of positive controls. The cytokine was not detected in 5 of 6 samples in the presence of mogamulizumab, whereas in the remaining sample, IFN-γ was detected at a level similar to that observed with [redacted] in 1 of 6 samples in the presence of the maximum concentration (10,000 ng/mL) of mogamulizumab.

From these results, the applicant explained as follows:
Although the obtained results suggested that the effect of mogamulizumab on cytokine release was weaker than that of the low-activity positive control [redacted], the maximum concentration of mogamulizumab used in the above study (10,000 ng/mL) was lower than the maximum plasma concentration of the drug reached following the initial administration in the Japanese phase II study (Study 0761-002) conducted to determine the proposed dosage and administration (16,622 ± 3324 ng/mL [mean ± SD]). In addition, in the Japanese phase I study (Study 0761-0501) and in the Japanese phase II study (Study 0761-002), adverse events suspected of being caused by cytokine release (e.g., infusion related reaction, pyrexia, chills, rash) occurred, albeit not serious. Therefore, it cannot be excluded that mogamulizumab may cause cytokine release in ATL patients. Information will be provided in an appropriate manner to clinical practice regarding the possibility of adverse events suspected of being due to cytokine release caused by mogamulizumab.

3.(i).A.(3) Safety pharmacology
The effects of mogamulizumab on the central nervous system, cardiovascular system, respiratory system, and renal function were investigated in single-dose toxicity studies and repeated-dose toxicity studies using cynomolgus monkeys [see "3.(iii).A.(1) Single-dose toxicity study and 3.(iii).A.(2) Repeated-dose toxicity studies"].

3.(i).A.(3).1) Effect on the central nervous system ([redacted]03, [redacted]-033, [redacted]27, [redacted]61)

Mogamulizumab was administered intravenously to cynomolgus monkeys (5 each of males and females per group) for 4 weeks at a dose of 0.05, 1.2, or 40 mg/kg/week or for 13 weeks at a dose of 2.5, 10, or 40 mg/kg/week to investigate the effect on general symptoms, body temperature, neurobehavioral parameters (behavior, clinical sign observation, reflex, motility/sensation, expression, pupil, visual field, sense of equilibrium, grasping, swallowing, proprioceptive sensibility) (in 4-week study only) and electrophysiological test parameters (central nervous system, brain stem auditory evoked response, visual evoked potentials, somatosensory evoked potentials; peripheral nervous system, motor conduction, F waves, and sural nerve conduction) (in 4-week study only). No changes suggestive of the effect of mogamulizumab were observed in any of the parameters tested.

Mogamulizumab was administered intravenously or subcutaneously in a single dose of 1.2 or 10 mg/kg to cynomolgus monkeys (3 males per group) or in a single dose of 10 mg/kg to cynomolgus monkeys (5 males per group), and the effects on general conditions were investigated. Results showed no changes suggestive of the effect of mogamulizumab.

3.(i).A.(3).2) Effect on the cardiovascular system ([redacted]03, [redacted]-033, [redacted]27, [redacted]61)

Mogamulizumab was administered intravenously to cynomolgus monkeys (5 each of males and females per group) for 4 weeks at a dose of 0.05, 1.2, or 40 mg/kg/week or for 13 weeks at a dose of 2.5, 10, or 40 mg/kg/week, and effects on blood pressure systolic, blood pressure diastolic, mean arterial pressure (in 4-week study only), heart rate, electrocardiogram (PR interval [13-week study only], RR interval, QT/QTc interval) were investigated. No changes suggestive of the effect of mogamulizumab on the cardiovascular system were observed.

Mogamulizumab was administered in a single dose intravenously or subcutaneously at a dose of 1.2 or 10 mg/kg to cynomolgus monkeys (3 males per group) or at a dose of 10 mg/kg to cynomolgus monkeys (5 males per group), and the effect on heart rate was investigated under ketamine sedation. No changes suggestive of the effect of mogamulizumab on the heart rate were observed.

3.(i).A.(3).3) Effect on the respiratory system ([redacted]03, [redacted]27, [redacted]61)

Mogamulizumab was administered intravenously to cynomolgus monkeys (5 each of males and females per group) at a dose of 0.05, 1.2, and 40 mg/kg/week for 4 weeks, and the effect on the respiratory pattern and on blood carbon dioxide (CO_2) concentration was investigated. Results showed no changes suggestive of the effect of mogamulizumab on the respiratory system.

Mogamulizumab was administered in a single dose intravenously or subcutaneously to cynomolgus monkeys (3 males per group) at a dose of 1.2 or 10 mg/kg, or to cynomolgus monkeys (5 males per group) at a dose of 10 mg/kg, and the effect on the respiratory rate and blood CO_2 concentration was investigated under ketamine sedation. No changes suggestive of the effect of mogamulizumab on the respiratory system were observed.

3.(i).A.(3).4) Effect on renal function ([redacted]03, [redacted]-033, [redacted]27, [redacted]61)

Mogamulizumab was administered intravenously to cynomolgus monkeys (5 each of males and females per group) for 4 weeks at a dose of 0.05, 1.2, or 40 mg/kg/week or for 13 weeks at a dose of 2.5, 10, or 40 mg/kg/week, and clinical chemistry tests (urea nitrogen, creatinine, electrolytes) and urinalysis were performed. None of the parameters tested showed changes suggestive of the effect of mogamulizumab on renal function.

Mogamulizumab was administered intravenously or subcutaneously in a single dose of 1.2 or 10 mg/kg to cynomolgus monkeys (3 males per group) or in a single dose of 10 mg/kg to cynomolgus monkeys (5 males per group), and clinical chemistry tests (urea nitrogen, creatinine, electrolytes). None of the parameters tested showed changes suggestive of the effect of mogamulizumab on renal function.

3.(i).B. Outline of the review by PMDA

Based on the submitted data and on the following review, PMDA has concluded that mogamulizumab is expected to be effective for CCR4-positive ATL.

Mechanism of action of mogamulizumab and growth suppressing effect on CCR4-positive ATL cells

Based on the findings that (i) mogamulizumab exhibited ADCC activity in a manner dependent on the expression level of CCR4 protein, (ii) mogamulizumab did not affect the binding of TARC to CCR4, suggesting that the drug did not inhibit the CCR4-mediated signal transduction system, (iii) mogamulizumab had only a minor effect on the expression level of CCR4 protein on the cell membrane, and (iv) mogamulizumab did not induce CDC activity, the applicant explained that mogamulizumab suppresses the growth of CCR4-positive ATL cells mainly via ADCC activity.

PMDA, while admitting that the available data suggest that mogamulizumab-induced ADCC activity is mainly involved in the mechanism of action, asked the applicant to further discuss the possibility that mogamulizumab may suppress the growth of ATL cells via other mechanism.

The applicant responded as follows:

(a) Inhibition of the function of CCR4 expressed on ATL cells

Dendritic cells of the skin, while secreting CCR4 ligands, are involved in the migration of CCR4-expressing cells to the skin (*Clin Cancer Res* 2003;9:3625-34, *J Leukoc Biol* 2001;69:785-93, *Am J Pathol* 2002;160:347-55). Therefore, mogamulizumab may affect the infiltration of CCR4-positive ATL cells into the skin. However, at the moment, the relationship between the inhibition of CCR4 expressed on ATL cells and suppression of the growth of CCR4-positive ATL cells is unclear.

(b) Inhibition of the function of CCR4 expressed on immune cells

In light of the findings that Th2 cells and regulatory T cells (Treg) express CCR4 (*J Exp Med* 2001;194:847-53, *J Immunol* 2007;178:4891-900, *Cancer Res* 2006;66:5716-22) and that administration of mogamulizumab resulted in a decrease in the number of Th2 cells and Treg cells in ATL patients, mogamulizumab may act on CCR4-expressing Th2 cells and Treg cells, thereby suppressing ATL cells. However, at the moment, it is unclear how the decrease in the number of CCR4-positive Th2 cells and Treg cells affects the overall immune function. As regards the effect of mogamulizumab on the overall immune function, data will be carefully collected from the results of ongoing clinical studies, etc.

PMDA considers as follows:

Although it is unclear how the difference between the *in vitro* ADCC activity observed under allogenic conditions and the activity observed under autologous conditions affects the difference in clinical effect, given the finding that mogamulizumab induced ADCC activity against CCR4-positive ATL cells under autologous conditions [see "3.(i).A.(1).1).ii) ADCC activity against tumor cells derived from ATL patients"], the explanation of the applicant that mogamulizumab suppresses the growth of ATL cells via ADCC activity is acceptable. However, for reasons described below, uncertainty remains on the mechanism of suppression of the growth of ATL cells by mogamulizumab. Therefore, it is desirable that the applicant actively pursues the issue and accumulates additional data.

- The applicant explained that mogamulizumab does not have neutralizing activity against CCR4 [see "3.(i).A.(1).2).iv).a. Effect on the binding of CCR4 ligand (TARC)"]. However, the neutralizing activity was studied only on TARC and the effect of mogamulizumab on the binding of MDC, another CCR4 ligand, to the receptor remains unknown.

- The function of CCR4 in ATL cells, such as the possible involvement of CCR4-mediated signal transduction in the growth of CCR4-positive ATL cells, has not been elucidated. As a result, it is unclear how the inhibition of this function by mogamulizumab affects the cells.

- It is unknown how the mogamulizumab-induced decrease in the number of CCR4-expressing Th2 cells and Treg cells affects the overall immune function.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A. Summary of the submitted data

PK of mogamulizumab in animals was investigated using cynomolgus monkeys.

3.(ii).A.(1) Analytical method

Mogamulizumab in the serum or plasma was measured by ELISA using [redacted] peptide and a secondary antibody recognizing human IgG, or by ELISA using immobilized anti-mogamulizumab antibody and peroxidase-labeled anti-mogamulizumab antibody.

Anti-mogamulizumab antibody was measured by ELISA using immobilized mogamulizumab and biotin-labeled mogamulizumab, or by electrochemical luminescence (ECL) using biotin-labeled mogamulizumab and ruthenium-labeled mogamulizumab. Neutralizing antibody against mogamulizumab was measured by ECL using [redacted] and [redacted] of [redacted]-labeled [redacted].

3.(ii).A.(2) Changes in blood concentration over time

3.(ii).A.(2).1) Single-dose administration

^{125}I-labeled mogamulizumab (1 mg/kg) was administered to male cynomolgus monkeys intravenously in a single dose, and total radioactivity concentration and mogamulizumab concentration in the plasma were measured. The $t_{1/2}$ of radioactivity was 5.42 days, AUC was 105 μg eq·day/mL, CL was 9.86 mL/day/kg, and V_{ss} was 67.6 mL/kg.

The applicant explained the results as follows:
Due to the fact that radioactivity in the fraction precipitated from the plasma by trichloroacetic acid (TCA) treatment was 97.2% to 100.1% of the total radioactivity in the plasma, most of the plasma radioactivity may be derived from ^{125}I-labeled mogamulizumab or other macromolecular fractions derived from ^{125}I-labeled mogamulizumab. In addition, plasma mogamulizumab concentration at 336 hours after administration was higher than the value calculated from the total radioactivity in 2 of 3 animals (concentration ratio, 2.26 and 2.54, respectively), suggesting that ^{125}I was removed from some portion of mogamulizumab molecules in the circulation. In the remaining animal (concentration ratio, 0.14), plasma radioactivity concentration during the elimination phase decreased more rapidly compared with the above 2 animals, which suggests that anti-mogamulizumab antibody may have been produced [Note by PMDA: Anti-mogamulizumab antibody was not investigated in this study.].

Mogamulizumab (0.0000725, 0.001, 0.01, 0.1, or 1 mg/kg) was administered to male cynomolgus monkeys intravenously in a single dose, and plasma mogamulizumab concentration was measured. Plasma mogamulizumab concentration was below the lower limit of quantitation in ≤0.001 mg/kg dose groups at most of the measuring time points, whereas in 0.01 to 1 mg/kg groups, it was eliminated in a mostly biphasic manner. PK parameter values were as shown in the table below. Anti-mogamulizumab antibody was detected in 1 each out of 3 animals in the 0.0000725 and

0.001 mg/kg groups and in all animals in the ≥0.01 mg/kg dose groups.

PK parameter values following single dose intravenous administration of mogamulizumab to cynomolgus monkeys

Dose (mg/kg)	$t_{1/2\alpha}$ (day)	$t_{1/2\beta}$ (day)	$AUC_{0-\infty}$ (μg·day/mL)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.01	0.355 ± 0.092	3.81 ± 0.33	1.09 ± 0.20	9.36 ± 1.86	48.6 ± 6.7
0.1	0.413 ± 0.197	9.49 ± 3.88	16.2 ± 5.0	6.65 ± 2.41	79.3 ± 9.2
1	0.418 ± 0.094	13.9 ± 1.0	268 ± 15	3.74 ± 0.21	73.2 ± 3.7

Mean ± SD, n = 3

Mogamulizumab (10 mg/kg) was administered to male cynomolgus monkeys in a single dose intravenously or subcutaneously, and serum mogamulizumab concentration was measured (see the table below). Bioavailability following subcutaneous administration, calculated by AUC ratio in animals without anti-mogamulizumab production, was 91.9%.

PK parameter values of mogamulizumab following single dose intravenous or subcutaneous administration to cynomolgus monkeys

Route of administration	AUC_{last} (μg·day/mL)	AUC_{last} (μg·day/mL) in animals without anti-mogamulizumab antibody production	Animals with anti-mogamulizumab antibody production
i.v.	3790 ± 570	4090 ± 540*[1]	2/5*[3]
s.c.	3740 ± 1140	3760*[2]	3/5*[4]

Mean ± SD, n = 5
*[1] n = 3
*[2] SD not calculated because n = 2
*[3] Neutralizing antibody detected
*[4] Neutralizing antibody detected in 2 animals

3.(ii).A.(2).2) Repeated administration

Mogamulizumab (0.05, 1.2, or 40 mg/kg) was administered intravenously to male and female cynomolgus monkeys once weekly for 4 weeks, and plasma mogamulizumab concentration was measured. In the 0.05 mg/kg group, anti-mogamulizumab antibody was detected and plasma mogamulizumab concentration following repeated administration decreased more rapidly than following the initial administration. In the 1.2 and 40 mg/kg groups, in contrast, $AUC_{0-\infty,day1}$ following the initial administration was almost the same as $AUC_{0-7d,day22}$ following the last administration (range of $AUC_{0-7d,day22}/AUC_{0-\infty,day1}$ ratio: 0.96-1.24). No sex difference was observed in PK parameters in any of the treatment groups. Accumulation factors calculated from the ratio (final administration/initial administration) of plasma mogamulizumab concentration at 7 days after administration (C_{7d}) in the 1.2 and 40 mg/kg groups were ranging from 2.04 to 3.12. In animals in which anti-mogamulizumab antibody was detected, plasma mogamulizumab concentration decreased more rapidly compared with animals without anti-mogamulizumab antibody. Based on the results, the applicant explained that anti-mogamulizumab antibody affects the PK of the drug.

Mogamulizumab (2.5, 10, or 40 mg/kg) was administered intravenously to male and female cynomolgus monkeys once weekly for 13 weeks, and plasma mogamulizumab concentration was measured. C_{7d} was almost constant from Day 43 (sixth dose) in the 2.5 mg/kg group, from Day 71 (10th dose) in the 10 and 40 mg/kg groups. AUC_{0-7d} increased almost dose-proportionally. No sex differentiation was observed (see the table below). No anti-mogamulizumab antibody was detected in any of the animals.

PK parameter values of mogamulizumab following repeated intravenous administration to cynomolgus monkeys

Dose (mg/kg)		$C_{7d, day8}$ (μg/mL)	$C_{7d, day43}$ (μg/mL)	$C_{7d, day71}$ (μg/mL)	$C_{7d, day85}$ (μg/mL)	$C_{7d, day92}$ (μg/mL)	$AUC_{0\text{-}7d, day1}$ (μg·day/mL)	$AUC_{0\text{-}7d, day85}$ (μg·day/mL)
2.5	M	26.9 ± 2.0	79.9 ± 9.8	83.8 ± 20.8	80.5 ± 14.9	82.1 ± 16.0	259 ± 25	734 ± 109
	F	23.7 ± 3.0	75.3 ± 11.3	78.2 ± 21.2	79.7 ± 22.9	78.2 ± 14.3	228 ± 27	716 ± 106
10	M	77.9 ± 14.5	186 ± 72	364 ± 98	356 ± 80	335 ± 60	987 ± 88	2860 ± 421
	F	73.1 ± 8.7	136 ± 68	254 ± 143	274 ± 119	264 ± 98	907 ± 53	2269 ± 631
40	M	249 ± 26	872 ± 331	1339 ± 543	1476 ± 526	1498 ± 444	2825 ± 296	13,529 ± 3271
	F	237 ± 42	944 ± 256	1334 ± 314	1263 ± 296	1264 ± 282	2664 ± 341	10,984 ± 1763

Mean ± SD, n = 5

The applicant explained as follows:
Among the doses administered to investigate the PK of mogamulizumab, ≤0.1 mg/kg doses showed an increase in CL and decrease in V_{ss}. Elimination mediated by the antigen CCR4 and/or increased elimination rate caused by anti-mogamulizumab antibody appeared to have contributed to these observations. Animals without detectable anti-mogamulizumab antibody did not show any marked changes in PK after repeated administration.

3.(ii).A.(3) Distribution

^{125}I-labeled mogamulizumab (1 mg/kg) was administered to male cynomolgus monkeys intravenously in a single dose, and radioactivity in tissues was measured at 4, 24, and 336 hours after administration. Radioactivity was highest in the plasma, followed in decreasing order by the blood, spleen at all measuring time points. The radioactivity distributed in tissues other than the plasma and blood was up to 4.9% of the dose, and tissue/plasma ratio of radioactivity at each time point was 0.26 at the maximum (spleen). From these results, the applicant explained that mogamulizumab is distributed in tissues only at low levels.

Mogamulizumab (40 mg/kg) was administered intravenously to pregnant cynomolgus monkeys once weekly for 18 weeks from Gestation Day 20 to 139. The mogamulizumab concentration in fetal plasma on Gestation Day 140 was 983 μg/mL, and the ratio of concentration in fetal plasma to that of maternal plasma (1700 μg/mL) was 0.58. Anti-mogamulizumab antibody was not detected in any of the fetuses (10 animals in all).

Excretion of mogamulizumab into breast milk was not investigated, but the applicant explained that since mogamulizumab is an antibody of IgG1 class, it may be excreted in breast milk.

