Report on the Deliberation Results

November 29, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ebglyss Subcutaneous Injection 250 mg Autoinjectors Ebglyss Subcutaneous Injection 250 mg Syringes
Non-proprietary Name	Lebrikizumab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	March 3, 2023

Results of Deliberation

In its meeting held on November 27, 2023, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2023
Pharmaceuticals and Medical Devices Agency

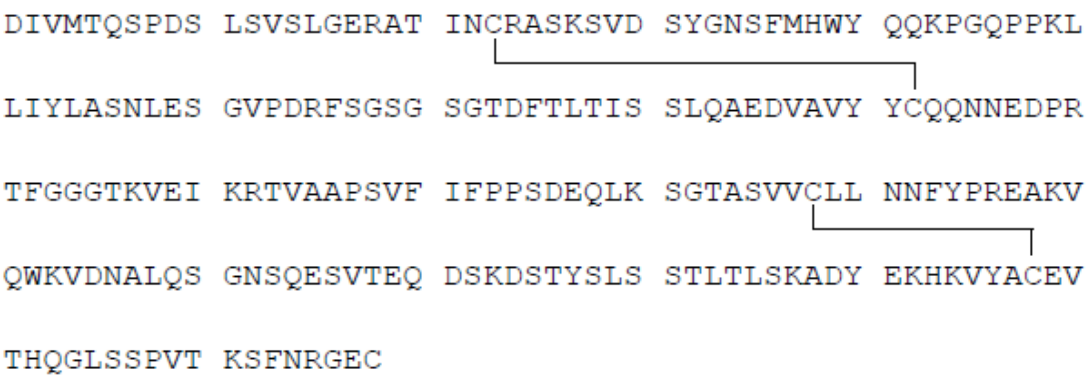
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ebglyss Subcutaneous Injection 250 mg Autoinjectors Ebglyss Subcutaneous Injection 250 mg Syringes
Non-proprietary Name	Lebrikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	March 3, 2023
Dosage Form/Strength	Injection: Each syringe contains 250 mg of lebrikizumab (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Lebrikizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-13 monoclonal antibody and framework regions and constant regions derived from human IgG4, whose amino acid residue at position 226 in the H-chain is substituted by Pro. Lebrikizumab is produced in Chinese hamster ovary cells. Lebrikizumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ4-chains) consisting of 445 amino acid residues each and 2 L-chains (κ-chains) consisting of 218 amino acid residues each.

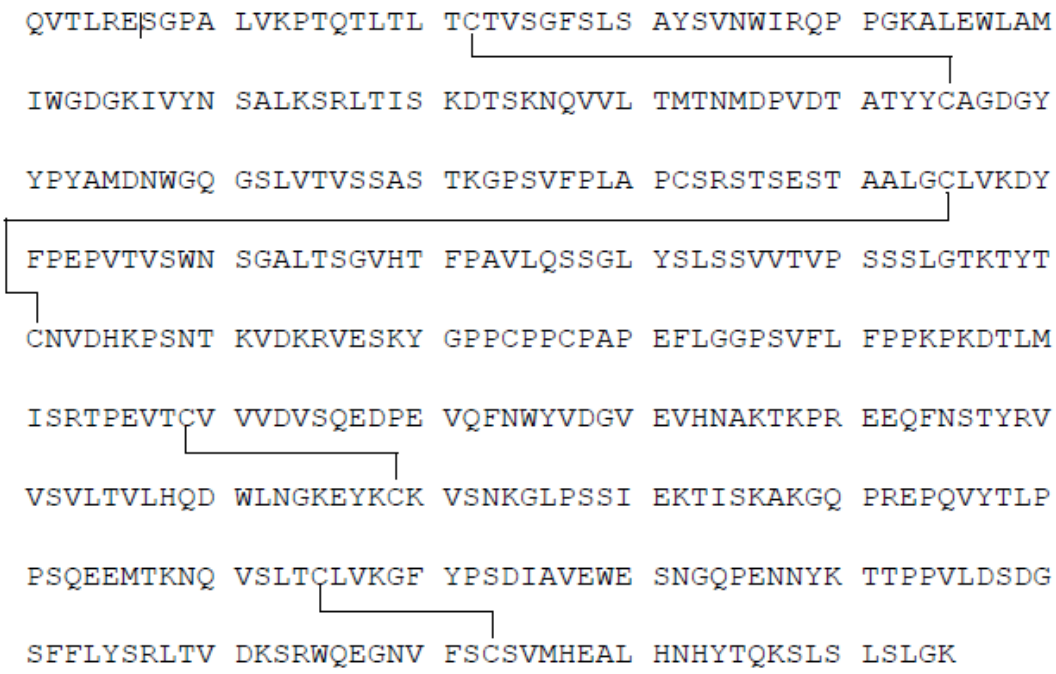
Structure

Amino acid sequence:

L chain

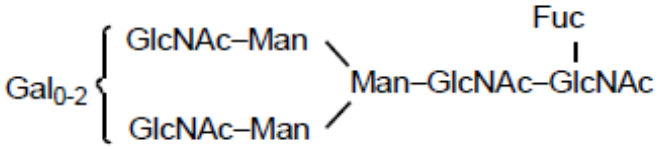


H chain



Intrachain disulfide bonds:	Solid lines shown above
Interchain disulfide bonds:	C218 in L-chain-C132 in H-chain, C224 in H-chain-C224 in H-chain, C227 in H-chain-C227 in H-chain
Pyroglutamic acid (partial):	Q1 in H-chain
Glycosylation site:	N295 in H chain
Partial processing:	K445 in H-chain

Putative structure of main carbohydrate chain:



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

Molecular formula: $C_{6434}H_{9972}N_{1700}O_{2034}S_{50}$ (protein portion consisting of 4 chains)
(H chain) $C_{2177}H_{3373}N_{567}O_{672}S_{18}$
(L chain) $C_{1040}H_{1617}N_{283}O_{345}S_{7}$
Molecular weight: Approx. 148,000

Items Warranting Special Mention

None

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of atopic dermatitis not responding adequately to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. The safety of the product in clinical use should be further investigated in the post-marketing surveillance.

Indication

Atopic dermatitis not responding adequately to conventional treatments

Dosage and Administration

The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals after Week 4, administered by subcutaneous injection. After Week 4, the 250 mg may be administered subcutaneously at 4-week intervals, according to the patient's condition.

Approval Condition

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

Attachment

Review Report (1)

October 26, 2023

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

Product Submitted for Approval

Brand Name	Ebglyss Subcutaneous Injection 250 mg Autoinjectors Ebglyss Subcutaneous Injection 250 mg Syringes
Non-proprietary Name	Lebrikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	March 3, 2023
Dosage Form/Strength	Injection: Each syringe contains 250 mg of lebrikizumab (genetical recombination).
Proposed Indication	Atopic dermatitis not responding adequately to conventional treatments

Proposed Dosage and Administration

The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals from Week 4 to 16, administered by subcutaneous injection. Thereafter, the maintenance dose of 250 mg is administered subcutaneously at 4-week intervals. After Week 16, the 250 mg dosing interval may be changed to 2 weeks or 8 weeks as appropriate, according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

Lebrikizumab (genetical recombination) (hereinafter referred to as lebrikizumab), the active ingredient of Ebglyss Subcutaneous Injection 250 mg Autoinjectors and Ebglyss Subcutaneous Injection 250 mg Syringes, is an anti-human interleukin (IL)-13 humanized immunoglobulin (Ig)G4 monoclonal antibody discovered by Tanox, Inc. (currently Genentech, Inc.). Lebrikizumab binds to IL-13, resulting in the inhibition of IL-13 signal transduction mediated by IL-13Rα1/IL-4Rα receptor complex.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic eczema with recurrent aggravation and remission. Treatment of AD depends on the symptoms and characteristics of individual patient, and basically includes drug therapy, external therapy/skin care for physiological abnormalities of the skin, and search for and countermeasures for aggravating factors (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021, edited by Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis, Japanese Dermatological Association/Japanese Society of Allergology [Clinical Practice Guidelines for AD 2021]).

In the drug therapy of AD, the basic treatment is control of the disease with topical anti-inflammatory drugs such as topical corticosteroids (TCS), tacrolimus ointment (topical calcineurin inhibitor [TCI]), and delgocitinib ointment (topical Janus kinase [JAK] inhibitor), with continuous use of topical skin moisturizers (Clinical Practice Guidelines for AD 2021). If these topical treatments are not adequately effective or the topical treatment is intolerable to the patients, the use of oral cyclosporine (intermittent administration), dupilumab (human anti-IL-4Rα subunit antibody), or baricitinib (oral JAK inhibitor) is considered. Short-term use of oral corticosteroid is considered during the acute exacerbation phase and for the introduction of remission from severe/severest symptoms (Clinical Practice Guidelines for AD 2021). In recent years, the following options have been added for the treatment of AD: (1) Difamilast ointment (topical phosphodiesterase 4 [PDE4] inhibitor) as an anti-inflammatory topical drug, (2) upadacitinib hydrate, abrocitinib (oral JAK inhibitors), and tralokinumab (human anti-human IL-13 monoclonal antibody) as systemic therapeutic agents, and (3) nemolizumab (monoclonal antibody against human anti-human IL-31 receptor A) for the treatment of AD-associated pruritus.

Multiple cytokines such as IL-4, IL-13, and IL-22 are involved in the pathophysiology of AD. Lebrikizumab was developed in expectation of the therapeutic effect for AD based on the inhibition of IL-13-mediated signal transduction pathway.