3.(ii).A.(4) Metabolism and excretion

The applicant thinks that, as is the case with endogenous IgG, mogamulizumab is degraded into low molecular weight peptides and amino acids, which are then excreted into urine or reused in the body. The applicant explained that studies on metabolism and excretion of mogamulizumab were omitted by referring to the guideline, "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PMSB/ELD Notification No. 326 dated February 22, 2000).

3.(ii).B. Outline of the review by PMDA

Based on the submitted data and the following review, PMDA has concluded that the applicant's discussions on PK are acceptable.

3.(ii).B.(1) Effect of anti-mogamulizumab antibody on the PK of mogamulizumab

PMDA asked the applicant to discuss the possibility that mogamulizumab in test samples, within the range of the concentration observed in each study, may have affected the measurement of anti-mogamulizumab antibody.

The applicant responded as follows:
Concentrations of mogamulizumab that affected the measurement of anti-mogamulizumab antibody were investigated using the two different methods (ELISA, ECL). The interfering concentration was ≥100 ng/mL for ELISA and ≥50 μg/mL for ECL. Based on these interfering concentrations and the actual mogamulizumab concentrations observed at the time points for anti-mogamulizumab antibody measurements, it is suggested that mogamulizumab may have interfered with anti-mogamulizumab antibody measurements in the 40 mg/kg group in the 4-week repeated-dose study (Study [redacted]03), and in all animals at all measuring points in the 13-week repeated-dose study and the study in pregnant cynomolgus monkeys (Studies [redacted]-033, [redacted]-049). However, in the single-dose studies (Studies [redacted]-01, [redacted]61) and in the 0.05 and 1.2 mg/kg groups in the 4-week repeated-dose study (Study [redacted]03), anti-mogamulizumab antibody was measured at time points where mogamulizumab was below the interfering concentration, though interference was likely at some measuring points. Therefore, evaluation is possible from the data obtained, regarding the production of anti-mogamulizumab antibody.

PMDA asked the applicant to explain the difference in PK parameter values of mogamulizumab between animals with detectable anti-mogamulizumab antibody and animals without anti-mogamulizumab antibody.

The applicant responded as follows:
The percentage of animals with a detectable level of anti-mogamulizumab antibody varied among different doses and among different studies. Therefore, PK parameter values were compared between animals with a detectable level of anti-mogamulizumab antibody and animals without anti-mogamulizumab antibody in the 1.2 mg/kg group of the 4-week repeated-dose study (Study [redacted]03), where the PK parameter values were calculated for animals with and without the detection of anti-mogamulizumab antibody after the animals were treated with the same dose in the same study. As a result, $C7_{d,\ Day28}$, $C_{max,\ Day22}$, $AUC_{0\text{-}7d,\ Day22}$, and $t_{1/2\beta}$ were lower, and CL was higher, in animals with anti-mogamulizumab antibody than in animals without, while V_{ss} was not significantly different between these animal groups (see the table below). These results suggest that the faster elimination rate of mogamulizumab from the plasma in animals with anti-mogamulizumab antibody compared with animals without anti-mogamulizumab antibody was due to the increased CL accompanying the anti-mogamulizumab antibody production.

PK parameter values of mogamulizumab in animals with and without detectable level of anti-mogamulizumab antibody

Anti-mogamulizumab antibody	n	$C7_{d,\ day28}$ (μg/mL)	$C_{max,\ day22}$ (μg/mL)	$AUC_{0\text{-}7d,\ day22}$ (μg·day/mL)	$t_{1/2\beta}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Animals without anti-mogamulizumab antibody	6	28.6 ± 9.4	48.5 ± 6.3	242 ± 51	13.6 ± 4.7	4.15 ± 1.70	70.3 ± 7.0
Animals with anti-mogamulizumab antibody	4	16.3 ± 11.1	42.8 ± 5.8	168 ± 58	9.90 ± 3.28	5.71 ± 0.91	74.5 ± 19.8

Mean ± SD

PMDA considers as follows:
At some measuring points in the 1.2 mg/kg group of the 4-week repeated-dose study (Study [redacted]03), mogamulizumab in test samples may have affected the measurement of anti-mogamulizumab antibody. Therefore, the systemic exposure level may decrease because of the increase in the CL of mogamulizumab caused by anti-mogamulizumab antibody, although the submitted data are too limited to fully evaluate the effect of anti-mogamulizumab antibody on the

PK of mogamulizumab.

3.(iii) Summary of toxicology studies

3.(iii).A. Summary of the submitted data

Major toxicology studies on mogamulizumab were conducted using cynomolgus monkeys, an animal species that shows cross reactivity to mogamulizumab.

3.(iii).A.(1) Single-dose toxicity

Mogamulizumab (0.01, 0.5, 4, 20, or 100 mg/kg) was administered to male and female cynomolgus monkeys intravenously in a single dose. No toxic findings or deaths were observed at any doses, from which the approximate lethal dose was determined to be >100 mg/kg. Immunophenotyping of blood lymphocytes by FCM showed a decrease in CCR4-positive T cells (CD3-positive/CD4-positive/CCR4-positive, CD3-positive/CD8-positive/CCR4-positive) and a decrease in CD3-positive/CD25-positive T cells accompanying the decrease in CD3-positive/
CD4-positive/CCR4-positve T cells in all groups. These changes were judged to be due to the pharmacological action of mogamulizumab.

3.(iii).A.(2) Repeated-dose toxicity

3.(iii).A.(2).1) 4-Week repeated-dose intravenous toxicity study

Mogamulizumab (0 [vehicle control], 0.05, 1.2, or 40 mg/kg) was administered intravenously to male and female cynomolgus monkeys intravenously once weekly for 4 weeks, followed by a recovery period of approximately 3 months. There was no death caused by mogamulizumab administration. In the ≥1.2 mg/kg dose groups, histopathological examination of the brain and the spinal cord showed unilateral axonal degeneration. However, similar changes were observed in animals in the control group and in the same imported colony as that of the animals used for this study, and hence it was concluded that there is no relationship between the axonal degeneration of the central nervous system and mogamulizumab administration. Immunophenotyping of blood lymphocytes by FCM showed a decrease in CCR4-positive T cells (CD3-positive/CD4-positive/CCR-4 positive, CD3-positive/CD8-positive/CCR4-positive) and natural killer cells (NK cells, CD3-negative/CD16-positive cells), but the change was reversible during the washout period. The decrease in CCR4-positive T cells was attributed to the pharmacological effect of mogamulizumab, and is therefore not considered to be a toxic effect. Also, the decrease in NK cells was not considered to be a toxic effect for the following reasons: (i) there was no effect on lymphatic organs or tissues, with no change in the infectivity observed, (ii) reversibility was observed, and (iii) the change was within the laboratory background range.

T-cell-dependent antibody production was investigated by sensitizing the animals to keyhole limpet hemocyanin (KLH) during the treatment period and to KLH and tetanus toxoid (TT) during the washout period. Mogamulizumab had no effect.

From these results, the no observed adverse effect level (NOAEL) was determined to be 40 mg/kg/week.

At the NOAEL in the 4-week repeated-dose toxicity study (40 mg/kg/week), the exposure level ($AUC_{0\text{-}7d}$, 8,630,000 ng·day/mL in males and 8,620,000 ng·day/mL in females) was approximately 33 times the exposure level ($AUC_{0\text{-}7d}$, 262.392 μg·day/mL) in repeated administration at the recommended clinical dose (1.0 mg/kg/week) to Japanese ATL patients (Study 0761-002).

3.(iii).A.(2).2) 13-Week repeated-dose intravenous toxicity study

Mogamulizumab (0 [vehicle control], 2.5, 10, or 40 mg/kg) was administered intravenously to

male and female cynomolgus monkeys once weekly for 13 weeks, followed by a recovery period of approximately 3 months after the last administration. There were no deaths caused by mogamulizumab administration. Changes in laboratory parameters suggestive of inflammatory changes and an increase in spleen weight were observed in 1 of 10 animals in the 40 mg/kg group. However, these findings were not judged as toxic effects because the changes occurred only in 1 animal and no abnormality was observed in general conditions, body temperature, blood smear test, or histopathological examination in this animal. CCR4-positive T cells were not evaluated by immunophenotyping of blood lymphocytes by FCM. A decrease in the mean NK cell count was observed in males of the 40 mg/kg group at Week 13. However, this change was not judged to be a toxic effect because the lowest level in individual animals during the treatment period was not significantly lower than that in the control group and the observed change was within the laboratory background range.

Based on the above results, the NOAEL was determined to be 40 mg/kg/week.

3.(iii).A.(3) Genotoxicity

Mogamulizumab is an antibody, a class of drugs that is unlikely to cause genotoxicity and may be exempt from the requirement of genotoxicity tests. Therefore, no genotoxicity study was conducted.

3.(iii).A.(4) Carcinogenicity

Mogamulizumab does not cross-react with CCR4 of animal species widely used in carcinogenicity studies such as mice and rats. Therefore, no carcinogenicity study was conducted.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Embryo-fetal development

Mogamulizumab (0 [vehicle control] or 40 mg/kg) was administered intravenously to pregnant cynomolgus monkeys once weekly from Gestation Day 20 to 139, and cesarean section was performed on Gestation Day 140. Fetal death (Gestation Day 100) and abortion (Gestation Day 106) were observed in 1 each out of 12 animals in the mogamulizumab group. However, they were judged as accidental changes and not as toxicity findings caused by mogamulizumab administration, for the following reasons: (i) the incidence of fetal death or abortion (2 of 12 animals, 16.7%) was within the laboratory background range, (ii) torsion and constriction of the umbilical cord were observed in the dead fetus, and (iii) in the aborted case, changes suggestive of the immunosuppressive effect of mogamulizumab were not observed although suppurative haemorrhagic placentitis probably caused by ascending infection was observed. In the mogamulizumab group, mogamulizumab concentration in fetal blood (on Gestation Day 140) was approximately 0.6 times the mogamulizumab concentration in maternal blood, showing transfer to fetuses. Immunophenotyping of blood lymphocytes by FCM showed a decrease in CCR4-positive cells both in maternal animals and in fetuses, and these changes were judged as pharmacological action of mogamulizumab.

Based on the above results, for general toxicity and reproductive competence in maternal animals and for fetuses, the NOAEL was determined to be 40 mg/kg/week.

3.(iii).A.(6) Local tolerance

Local tolerance was evaluated based on the results of the single and repeated-dose toxicity studies in cynomolgus monkeys, the study for effects on embryo-fetal development, and the bridging single-dose toxicity study [see “3.(iii).A.(7).5) Bridging single-dose toxicity study by intravenous and subcutaneous administration”]. Changes in general conditions or histopathology at the administration site observed in these studies include skin wounds and red blotches, dry skin, dermatitis, subcutaneous haemorrhage, subcutaneous oedema, muscle degeneration, parasitosis, infiltration of mononuclear cells in perivascular region, hyperplasia of venous endothelial cells,

epidermal hyperplasia, intradermal haemorrhage, folliculitis, and brown pigmentation in perivascular region. None of the findings were dose-correlated and were not clearly different from those observed in the control group. Therefore, they were considered to be accidental changes or changes caused by the procedure of administration, blood sampling, or retention of animals, which did not suggest the local irritability of mogamulizumab.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Antigenicity

Production of antibody against mogamulizumab in the plasma was investigated in the single-dose and repeated-dose toxicity studies in cynomolgus monkeys, the study for effects on embryo-fetal development (dams and fetuses), and the bridging single-dose toxicity study. Anti-mogamulizumab antibody was detected in some animals in the 0.05 and 1.2 mg/kg/week groups in the 4-week repeated-dose study and in the bridging single-dose toxicity study (dose, 10 mg/kg), but not in the 40 mg/kg/week group in the 4-week repeated-dose study. In these studies, no effect was observed that was suspected of being caused by antibody production. In the single-dose toxicity study, the 13-week repeated-dose toxicity study, and the study for effects on embryo-fetal development, no anti-mogamulizumab antibody was detected in any of the animals.

3.(iii).A.(7).2) Immunotoxicity

The effect on the immune system was investigated in the single-dose and repeated-dose toxicity studies in cynomolgus monkeys, the study for effects on embryo-fetal development, and the bridging single-dose toxicity study. All studies showed a decrease in CCR4-positive T cells in the blood, which was judged as the effect of the pharmacological action of mogamulizumab. In the 4-week repeated-dose toxicity study, a decrease in NK cells in the blood was observed. No other effect of mogamulizumab on the immune system was observed either in the histopathological examination of the immune organs or tissues or in the evaluation of T cell-dependent antibody (IgG, IgM) production after sensitization to KLH and TT in the 4-week repeated-dose toxicity study. Therefore, no independent immunotoxicity study was conducted.

3.(iii).A.(7).3) Mechanism of toxicity (effect on the central nervous system)

In the 4-week repeated-dose toxicity study, axonal degeneration of brain (brain stem) and of the spinal cord was observed in mogamulizumab group. Therefore, in order to investigate the reproducibility and the mechanism of the axonal degeneration of the central nervous system, mogamulizumab (1.2 mg/kg) was administered intravenously to male cynomolgus monkeys once weekly for 4 weeks, and histopathological examination for the brain, spinal cord, and peripheral nerves was performed. As a result, no abnormal findings were observed.

3.(iii).A.(7).4) Tissue cross-reactivity

A tissue cross reactivity study was conducted using normal tissues of humans and cynomolgus monkeys. Results of the tissue cross reactivity study in cynomolgus monkeys were almost identical to those observed in humans.

Immunohistochemical staining was performed on fresh frozen array samples of the whole body's organs and tissues of humans and the fresh frozen organs and tissues of the whole body of cynomolgus monkeys, using biotin-labeled mogamulizumab. Mogamulizumab-specific positive reaction was observed in the cell membrane and the cytoplasm of some mononuclear cells (lymphocytes) in the blood smear samples, colon, esophagus, stomach, liver, lymph nodes, parathyroid gland, spleen, and tonsil. Mogamulizumab-specific staining was observed also in the cell membrane of monocytes (lymphocytes) in the pancreas and in the cytoplasm of macrophages in the placenta (Hofbauer cells). In cynomolgus monkeys, mogamulizumab-specific positive reaction was observed in the cell membrane and the cytoplasm of some mononuclear cells (lymphocytes) in the blood smear samples, colon, stomach, liver, lymph nodes, spleen, thymus, and tonsil. Mogamulizumab-specific staining was observed also in the cytoplasm of macrophages in the

placenta (Hofbauer cells).

3.(iii).A.(7).5) Bridging single-dose toxicity study by intravenous and subcutaneous administration

Two sets of single-dose intravenous and subcutaneous toxicity studies were conducted in cynomolgus monkeys (dose, 0-10 mg/kg). In both studies, approximate lethal dose was determined to be >10 mg/kg for both intravenous administration and for subcutaneous administration. Of the 2 studies, 1 study included immunophenotyping of blood lymphocytes by FCM. In the study, a decrease in CCR4-positive T cells was observed both in the intravenous administration group and in the subcutaneous administration group. The change was reversible and judged to be a pharmacological effect of mogamulizumab.

3.(iii).B. Outline of the review by PMDA

Mogamulizumab administration caused a decrease in NK cells and in CCR4-positive cells, but both changes were reversible. As regards the axonal degeneration of brain and the spinal cord observed in the repeated-dose toxicity study, PMDA accepts the applicant's view that the observation is not causally related to mogamulizumab. Regarding the transfer of mogamulizumab to fetuses, the information should be supplied to clinical practice in an appropriate manner.

3.(iii).B.(1) Axonal degeneration of brain and the spinal cord

PMDA asked the applicant to explain the relationship between mogamulizumab and axonal degeneration of brain and the spinal cord observed in the 4-week repeated-dose administration study.

The applicant responded as follows:

In the 4-week repeated-dose administration toxicity study, axonal degeneration of the brain and the spinal cord was observed throughout the study period in 5 of 30 animals (17%) in the mogamulizumab group and in 1 of 10 animals (10%) in the control group. In this study, decreases in CCR4-positive T cell count and in NK cell count were observed, but no correlation was observed between these decreases and the occurrence or severity of axonal degeneration. Histopathological changes caused by systemic exposure to a drug are generally considered to occur bilaterally in bilateral organs or symmetrical organs, whereas the axonal degeneration observed in this study was unilateral in all affected animals. In addition, the axonal degeneration was accompanied by glial cell hypertrophy, gliosis, or gitter cell infiltration which are considered to be reparative changes. These observations suggest that the axonal degeneration had already been present before animals were subjected to the study. Also, axonal degeneration was observed in 1 of 10 animals (10%) in the control group as well, whereas no similar changes were observed in the 13-week repeated-dose toxicity study with a longer treatment period than in the 4-week study. Furthermore, axonal degeneration was observed in a total of 10 of 80 animals (13%) in the imported colony including the animals used in the present study. The breakdown of the affected animals was 6 of 40 animals (15%) in animals used in the toxicity study on mogamulizumab and in 4 of 40 animals (10%) in the remaining animals, showing no significant difference in the incidence of axonal degeneration between the 2 groups. Based on the above results, it was concluded that axonal degeneration was not causally related to mogamulizumab administration.

PMDA accepted the applicant's response by also taking into account the fact that abnormal findings, including axonal degeneration, were not detected in the histopathological examination of the brain, spinal cord, and peripheral nerves in the study on the effect on the central nervous system.

3.(iii).B.(2) Decrease in CCR4-positive T cells observed in fetuses

PMDA asked the applicant to explain the toxicological significance of the decrease in CCR4-positive T cells in fetuses observed in the embryo-fetal study.

The applicant responded as follows:
In the embryo-fetal study, fetuses in the mogamulizumab group showed a decrease in CCR4-positive T cells, which was considered to be the pharmacological action of mogamulizumab, but no other abnormal findings were observed. The decrease in CCR4-positive T cells in fetal blood did not affect the survival or development of fetuses, and was therefore not a toxic finding.

PMDA has confirmed that the transfer of mogamulizumab to fetuses is appropriately described in the package insert as information.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A. Summary of the submitted data

4.(i).A.(1) Mogamulizumab assay method

Mogamulizumab in human plasma was measured by ELISA using [redacted] peptide, biotin-labeled anti-human IgG (secondary antibody), and horseradish peroxidase (HRP)-labeled avidin.

4.(i).A.(2) Measurement of anti-mogamulizumab antibody

Anti-mogamulizumab antibody in human plasma was measured by ELISA using immobilized mogamulizumab, biotin-labeled mogamulizumab, and HRP-labeled avidin.