In Japan, a Japanese phase III study was conducted from March 2021 in patients with AD, and the applicant has recently submitted an application for marketing approval of lebrikizumab based on the results of the above study. As of September 2023, lebrikizumab is not approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Hybridoma cells were generated by the fusion of [redacted] cells and [redacted] cells immunized with protein antigen prepared by combining mutant [redacted] human IL-13 with human [redacted]. A hybrid clone was selected using

[redacted] as the index, and the variable regions of the heavy and light chains of [redacted] obtained from the clone were optimized and humanized, and the gene expression construct was generated using gene fragments consisting of the constant region of human κ chain and the constant region of human IgG4. The gene expression complex thus generated was introduced into Chinese hamster ovary (CHO) cells, and the clone best-suited for the manufacture of lebrikizumab was selected and used for the preparation of master cell bank (MCB) and working cell bank (WCB).

The characterization and purity of the MCB, WCB, and cells at the limit of in vitro cell age (CAL) were conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. Results confirmed the genetic stability during the production of lebrikizumab. Except for endogenous retroviruses-like particles commonly observed in rodent-derived cell lines, viral or non-viral adventitious agents were not detected within the range of tests performed.

The MCB and WCB are stored in vapor phase in liquid nitrogen. There is no plan for regeneration of the MCB or WCB.

2.1.2 Manufacturing process

The drug substance manufacturing process consists of seed culture, inoculation culture, production culture, harvesting, [redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, [redacted] chromatography, [redacted] filtration, [redacted], and dispensing/freezing/storage/testing.

Critical steps include [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] processes.

The process validation of the manufacturing process for the drug substance was conducted on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except for CHO cells, the host cells, are used in the manufacturing process of the drug substance.

Purity tests were performed on the MCB, WCB, and CAL [see Section 2.1.1]. The unprocessed bulk before harvesting on commercial-scale was subjected to bioburden testing, mycoplasma testing, *in vitro* virus testing, and mouse minute virus testing. No contamination with either viral or non-viral adventitious agents was detected within the range of the tests performed. These tests on the unprocessed bulk before harvesting are included in in-process control tests.

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

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	Simian virus 40
[redacted] chromatography	[redacted]	[redacted]	[redacted]
[redacted] virus inactivation	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]
[redacted] filtration	[redacted]	[redacted]	[redacted]
Overall viral reduction factor	≥21.19	10.39	≥11.26

2.1.4 Manufacturing process development

The following are the main changes made to the manufacturing process during the development of the drug substance (each manufacturing process is referred to as Process A, Process B, Process C, Process D, Process E, or proposed process). The formulations used for each clinical study were manufactured from the drug substances prepared by the following processes: Process D and Process E for the phase I study, Process D for the phase II study, and Process E for the phase III study.

- Process A to Process B: Changes in [redacted], [redacted] and [redacted]
- Process B to Process C: Change in [redacted], introduction of [redacted], and changes in production scale, [redacted], and [redacted]
- Process C to Process D: Changes in [redacted] and [redacted]
- Process D to Process E: Changes in [redacted] and [redacted]
- Process E to proposed process: Changes in [redacted] and production scale, and addition of [redacted]

After these manufacturing process changes, the comparability assessment of quality attributes showed that the post-change drug substance was comparable to the pre-change drug substance.

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Lebrikizumab was subjected to characterization tests described in Table 2.

Table 2. Parameters for characterization

Primary/higher-order structure	Amino acid sequence, N- and C-terminal amino acid sequences, posttranslational modification ([redacted], [redacted], [redacted], Impurity H, [redacted]), disulfide bonds, free sulfhydryl group content, secondary structure, tertiary structure, quaternary structure, thermal stability
Physicochemical properties	Molecular weight, size variants, charge variants, isoelectric point, IgG subclass analysis, absorption coefficient
Carbohydrate structure	Glycosylation rate, oligosaccharide profile, carbohydrate structure analysis, sialic acid content
Biological properties	IL-13-binding affinity, Fcγ receptor (I, IIa, IIIa)-binding affinity, C1q-binding activity, FcRn-binding affinity, IL-13-binding inhibitory activity, IL-13 inhibitory activity

Lebrikizumab was investigated for its biological properties, including the following:

- Binding affinity to IL-13, Fcγ receptor, and neonatal Fc receptor (FcRn) was confirmed by surface plasmon resonance (SPR). Binding affinity to FcRn was confirmed for [redacted] as well.
- Complement component 1, q subcomponent (C1q)-binding activity was confirmed by enzyme-linked immunosorbent assay (ELISA).

- The inhibitory activity of lebrikizumab against binding of IL-13 with IL-13Rα1 and IL-13Rα2 was investigated by ELISA. Lebrikizumab did not inhibit the binding of IL-13 with IL-13Rα1 or IL-13Rα2.
- IL-13-inhibitory activity was confirmed based on [redacted] expression level in the [redacted]-expressing cell line ([redacted]).

2.1.5.2 Product-related substances/Product-related impurities

On the basis of the results of characterization in Section 2.1.5.1, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. High molecular weight forms, low molecular weight forms, Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, and Impurity H were identified as product-related impurities. Among product-related impurities, high molecular weight forms, low molecular weight forms, and Impurity A, Impurity B, Impurity C, and Impurity D are controlled by the specifications for the drug substance and the drug product. No constant control is required for other product-related impurities because their levels have remained constantly low in the past manufacturing experiences.