4.(i).A.(3) Test for CCR4 expression

4.(i).A.(3).1) Flow cytometry

CCR4 expression in peripheral blood was confirmed by FCM. Fluorescein isothiocyanate (FITC)-labeled murine anti-CCR4 monoclonal antibody (KM2160), phycoerythrin (PE)-labeled anti-CD25 antibody, and peridininchlorophyll protein (PerCP)-labeled anti-CD4 antibody were added to the peripheral blood and the mixture was incubated. After hemolysis, CCR4 (KM2160)-positive/CD25-positive fraction in CD4-positive lymphocyte fraction was analyzed by FCM.

4.(i).A.(3).2) Immunohistochemical staining

CCR4 expression in tumor tissue was confirmed by immunohistochemistry (IHC). Thin sections of formalin-fixed and paraffin-embedded tumor tissue were incubated with murine anti-CCR4 monoclonal antibody (KM2160), after which CCR4 was detected by linked streptavidin-biotin (LSAB) method.

4.(i).B. Outline of the review by PMDA

4.(i).B.(1) Effect of mogamulizumab in samples on the measurement of anti-mogamulizumab antibody

PMDA asked the applicant to explain the possibility that mogamulizumab in test samples, within the range of the concentration observed in each study, may have affected the measurement of anti-mogamulizumab antibody.

The applicant responded as follows:
Concentrations of mogamulizumab that affected the anti-mogamulizumab antibody assay method in clinical studies were investigated. As a result, the presence of mogamulizumab at concentrations of 100, 1000, and 10,000 ng/mL decreased the observed value of anti-mogamulizumab antibody to 56.5%, 4.2%, and 1.7%, respectively, of the value observed in the absence of mogamulizumab. In the Japanese phase II study conducted using the proposed dosage and administration (Study 0761-002), plasma mogamulizumab concentration at 28 days after 8 doses administered intravenously at 1.0 mg/kg once weekly was 16,107 ± 6,088 ng/mL, suggesting that mogamulizumab might have

affected the measurement of anti-mogamulizumab antibody. However, no decrease in the exposure level of mogamulizumab by multiple-dose administration was observed in any of the subjects who received 8 doses of mogamulizumab in this study.

PMDA considers that the effect of anti-mogamulizumab antibody on the PK, efficacy, and safety of mogamulizumab should be judged carefully, taking into account the above issue regarding the anti-mogamulizumab antibody assay system used in clinical studies.

The applicant explained the new anti-mogamulizumab antibody assay method as follows:
One of the anti-mogamulizumab antibody assay methods used in clinical studies (ECL) is less susceptible to the effect of mogamulizumab in assay samples. Therefore, a similar assay method was investigated for the measurement of human samples. It has been confirmed that the new assay method is not affected even in the presence of 24.6 μg/mL mogamulizumab. This assay method is already being used in the ongoing foreign clinical study, and the validation study of this assay method in Japanese facilities is expected to be completed by the end of [redacted] 20[redacted].

4.(ii) Summary of clinical pharmacology studies

4.(ii).A. Summary of the submitted data

PK of mogamulizumab in humans was investigated in healthy adults and cancer patients.

4.(ii).A.(1) Foreign phase I study (Study 0761-EU-001) [[redacted] 20[redacted] to [redacted] 20[redacted]]

Placebo or mogamulizumab (0.0001, 0.0003, 0.001, or 0.003 mg/kg) was administered to 32 non-Japanese healthy adult males (25 included in the PK analysis) intravenously in a single dose to investigate the PK of mogamulizumab. Plasma mogamulizumab concentration was below the lower limit of quantitation (10 ng/mL) in all subjects in ≤0.0003 mg/kg groups. In the 0.001 mg/kg group, the values were measurable only at several time points immediately after administration. C_{max} in the 0.003 mg/kg group (59.2 ng/mL) was 2.92 times that in the 0.001 mg/kg group (20.3 ng/mL), a value close to the dose ratio. In this study, the PK of mogamulizumab was also investigated in patients with seasonal allergic rhinitis following [redacted] administration of mogamulizumab at [redacted] mg/kg. Results were similar to those observed in healthy adult males.

4.(ii).A.(2) Japanese phase I study (Study 0761-0501) [February 2007 to October 2008]

Mogamulizumab (0.01, 0.1, 0.5, or 1.0 mg/kg) was administered to a total of 16 patients with CCR4-positive ATL or with CCR4-positive PTCL, intravenously once weekly for 4 doses to investigate the PK of the drug (see the table below). C_{max} and C_{trough} of mogamulizumab increased with multiple doses. CL was similar among all treatment groups except 0.1 mg/kg group, and V_{ss} was constant regardless of dose and similar to the blood volume (5200 mL/70 kg [74.3 mL/kg], *Pharm Res* 1993;10:1093-5). The mean cumulative coefficient of C_{trough} was higher in the 0.1 mg/kg group than in other groups. The applicant explained that the difference was due to the higher C_{trough} value in 1 out of 3 patients (3.97, 7.58, 29.4).

PK parameters of mogamulizumab following intravenous administration

Dose (mg/kg)	Administration	C_{max} (ng/mL)	C_{trough} (ng/mL)	$AUC_{0\text{-}7days}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
0.01 (n = 3)	First	206 ± 23.1	41.0 ± 39.0	14.9 ± 7.67	80 ± 52	0.240 ± 0.016	108 ± 49.1
	Fourth	350 ± 47.8*2	158 ± 7.4*2	36.6 ± 2.99*2	179 ± 40*2		
	Cumulative coefficient*1	1.63 (1.38, 1.87)*2	2.11*3	3.42 (1.76, 5.08)*2	–		
0.1 (n = 4)	First	1832 ± 334	255 ± 447	87.6 ± 93.7	74 ± 85*4	0.708 ± 0.646*4	112 ± 41.4*4
	Fourth	2807 ± 1665*4	1515 ± 1873*4	328 ± 322*4	201 ± 196*4		
	Cumulative coefficient*1	1.39 (0.96, 2.13)*4	13.7 (3.97, 29.4)*4	3.48 (2.03, 5.24)*4	–		
0.5 (n = 3)	First	8353 ± 1993	2985 ± 606	762 ± 131	141 ± 23*2	0.237 ± 0.050	116 ± 31.0
	Fourth	15,181 ± 872	6825 ± 873	1626 ± 142	332 ± 122		
	Cumulative coefficient*1	1.89 (1.52, 2.42)	2.32 (2.09, 2.75)	2.15 (1.97, 2.34)	–		
1.0 (n = 6)	First	21,758 ± 3495	7544 ± 3009	1901 ± 467	–	0.144 ± 0.032	103 ± 20.3
	Fourth	40,428 ± 5351*5	19,517 ± 4265*5	4190 ± 545*5	462 ± 51*5		
	Cumulative coefficient*1	1.95 (1.61, 2.09)*5	3.53 (2.19, 7.58)*5	2.43 (2.24, 2.78)*5	–		

Mean ± SD, *1 Mean (minimum, maximum), *2 n = 2, *3 n = 1, *4 n = 3, *5 n = 5

The applicant explained that when a power model ($\log_{10}$[PK parameter]) = $\mu + \beta \times \log_{10}$[dose]) is applied to C_{max} and $AUC_{0\text{-}7\ days}$, the 95% confidence interval of β does not include 0 but includes 1 for both C_{max} and $AUC_{0\text{-}7\ days}$, demonstrating a linear relationship within the dose range from 0.01 to 1.0 mg/kg.

4.(ii).A.(3) Japanese phase II study (Study 0761-002) [June 2009 to July 2010]

Mogamulizumab (1.0 mg/kg) was administered to 27 patients with CCR4-positive ATL intravenously once weekly for a total of 8 doses to investigate the PK of the drug (see the table below). C_{max} and C_{trough} increased with multiple doses, and did not reach a steady state even after the eighth dose. $t_{1/2}$ after the eighth dose was similar to that observed with IgG1 in general (approx. 21 days, *J Clin Invest* 1970;49:673-80). The applicant explained that C_{max}, C_{trough}, and $AUC_{0\text{-}7days}$ after the initial dose were not significantly different from the results obtained in the Japanese Study 0761-0501. The applicant also explained that C_{max} and C_{trough} values after the eighth dose, estimated from the 2-compartment open-model analysis based on the mean plasma drug concentration, were 40,993 ng/mL and 29,546 ng/mL, respectively, which were almost the same as the mean observed values, suggesting that multiple doses have little effect on the PK of mogamulizumab.

PK parameters of mogamulizumab after intravenous administration at 1.0 mg/kg

Administration	N	C_{max} (ng/mL)	C_{trough} (ng/mL)	$AUC_{0\text{-}7days}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
First	27	16,622 ± 3324	5152 ± 3714*2	1427 ± 571*2	124 ± 92*3	0.211 ± 0.096	99.7 ± 37.5
Eighth	5	42,943 ± 14,240	33,638 ± 10,572*4	6297 ± 1812*4	422 ± 147		
Cumulative coefficient*1	5	2.25 (1.74, 3.09)	3.56 (3.24, 3.86)*5	2.87 (2.50, 3.12)*5	–		

Mean ± SD, *1 Mean (minimum, maximum), *2 n = 19, *3 n = 23, *4 n = 4, *5 n = 3

4.(ii).A.(4) Anti-mogamulizumab antibody

In the Japanese Study 0761-0501 and the Japanese Study 0761-002, anti-mogamulizumab antibody concentration in the plasma was below the lower limit of quantitation (5.0 ng/mL) in all subjects.

In the foreign Study 0761-EU-001 in which mogamulizumab (0.0001-0.003 mg/kg) was administered intravenously in a single dose to 25 healthy adults and 18 patients with seasonal allergic rhinitis, anti-mogamulizumab antibody was detected in the following 2 healthy subjects, whereas it was below the lower limit of quantitation (7.5 ng/mL) in the remaining 41 subjects.

- In 1 subject in the 0.0003 mg/kg group, anti-mogamulizumab antibody was detected (28.0 ng/mL) from before administration, and the concentration remained mostly at a constant level (23.6-26.6 ng/mL) up to 57 days after administration. The plasma mogamulizumab concentration in this subject was below the lower limit of quantitation (10 ng/mL) at all blood sampling points, as was the case with other subjects in the same cohort. Since the subject had no past history of mogamulizumab administration and anti-mogamulizumab antibody concentration did not change between before and after administration, the applicant considers that the result of the anti-mogamulizumab antibody test in this subject is a "false positive."

- In 1 subject in the 0.003 mg/kg group, anti-mogamulizumab antibody was detected from the 29th day after administration; the concentration reached the maximum level (29.6 ng/mL) at 57 days after administration and was detected up to 6 months after administration (11.9 ng/mL). In this subject, mogamulizumab was detected in the plasma up to 15 days after administration. The plasma level changed over time in a similar manner as observed in antibody-negative subjects in the same cohort and decreased below the lower limit of quantitation (10.0 ng/mL) from the 22nd day after administration.

4.(ii).A.(5) Discussion by the applicant

4.(ii).A.(5).1) Effect of background factors on the PK of mogamulizumab

C_{max}, $AUC_{0\text{-}7days}$, and $t_{1/2}$ after the first, fourth, and eighth doses of mogamulizumab in subjects in the 1.0 mg/kg group in the Japanese clinical study were compared between sexes (14 males, 19 females) and among different age groups (20 patients aged <65 years, 9 patients aged 65-74 years, 4 patients aged ≥75). As a result, difference in sex or age had no significant effect on the PK of mogamulizumab.

Since mogamulizumab is an antibody protein of the IgG1 class with molecular weight of approximately 149,000, it is inferred that the kidneys are not involved in the elimination of mogamulizumab, and reticuloendothelial cells rather than the liver are mainly involved (*Clinical pharmacology of therapeutic proteins* 1st ed. Pine House Publishers. 2006, *Drug Dev Res.* 2004;61:108-20). Therefore, renal or hepatic function is unlikely to significantly affect the clearance of mogamulizumab.

4.(ii).A.(5).2) Relationship among mogamulizumab dose, PK, and efficacy

In ATL patients, the best results achieved in the peripheral blood was CR in all of those evaluated for efficacy, except in 1 patient (PR) in the 0.1 mg/kg group. As regards the best results in the target lesion and skin lesion, no clear conclusion was reached regarding the relationship among mogamulizumab dose, PK, and efficacy because of the limited number of patients with each lesion.

4.(ii).B. Outline of the review by PMDA

4.(ii).B.(1) Factors affecting the PK of mogamulizumab

4.(ii).B.(1).1) CCR4-positive cells and ATL cells

PMDA asked the applicant to explain whether or not there is any relationship between the percentage or number of CCR4-positive cells and PK parameter values of mogamulizumab.

The applicant responded as follows:
In ATL patients in whom peripheral blood CCR4-positive cells were detected, a correlation was observed between the number of CCR4-postive cells and the number of ATL cells before mogamulizumab administration ($R^2 = 0.9675$). Therefore, the number of ATL cells, in addition to the percentage and the number of CCR4-positive cells, was investigated for correlation with PK parameters of mogamulizumab.

i) Percentage and number of CCR4-positive cells

Investigation of the relationship between the percentage of CCR4-positive cells and PK parameters (C_{max}, C_{trough}, $AUC_{0\text{-}7days}$) following the initial dose showed that C_{max} was constant among patients in the same dose group regardless of the percentage of CCR4-positive cells, whereas C_{trough} and $AUC_{0\text{-}7days}$ were low in some patients with a higher percentage of CCR4-positive cells. Since mogamulizumab binds to CCR4 specifically, it was considered that, in patients with a higher percentage of CCR4-positive cells in the blood, plasma mogamulizumab concentration decreased by binding to CCR4-positive cells if the plasma mogamulizumab concentration was low. No relationship was observed between the percentage of CCR4-positive cells before the second dose, before the fifth dose, and at 7 days after the eighth dose and C_{max} or C_{trough} after each administration.

The relationship between the number of CCR4-positive cells and PK parameters (C_{max}, C_{trough}, $AUC_{0\text{-}7days}$) was investigated based on the results of the Japanese phase II study (1.0 mg/kg). C_{max} and $AUC_{0\text{-}7days}$ after the initial dose were similar among patients regardless of the number of CCR4-positive cells, whereas C_{trough} after the initial dose was low in some patients. No correlation was observed between the number of CCR4-positive cells before the second dose, before the fifth dose, or on day 7 after the eighth dose and C_{max}. C_{trough} after the fifth and subsequent doses was similar in all patients regardless of the number of CCR4-positive cells.

The difference in the relationship of CCR4-positive cells with PK parameters observed between after the initial dose and after multiple-dose administration was considered to be due to the decrease in the percentage and the number of CCR4-positive cells with multiple-dose administration, resulting in suppression of the decrease in mogamulizumab concentration caused by the binding to CCR4-positive cells.

ii) Number of ATL cells

The relationship between the number of ATL cells and PK parameters at the time closest to the timing of ATL cell counting (first to eighth doses) was investigated. C_{max} was consistent among patients in the same dose group regardless of the number of ATL cells after each dose. In the 0.1 mg/kg group, C_{trough} tended to be lower in patients with a higher number of ATL cells up to the fourth dose, whereas in the 1.0 mg/kg group, C_{trough} was low in some patients after the first dose but approached a similar level in all patients with multiple-dose administration.

As shown in i) and ii) above, C_{max} of mogamulizumab (plasma concentration immediately after each dose) had no effect on the percentage or number of CCR4-positve cells or on the number of ATL cells, whereas, in patients who showed high values in these parameters, C_{trough} and $AUC_{0\text{-}7days}$ tended to be low. In the group treated with 1.0 mg/kg as the proposed dose, C_{trough} and $AUC_{0\text{-}7days}$ after the first dose were low in some patients in whom the percentage and the number of CCR4-positve cells and the number of ATL cells were high. However, with multiple-dose

administration, the number of ATL cells, etc., decreased and, from immediately before the fourth dose, C_{trough} and $AUC_{0\text{-}7days}$ appeared to be seldom affected by these test parameter values.

PMDA considers as follows:
The percentage of CCR4-positive cells before the second dose, before the fifth dose, and on day 7 after the eighth dose (range 0.96%-71.7%, 1.03%-18.2%, 2.78%-33.9%, respectively) and the number of CCR4-positive cells (range 2-747, 2-35, 3-40/μL) converged to a low level with multiple-dose administration. The number of ATL cells also tended to decrease markedly with multiple-dose administration. Therefore, results obtained after the fifth and subsequent doses in particular do not allow clear assessment of the relationship between each test parameter value and PK parameter values.

Although C_{trough} and $AUC_{0\text{-}7days}$ after the first dose were low in some patients treated with the proposed dose of 1.0 mg/kg, the submitted data did not show any consistent tendency between C_{trough} or $AUC_{0\text{-}7days}$ and the percentage and the number of CCR4-positive cells or the number of ATL cells. Therefore, at the moment, it is unclear which factors might affect the PK of mogamulizumab after administration at 1.0 mg/kg. In addition, the study was conducted in only a very limited number of patients other than those in the 1.0 mg/kg group. Therefore, it is unclear how the number of ATL cells, etc., affect the PK of mogamulizumab.

4.(ii).B.(1).2) Anti-mogamulizumab antibody
PMDA considers as follows:
In the anti-mogamulizumab antibody assay used in clinical studies, mogamulizumab present in the test samples affected the results of the assay [see "4.(i).B.(1) Effect of mogamulizumab in samples on the measurement of anti-mogamulizumab antibody"], and, at most of the measuring points, the observed level of anti-mogamulizumab antibody was possibly estimated to be very much lower than the actual level. Therefore, at the moment, the effect of anti-mogamulizumab antibody on the PK of mogamulizumab is unclear.

4.(ii).B.(2) Relationship between PK and safety
No clear conclusion has been reached regarding the relationship between the PK of mogamulizumab and the efficacy [see "4.(ii).A.(5).2) Relationship among mogamulizumab dose, PK, and efficacy"].

PMDA asked the applicant to discuss the relationship between the PK of mogamulizumab and safety.

The applicant responded as follows:
Among the adverse events that occurred with 10% or higher incidence in the Japanese Study 0761-002 which was conducted using the proposed dosage regimen, events that included Grade 3 or higher severity (infusion related reaction, lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, platelet count decreased, GTP increased, ALT increased, AST increased, blood LDH increased, haemoglobin decreased, hypophosphataemia, hypercalcaemia, hypokalaemia, hypoxia, rash, pruritus) were examined for the effect on the distribution of C_{max} and $AUC_{0\text{-}7days}$ after the first administration in affected patients classified by the worst grade. As a result, none of the events showed a relationship between the worst grade and C_{max} or $AUC_{0\text{-}7days}$, which suggests that there is no correlation between the PK parameter values after administration of mogamulizumab at 1.0 mg/kg and the safety.

PMDA considers as follows:
Although the submitted study results do not show any clear relationship between the PK of mogamulizumab and the safety, the currently available data provide only limited information obtained from a very few patients. Therefore, it is practically impossible to conclude that PK and

safety are not correlated solely based on these results. The relationship between the PK of mogamulizumab and safety should be investigated in further detail when new data are accumulated from clinical studies including the currently ongoing clinical study in treatment-naive ATL patients, and appropriate measures such as provision of information should be taken.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

As the efficacy and safety evaluation data, the results from a total of 2 studies, 1 each of Japanese phase I and phase II studies, were submitted. As the reference data, the results from 1 foreign phase I clinical study were submitted.

List of clinical studies on efficacy and safety

Category	Region	Study	Phase	Study patients	No. of subjects enrolled	Outline of dosage and administration	Main endpoints
Evaluation	Japan	0761-0501	I	Patients with recurrent or relapsed CCR4-positive ATL or PTCL	16	Mogamulizumab (0.01, 0.1, 0.5, 1.0 mg/kg) administered intravenously, once weekly for 4 doses	Safety, PK
		0761-002	II	Patients with recurrent or relapsed CCR4-positive ATL	28	Mogamulizumab (1.0 mg/kg) administered intravenously, once weekly for 8 doses	Antitumor effect, Safety, PK
Reference	Foreign country	0761-EU-001	I	Healthy adults and patients with seasonal allergic rhinitis (SAR)	55	Healthy adults: Placebo or mogamulizumab (0.0001, 0.0003, 0.001, 0.003 mg/kg) administered intravenously in a single dose SAR patients: Placebo or mogamulizumab ([redacted], [redacted], [redacted] mg/kg) administered [redacted]	Safety, PK

The clinical studies were summarized below.
The main adverse events excluding deaths observed in each clinical study are described in "4.(iv) Adverse events observed in clinical studies", and results of PK studies in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

[Evaluation data]

(1) Japanese phase I study (5.3.5.2-1: Study 0761-0501) [February 2007 to October 2008]

An open-label, uncontrolled study in patients with recurrent or relapsed*[1] CCR4-positive ATL and in patients with recurrent or relapsed CCR4-positive PTCL (including MF, etc.) (target sample size, 15) was conducted at 6 centers in Japan to investigate the maximum tolerated dose*[2] (MTD), safety, and PK of mogamulizumab.

*[1] The occurrence of the disease after complete response (CR) achieved by chemotherapy was defined as "recurrence," and aggravation after uncertain complete response (CRu) or partial response (PR) was defined as "relapse."
*[2] When dose-limiting toxicity (DLT) occurred in 3 out of 3 patients or in 3 out of 6 patients, dose increase was to be cancelled and the dose showing the DLT was to be regarded as MTD.

Mogamulizumab (0.01, 0.1, 0.5, or 1.0 mg/kg) was to be intravenously administered once weekly for 4 doses.

All of the 16 patients enrolled in this study (3 patients in 0.01 mg/kg group, 4 patients in 0.1

mg/kg group, 3 patients in 0.5 mg/kg group, 6 patients in 1.0 mg/kg group) were treated with mogamulizumab and included in the safety analysis set.

DLT occurred in 1 of 6 patients in the 1.0 mg/kg group (neutrophil count decreased/febrile neutropenia/rash), but MTD was not reached. In accordance with the pre-determined rule, the recommended dose for the phase II study was determined to be 1.0 mg/kg. No death occurred during the treatment period or within 30 days after the last administration.

(2) Japanese phase II study (5.3.5.2-9: Study 0761-002) [June 2009 to July 2010]

An open-label, uncontrolled study in patients with recurrent or relapsed CCR4-positive ATL (target sample size, 25) was conducted at 17 centers in Japan to evaluate the efficacy and safety of mogamulizumab.

Mogamulizumab (1.0 mg/kg) was to be intravenously administered once weekly for 8 doses.

Of 28 patients enrolled in the study, 27 patients were treated with mogamulizumab and included in the safety analysis set. Of these, 1 patient was found to be ineligible after the start of the study because of double cancers and was withdrawn from the study. The remaining 26 patients were included in the efficacy analysis set.

As regards efficacy, the anti-tumor effect evaluated as the combined best response of peripheral blood lesion (the primary endpoint) and of non-peripheral-blood lesions (overall best response, centralized assessment [image reading committee and anti-tumor effect assessing committee]) was as follows.

Anti-tumor effect (overall best response, centralized assessment)*

Acceptance criteria	Number of patients (%) (n = 26)
CR	8 (30.8)
CRu	0
PR	5 (19.2)
SD	2 (7.7)
PD	11 (42.3)
NE	0
Number of responders (response rate) [95% CI]	13 (50.0) [29.9, 70.1]

CR, complete response; CRu, uncertain complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

* The anti-tumor effect was evaluated according to the "criteria for anti-tumor effect evaluation" stipulated in the protocol, as follows.

[Evaluation of effect in peripheral blood]

CR, The percentage of abnormal lymphocytes is <5% and the number of lymphocytes (observed value) is <4000/mm^3; PR, The number of abnormal lymphocytes (observed value) has decreased by ≥50% from baseline; SD, Response less than PR but not PD; PD, The number of abnormal lymphocytes (observed value) has increased by ≥50% from the minimum level and the number of lymphocytes (observed value) is ≥4000/mm^3.

[Assessment of best response in peripheral blood]

To be assessed based on the change over time in the efficacy evaluated at each evaluating time point according to the rules described in (i) to (iii) below.

(i) CR or PR observed before PD, CR or PR; (ii) PD observed before restaging after fourth dose, except (i), PD; (iii) other than (i) and (ii) above, SD

[Assessment of response of non-peripheral-blood lesion]

Response is assessed based on the results of the evaluation as described in (i) to (viii) below, according to the "Table for the assessment of the response of non-peripheral-blood lesion".

(i) Assessment of response of target lesion (CR, ≥75% decrease in the sum of the products of the greatest diameters, with no swollen lymph nodes exceeding 1.5 cm in diameter and with complete disappearance of extranodal lesions; CRu, ≥75% decrease in the sum of the products of the greatest diameters; PR, ≥50% decrease in the sum of the products of the greatest diameters; SD, less than PR but not PD; PD, ≥50% increase in the sum of the products of the greatest diameters, or appearance of a new lesion)

(ii) Assessment of response of nodal, non-target lesions
(iii) Assessment of extranodal, non-target lesions
(iv) Assessment of skin lesion (assessed based on both the affected area and the symptoms according to Physician's Global Assessment of Clinical Condition [PGA] [*J Clin Oncol* 2001;19:2456-71])
(v) Assessment of response of hepatomegaly and splenomegaly
(vi) Assessment of bone-marrow infiltration
(vii) Assessment of gastrointestinal lesion
(viii) Appearance of new lesion
[Assessment of best response of non-peripheral-blood lesions]
Among the assessment of response of non-peripheral-blood lesions made at each staging, the best result observed is handled as the best response of non-peripheral-blood lesions. In a similar manner, the best response is assessed for the target lesion and skin lesion.
[Assessment of overall best response]
The assessment is made according to the "Table for the assessment of the best response" shown below.

Table for the assessment of the response of non-peripheral-blood lesion

Overall response	Target lesion	Non-target lesion		Skin lesion	Hepatomegaly Splenomegaly	Bone marrow infiltration	New lesion
		Nodal	Extranodal				
CR	CR	Normal	Disappeared	CR	Disappeared	Negative	None
CRu	CR	Normal	Disappeared	CR	Disappeared	Uncertain	None
	CRu	Normal	Disappeared	CR	Disappeared	Negative or uncertain	None
PR	CR	Normal	Disappeared	CR	Disappeared	Positive	None
	CRu	Normal	Disappeared	CR	Disappeared	Positive	None
	PR	Normal or not enlarged	Disappeared or not enlarged	PR	Disappeared or not aggravated	Irrelevant (test not required)	None
SD	Other than CR, CRu, PR, PD, and NE						
PD	PD	Enlarged	Enlarged	PD	Aggravated	Turned positive after negative conversion	Yes
NE	–	Not evaluable	Not evaluable	–	Not evaluable	–	–

Table for the assessment of the best response

		The best response of non-peripheral-blood lesion					
		CR	CRu	PR	SD	PD	NE
Best response of peripheral blood	CR	CR	CRu	PR	SD	PD	NE
	PR	PR	PR	PR	SD	PD	NE
	SD	SD	SD	SD	SD	PD	NE
	PD	PD	PD	PD	PD	PD	NE

As regards safety, no death occurred during the study period or within 30 days after the last administration.

[Reference data]

(1) Foreign phase I study (5.3.3.1-1: Study 0761-EU-001) [[redacted] 20[redacted] to [redacted] 20[redacted]]

A double-blind, randomized, single-dose study was conducted at 1 center overseas in healthy adult male subjects and in male patients with seasonal allergic rhinitis (SAR) to evaluate the safety and PK for single-dose intravenous administration of mogamulizumab (target sample size, 6 subjects in mogamulizumab group and 2 subjects in placebo group for each cohort). Of 55 subjects enrolled in the study, 43 patients were treated with mogamulizumab. No death occurred during the treatment period or within 30 days after the last dose.

4.(iii).B. Outline of the review by PMDA

4.(iii).B.(1) Efficacy

As a result of the following review, PMDA has concluded that mogamulizumab is expected to be effective for patients with recurrent or relapsed CCR4-positive ATL.

4.(iii).B.(1).1) Efficacy endpoints and results of efficacy evaluation

In Study 0761-002, the acceptance criteria for efficacy was established by referring to the criteria for assessing the anti-tumor effect against non-Hodgkin's lymphoma recommended by the National Comprehensive Cancer Network (NCCN) and by the Japan Clinical Oncology Group (JCOG) and to the acceptance criteria discussed at the 13th International Conference on Human Retrovirology (*J Clin Oncol* 2009;27:453-9, hereafter referred to as the "criteria of the International Conference on Human Retrovirology"), and the best response that met these criteria was established as the primary efficacy endpoint.

In Study 0761-002, the rate of the best response was 50.0% (13 of 26 patients [95% confidential interval (CI), 29.9%, 70.1%]). The response rate by lesion site was 100% (13 of 13 patients) for peripheral blood lesion and 38.1% (8 of 21 patients) for non-peripheral-blood lesion. The response rate by disease type was 42.9% (6 of 14 patients) for acute type, 33.3% (2 of 6 patients) for lymphoma type, and 83.3% (5 of 6 patients) for chronic type with poor prognostic factor (any of LDH high, BUN high, or albumin low [*Adult T-cell Leukaemia*. Oxford University Press; 1994]).

The applicant explained the efficacy of mogamulizumab in patients with recurrent or relapsed CCR4-positive ATL as follows:

For the target patients in this study, i.e., patients with recurrent or relapsed CCR4-positive ATL for which no standard treatment has been established, the fact that response is obtained is in itself clinically meaningful. A total of 26 efficacy-evaluable patients in Study 0761-002 were divided into two groups: responders and non-responders, and their PFS and OS were estimated according to the Kaplan-Meier method. Results showed that, in responders, the median PFS and OS were not reached, whereas in non-responders, median PFS and OS were 25 days and 225 days, respectively. These results clearly show that positive response contributes to the prolonged survival in ATL patients.

PMDA considers the efficacy of mogamulizumab in patients with recurrent or relapsed CCR4-positive ATL as follows:

The finding in Study 0761-002 that the response was obtained in patients with recurrent or relapsed CCR4-positive ATL for which no standard treatment has been established raises the expectation of a decrease in tumor mass with resultant improvement in symptoms and a certain treatment-free period. Therefore, the treatment has a certain clinical significance, and the response rate based on the overall best response may be used as an exploratory index for efficacy evaluation in the patients. PMDA has also concluded, from the results of the study, that mogamulizumab is expected to be effective for patients with recurrent or relapsed CCR4-positive ATL. On the other hand, results of analysis performed according to the criteria of the International Conference on Human Retrovirology could not be confirmed because of the unavailability of data required for the analysis.

The applicant's explained that achieving a response contributes to prolonged survival, based on the results from the Kaplan-Meier analysis for responders and non-responders. However, the applicant's claim is inappropriate because discussing the life-prolonging effect of responders versus non-responders is problematic for the following reasons: (i) comparison of groups stratified based on response or non-response may have produced a bias in the distribution of prognostic factors, and (ii) responders would survive until response is observed and, therefore, responders may tend to survive longer regardless of the presence or absence of the life-prolonging effect. In providing information related to the efficacy of mogamulizumab, adequate caution should be exercised to avoid misunderstanding at clinical practice, by interpreting the study results in an appropriate manner. Also, since the therapeutic effect may vary depending on the disease type of ATL (*Blood* 2011;118:1736-45), information on efficacy by disease type and by disease site obtained from the study should be provided in an appropriate manner.

4.(iii).B.(2) Safety

Based on the following review, PMDA considers that adverse events requiring caution in administering mogamulizumab include haematotoxicity (bone marrow depression), infusion reaction, infection/immune system disorder, skin disorder, tumor lysis syndrome, hepatic dysfunction, and cardiac dysfunction, and that caution should be exercised against the occurrence of these adverse events in administering mogamulizumab.

Based on the above, PMDA has concluded that mogamulizumab is tolerable provided that monitoring for, and control of, adverse events and temporary withdrawal and discontinuation, etc., are performed appropriately by physicians with sufficient knowledge and experience of cancer chemotherapy for hematopoietic organ tumor. However, since only limited safety information is available at the moment, it is necessary to collect and provide information continuously after the market launch.

4.(iii).B.(2).1) Haematotoxicity (bone marrow depression)

Haematotoxicity observed in Studies 0761-0501 and 0761-002 was as follows. Adverse events leading to study drug postponement occurred in 1 subject with Grade 4 platelet count decreased. There were no serious adverse events or adverse events leading to study drug discontinuation. Intervening treatment was required for neutrophil count decreased of Grade 3 to 4 in 1 subject each and for platelet count decreased of Grade 4 in 1 subject. Neutrophil count decreased in 2 subjects resolved following G-CSF administration. Platelet transfusion was performed in the subject with platelet count decreased. Follow-up of the adverse event was judged unnecessary because post-trial treatment had commenced.

Haematotoxicity observed in Studies 0761-0501 and 0761-002

PT	Study 0761-0501 No. of subjects (%) (N = 16)		Study 0761-002 No. of subjects (%) (N = 27)	
	All grades	≥ Grade 3	All grades	≥ Grade 3
Lymphocyte count decreased	15 (93.8)	10 (62.5)	26 (96.3)	20 (74.1)
White blood cell count decreased	10 (62.5)	2 (12.5)	18 (66.7)	8 (29.6)
Neutrophil count decreased	10 (62.5)	3 (18.8)	14 (51.9)	5 (18.5)
Platelet count decreased	9 (56.3)	0	14 (51.9)	5 (18.5)
Haemoglobin decreased	1 (6.3)	0	8 (29.6)	1 (3.7)

PMDA considers as follows:

Administration of mogamulizumab causes haematotoxicity with a high incidence, requiring caution. However, intervening treatment was required in only 3 subjects, and drug withdrawal alone was sufficient for recovery in the majority of patients. All events that required treatment also resolved. In addition, in the subject who had Grade 4 platelet count decreased leading to study drug suspension, treatment was able to resume after recovery. Based on these results, PMDA considers that haematotoxicity caused by mogamulizumab is tolerable provided that subjects receive treatment and management similar to those given in clinical studies.

4.(iii).B.(2).2) Infusion reaction

The applicant explained that the adverse event “infusion related reaction” observed in clinical studies is synonymous with “infusion reaction” used in the package insert, etc.

Infusion reaction was observed in 13 of 16 patients (81.3%) in Study 0761-0501 and in 24 of 27 patients (88.9%) in Study 0761-002. Details of the incidence of infusion reaction in Study 0761-002 were as follows.

In Study 0761-002, events that were observed in at least 10% of patients and classified as infusion reaction were pyrexia (77.8% [21 of 27 patients]), chills (59.3% [16 of 27 patients]), tachycardia (29.6% [8 of 27 patients]), blood pressure increased (22.2% [6 of 27 patients]), nausea (18.5% [5

of 27 patients]), hypoxia (14.8% [4 of 27 patients]), and vomiting (11.1% [3 of 27 patients]), of which those of Grade 3 or above were hypoxia in 3 patients (all Grade 3). Infusion reaction occurred after the first dose in all 24 affected patients. Multiple infusion reaction occurred in 3 patients (twice in 2 patients, 3 times in 1 patient), all of which were Grade 2 or below.

As regards the timing of occurrence, infusion reaction occurred frequently particularly during the period from 0.5 to 2 hours after the first dose (70.8%, 17 of 24 patients). The reaction occurred within 2 hours after the start of the second dose in 2 of 3 patients (2 patients with 2 occurrences and 1 patient with 3 occurrences). As regard the occurrences after the third and subsequent doses, the reaction occurred within 2 hours after the start of the sixth dose (1 patient with 3 occurrences). Mogamulizumab administration was suspended temporarily after the first dose in 7 patients because of the infusion reaction, but resumed on the same day in all patients at the pre-determined dose. After the second and subsequent doses, however, temporary suspension did not occur in any of the 26 patients.

PMDA asked the applicant to explain prior drug administration and measures for the infusion reaction.

The applicant responded as follows:
In Japanese clinical studies, an antihistaminic agent and an antipyretic analgesic agent were administered to prevent infusion reaction at 30 minutes before mogamulizumab administration. The prior drug administration for the second and subsequent doses was the same as for the first dose in 3 patients who had multiple infusion reactions. In patients with infusion reaction, mogamulizumab administration was suspended temporarily or given at a reduced infusion rate, and the patients were treated with antihistaminic agents, antipyretic analgesic agents, corticosteroids, etc. As a result, administration of mogamulizumab at the pre-determined dose was completed even in patients for whom administration was temporarily suspended. The applicant considered that, although risk factors for infusion reaction are not identified, addition of a corticosteroid (intravenous) could reduce or alleviate infusion reaction. Therefore, in the ongoing Japanese study in treatment-naïve ATL patients (Study 0761-003), prior administration of an antihistaminic agent, an antipyretic analgesic agent, and a corticosteroid (intravenous) before the first dose was specified in the protocol.

The proposed package insert cautions that, if after resumption of administration, infusion reaction occurs again requiring treatment suspension, mogamulizumab should be discontinued and should never be re-administered. Information on specific measures to cope with the incidence of infusion reaction is planned to be provided using information leaflets.