2.1.5.3 Process-related impurities

Host cell DNA, host cell protein (HCP), Impurity I, Impurity J, Impurity K, Impurity L, and Impurity M were identified as process-related impurities. All process-related impurities have been shown to be adequately removed in the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping and IL-13-inhibitory activity), osmolality, pH, purity (size exclusion chromatography [SEC] and capillary electrophoresis-sodium dodecyl sulphate [CE-SDS] [[redacted]]), charge heterogeneity (capillary isoelectric focusing [cIEF]), bacterial endotoxins, microbial limits, [redacted], potency (IL-13-inhibitory activity), and assay (ultraviolet and visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows the main stability studies conducted on the drug substance.

Table 3. Summary of main stability tests on drug substance

	Manufacturing process for drug substance	Number of batches	Storage condition	Study period	Storage form
Long-term testing	[redacted]	3	−20 ± 5°C	60 months	Hastelloy container
		4		18 months[a)]	
Accelerated testing	[redacted]	3	5 ± 3°C	6 months	
		4		12 months[b)]	
Long-term testing	[redacted]	4	−86°C to −70°C ([redacted])	18 months[c)]	Polycarbonate container with [redacted] polypropylene copolymer screw cap
Accelerated testing	[redacted]	3	5 ± 3°C	12 months	
Stress testing (light)	[redacted]	1	Overall illuminance of ≥1.2 million lux•h, and integrated near ultraviolet energy of ≥250 W•h/m^2		Glass vial

a) Study completed up to [redacted] months for [redacted] batches. The stability study is ongoing up to [redacted] months.
b) Study completed up to [redacted] months for [redacted] batches.
c) Study completed up to [redacted] months for [redacted] batches. The stability study is ongoing up to [redacted] months.

Neither the long-term testing nor the accelerated testing showed any clear changes in quality attributes throughout the study period.

The stress testing (light) showed that the drug substance was photolabile.

On the basis of the above findings, the shelf life for the drug substance was proposed to be 60 months when stored at ≤−20°C in a Hastelloy container and 18 months when stored at −86°C to −70°C in a polycarbonate container with [redacted] polypropylene copolymer screw cap.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is aqueous injection containing 250 mg of lebrikizumab per syringe (2.25 mL). The proposed drug product is available in 2 containers: (1) the drug solution-containing glass syringe with a needle and a needle safety device (a pre-filled syringe) and (2) the drug solution-containing glass syringe with a needle and a pre-filled pen (an autoinjector [AI]). Both are combination products.

The excipients in both drug products are L-histidine, glacial acetic acid, sucrose, polysorbate 20, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the pre-filled syringe consists of thawing of the drug substance, drug solution preparation, sterile filtration, filling/capping, inspection, labeling/assembling, and packaging/testing.

The manufacturing process for the AI consists of thawing of the drug substance, drug solution preparation, sterile filtration, filling/capping, inspection, assembling, and labeling/packaging/testing.

[redacted] and [redacted] processes are defined as the critical steps for both drug products.

The process validation of the manufacturing process for the drug product was conducted on a commercial scale.

2.2.3 Manufacturing process development

The following are main changes in the manufacturing process during the development of the drug product (each process is referred to as Process 1, Process 2, Process 3, Process 4, and proposed process). The formulation manufactured by Process 4 was used in the phase I and II studies. The formulation manufactured by the proposed process was used in the phase III study.

- Process 1 to Process 2: Change in formulation and [redacted]
- Process 2 to Process 3: Change in formulation, [redacted], [redacted], and [redacted]
- Process 3 to Process 4: Change in formulation and [redacted]
- Process 4 to proposed process: Change in [redacted], [redacted], and [redacted]

In association with a change of the manufacturing process from Process 4 to the proposed process, comparability assessment of quality attributes showed that the post-change drug product was comparable to the pre-change drug product.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted] liquid chromatography and IL-13-inhibitory activity), pH, purity (SEC, CE-SDS [[redacted]]), charge heterogeneity (cIEF), foreign insoluble matter, insoluble particulate matters, sterility, potency (IL-13-inhibitory activity), and assay (ultraviolet and visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows a summary of the main stability studies for the drug product.

Table 4. Summary of the main stability tests on drug product

	Dosage form	Manufacturing process for drug product[a)]	Number of batches	Storage condition	Study period	Storage form
Long-term testing	Syringe	Proposed process	3	5 ± 3°C	36 months	Glass syringe with a stainless steel needle and a bromobutyl rubber plunger[c)]
	AI	Proposed process	4		[redacted] months[b)]	
Accelerated testing	Syringe	Proposed process	3	25°C/60%RH	6 months	
	AI	Proposed process	4			
Photostability testing	AI	Proposed process	1	Overall illuminance of ≥1.2 million lux•h, or integrated near ultraviolet energy of ≥200 W•h/m^2		

a) The drug substance was manufactured by [redacted].
b) Study completed up to [redacted] months for [redacted] batches. The stability study is ongoing up to [redacted] months.
c) [redacted]

The long-term testing did not show any clear changes in quality attributes throughout the study period.