In the post-marketing surveillance, infusion reaction will be included in a priority item, and investigation will be carried out to identify the risk factors for the adverse event.

PMDA considers as follows:
Infusion reaction was observed after the first dose of mogamulizumab in all affected patients except in 1 patient in Study 0761-0501. However, judging from the findings that the adverse event was Grade 2 or below except 3 patients with Grade 3 hypoxia, that the symptom improved after temporary suspension of administration or treatment with an antihistaminic agent, etc., and that, in 3 patients with multiple occurrences, treatment discontinuation was not required even without change in prior drug use, the infusion reaction after mogamulizumab administration can be controlled by appropriate prior drug use and measures taken in case of occurrence. However, in light of the reported occurrence of Grade 3 hypoxia, information should be provided, and caution raised, to clinical practice appropriately using the package insert and information leaflets regarding the occurrence of infusion reaction (time of onset and duration after the start of administration), prior drug treatment given to prevent infusion reaction and measures taken for

the reaction in Japanese clinical studies. The applicant explained that adding a corticosteroid (intravenous) to the prior drug administration may reduce or alleviate infusion reaction. However, necessity of prior administration of a corticosteroid (intravenous) is unclear at the moment. Therefore, infusion reaction should be dealt accordingly to the prior drug use and the treatment methods used in Japanese clinical studies submitted for approval application. When new information becomes available from ongoing clinical studies, etc., it should be provided without delay.

4.(iii).B.(2).3) Infection/immune system disorder

Infection-related adverse events (date of onset) include herpes zoster (Day 96), nasopharyngitis (Day 36), and skin infection (Day 44) in 1 patient each in Study 0761-0501, and nasopharyngitis in 4 patients (Days 6, 15, 42, 68), pharyngitis in 2 patients (Days 5, 47), oral herpes (Day 40), bronchopulmonary aspergillosis (Day 12), cytomegalovirus infection (Day 11), and urinary tract infection (Day 73) in 1 patient each in Study 0761-002.

In Study 0761-0501, in 1 patient who had recurrent ATL after completion of the fourth dose and received mogamulizumab again, hepatitis B occurred on Day 18 after the resumption of the administration (HBs antigen was negative, HBV-DNA was not detected, and anti-HBc antibody was positive before study participation; AST, ALT, bilirubin, and ALP increased, HBs antigen turned positive, and HBV-DNA levels exceeded the limit of detection after mogamulizumab administration). The patient recovered after treatment with an anti-viral drug and liver-supporting agents.

Of the above events, a causal relationship with mogamulizumab was not ruled out for herpes zoster, cytomegalovirus infection, oral herpes, and hepatitis B.

PMDA asked the applicant to explain the measures to call attention to infection, including preventive drug administration.

The applicant responded as follows:

Essential prophylactic drugs were anti-tuberculosis drugs (only in patients with a history of tuberculosis) in Study 0761-0501 and anti-tuberculosis drugs (only in patients with a history of tuberculosis) and ST combination drug (in all patients) in Study 0761-002. Antiviral drugs and antifungal drug were administered as necessary. In Study 0761-0501 (except in PTCL patients) and in Study 0761-002, ST combination drug was administered to 10 of 13 patients (76.9%) and 27 of 27 patients (100%), respectively, anti-tuberculosis drugs to 2 of 13 patients (15.4%) and 7 of 27 patients (25.9%) including those without a history of tuberculosis, antifungal drugs to 7 of 13 patients (53.8%) and 22 of 27 patients (81.5%), and antiviral drugs to 1 of 13 patients (7.7%) and 17 of 27 patients (63.0%). The concomitant drugs were used in the same manner as used for the prevention of infection in routine medical practice. After the market launch, caution will be raised about the methods for preventing Pneumocystis pneumonia, tuberculosis, herpes zoster, and fungal infection, by means of information leaflets, etc.

The onset of hepatitis B in 1 patient appears to be due to the reactivation of hepatitis B virus (HBV). Therefore, screening for HBs antigen, anti-HBs antibody, and anti-HBc antibody, and proper use of anti-HBV drug will be recommended and caution will be raised according to the “Guideline for prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection” (*Kanzo* 2009;50:38-42 [Note by PMDA: Revised on September 26, 2011]).

Mogamulizumab acts on normal Th2 and Treg cells as well, reducing their number for a certain period even after the end of administration. However, the effect of this phenomenon on immunity is currently unclear. Relevant information will be continuously collected for further investigation.

PMDA considers the occurrence and prevention of infection as follows:
In Study 0761-002, infection occurred within the study period (on or before Day 78) in all of 10 affected patients and, in 8 patients, infection occurred during the course of treatment with mogamulizumab (on or before Day 57). Of the 10 patients, only 1 patient developed an infection (oral herpes) even after prophylactic administration. ST combination drug was administered to all patients and antituberculosis drugs were administered to all of those with a history of tuberculosis. Neither Pneumocystis pneumonia nor tuberculosis was observed. Mogamulizumab administration was deferred in 1 patient but resumed after recovery. There were no patients who discontinued the study.

Although the relationship between the mechanism of action of mogamulizumab and the occurrence of infection is unclear, decreased lymphocytes are observed with a high incidence after mogamulizumab administration, raising a concern about the occurrence and aggravation of infection. Therefore, it is necessary to advise caution to take appropriate measures including prophylactic administration, by providing information regarding the rules for prophylactic administration against infection in Japanese clinical studies and the incidence of infection, by means of information leaflets, etc.

The causal relationship of mogamulizumab with hepatitis B that was suspected of being caused by reactivation of HBV cannot be ruled out. Therefore, patients should undergo HBV infection screening before mogamulizumab administration. When mogamulizumab is to be administered to patients infected with HBV, sufficient information should be provided, and caution advised, regarding the screening for anti-HBs antibody and anti-HBc antibody, monitoring during mogamulizumab administration, and measures to be taken in the event of the occurrence of hepatitis B, by means of information leaflets, etc.

After the market launch, information should be collected regarding the use or non-use of prophylactic drugs against infection, and the details of the administration if such is the case, under routine use of mogamulizumab, the incidence of infection, and the relationship between mogamulizumab and HBV reactivation.

4.(iii).B.(2).4) Skin disorder

Skin disorders observed were rash in 4 patients (25.0%), pruritus in 3 patients (18.8%), and acne in 1 patient (6.3%) in Study 0761-0501; and rash in 14 patients (51.9%), pruritus in 4 patients (14.8%), hyperhidrosis in 2 patients (7.4%), dermatitis, dermatitis contact, eczema, eczema nummular, erythema, erythema nodosum, and Stevens-Johnson syndrome (SJS) in 1 patient each (3.7%) in Study 0761-002. Skin disorders of Grade 3 or above were rash in 1 patient in Study 0761-0501 and rash in 4 patients and pruritus, eczema, and SJS in 1 patient each in Study 0761-002. No Grade 4 events were observed. Serious events were rash in 1 patient in Study 0761-0501 and rash in 4 patients and SJS in 1 patient in Study 0761-002. Skin disorders requiring the postponement of administration were not observed in Study 0761-0501, whereas in Study 0761-002, rash in 3 patients and eczema nummular in 1 patient required the postponement of administration. In Study 0761-0501, there were no skin disorders leading to the discontinuation of administration, whereas in 0761-002 study, rash in 1 patient resulted in the discontinuation of administration. In the patient with SJS, cytomegalovirus antigen (C7-HRP) was positive and cytomegalovirus DNA level was high at the onset of SJS. Although both drug and virus were suspected as the causative agent, the cause was not identified.

The applicant explained that the characteristic feature of mogamulizumab-induced skin disorders is that they do not become aggravated with continued administration.

PMDA asked the applicant to explain the reasons for concluding that continued administration of mogamulizumab does not cause aggravation of the drug-induced skin disorders and what

measures should be taken for the disorders.

The applicant responded as follows:
The conclusion that continued administration does not cause aggravation of mogamulizumab-induced skin disorders is based on the view provided by the "skin symptoms review committee" which is established by the applicant and consists of external experts in dermatology. The committee provided the following view regarding the characteristics and clinical course of mogamulizumab-induced skin disorders.

- Clinical findings of skin symptoms observed following mogamulizumab are classified into the following 4 types: (i) small papula, (ii) small papula with cyst inflammation, (iii) infiltrative erythema, and (iv) erythroderma.

- Major histopathological findings are classified into two major categories, "interface dermatitis" and "spongiotic dermatitis." Skin disorders accompanied by petechiae, papule, or cyst inflammation tend to be "spongiotic dermatitis," while those accompanied by erythema tend to be "interface dermatitis." However, it is difficult to differentiate drug eruption from ATL-induced eruption from histopathological findings alone.

- Usually, allergic drug eruptions show dramatic aggravation of symptoms with multiple-dosing of the causative drug, precluding further administration. In contrast, mogamulizumab-induced rash did not show any dramatic aggravation in symptoms with multiple-dosing although aggravation (from Grade 1 to Grade 2 or 3, or from Grade 2 to Grade 3) was observed in some patients. Furthermore, in some patients, mogamulizumab-induced skin diseases can be controlled by oral corticosteroid, or spontaneous recovery may be achieved.

Based on the comprehensive review of the above findings, the applicant concluded that, as opposed to usual drug eruptions, mogamulizumab-induced skin diseases are unlikely to become dramatically aggravated even after continued administration.

In Study 0761-002, to control "skin and subcutaneous tissue disorders" (MedDRA SOC), topical corticosteroids, anti-allergic drugs, or anti-histaminic drugs were mainly used for symptoms of Grade 2 or below, and oral or topical corticosteroid for those of Grade 3 or above.

On the basis of the above, treatment with corticosteroid (oral, topical, intravenous), anti-allergic drugs, and antihistaminic drugs will be recommended as measures to address skin diseases after the market launch, and caution will be raised using information leaflets, requesting that in patients with skin disorder of Grade 3 or above, mogamulizumab be postponed until symptoms improve to Grade 2 or below and that patients undergo skin biopsy as necessary and visit a dermatologist.

PMDA considers as follows:
Mogamulizumab-induced skin disorders occurred with a high incidence, with severity of Grade 3 or above in some cases. Therefore, it is necessary to appropriately advise caution and provide information about the incidence of skin disorders including SJS and measures to be taken, using information leaflets, etc. As regards the applicant's explanation that mogamulizumab-induced skin disorders do not become serious even after multiple-dosing, no such conclusion can be reached at the moment because of the limited number of patients studied. Given that mogamulizumab administration caused SJS, a disorder that may become serious, and that administration was deferred in a patient in the clinical study, it is necessary to carefully consider the measures to be taken in the event of skin disorder and necessity of postponing mogamulizumab administration, in collaboration with a dermatologist as necessary. In addition, additional information should be collected after the market launch, regarding the incidence of skin disorders and measure taken, including the postponement of administration.

4.(iii).B.(2).5) Tumor lysis syndrome (TLS)

Preventive measures against tumor lysis syndrome (TLS) (transfusion, diuretic, inhibitor of uric acid formation) were performed in 6 of 16 patients (37.5%) in Study 0761-0501 and in 15 of 27 patients (55.6%) in Study 0761-002.

TLS was not observed in Study 0761-0501, whereas in 0761-002 study, TLS occurred in 1 patient (Grade 3) after the first dose. This patient had received preventive measures against TLS (allopurinol 100 mg, per oral, 3 times daily). Treatments given after the onset of TLS (transfusion, low molecular weight heparin, allopurinol) resulted in the recovery from the event, and no recurrence of TLS was observed after the second and subsequent doses.

PMDA considers as follows:

TLS has so far been observed in only 1 patient, and risk factors for mogamulizumab-induced TLS are therefore unknown at the moment. However, since TLS, once manifested, may become serious, it is necessary to take appropriate measures to prevent and treat TLS by referring to general risk factors of TLS such as tumor mass and renal function (*J Clin Oncol* 2008;26:2767-78). Therefore, it is necessary to provide detailed information about the status of supportive therapy for TLS in clinical studies of mogamulizumab and to advise caution to take appropriate measures.

4.(iii).B.(2).6) Hepatic dysfunction

The incidence of hepatic function in Studies 0761-0501 and 0761-002 was as shown in the following table. The only serious adverse event observed was hepatitis B in 1 patient described in "4.(iii).B.(2).3) Infection/immune system disorder." There were no adverse events leading to the discontinuation of administration. Mogamulizumab administration was deferred in 2 patients with γ-GTP increased and 1 patient with ALT increased/AST increased in Study 0761-002. All events resolved after the postponement of administration.

Abnormal hepatic function values observed in Studies 0761-0501 and 0761-002

PT	Study 0761-0501 No. of patients (%) (N = 16)		Study 0761-002 No. of patients (%) (N = 27)	
	All grades	≥ Grade 3	All grades	≥ Grade 3
ALT increased	5 (31.3)	1 (6.3)	11 (40.7)	2 (7.4)
AST increased	5 (31.3)	1 (6.3)	11 (40.7)	2 (7.4)
Blood ALP increased	5 (31.3)	0	7 (25.9)	0
Blood LDH increased	4 (25.0)	0	10 (37.0)	3 (11.1)
Blood γ-GTP increased	1 (6.3)	1 (6.3)	4 (14.8)	3 (11.1)
Hyperbilirubinaemia	1 (6.3)	0	2 (7.4)	0
Cholangitis	0	0	1 (3.7)	0
Hepatitis B*	1 (6.3)	0	0	0

* After re-administration

PMDA considers as follows:

Hepatic dysfunction occurred after mogamulizumab administration, but there were only few Grade 3 or higher-grade events and they resolved after postponement of administration. In addition, there were no patients who discontinued the administration because of hepatic dysfunction. These results suggest that the adverse events are tolerable when addressed in a similar manner as in clinical studies. It is necessary to provide information on the incidence of hepatic dysfunction and measures taken in clinical studies and to collect further information after the market launch.

4.(iii).B.(2).7) Cardiac dysfunction

The applicant explained the risk of QT/QTc interval prolonged and cardiac dysfunction as follows:

Adverse events related to cardiac function included tachycardia (4 patients [25.0%]), left ventricular dysfunction (3 patients [18.8%]), electrocardiogram QT prolonged (2 patients [12.5%]), and heart rate increased (2 patients [12.5%]) in Study 0761-0501, and tachycardia (8 patients [29.6%]), ventricular extrasystoles (2 patients [7.4%]), congestive cardiac failure, left ventricular dysfunction, left atrial dilatation, and heart rate increased (1 patient each [3.7%]) in Study 0761-002. Electrocardiogram QT prolonged in 1 patient and cardiac failure congestive in 1 patient were Grade 2, whereas all other events were Grade 1. Grade 2 cardiac failure congestive, tachycardia, ventricular extrasystoles, and heart rate increased were events mainly related to infusion reaction.

Electrocardiogram QT prolonged in 2 patients was a mild, transient change without subjective symptoms. One patient who experienced Grade 2 electrocardiogram QT prolonged had had Grade 1 QT/QTc intervals prolonged before the first dose of mogamulizumab. In 5 patients who had concurrent cardiac disease as a background factor, QT/QTc interval prolonged was not observed. In light of the findings that QT/QTc interval prolonged did not occur in Study 0761-EU-001, that CCR4 is not expressed in human heart, and that no signs of QT/QTc interval prolonged were observed in nonclinical studies, mogamulizumab appears to have only a small risk of causing prolonged QT/QTc interval. However, information will be provided and caution advised about QT/QTc interval prolonged as is the case with other cardiac dysfunctions.

PMDA considers as follows:
Based on the incidence of the QT/QTc interval prolonged and information obtained in nonclinical studies, it is unnecessary at the moment to perform periodical electrocardiography in all patients treated with mogamulizumab. However, since cardiac dysfunction occurred mainly associated with infusion reaction, patients should be closely monitored during administration and, in patients with cardiac dysfunction or abnormal ECG changes, caution should be exercised to pay particular attention to the occurrence of QT/QTc interval prolonged.

4.(iii).B.(2).8) Others

a. Secondary malignant tumor

In foreign Study 0761-EU-001, B cell lymphoma (stage IV follicular lymphoma) was observed in 1 healthy adult subject at 65 days after receiving 0.001 mg/kg mogamulizumab. In Japanese clinical studies, in contrast, no malignant tumor other than the primary disease was observed.

PMDA asked the applicant to explain the necessity of advising caution against the occurrence of secondary malignant tumor caused by mogamulizumab.

The applicant responded as follows:
As regards follicular lymphoma observed in Study 0761-EU-001, the investigator and the sponsor has considered that its causal relationship with mogamulizumab cannot be ruled out completely. However, it is extremely unlikely that mogamulizumab acts as a major cause of secondary malignant tumor because (i) the drug acts by inducing ADCC activity and is unlikely to cause secondary malignant tumor due to DNA damage and (ii) no secondary malignant tumor was detected in other clinical studies. Therefore, at the moment, it is unnecessary to raise caution about secondary malignant tumor. However, since mogamulizumab has been administered to only a limited number of patients, information will be collected after the market launch and caution will be advised as necessary.

PMDA considers the risk of secondary malignant tumor as follows:
Mogamulizumab has been administered to only a small number of patients in clinical studies and the patients have been observed for a limited period of time, precluding accurate assessment of the risk of secondary malignant tumor. However, since follicular lymphoma reported in foreign Study 0761-EU-001 usually progresses only gradually, it is unlikely that the adverse event is

related to mogamulizumab. Therefore, the applicant's response that it is unnecessary, at the moment, to raise caution against secondary malignant tumor is acceptable. However, there is a report that CCR4-expressing Th2 and Treg cells are involved in the clinical course of lymphoma (*Hematol Oncol* 2009;27:31-9, *Blood* 2006;108:2957-64), suggesting that the observed follicular lymphoma may have been a lymphoproliferative diseases that occurred after mogamulizumab administration. Therefore, consideration should be given to collecting information on the occurrence of secondary malignant tumor from the ongoing comparative study in treatment-naive patients.

b. Anti-mogamulizumab antibody

In foreign Study 0761-EU-001 (single-dose intravenous administration), anti-mogamulizumab antibody was detected in 2 healthy adult subjects. In contrast, in Japanese clinical studies, anti-mogamulizumab antibody was not detected.

PMDA asked the applicant to explain the safety in patients who produced anti-mogamulizumab antibody.

The applicant responded as follows:

In 1 patient in whom anti-mogamulizumab antibody was produced (in 0.003 mg/kg mogamulizumab group), the antibody was detected from the 29th day of mogamulizumab administration, but no allergic reactions or anaphylactoid symptoms (e.g., polyuria, dyspnoea, hypotension, encephalitis, syncope, unconsciousness, urticaria, flushing, angioedema) were observed for approximately 16 months until anti-mogamulizumab antibody decreased below the lower limit of quantitation. The other patient (in 0.0003 mg/kg mogamulizumab group) was anti-mogamulizumab antibody-positive from before mogamulizumab administration, and was therefore judged as "pseudo-positive." No allergic reaction was observed in this patient either.

However, at the moment, safety in patients with anti-mogamulizumab antibody cannot be fully ensured. If, after the market launch, allergic reactions and accompanying symptoms suggestive of adverse reactions due to anti-mogamulizumab antibody are observed, the applicant will perform test for anti-mogamulizumab antibody on such patients, and collect safety information. Since in the current assay method, mogamulizumab in samples may affect the results of the assay, a new assay method not affected by mogamulizumab is under investigation.

PMDA considers as follows:

Anti-mogamulizumab antibody was produced in only 2 patients. In addition, patients with or without anti-mogamulizumab antibody cannot necessarily be clearly differentiated from each other because of the problem in the anti-mogamulizumab antibody assay method [see "4.(i).B.(1) Effect of mogamulizumab in samples on the measurement of anti-mogamulizumab antibody"]. Therefore, safety in patients with anti-mogamulizumab antibody is currently unclear. It is necessary to promptly establish a new assay method so that the state of anti-mogamulizumab antibody production and the safety in patients with anti-mogamulizumab antibody can be accurately evaluated. Also, since the clinical significance of anti-mogamulizumab antibody production is unknown, if the production is observed in mogamulizumab-treated patients after the market launch, safety information should be collected from such patients for investigation and provided to clinical practice in an appropriate manner.

4.(iii).B.(3) Clinical positioning

The applicant explained the clinical positioning as follows:

In ATL patients, performance status, LDH high, age of ≥40 years, calcium high, and total number of lesions are known to be poor prognostic factors. Particularly chronic-type ATL with LDH high, BUN high, or albumin low is classified as chronic ATL with poor prognostic factors; thus, presence or absence of poor prognostic factors markedly affects the treatment option. ATL

patients who are candidates for aggressive treatment are those with acute ATL, lymphoma-type ATL, or chronic ATL with poor prognostic factors.

Mogamulizumab is intended to be administered to patients with recurrent or relapsed CCR4-positive ATL of acute type, lymphoma type, or chronic type with poor prognostic factors (LDH high, BUN high, or albumin low). There is no effective treatment for these patients and reports of treatment results are limited. According to the results of clinical studies of already approved drugs available at the time of their approval, the response rates for acute type and lymphoma type to pentostatin (brand name, Coforin for intravenous injection 7.5 mg), studied in patients with unknown prior treatment, were 23.5% (4 of 17 patients) and 33.3% (1 of 3 patients), respectively, with an overall response rate being 25.0% (5 of 20 patients) (data from the package insert of Coforin for intravenous injection 7.5 mg). These results show that the response rate to mogamulizumab is comparable to or higher than the rate to pentostatin. Sobuzoxane (brand name, Perazolin Fine Granules 400 mg, 800 mg) was effective only in treatment-naive patients (*Cancer* 1993;71:2217-21). Treatment regimens used in combination chemotherapy for secondary and subsequent treatments include CDE-11 (irinotecan, dexamethasone, etoposide), EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), and CHASE (cyclophosphamide, etoposide, cytarabine, dexamethasone), but these regimens have not shown any clear evidence of efficacy and are not indicated for quite a few patients for reasons of age limit, etc.

On the basis of the above, mogamulizumab is considered to be positioned as the first-line drug for patients with recurrent or relapsed CCR4-positive ATL of acute type, lymphoma type, or chronic type with poor prognostic factors. Since patients with ATL of smoldering type or chronic type without poor prognostic factors are also sometimes treated with combination chemotherapy if they have nodal/tumoral skin lesion, mogamulizumab is indicated for these patients as well if CCR4 is expressed.

PMDA has confirmed the following regarding the treatment policy for ATL, based on the standard textbooks (*Williams Hematology* 7th ed. *Harrison's Internal Medicine* 17th ed.), overseas clinical practice guideline (NCCN *Clinical Practice Guidelines in Oncology Non-Hodgkin's Lymphomas.* v.3. 2011; hereafter referred to as "NCCN Guideline"), and most recent publications. PMDA also confirmed that information provided by National Cancer Institute Physician Data Query (NCI-PDQ®) regarding ATL treatment was mostly derived from clinical studies.

- Treatment of ATL has been investigated based on the disease type and presence/absence of poor prognostic factors, and in patients who are candidates for aggressive treatment, namely those with ATL of acute type, lymphoma type, or chronic type with poor prognostic factors, participation in clinical studies, potent combination chemotherapy, and allogeneic hematopoietic stem cell transplantation are recommended (*J Clin Oncol* 2009;27:453-9, *Blood* 2011;118:1736-45). Patients with chronic ATL are considered to have poor prognosis if they have LDH high, BUN high, or albumin low (*Adult T-cell leukemia* Oxford University Press, 1994).

- As regards for treatment-naive ATL patients, foreign published literature (*J Clin Oncol* 2010;28:4177-83, *Blood* 2011;118:1736-45) and NCCN Guideline recommend participation in clinical studies and concomitant use of zidovudine with IFN-α (hereafter referred to as "AZT/IFN therapy") for acute type, combination chemotherapy and participation in clinical studies for lymphoma type, and participation in clinical studies, AZT/IFN therapy, and follow-up for chronic and smoldering type.

- The internationally agreed treatment policy for treatment-naive ATL patients recommends participation in clinical studies, whereas the usefulness of VCAP-AMP-VECP regimen

(mLSG15 regimen) was reported in a Japanese phase III study (Study JCOG9801) in these patients (*J Clin Oncol* 2007;25:5458-64). In Japan, this regimen is usually administered as the primary treatment with consideration given to age and disease state (*Blood* 2011;118:1736-45, *Eur J Haematol* 2008;80:185-96, *J Clin Exp Hematop* 2010;50:9-25).

- For relapsed or refractory ATL, there is no widely accepted treatment policy. Possible options are participation in clinical studies (concomitant use of arsenic trioxide with IFN-α, bortezomib, forodesine, histone deacetylase inhibitor, target therapy against surface molecules [e.g., CD25, CD2, CD52, CCR4], angiogenic inhibitor, etc.) and, if feasible, allogeneic bone-marrow transplantation (*J Clin Oncol* 2009;27:453-9, *Blood* 2011;118:1736-45, *J Clin Exp Hematop* 2010;50:9-25, NCCN Guideline).

PMDA considers the clinical positioning of mogamulizumab as follows:
The submitted clinical study data suggest that mogamulizumab has some clinical significance in patients with recurrent or relapsed CCR4-positive ATL of acute type, lymphoma type, or chronic type with poor prognostic factors. However, no clinical data are available on the comparison of the efficacy between mogamulizumab and other treatment options, and already approved drugs were compared with external controls only. Therefore, the clinical positioning of mogamulizumab relative to other treatment options in the above patients remains unclear. On the basis of the above, PMDA has concluded that mogamulizumab can be positioned as one of the treatment options for patients with recurrent or relapsed CCR4-positive ATL of acute type, lymphoma type, or chronic type with poor prognostic factors. As regards patients with ATL of smoldering type or chronic type without poor prognostic factors who have nodal/tumoral skin lesions, no clinical data have been submitted. Therefore, there is no justification for strongly recommending administration to these patients.

Regarding for treatment-naive ATL patients, no clinical results of mogamulizumab have been available at the moment, but PMDA confirmed that a Japanese phase II study (Study 0761-003) is currently ongoing to investigate the efficacy and safety of concomitant use of mogamulizumab using mLSG15 regimen as the control and that the study will be completed in the [redacted] or [redacted] quarter of 20[redacted].

4.(iii).B.(4) Indications
Based on the following review in addition to the results of reviews in "4.(iii).B.(1) Efficacy, 4.(iii).B.(2) Safety, and 4.(iii).B.(3) Clinical positioning," PMDA has concluded that the indication for mogamulizumab should be "relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma." Also, the following caution statements should be included in the Precaution for Indications section of the package insert.

- The disease to be treated with mogamulizumab should be diagnosed by a physician or a clinical center that is well experienced in pathological diagnosis.

- Patients should be tested for CCR4 antigen by IHC or FCM, and only those who are CCR4-antigen positive should be treated with mogamulizumab.

- The physician 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.(iii).B.(4).1) Indications
Since no clinical study data have been available on patients other than those with recurrent or relapsed ATL (refractory to primary treatment), the applicant considers that administration of

mogamulizumab to these patients is not recommended. Thus, the applicant explained that "recurrent/relapsed CCR4-positive adult T-cell leukemia lymphoma" will be proposed as the indication for the product, and that caution will be advised to use the drug only in patients with recurrent or relapsed ATL after chemotherapy.

Regarding the establishment of indications, PMDA considers as follows:
Patients for whom mogamulizumab administration is recommended are as described in "4.(iii).B.(3) Clinical positioning." However, treatment for ATL is determined based on the disease type and presence or absence of poor prognostic factors, and patients with disease types other than those investigated in Japanese clinical studies and patients without poor prognostic factors experience very gradual progression of the disease and therefore do not usually receive aggressive treatment. In addition, mogamulizumab is used by physicians with thorough knowledge and experience in chemotherapy of hematopoietic organ tumor. Taking these facts into account, it is expected that patients are selected appropriately if the sponsor (i.e., the applicant) provides such physicians with accurate information on patients to be enrolled in clinical studies. In Japanese clinical studies, patients refractory to primary treatment were excluded. At the current clinical practice, the choice for the secondary treatment for ATL does not depend on the response to the primary treatment, and there is no sufficient pharmacological data suggesting that the efficacy of mogamulizumab depends on the response to the primary treatment given previously.

For these reasons, PMDA considers that there is little need to include disease type or presence/absence of poor prognostic factors as criteria in the indications and that it is unnecessary to exclude patients who did not respond to the primary treatment. PMDA judges that the "relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma" as the indication for mogamulizumab is appropriate. In order to facilitate appropriate patient inclusion, it will be necessary to advise caution and to provide information about the disease type and presence/absence of poor prognostic factors in patients to be enrolled in clinical studies, using information leaflets including the package insert.

Regarding the use of mogamulizumab in patients after allogeneic hematopoietic stem cell transplantation, the applicant explained as follows:
Since both immune-enhancing Th2 cells and immune-suppressing Treg cells express CCR4, it is expected that these cells decrease in number following treatment with mogamulizumab. Although the effect of mogamulizumab on these cells has not been fully elucidated, the immunosuppressive effect of Treg cells may be cancelled by the reduction in Treg cells. If mogamulizumab is administered to patients who have received transplantation such as allogeneic hematopoietic stem cell transplantation, a possibility of delayed graft-versus-host disease (GVHD) cannot be excluded. Therefore, these patients were excluded from Japanese clinical studies. Accordingly, caution will be advised that the efficacy and safety of mogamulizumab in patients who have received allogeneic hematopoietic stem cell transplantation has not been established, and therefore that the use of the drug in these patients should be decided based on the careful assessment of risk-benefit profile.

PMDA considers the use of mogamulizumab in patients after allogeneic hematopoietic stem cell transplantation as follows:
In addition to the fact that the effect of mogamulizumab on Th2- and Treg-mediated immune function is unknown, there is no clear evidence of the occurrence of adverse events caused by this mechanism. Therefore, there is currently no sufficient reason for considering that the use of mogamulizumab to treat these patients is inappropriate. However, it is necessary to provide the following information to clinical practice using information leaflets, etc.: (i) in light of reports suggesting the relationship between Treg cells and GVHD (*Blood* 2011;118:5671-80, *Blood* 2009;113:4458-67, *Nat Med* 2003;9:1144-50), it is theoretically plausible that mogamulizumab affects the immune system by acting on these cells, causing GVHD for example; (ii) depending

on the concomitant drugs such as immunosuppressive agents, the risk of mogamulizumab-induced infection may be enhanced in these patients; and (iii) mogamulizumab has never been used in these patients because they were excluded from Japanese clinical studies. Also, it is necessary to collect information on the safety of mogamulizumab in these patients from post-marketing experience and from published reports including those of nonclinical studies.

4.(iii).B.(4).2) Test for CCR4 expression

In Study 0761-002, CCR4 expression was measured at the centralizing test facility by FCM of whole blood in patients who had tumor cells mainly in the peripheral blood and by IHC of tissue sections collected by biopsy in patients who had tumor cells mainly in lymph nodes or the skin. Results of the test were judged by the FCM evaluator and histopathology evaluator, respectively.

PMDA asked the applicant to explain the appropriateness of administering mogamulizumab when the results of FCM differ from those of IHC.

The applicant responded as follows:

In patients with both peripheral blood lesion and non-peripheral-blood lesion, both tests for CCR4 expression may be performed, and the result may possibly be different between the 2 testing methods. However, given the report that ATL cells are monoclonal (*Proc Natl Acad Sci* 1984;81:2534-7), if a patient is judged as CCR4-positive by either of the tests, it is considered that CCR4-positive ATL cells are present in the other lesion, warranting the administration of mogamulizumab. However, in 44 patients (including non-enrolled patients) who received both tests in Study 0761-002, there were no cases that were positive for one test and negative for the other, which suggests that both tests are unlikely to give different results from each other.

PMDA has concluded that, if CCR4 expression is confirmed either by FCM or by IHC, such patients may be selected as eligible for treatment with mogamulizumab.

4.(iii).B.(5) Dosage and administration

Based on the results of the following review, PMDA has concluded that the proposed dosage and administration, “The usual adult dosage is 1 mg/kg/dose of Mogamulizumab (Genetical Recombination) intravenously infused once weekly for 8 doses,” is acceptable. PMDA has also concluded that it is appropriate to advise caution and provide information on the following in the “Precautions for Dosage and Administration” section of the package insert.

[Precautions for Dosage and Administration]

- Infusion reaction (e.g., pyrexia, chills, tachycardia) may occur after mogamulizumab administration. Prior treatment with an anti-histaminic drug and an antipyretic analgesic agent, etc. should be performed 30 minutes before mogamulizumab administration in order to alleviate these symptoms.

- Patients should be carefully monitored. If an 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 recurred, administration should be discontinued immediately, and retreatment should not be performed.

- The efficacy and safety of concomitant use of mogamulizumab with other antineoplastic drugs has not been established.

- 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 mL of saline, and infuse the solution over 2 hours.

4.(iii).B.(5).1) Method of administration

The applicant explained the reason for determining the recommended dose in Study 0761-002 to be 1.0 mg/kg, as follows:

Generally, MTD of antibody drugs remains undetermined in phase I studies, and the maximum dose tested is determined as the dose recommended for phase II studies (*Blood* 1994;84:2457-66, *J Clin Oncol* 1997;15:3266-74, *J Clin Oncol* 2007;25:2564-9). In such cases, it is important to know whether or not patients are exposed to a sufficient amount of the antibody relative to the amount of the antigen. In Study 0761-0501, $t_{1/2}$ of mogamulizumab after the fourth dose in the 1.0 mg/kg group was similar to that of human IgG in general, which suggests that the amount of mogamulizumab sufficiently exceeds the amount of the antigen within the body. In the same study, C_{trough} in the 1.0 mg/kg group after the first and the fourth dose was 7.54 and 19.5 μg/mL, respectively, and plasma mogamulizumab concentration after 1.0 mg/kg administration was the same as or higher than the concentration that showed sufficient ADCC activity in *in vitro* tests using specimens collected from ATL patients (10 μg/mL). Moreover, in the 1.0 mg/kg group of this study, skin disorders (rash, pruritus) tended to occur more frequently and severe adverse events (rash, febrile neutrophils decreased) occurred, compared with 0.01 to 0.5 mg/kg groups. Based on the collective judgment of the above findings, 1.0 mg/kg is considered to be a dose close to MTD in ATL patients.

Since a sufficiently high clinical effect (response rate 50% [13 of 26 patients]) was obtained at 1.0 mg/kg in Study 0761-002, there is no plan to investigate the efficacy at doses exceeding 1.0 mg/kg.

PMDA considers dosage and administration as follows:

In vitro studies using specimens collected from ATL patients were not conducted at the concentration of >10 μg/mL, and ADCC activity at higher concentrations is therefore unknown. Also, no clear conclusion has been obtained regarding the relationship among mogamulizumab dose, PK, and efficacy. The possibility cannot be therefore excluded that a higher degree of clinical efficacy may be obtained at doses of >1.0 mg/kg, which are expected to provide higher exposure level. In addition, the dose 1.0 mg/kg is not judged as the MTD. These results suggest that there remains room to study the efficacy at higher doses. However, based on the results of the reviews in “4.(iii).B.(1) Efficacy” and in “4.(iii).B.(2) Safety,” PMDA has concluded that, at the moment, it is appropriate to determine 1.0 mg/kg as the dose for mogamulizumab

administered to ATL patients once weekly.

Also, PMDA concluded that caution should be advised in the package insert, etc., regarding the method for the preparation of drug solution and the infusion rate, based on the results of the study.

4.(iii).B.(5).2) Dosing schedule, etc.

The applicant explained the determination of the dosing schedule of mogamulizumab, etc., as follows:

In Study 0761-002, the dosing schedule was set at up to 8 doses by taking into account the results of Study 0761-0501 which confirmed the tolerability and safety of 4 doses of mogamulizumab and the maximum dosing schedule approved for rituximab (genetical recombination), an antibody drug for CD20-positive B-cell non-Hodgkin's lymphoma. Since mogamulizumab has never been administered continuously for >8 doses, the "Dosage and Administration" section will include the caution that the dosing schedule is up to 8 doses. At the moment, there is no plan for clinical development of mogamulizumab administered continuously for >8 doses.

In Studies 0761-0501 and 0761-002, if ATL recurrence or relapse occurred in patients who had shown a response after completing 4 doses (Study 0761-0501) or 8 doses (Study 0761-002), they were allowed to receive retreatment with mogamulizumab by the same dosage regimen as in the initial treatment, provided that anti-mogamulizumab antibody was undetectable.

The applicant explained retreatment in clinical studies, as follows:

Mogamulizumab was readministered in 1 patient each in Studies 0761-0501 and 0761-002. The patient receiving retreatment (0.01 mg/kg group) in Study 0761-0501 discontinued the study medication because of hepatic dysfunction before the third dose in the retreatment, with the overall best response unknown. The patient receiving the retreatment in Study 0761-002 achieved PR after completing the fourth dose in the retreatment but was judged as PD after completing the sixth dose, whereupon the treatment was discontinued. Thus, the efficacy and safety of retreatment with mogamulizumab is unclear from the currently available data of clinical studies.