The accelerated testing showed the following tendencies: (1) An increase in the peak of the high molecular weight form and a decrease in the main peak in SEC, (2) an increase in the peak of the low molecular weight form and a decrease in the main peak in CE-SDS ([redacted]), and (3) an increase in [redacted] and a decrease in the main peak in cIEF.

Photostability testing showed that the drug product was photolabile.

On the basis of the above, a shelf life of 36 months and 24 months was proposed for the pre-filled syringe and the AI, respectively, when stored in a glass syringe with a stainless-steel needle and a bromobutyl rubber plunger (primary container) at 2°C to 8°C, protected from light. The shelf life of the AI is proposed with [redacted] taken into account.

2.3 Quality control strategy

The quality control strategy was designed based on the following investigations:

- Identification of critical quality attributes (CQAs):
  Regarding the quality of product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on the information obtained during the process of the development of lebrikizumab and related findings:
  CQA of drug substance: Potency, high molecular weight form, low molecular weight form, Impurity A, Impurity B, Impurities C and D, Impurity E, Impurity F, Impurity G, Impurity H, host cell DNA, HCP, Impurity J, Impurity I, Impurity M, microbiological safety, viral safety/adventitious agents, identification, description, protein content, pH, and osmolality
  CQAs of the drug product: Potency, high molecular weight form, low molecular weight form, Impurity A, Impurity B, Impurities C and D, Impurity M, microbiological safety, insoluble particulate matters, identification, description, protein content, pH, osmolality, and dose
- Process characterization:
  The processes affecting CQAs were identified and, in these processes, process control parameters significantly affecting CQAs and process performance were identified by means of risk assessment, etc. The acceptable range was confirmed.
- Establishment of the control methods:
  On the basis of the knowledge on the process including the above process characterization, results of batch analysis, data on stability studies, etc., the methods for controlling the quality attributes of lebrikizumab were established by the combination of the process parameters, in-process control, specifications, etc. [for the control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

2.R Outline of the review conducted by PMDA

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

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

The applicant submitted the results of the following primary pharmacodynamic studies: (1) Binding to IL-13, (2) effects on the binding of IL-13 with IL-4Rα, IL-13Rα1, and IL-13Rα2, (3) the effect on IL-13 signal transduction, and (4) the effect on the murine inflammation model. The applicant also submitted the results of *in vitro* studies on the effect on the cardiovascular system which were conducted as safety pharmacology studies. The effect on the cardiovascular system was investigated in a repeated-dose toxicity study in monkeys, and effects on the cardiovascular, central nervous, and respiratory

system were investigated in a fertility study in monkeys [see Sections 5.2 and 5.5], albeit not conducted as safety pharmacology studies per se.

Pharmacological parameters are expressed in means unless specified otherwise. In this section, the species name of IL-13, IL-4, IL-4Rα, IL-13Rα1, and IL-13Rα2 is omitted if they are of human origin.

3.1 Primary pharmacodynamics

3.1.1 Binding to IL-13 (CTD 4.2.1.1.1 to 4.2.1.1.3)

Binding of lebrikizumab to IL-13 and IL-4 was investigated by ELISA. Results showed that lebrikizumab bound to IL-13 but not to IL-4. Results also showed that lebrikizumab did not cross-react with murine or rat IL-13.

Binding of lebrikizumab to human and cynomolgus monkey IL-13 was investigated by SPR. Results showed that K_D of lebrikizumab to human and cynomolgus monkey IL-13 was 31 pmol/L and <0.67 pmol/L, respectively.

3.1.2 Effect on binding of IL-13 to IL-13Rα1, IL-13Rα2, and IL-4Rα (CTD 4.2.1.1.4 and 4.2.1.1.5)

The effect of lebrikizumab on the binding of IL-13 to IL-13Rα1 or IL-13Rα2 was investigated by ELISA. Results showed that lebrikizumab did not inhibit the binding of IL-13 to IL-13Rα1 or IL-13Rα2 over the concentration range investigated.[1)]

X-Ray crystallography of the complex of Fab fragment of lebrikizumab with human IL-13 suggested that IL-13 amino acid sequence ([redacted])[2)] presumed to be essential for interaction with lebrikizumab is located at the binding site of IL-13 with IL-4Rα (*J Mol Biol.* 2013;425:1330-9).

3.1.3 Effect on IL-13 signal transduction (CTD 4.2.1.1.6 and 4.2.1.1.7)

The inhibitory effect of lebrikizumab against IL-13 (2 μg/mL)-stimulated STAT6 phosphorylation in human erythroleukemia cell line TF-1 was investigated by flow cytometry. Phosphorylated STAT6 was undetectable in cells treated with lebrikizumab (2 μg/mL). The effect of lebrikizumab on IL-13 (20 ng/mL)-stimulated TF-1 cell growth was investigated using intracellular ^{3}H-thymidine uptake as the index. Lebrikizumab inhibited IL-13-induced TF-1 cell growth in a concentration-dependent manner over the concentration range investigated (2.5 fg/mL to 2.5 μg/mL).