PMDA considers the dosing schedule of mogamulizumab as follows:

PMDA understands that the upper limit of dosing schedule in Study 0761-002 was determined mainly by referring to the approved dosage regimen for rituximab and not based on the clinical pharmacology of mogamulizumab itself. However, since the efficacy and safety of mogamulizumab is unknown for >8 doses, PMDA considers it acceptable to set the dosing schedule of up to 8 doses as the dosage regimen in keeping with the dosage regimen in Study 0761-002. Also, PMDA has concluded that detailed information should be appropriately provided using information leaflets, etc. on the clinical course of patients who received retreatment for recurrence or relapse of ATL after having responded to mogamulizumab treatment in clinical studies. In addition, since retreatment was performed in very limited number of patients, safety information, etc., of retreatment should be collected and provided to clinical practice appropriately if there are retreatment cases after the market launch.

4.(iii).B.(5).3) Criteria for temporary withdrawal and discontinuation

Regarding the cautions against infusion reaction and skin disorders and their treatments, the applicant explained as follows:

Measures will be taken as described in the "4.(iii).B.(2) Safety." section. For serious skin disorders such as SJS, caution will be raised to take appropriate measures and withdraw the drug temporarily.

PMDA accepted the applicant's explanation regarding the caution against infusion reaction and its treatment. Regarding the section "Precautions for Dosage and Administration," PMDA judges it necessary to advise caution regarding when to withdraw the drug temporarily or discontinue the treatment in case of occurrence.

In contrast, no discontinuation criteria for skin disorders are established, and judgment of treatment discontinuation or postponement after appropriate treatment will be given in a similar manner as in adverse events other than infusion reaction. In addition, based on the incidence of skin disorders, their treatments, and clinical courses in clinical studies, PMDA has concluded that there is little need to raise caution against skin disorders in particular in the "Precautions for Dosage and Administration" section.

4.(iii).B.(5).4) Concomitant use with other antineoplastic drugs

The applicant explained concomitant use of mogamulizumab with other antineoplastic drugs as follows:

Since the safety and efficacy of concomitant use of mogamulizumab with other antineoplastic drugs has not been established at the moment, caution will be advised for not co-administering the drug with other antineoplastic drugs. A combination therapy study of mogamulizumab and mLSG15 regimen (Study 0761-003) is ongoing in treatment-naive ATL patients.

PMDA accepted the explanation of the applicant. Also, PMDA considers that if safety-related information is obtained in additional clinical studies, etc., regarding the concomitant use of mogamulizumab with other antineoplastic drugs, the information should be provided in an appropriate manner.

4.(iii).B.(6) Post-marketing investigations

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

The applicant plans to conduct a post-marketing surveillance of all patients treated with mogamulizumab using the central registration system in order to (i) detect unexpected adverse drug reactions, (ii) grasp the incidence of adverse drug reactions, (iii) identify factors that may affect the safety and efficacy, and (iv) investigate priority surveillance items etc., for actual use after the market launch, thereby to confirm the safety and efficacy of the drug.

On the basis of safety information obtained from Japanese clinical studies, the priority surveillance items will include infection reaction, skin disorders (e.g., rash, pruritus, hyperhidrosis, dermatitis, eczema, erythema), infection (including reactivation of HBV), and TLS, as well as immune disorders (e.g., deterioration of autoimmune diseases) which may be induced by suppression of Treg cells by mogamulizumab, albeit not observed in clinical studies in Japan and overseas.

The target sample size was set at 600 patients for the following reasons: (i) at least 300 patients are needed to detect, with a ≥95% probability, adverse reactions that occur with an incidence of 1%, a rate lower than that of the adverse event with the lowest frequency observed in clinical studies (2.3%, observed in 1 out of a total of 43 patients in Japanese clinical studies), and (ii) in order to analyze the efficacy of the drug for low-frequency disease types, i.e., lymphoma-type ATL and chronic ATL with poor prognostic factors (each accounting for 23.1% of all patients in Study 0761-002), in approximately 100 patients, data from approximately 600 patients have to be collected with allowance for those excluded from analysis (approx. 20%). As a result of the estimation of the number of patients treatable with mogamulizumab based on the number of patients who develop ATL annually, the recruitment period necessary to collect 600 patients is set at 3 years.

The observation period will consist of up to 8 weeks (approx. 2 months) of treatment period for 8 doses of mogamulizumab, 1 month of post-treatment period, and a follow-up period, resulting in a total of 8 months. The follow-up period was determined by taking into account the fact that rash, a skin disease which occurred with the highest incidence in clinical studies among skin diseases included in the priority surveillance items, develops during the last half of the

administration period and persists for a long period of time (median maximum duration, 118.5 days [approx. 4 months]).

As regards efficacy, information on the response rate judged by attending physicians and survival rate 8 months after the start of treatment will be collected.

PMDA considers the submitted plan for post-marketing surveillance as follows:
Since safety information of mogamulizumab in Japanese ATL patients is limited at the moment, it is necessary to collect information promptly. Therefore, an all-case post-marketing surveillance should be conducted in a certain number of patients after the market launch.

The following information should be collected in addition to priority surveillance items proposed by the applicant:

- Time of onset of events possibly related to immune disorders (e.g., infection, exacerbation of autoimmune disease)

- Information required for the evaluation of the relationship between mogamulizumab administration and immune disorders (e.g., conditions of ATL)

- Whether or not screening for anti-HBs antibody and anti-HBc antibody is performed

- Information on haematotoxicity and hepatic dysfunction

- Effect of anti-mogamulizumab antibody on the safety and efficacy of mogamulizumab, if the antibody assay is performed

- Safety and efficacy of mogamulizumab administration after allogeneic hematopoietic stem cell transplantation, if performed

- Safety and efficacy of retreatment with mogamulizumab for ATL recurrence or relapse after response to the initial treatment with mogamulizumab

The target sample size is set to allow efficacy evaluation in each disease type including those with relatively rare occurrence. However, since the primary objective of this surveillance is to promptly collect safety information on actual use and a certain level of efficacy evaluation has already been performed based on the submitted data, it is sufficient to set the target sample size as that which allows the collection of safety information during routine use, and to plan a supplementary investigation for efficacy within the set range.

The observation period should be set to allow the assessment of the incidence of adverse events related to the prolonged immune disorders caused by mogamulizumab. The applicant explained that herpes zoster occurred at approximately 3 months after the end of administration and within 6 months after the last administration in Study 0761-0501 and that it is possible to collect information on immunosuppression-related adverse events during the currently planned observation period (up to 6 months after the last administration). Therefore, the observation period planned by the applicant will be sufficient. However, since mogamulizumab is administered for up to 2 months, information available at least 2 months after the start of treatment should be collected promptly and be provided to clinical practice in an appropriate manner.

Also, based on the interim analysis to be carried out at the above timing, etc., necessity of changing the surveillance plan, including the target sample size and the observation period, should be considered as required.

4.(iv) Adverse events observed in clinical studies

Deaths reported in clinical studies submitted as the safety evaluation data were described in "4.(iii) Summary of clinical efficacy and safety." Other main adverse events were shown below.

4.(iv).1) Japanese phase I study (Study 0761-0501)

Adverse events were observed in 16 of 16 patients (100%), and those for which a causal relationship with mogamulizumab could not be ruled out were observed in 16 of 16 patients (100%). Adverse events with an incidence of ≥20% were as shown in the following table.

Adverse events (incidence ≥ 20%) in Study 0761-0501: number of patients (%)

	0.01 mg/kg		0.1 mg/kg		0.5 mg/kg		1.0 mg/kg		All	
SOC PT	All grades N = 3	≥ Grade 3 N = 3	All grades N = 4	≥ Grade 3 N = 4	All grades N = 3	≥ Grade 3 N = 3	All grades N = 6	≥ Grade 3 N = 6	All grades N = 16	≥ Grade 3 N = 16
All AEs	3 (100)	1 (33.3)	4 (100)	3 (75.0)	3 (100)	2 (66.7)	6 (100)	5 (83.3)	16 (100)	11 (68.8)
Cardiac disorders										
Tachycardia	1 (33.3)	0	3 (75.0)	0	0	0	0	0	4 (25.0)	0
General disorders and administration site conditions										
Infusion related reaction	3 (100)	0	3 (75.0)	0	3 (100)	0	4 (66.7)	0	13 (81.3)	0
Pyrexia	2 (66.7)	0	4 (100)	0	2 (66.7)	0	4 (66.7)	0	12 (75.0)	0
Chills	1 (33.3)	0	4 (100)	0	0	0	4 (66.7)	0	9 (56.3)	0
Fatigue	1 (33.3)	0	1 (25.0)	0	1 (33.3)	0	1 (16.7)	0	4 (25.0)	0
Investigations										
Lymphocyte count decreased	2 (66.7)	1 (33.3)	4 (100)	2 (50.0)	3 (100)	2 (66.7)	6 (100)	5 (83.3)	15 (93.8)	10 (62.5)
Neutrophil count decreased	1 (33.3)	0	2 (50.0)	1 (25.0)	3 (100)	1 (33.3)	4 (66.7)	1 (16.7)	10 (62.5)	3 (18.8)
White blood cell count decreased	1 (33.3)	0	2 (50.0)	0	3 (100)	1 (33.3)	4 (66.7)	1 (16.7)	10 (62.5)	2 (12.5)
Platelet count decreased	3 (100)	0	2 (50.0)	0	1 (33.3)	0	3 (50.0)	0	9 (56.3)	0
ALT increased	1 (33.3)	0	2 (50.0)	1 (25.0)	0	0	2 (33.3)	0	5 (31.3)	1 (6.3)
AST increased	1 (33.3)	0	2 (50.0)	1 (25.0)	0	0	2 (33.3)	0	5 (31.3)	1 (6.3)
Blood ALP increased	1 (33.3)	0	3 (75.0)	0	0	0	1 (16.7)	0	5 (31.3)	0
Blood LDH increased	0	0	1 (25.0)	0	1 (33.3)	0	2 (33.3)	0	4 (25.0)	0
Respiratory, thoracic and mediastinal disorders										
Hypoxia	1 (33.3)	0	2 (50.0)	0	0	0	1 (16.7)	0	4 (25.0)	0
Skin and subcutaneous tissue disorders										
Rash	1 (33.3)	0	0	0	0	0	3 (50.0)	1 (16.7)	4 (25.0)	1 (6.3)

Serious adverse events were observed in 3 of 16 patients (18.8%), breakdown of which was herpes zoster, hypoxia, and rash in 1 patient (6.3%) each. Of these, a causal relationship with mogamulizumab could not be ruled out for herpes zoster and rash. There were no adverse events leading to treatment discontinuation.

In 1 patient who received retreatment, hepatitis B occurred as a serious adverse event and AST increased occurred as an adverse event leading to treatment discontinuation.

4.(iv).2) Japanese phase II study (Study 0761-002)

Adverse events were observed in 27 of 27 patients (100%), and those for which a causal relationship with mogamulizumab could not be ruled out were observed in 27 of 27 patients (100%). Adverse events with an incidence of 10% or more were as shown in the following table.

Adverse events in Study 0761-002 (incidence ≥ 10%, number of patients (%))

SOC PT	All grades N = 27	≥ Grade 3 N = 27
All AEs	27 (100)	26 (96.3)
Cardiac disorders		
Tachycardia	8 (29.6)	0
Gastrointestinal disorders		
Nausea	5 (18.5)	0
Vomiting	5 (18.5)	0
Constipation	3 (11.1)	0
General disorders and administration site conditions		
Infusion related reaction	24 (88.9)	1 (3.7)
Pyrexia	23 (85.2)	0
Chills	16 (59.3)	0
Infections and infestations		
Nasopharyngitis	4 (14.8)	0
Investigations		
Lymphocyte count decreased	26 (96.3)	20 (74.1)
White blood cell count decreased	18 (66.7)	8 (29.6)
Neutrophil count decreased	14 (51.9)	5 (18.5)
Platelet count decreased	14 (51.9)	5 (18.5)
ALT increased	11 (40.7)	2 (7.4)
AST increased	11 (40.7)	2 (7.4)
Blood LDH increased	10 (37.0)	3 (11.1)
Haemoglobin decreased	8 (29.6)	1 (3.7)
γ-GTP increased	4 (14.8)	3 (11.1)
Blood ALP increased	7 (25.9)	0
Blood creatinine increased	6 (22.2)	0
Blood pressure increased	6 (22.2)	0
Weight increased	6 (22.2)	0
Blood albumin decreased	5 (18.5)	0
Blood sodium decreased	4 (14.8)	0
Weight decreased	4 (14.8)	0
Blood pressure decreased	3 (11.1)	0
Protein total decreased	3 (11.1)	0
Red blood cell count decreased	3 (11.1)	0
Blood phosphorus decreased	3 (11.1)	0
Metabolism and nutrition disorders		
Hypoalbuminaemia	7 (25.9)	0
Hypophosphataemia	5 (18.5)	2 (7.4)
Hypercalcaemia	5 (18.5)	1 (3.7)
Hypokalaemia	5 (18.5)	1 (3.7)
Hyperuricaemia	4 (14.8)	0
Decreased appetite	3 (11.1)	0
Nervous system disorders		
Headache	3 (11.1)	0
Psychiatric disorders		
Insomnia	4 (14.8)	0
Renal and urinary disorders		
Proteinuria	4 (14.8)	0
Respiratory, thoracic and mediastinal disorders		

SOC PT	All grades N = 27	≥ Grade 3 N = 27
Hypoxia	5 (18.5)	3 (11.1)
Skin and subcutaneous tissue disorders		
Rash	14 (51.9)	4 (14.8)
Pruritus	4 (14.8)	1 (3.7)

Serious adverse events were observed in 6 of 27 patients (22.2%), and the breakdown of which was rash in 4 patients (14.8%), SJS in 1 patient (3.7%), and pharyngitis in 1 patient (3.7%). Of these, a causal relationship with mogamulizumab could not be ruled out for rash in 4 patients and for SJS in 1 patient.

An adverse event leading to treatment discontinuation was observed in 1 of 27 patients (3.7%) which was rash. The causal relationship of the event with mogamulizumab could not be ruled out.

4.(iv).3) Foreign phase I study (Study 0761-EU-001)

Adverse events were observed in 21 of 25 healthy adult subjects (84%) and in 11 of 18 SAR patients (61%). Treatment-related adverse events were observed in 17 of 25 healthy adult subjects (68%) and in 7 of 18 SAR patients (39%).

Adverse events that occurred in ≥2 subjects were nasopharyngitis in 9 of 25 subjects (36%), abdominal pain upper, diarrhoea, nasal congestion, sore throat, injection site paraesthesia, and headache in 2 subjects each (8%) among healthy adult subjects; and headache in 4 of 18 patients (22%), nasopharyngitis in 3 of 18 patients (17%), and nausea in 2 of 18 patients (11%) among seasonal allergic rhinitis (SAR) patients.

The serious adverse event in healthy adult subjects was B cell lymphoma observed in 1 of 25 subjects (4%), for which a causal relationship with mogamulizumab could not be ruled out. In SAR patients, no serious adverse events were observed.

There were no adverse events leading to treatment discontinuation.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based compliance assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA’s conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-1, 5.3.5.2-4, 5.3.5.2-9). As a result, protocol deviations (some tests left unperformed) were found at some clinical trial sites. Thus, PMDA has concluded that although there are several items requiring improvements, the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of mogamulizumab in patients with “relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma” has been demonstrated and its safety

of mogamulizumab is acceptable in view of its observed benefits. Mogamulizumab has a clinical significance as a new treatment option for relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma. As regards indications, dosage and administration, and items to be investigated after the market launch, PMDA will discuss them in further detail at the Expert Discussion. Taking account of the comments from the Expert Discussion, mogamulizumab may be approved if it can be concluded that there are no particular problems.

Review Report (2)

January 16, 2012

I. Product Submitted for Registration

[Brand name]	Poteligeo Injection 20 mg
[Non-proprietary name]	Mogamulizumab (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	April 26, 2011

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for registration, 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) Efficacy

PMDA considers that mogamulizumab has a certain level of clinical significance, judging from the response obtained in patients with recurrent or relapsed CC chemokine receptor 4 (CCR4)-positive adult T-cell leukemia lymphoma (ATL) in the phase II study (Study 0761-002) which is the major clinical study in this submission, and has concluded that it is appropriate to use the response rate based on the overall best response as the index for efficacy evaluation.

Based on the results of the study, PMDA has concluded that mogamulizumab is expected to be effective in treating patients with recurrent or relapsed CCR4-positive ATL. PMDA has also concluded that information should be provided appropriately using information leaflets, etc., regarding the data obtained in the above study which demonstrate the efficacy in patients with different disease types and with different lesion sites obtained in the above study.

The above conclusions of PMDA were supported by the expert advisers. The expert advisers commented that the following caution should be noted: ATL cells sometimes infiltrates into the central nervous system, but the distribution rate of mogamulizumab in the central nervous system observed in non-clinical studies was low, and therefore the drug may not exhibit an antitumor effect in the central nervous system.

Based on the results of the comments from the Expert Discussion, PMDA considers as follows: Since distribution of mogamulizumab into the spinal fluid has not been investigated and the efficacy of mogamulizumab in the central nervous system remains unknown, it is necessary to collect relevant information from published reports, etc., after the market launch, and appropriately provide information to the medical practice if new findings become available. Also, the fact that distribution of mogamulizumab into the spinal fluid has not been investigated should be appropriately informed to clinical setting using information leaflets, etc., together with the results of tissue distribution of mogamulizumab in non-clinical studies.

PMDA instructed the applicant to take appropriate actions to address the above issues, to which the applicant agreed.

(2) Safety

Based on the submitted clinical study data, PMDA has concluded that adverse events requiring particular attention in treatment with mogamulizumab are haematotoxicity (bone marrow

depression), infusion reaction, infection/immune system disorder, skin disorder, tumor lysis syndrome, hepatic dysfunction, and cardiac dysfunction. Caution should be exercised against the occurrence of these adverse events when using mogamulizumab. However, mogamulizumab is tolerable provided that monitoring for, and control of, adverse events and temporary withdrawal and discontinuation, etc., are performed appropriately by physicians with sufficient knowledge of, and experience in, treatment of hematopoietic organ malignant tumor.

The above conclusion of PMDA was supported by the expert advisers. The following comments were raised from the expert advisors:

- Taking into account the fact that target patients are those who have received combination chemotherapy and that it is known that ATL patients have compromised immune function, patients intended for treatment with mogamulizumab are likely to have haematopoietic disorders. Therefore, caution should be raised concerning mogamulizumab-induced haematotoxicity such as lymphocyte count decreased, neutrophil count decreased, and platelet count decreased.

- In light of the findings that an infusion reaction occurs with a high incidence even when prior treatments are given to prevent the reaction and that Grade 3 hypoxia developed in Study 0761-002, it is necessary to advise caution about the pretreatment against infusion reaction and treatment methods performed in Japanese clinical studies.

- Since the safety of continued treatment in patients who have developed skin disorder has not been established, caution should be advised on the incidence of skin disorders including Stevens-Johnson syndrome and treatment methods.

- Since the effect of mogamulizumab on the overall immune function, including the change in CCR4-positive helper type 2 T cells (Th2 cells) and regulatory T cells (Treg cells) which may be affected by mogamulizumab, are currently unknown, it is necessary to continuously collect information. The following points should be investigated after the market launch.

    - Since it is known that helper type 1 T cells (Th1 cells) and Th2 cells are known to regulate immune function through mutual suppression, the effect of mogamulizumab on changes in Th1 cells and on changes in the ratio of Th1 cells and Th2 cells caused by the changes in Th2 cells should be investigated.

    - Since it is known that a decrease in Treg cell count is related to the onset and aggravation of autoimmune disease and that HTLV-1-positive patients have autoimmune disease at a high rate, the relationship between mogamulizumab and the onset and aggravation of autoimmune disease should be investigated.

    - Since blood immunoglobulin concentration may decrease with the treatment-related immunosuppression in ATL patients, the necessity of administering immunoglobulin preparation together with mogamulizumab should be investigated.

PMDA asked the applicant to explain the effect of mogamulizumab on the ratio of Th1 cells to Th2 cells and on the onset or aggravation of autoimmune disease and to explain the decrease in blood immunoglobulin level and the use of immunoglobulin preparation in Japanese clinical studies.

The applicant responded as follows:

- In Japanese clinical studies, time-course change in the number of Th2 cells was analyzed by measuring CD4-positive/CCR4-positive cells but the change in Th1 cell count was not

measured. Therefore, the effect of mogamulizumab on the ratio of Th1 cells and Th2 cells remains unknown. Relevant information will be carefully collected in the ongoing clinical study (Study 0761-003), etc.

- As regards the effect of mogamulizumab on the onset or aggravation of autoimmune disease, a sarcoidosis-like response was observed in 1 patient in Study 0761-002, but improved at 136 days after the onset. Among patients enrolled in Japanese clinical studies, 2 patients had concurrent autoimmune diseases (rheumatoid arthritis and hypothyroidism, 1 each), which did not become aggravated during the study period. Therefore, the results of the Japanese clinical studies did not demonstrate the relationship between mogamulizumab and onset or aggravation of autoimmune disease. At the moment, no sufficient investigation has been carried out on the effect of mogamulizumab on the onset or aggravation of autoimmune disease. Thus, information will be collected from the ongoing clinical study (Study 0761-003), the post-marketing surveillance, etc.

- Since measurement of blood immunoglobulin level was not required in the Japanese clinical studies, no sufficient investigation was performed on the decrease in blood immunoglobulin level. There was no report of decreased blood immunoglobulin level after mogamulizumab administration in these studies.

PMDA considers as follows:
The applicant's response about the effect of mogamulizumab on the ratio of Th1/Th2 cells and the relationship between mogamulizumab and the onset or aggravation of autoimmune disease is acceptable.

It is unnecessary at the moment to uniformly require measurement of blood immunoglobulin level or administration of immunoglobulin preparation when using mogamulizumab, for the following reasons: (i) in the repeated-dose toxicity study in cynomolgus monkeys, mogamulizumab had no effect on the production of T cell-dependent antibodies (IgG, IgM) in animals sensitized to keyhole limpet hemocyanin or tetanus toxoid, and (ii) the necessity of measuring blood immunoglobulin level and of administering immunoglobulin preparation when decrease in blood immunoglobulin level is observed will generally be considered in each patient when appropriate.

Taking account of the comments from the Expert Discussion and based on the above discussion, PMDA instructed the applicant to provide information and advise caution to clinical practice regarding the safety of mogamulizumab including adverse events requiring particular caution, using the package insert, information leaflets, etc., to which the applicant agreed.

(3) Clinical positioning and indications
Based on the results of its review described in the "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety" sections of the Review Report (1), PMDA has concluded that mogamulizumab is positioned as a treatment option for recurrent or relapsed CCR4-positive ATL of acute type, lymphoma type, and chronic type of poor prognostic factors.

The above conclusion of PMDA was supported by the expert advisers. The following discussion was made regarding the indications and the use of mogamulizumab in patients who have received hematopoietic stem cell transplantation (HSCT).

1) Indications
PMDA has concluded that, for reasons described in the "4.(iii).B.(4) Indications" section of the Review Report (1), the indication for mogamulizumab should be "relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma" including cases unresponsive to the primary treatment instead of limiting to "recurrent or relapsed" cases, on the condition that caution is advised and

information is provided about the disease type and presence/absence of poor prognostic factors in ATL patients treated in the Japanese clinical studies, using the "Clinical Studies" section of the package insert and other information leaflets to allow selection of eligible patients. Also, PMDA has concluded that caution should be advised on the following points in the "Precautions for Indications" section.

- The disease to be treated with mogamulizumab should be diagnosed by a physician or a clinical center well experienced in pathological diagnosis.

- Patients should be tested for CCR4 antigen by flow cytometry or immunohistochemical staining, and only those who are CCR4-antigen positive should be treated with mogamulizumab.

- The physician should thoroughly understand the disease type and presence/absence of poor prognostic factors in patients enrolled in clinical studies by reading the description in "Clinical Studies" and become fully aware of the efficacy and safety of mogamulizumab before selecting patients to be treated with the drug.

The above conclusion of PMDA was supported by the expert advisers. In addition to the comment supporting the conclusion of PMDA, the following comments were raised from the expert advisors:

- Taking into account the fact that in many patients with advanced ATL, remission, even if achieved, lasts for only a short period of time, making it difficult to clearly differentiate "recurrence or relapse" from "nonresponse to primary treatment," mogamulizumab is expected to have a certain level of clinical efficacy even in patients with ATL nonresponsive to the primary treatment, judging from the results of mogamulizumab monotherapy in ATL patients in Study 0761-002.

- Recurrent or relapsed ATL may have a disease property different from that at the first onset. If the disease has shifted from a gradual clinical course to an acute type, mogamulizumab will be indicated.

- At the moment, there is no justification for actively selecting mogamulizumab for smoldering type or chronic type with poor prognostic factors. However, under the current situations where no standard treatment has been established for ATL patients, mogamulizumab may possibly be used in patients with these types of diseases, and the treatment may actually contribute to the improvement of their prognosis.

PMDA asked the applicant to explain the clinical study plan in patients with ATL of smoldering type or chronic type without poor prognostic factors (for which no clinical study data have been submitted) who have nodal/tumoral skin lesions. The applicant responded there was no plan for a clinical study on these disease types.

PMDA considers as follows:
There is no sufficient justification for actively recommending the use of mogamulizumab in patients with ATL of smoldering type or chronic type without poor prognostic factors who have nodal/tumoral skin lesions. Therefore, it is necessary to advise caution and provide information about the disease types and presence/absence of poor prognostic factors of patients treated in the Japanese clinical studies using information leaflets, etc. At the same time, information should be collected on the efficacy and safety of mogamulizumab in patients with disease types not treated in the Japanese clinical studies, from the post-marketing surveillance, published reports, etc., and if new information becomes available, it should be provided to medical practice in an appropriate

manner.

Taking account of the comments from the Expert Discussion, PMDA instructed the applicant to set the "Indications" and "Precautions for Indications" section as stated above, to which the applicant agreed.

2) Use in patients who have received hematopoietic stem cell transplantation

Regarding the use of mogamulizumab in patients after allogeneic HSCT, the applicant explained as follows:

Mogamulizumab may reduce the immunosuppressive effect of Treg cells by decreasing the number of these cells, and the effect of mogamulizumab on the possible onset of delayed type graft-versus-host disease (GVHD) is currently unknown. Therefore, there is a plan in which caution will be advised that the efficacy and safety of mogamulizumab has not been established in patients who have received allogeneic HSCT.

Regarding the use of mogamulizumab in patients who have received allogenic HSCT, PMDA has concluded that, at the moment, there is little need for defining these patients as ineligible for treating with mogamulizumab because there is no clear evidence of the effect of mogamulizumab on the immune system via Th2 or Treg cells or on the occurrence of adverse events mediated by this mechanism. However, it is necessary to provide the following information to clinical practice and to continuously collect relevant information on post-marketing experience for appropriate provision of the information.

- In light of reports suggesting the relationship between Treg cells and GVHD (*Blood* 2011;118:5671-80, *Blood* 2009;113:4458-67, *Nat Med* 2003;9:1144-50), it is theoretically plausible that mogamulizumab affects the immune system via Th2 or Treg cells in humans, causing GVHD for example.

- Depending on the concomitant drugs such as immunosuppressive agents administered after allogenic HSCT, the risk of mogamulizumab-induced infection may be enhanced in these patients.

- Mogamulizumab has never been used in these patients because they were excluded from Japanese clinical studies.

The above conclusion of PMDA was supported by the expert advisers. The expert advisors also commented as follows:

Since HSCT is a treatment option that is expected to be effective in ATL patients, it could be performed not only at the initial onset but also for recurrent or relapsed ATL. Therefore, it is necessary to continuously collect information, from published reports, etc., on the efficacy and safety of mogamulizumab in patients who receive HSCT after mogamulizumab administration.

PMDA asked the applicant to explain the experience of using mogamulizumab before HSCT.

The applicant responded as follows:

In Study 0761-002, there is no report of performing HSCT after mogamulizumab administration. In the ongoing clinical study in treatment-naive ATL patients (Study 0761-003), 3 patients received HSCT after mogamulizumab administration, as of December 19, 2011. However, no detailed information is available, such as post-HSCT follow-up, because in all of these patients, HSCT was performed after the end of the observation period.

Mogamulizumab may be used in patients with relapsed or refractory ATL during remission induction before transplantation or as a pre-treatment for transplantation. However,

mogamulizumab has been used before HSCT in only an extremely limited number of patients. Also, the possibility cannot be excluded that mogamulizumab may affect the occurrence of GVHD if HSCT is performed after the administration because mogamulizumab suppresses Th2 and Treg cells for a prolonged period. Hence, caution will be raised against post-transplantation complications such as GVHD using information leaflets, etc., and information on the safety of mogamulizumab used before HSCT will be collected in the post-marketing surveillance. There is no plan for conducting a clinical study of administering mogamulizumab as a means of remission induction therapy before transplantation or as a pretreatment for transplantation.

PMDA considers as follows:
Regarding the use of mogamulizumab before HSCT, there is little need for defining these patients as ineligible for treatment with mogamulizumab, as is the case with the use of mogamulizumab after HSCT, since there is no clear evidence of the effect of mogamulizumab on the immune system via Th2 or Treg cells or on the occurrence of adverse events mediated by this mechanism. However, it will be necessary to inform that there are no clinical data available on the efficacy and safety of mogamulizumab when used as a remission induction therapy or as a pretreatment for transplantation, and to collect information on the safety in patients treated with mogamulizumab before HSCT, not only from the post-marketing surveillance but also from the ongoing clinical study (Study 0761-003) and published reports and, when new information becomes available, to provide such information in an appropriate manner.

PMDA instructed the applicant to take appropriate actions regarding the above, to which the applicant agreed.

(5) Dosage and administration
Based on the review in the "4.(iii).B.(5) Dosage and administration" section of the Review report (1), PMDA has concluded that the dosage and administration statement should be "The usual adult dosage is 1 mg/kg/dose of Mogamulizumab (Genetical Recombination) intravenously infused once weekly for 8 doses." PMDA has also concluded that caution should be advised about the following in the "Precautions for Dosage and Administration" section.

- Infusion reaction (e.g., pyrexia, chills, tachycardia) may occur after mogamulizumab administration. Prior treatment with an anti-histaminic drug and an antipyretic analgesic agent, etc. should be performed 30 minutes before mogamulizumab administration in order to alleviate these symptoms.

- Patients should be carefully monitored. If infusion reaction occurs, 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 immediately, and retreatment should not be performed.

- The efficacy and safety of concomitant use of mogamulizumab with other antineoplastic drugs has not been established.

- 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 mL of saline, and infuse the solution over 2 hours.

The above conclusion of PMDA was supported by the expert advisers.

Taking account of the comments from the Expert Discussion, PMDA instructed the applicant to

establish the “Dosage and Administration” as above and include the above statement in the “Precautions for Dosage and Administration” section, and gave the following instructions, to which the applicant agreed.

- Provide information appropriately using information leaflets, etc., regarding the pretreatment with corticosteroid (intravenous) required to reduce or alleviate infusion reaction in the ongoing clinical study (Study 0761-003), the necessity of the pretreatment based on the study results, the incidence of infusion reaction, and treatment methods in Japanese clinical studies.

- Regarding the efficacy and safety of concomitant use of mogamulizumab with other antineoplastic drugs, information should be supplied appropriately when efficacy or safety data became available from the ongoing combination therapy study of mogamulizumab with mLSG15 regimen (Study 0761-003) or when new information is obtained from published reports.

(6) Post-marketing investigations

The applicant plans to conduct an all-case post-marketing surveillance of an 8-month observation period in a planned number of 600 patients for analysis, focused mainly on the confirmation of safety.

Based on the results of the review of the submitted plan for the post-marketing surveillance, as described in the “4.(iii).B.(6) Post-marketing investigations” section of the Review Report (1), PMDA has concluded as follows:

a. Since safety information of mogamulizumab in Japanese ATL patients is limited at the moment, it is necessary to collect information promptly. Therefore, the all-case post-marketing surveillance should be conducted in a certain number of patients after the market launch.

b. Since the primary objective of this surveillance is to promptly collect safety information during actual use and to promptly provide information obtained from the survey, the following actions will be appropriate:

    - The number of patients expected to be available for collecting safety information under actual use conditions may be set as the target sample size, and complementary efficacy information may be collected within this range.

    - An interim analysis should be carried out at an appropriate timing and information obtained should be provided to clinical practice. At the same time, based on the results of the interim analysis, etc., necessity of changing the surveillance plan, including the target sample size and the observation period should be examined.

c. The observation period should be set to allow the assessment of the incidence of adverse events related to the prolonged immune disorders caused by mogamulizumab. The applicant considers that it is possible to collect information on immunosuppression-related adverse events during the observation period of 8 months (up to 6 months after the last administration), judging from the time of the onset of infection in the clinical studies. The observation period planned by the applicant is appropriate.

d. The surveillance items established are largely acceptable, however, as described in “4.(iii).B.(6) Post-marketing investigations” section of the Review Report (1), information should be collected appropriately on 7 items added to the priority surveillance items proposed by the applicant.

The above conclusion of PMDA was supported by the expert advisers. The expert advisers also commented as follows:

- Since safety information of mogamulizumab in Japanese ATL patients is limited, information on adverse reactions, etc., obtained from the post-marketing surveillance should be promptly provided to clinical practice. Therefore, the target sample size in this surveillance should be set to allow the collection of safety information during actual use of mogamulizumab. Based on the results of the interim analysis, the necessity of changing the surveillance plan including the target sample size should be considered. If collection of more information or investigation of additional items is deemed necessary, an additional surveillance or study should be conducted as necessary.

- Excessive expectations from mogamulizumab may result in the requirement for treatment of many patients during a short period of time after the market launch. Therefore, it is important to appropriately provide to clinical practice not only the currently available efficacy and safety information but also potential risks such as the effect of mogamulizumab on the immune function as a whole and, at the same time, to establish a system that allows prompt collection of information immediately after the market launch.

- It is also necessary to collect safety information when mogamulizumab is concomitantly used with other antineoplastic drugs or used in patients of disease types not enrolled in the clinical studies.

- Patients receiving HSCT after mogamulizumab should be identified wherever possible, and post-transplantation safety information should be collected from these patients.

Taking account of the comments from the Expert Discussion, PMDA considers as follows:
It is necessary to reconsider the target sample size in the post-marketing surveillance as described in “b” above and to change the surveillance plan including the conduct of an interim analysis. It is necessary to design the surveillance plan so that safety information can be collected from patients who are treated with mogamulizumab in combination with other antineoplastic drugs, patients who have received HSCT after mogamulizumab administration, and patients with disease types not enrolled in the clinical studies, in addition to the information described in “d” above.

PMDA instructed the applicant as above, to which the applicant responded that the target sample size would be reduced to 300 to allow prompt collection of safety information during actual use, and other items in the surveillance plan would also be changed according to the instructions.

PMDA accepted the reply of the applicant.

III. Overall Evaluation

Based on the results of the review described above, PMDA has concluded that the product may be approved for the following indication and dosage and administration with the following conditions for approval after revision, provided that appropriate cautions will be included in the package insert and information concerning the proper use of mogamulizumab will be provided appropriately after the market launch, and the compliance with the proper use of mogamulizumab will be ensured 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. The re-examination period of mogamulizumab is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication] Relapsed or refractory CCR4-positive adult T-cell leukemia lymphoma

[Dosage and administration] The usual adult dosage is 1 mg/kg of Mogamulizumab (Genetical Recombination) intravenously infused once weekly for 8 doses.

[Conditions for approval]

Since the product has been studied in only a limited number of patients in Japan, a drug use-results survey should be conducted involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of patients treated with the product and, at the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product

[Warning]

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.

[Contraindications]

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

[Precautions for indications]

1. The disease to be treated with Mogamulizumab should be diagnosed by a physician or a clinical center well experienced in pathological diagnosis.
2. Patients should be tested for CCR4 antigen by flow cytometry or immunohistochemical staining, and only those who are confirmed to be CCR4-antigen positive should be treated with Mogamulizumab.
3. The physician 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.

[Precautions for dosage and administration]

1. Infusion reaction (e.g., pyrexia, chills, tachycardia) may occur after Mogamulizumab administration. Prior treatment with an anti-histaminic drug and an antipyretic analgesic agent, etc. should be performed 30 minutes before Mogamulizumab administration in order to alleviate these symptoms.
2. 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 (see “Important Precautions” and “Clinically significant adverse reactions”).
3. The efficacy and safety of concomitant use of Mogamulizumab with other antineoplastic drugs have not been established.
4. 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 mL of saline, and infuse the solution over 2 hours (see “Precautions in Use”).