3.1.4 Effect on a mouse model of airway inflammation (CTD 4.2.1.1.8)

The effect of lebrikizumab on airway inflammation induced by 5-day repeated intraperitoneal administration of IL-13[3)] (1 μg) to female C57BL/6 mice was investigated. Intraperitoneal administration of lebrikizumab for 4 days from the next day of the start of IL-13 administration caused

---

1) The concentration range of lebrikizumab investigated was 0.019 to 150 μg/mL (0.13-1,000 nmol/L) for the binding of IL-13 with IL-13Rα1 and 0.022 to 45.0 μg/mL (0.15-300 nmol/L) for the binding of IL-13 with IL-13Rα2.

2) Identified by the investigation conducted using the following: (1) Murine monoclonal antibody 228B/C containing the same complementarity determining region (CDR) as that of lebrikizumab; (2) mouse and cynomolgus monkey IL-13; and (3) mouse/monkey hybrid IL-13 generated by replacing the amino acid residue [redacted] to [redacted] of mouse IL-13 with the corresponding residue ([redacted]) of cynomolgus monkey.

3) Although lebrikizumab does not cross-react with IL-13 of rodents, human IL-13 reacts with mouse IL-13R. Accordingly, the effect of lebrikizumab was investigated by using human IL-13.

a decrease in IL-13-induced inflammatory cells and suppression of an increase in IL-13Rα2 mRNA expression level in the lung and an increase in transforming growth factor (TGF)-β1 in the bronchoalveolar lavage fluid.

3.2 Safety pharmacology (CTD 4.2.1.3.1, 4.2.3.2.1 to 4.2.3.2.3, and 4.2.3.5.1.2)

Using human fetal kidney-derived cell line HEK293 introduced with human *ether-a-go-go* related gene (hERG), the effect of lebrikizumab on hERG ion channel current was investigated by hERG potassium current patch clamp technique. Addition of lebrikizumab 0.2 and 6 mg/mL did not show an inhibitory effect.

Safety pharmacological parameters were investigated in 6-week, 13-week, and 9-month repeated-dose toxicity studies in cynomolgus monkeys and in a fertility study in male cynomolgus monkeys [see Sections 5.2 and 5.5]. Lebrikizumab was administered intravenously to cynomolgus monkeys at a dose of 0.95, 4.9, or 22.75 mg/kg once a week for 6 weeks, subcutaneously at a dose of 5 or 25 mg/kg once a week for 13 weeks, or intravenously at a dose of 1, 5, or 25 mg/kg once a week for 9 months. Results showed that lebrikizumab had no effect related to electrocardiogram parameters. Lebrikizumab was administered to male cynomolgus monkeys at a dose of 5 or 25 mg/kg once a week for 3 months. Results showed that no lebrikizumab-associated effects were observed in the cardiovascular system (heart rate and cardiac auscultation), the central nervous system (neurological tests, neurobehavioral assessment, and body temperature), or the respiratory system (respiratory rate and lung auscultation).

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of lebrikizumab against AD:
IL-13 is assumed to play vital roles in the pathogenesis of skin barrier dysfunction, dermal inflammation, allergic reactions, and lichenification (*J Clin Cell Immunol.* 2011;2:110, *J Allergy Clin Immunol.* 2017;139:S65-76, *J Drugs Dermatol.* 2016;15:165-71). Lebrikizumab is considered to exhibit its effect against AD by binding to IL-13, thereby inhibiting IL-13Rα1/IL-4Rα receptor complex-mediated IL-13 signal transduction.

On the basis of the data submitted, PMDA concluded that the effect of lebrikizumab to suppress the physiological activity of IL-13 was demonstrated and that lebrikizumab is expected to be effective against AD, a disease in which IL-13 is considered to be involved in pathogenesis.

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

The applicant submitted the following data relating to absorption and distribution of lebrikizumab: (1) Intravenous and subcutaneous administration studies and (2) reproductive and developmental toxicity studies, both in rats and cynomolgus monkeys. Serum lebrikizumab concentration was measured by ELISA (lower limit of quantitation,[4)] 25, 20, or 1.5 ng/mL), and serum anti-drug antibody (ADA) was measured by ELISA (lower limit of quantitation, 50 ng/mL) or by electrochemiluminescence immunoassay (detection sensitivity, 142 or 230 ng/mL). Since lebrikizumab is a monoclonal antibody, it is considered to be distributed mainly within blood vessels and in the interstitial fluid after entering the systemic circulation, with only limited extravascular distribution. Also, it is considered to be

4) The validation report on the serum lebrikizumab level measurement in the single subcutaneous dose study in rats was not submitted.

degraded into peptides and amino acids, which are then reused or excreted. Therefore, no studies were conducted on its distribution (other than distribution in fetuses or newborns), metabolism, or excretion.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1 and 4.2.3.1.1)

Table 5 shows the pharmacokinetic parameter values obtained following a single subcutaneous administration of 5 mg/kg of lebrikizumab (Process A or B) to male rats. No significant difference was observed in the results between Process A- and B-derived lebrikizumab. A decrease in serum lebrikizumab concentration was observed in rats expressing ADA.

Table 5 also shows pharmacokinetic parameter values obtained following a single intravenous administration of lebrikizumab to female cynomolgus monkeys at a dose of 1, 10, or 100 mg/kg. C_{max} increased in proportion to dose within the range investigated. AUC_{inf} increased roughly in proportion to dose within the range from 1 to 10 mg/kg, whereas the increase was less than the dose ratio over the range from 10 to 100 mg/kg. ADA expression was observed in 1 animal in the 1 mg/kg group, but had no significant effect on the exposure level.

Table 5. Pharmacokinetic parameter values following single-dose administration of lebrikizumab

Animal species	Route of administration	Dose (mg/kg)	N	C_{max} (μg/mL)	AUC_{inf} (μg•day/mL)	$AUC_{0\text{-}14\ day}$ (μg•day/mL)	t_{max} (day)	CL (mL/day/kg)	V_d (mL/kg)	$t_{1/2}$ (day)	No. of animals with ADA
Rat	s.c.	5 (Process A)	18 males[a)]	72.1 ± 10.6	1,590 ± 309	731 ± 120	3.9 ± 1.1	—	—	14.3 ± 4.7	2/20
		5 (Process B)	15 males[b)]	61.6 ± 8.2	1,340 ± 211	627 ± 66.1	4.0 ± 0.0	—	—	13.6 ± 4.1	5/20
Cynomolgus monkey	i.v.	1	2 females	27.2, 25.1	394, 405	—	—	2.54, 2.47	59.0, 65.5	16.1, 18.4	1/2
		10	2 females	212, 220	3,040, 4,720	—	—	3.29, 2.12	85.0, 77.6	17.9, 25.4	0/2
		100	2 females	2,080, 2,000	20,300, 22,300	—	—	4.93, 4.48	81.1, 60.7	11.4, 9.38	0/2

Mean ± standard deviation (SD) (individual value if N = 2)
a) Two ADA-positive animals were excluded.
b) Five ADA-positive animals were excluded.

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2.2 and 4.2.3.2.3)

Table 6 shows the trough serum lebrikizumab concentration and the incidence of ADA following a once weekly repeated intravenous or subcutaneous administration of lebrikizumab to male and female cynomolgus monkeys. No clear sex difference was observed in the pharmacokinetics. There was a tendency of accumulation with repeated administration. In the 9-month repeated intravenous dose toxicity study, serum lebrikizumab concentration showed a roughly dose-proportional increase within the range investigated and, in the 13-week repeated subcutaneous dose toxicity study, serum lebrikizumab concentration showed a tendency of dose-dependent increase. Serum lebrikizumab concentration decreased in animals with ADA.

Table 6. Pharmacokinetic parameter values following repeated-dose administration of lebrikizumab

Route of administration	Administration period	Dose (mg/kg/day)	Measuring time point	C_{trough} (μg/mL)		No. of animals with ADA	
				Male	Female	Male	Female
i.v.	9 months[a)]	1	Month 1	30.1 ± 5.21 (8)	33.3 ± 4.41 (8)	0	1
			Month 3	50.3 ± 12.4 (8)	54.2 ± 6.00 (7)[b)]		
			Month 9	45.1 ± 29.2 (4)	54.9 ± 5.30 (3)[b)]		
		5	Month 1	181 ± 15.7 (8)	163 ± 31.3 (7)[b)]	0	1
			Month 3	297 ± 29.9 (8)	236 ± 65.8 (7)[b)]		
			Month 9	309 ± 81.9 (4)	314 ± 34.7 (4)		
		25	Month 1	896 ± 74.5 (8)	897 ± 55.2 (8)	0	0
			Month 3	1,520 ± 192 (8)	1,310 ± 288 (8)		
			Month 9	1,420 ± 292 (4)	1,490 ± 296 (4)		
s.c.	13 weeks	5	Week 1	19.1 ± 12.2 (5)[c)]	22.4 ± 8.50 (5)[c)]	0	0
			Week 3	97.7 ± 44.4 (3)	97.8 ± 23.1 (3)		
			Week 13	419 ± 110 (3)[d)]	367 ± 43.7 (3)[d)]		
		25	Week 1	140 ± 49.0 (3)	229 ± 68.3 (3)	0	0
			Week 3	549 ± 23.1 (3)	616 ± 342 (3)		
			Week 13	1,420 ± 234 (3)	1,350 ± 113 (3)		

Mean ± SD (number of animals)

a) A total of 8 animals (4 each of males and females) of 16 animals (8 each of males and females) in each group were necropsied at 3 months post dose.
b) Except ADA-positive animals
c) Includes data of 4 animals (2 each of males and females) in the satellite group receiving lebrikizumab 5 mg/kg subcutaneously for 4 weeks.
d) Lebrikizumab 25 mg/kg was administered to all animals at Week 10 by mistake.

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.2.1)

In the study of embryo-fetal development, lebrikizumab 5, 15, or 50 mg/kg was administered subcutaneously once weekly from Gestation Day 20 to 48 in pregnant cynomolgus monkeys (n = 12/group[5)]) (5 times in total; the initial loading dose, subcutaneous administration at 15, 45, or 150 mg/kg in each dose group). The percentage (mean ± standard deviation [SD]) of the serum lebrikizumab concentration in fetal serum to that in the maternal animals at cesarean section (Gestation Day 100-102) was 29.5% ± 7.05%, 33.7% ± 8.70%, and 32.2% ± 7.97%, respectively, demonstrating that lebrikizumab crossed the placenta and was transferred into fetal circulation. ADA was detected in 2 each of maternal animals in the 5 mg/kg and 15 mg/kg groups and in 3 maternal animals in the 50 mg/kg group. A decrease in serum lebrikizumab concentration was observed in 1 animal each in the 5 mg/kg and 50 mg/kg groups.

4.2.2 Transfer to offspring (CTD 4.2.3.5.3.1)

In the study of effects on pre- and postnatal development, including maternal function, lebrikizumab 15 or 50 mg/kg was administered subcutaneously once weekly to pregnant cynomolgus monkeys (n = 16/group) from Gestation Day 35 to delivery or Gestation Day 168 (the initial loading dose, subcutaneous administration at 45 or 150 mg/kg in each dose group). Table 7 shows the serum lebrikizumab concentration in maternal animals and the offspring.

ADA was detected in 7 maternal animals and 3 offspring in the 15 mg/kg group and in 12 maternal animals and 4 offspring in the 50 mg/kg group at least at one measuring time point. Decreased serum lebrikizumab concentration was observed in some maternal animals.

5) Test animals showing ADA, abortion, or embryonal death were excluded from the analysis population (8 animals in the 5 mg/kg group, 9 animals in the 15 mg/kg group, 6 animals in the 50 mg/kg group).

Table 7. Serum lebrikizumab concentration in maternal animals and offspring (μg/mL)

	15 mg/kg		50 mg/kg	
	Maternal animals	Offspring	Maternal animals	Offspring
Gestation Day 42[a)]	534 ± 89.2 (16)		1,570 ± 263 (16)	
Gestation Day 133[a)]	564 ± 90.8 (15)		1,800 ± 432 (15)	
Postpartum/Postnatal Day 28	214 ± 111 (14)	264 ± 72.8 (14)	585 ± 271 (14)	663 ± 205 (14)
Postpartum/Postnatal Day 56	83.0 ± 50.1 (14)	141 ± 48.4 (14)	254 ± 180 (14)	380 ± 148 (14)
Postpartum/Postnatal Day 84	41.8 ± 24.2 (13)[b)]	70.6 ± 21.1 (14)	112 ± 77.6 (13)[b)]	219 ± 87.7 (14)
Postpartum/Postnatal Day 180	2.19 ± 2.59 (11)[b)]	6.70 ± 2.90 (14)	7.44 ± 8.08 (11)[b)]	20.5 ± 9.07 (14)

Mean ± SD (number of animals)
a) Samples were collected before lebrikizumab administration.
b) Data below the lower limit of quantitation were excluded.

4.R Outline of the Review Conducted by PMDA

PMDA's view:

PMDA has concluded that the *in vivo* behavior of lebrikizumab has been elucidated to a certain extent from the results of the nonclinical pharmacokinetic studies submitted. The package insert should include a precautionary statement regarding placental transfer and distribution in milk of lebrikizumab, taking account of the following: (1) Lebrikizumab was shown to cross the placenta in pregnant cynomolgus monkeys, and (2) human IgG is generally known to be distributed in milk, although no study was conducted on lebrikizumab distribution in milk.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicology studies of lebrikizumab were conducted: Single-dose toxicity studies, repeated-dose toxicity studies, reproductive and developmental toxicity studies, and tissue cross-reactivity studies. Since lebrikizumab binds to monkey IL-13 [see Section 3.1], toxicity studies of lebrikizumab were conducted in cynomolgus monkeys.

5.1 Single-dose toxicity

There were no acute symptoms or death up to the maximum dose of 100 mg/kg in the single-dose toxicity study in cynomolgus monkeys. The approximate lethal dose was estimated to be >100 mg/kg (Table 8).

Table 8. Summary of results of single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female cynomolgus monkeys	i.v.	1, 10, 100	None	>100	4.2.3.1.1

5.2 Repeated-dose toxicity

Repeated subcutaneous and intravenous dose toxicity studies were conducted in cynomolgus monkeys. No systemic toxicity associated with lebrikizumab administration was observed (Table 9). Decreased weights of thyroid gland and parathyroid observed in the lebrikizumab group of the 6-week repeated intravenous dose toxicity study were not accompanied by related abnormal findings, suggesting low toxicological significance. The decreased uterine weight observed in the lebrikizumab group of the 9-month repeated intravenous dose toxicity study may possibly be due to the varied extent of maturity of animals used, and no related abnormal findings were observed in the female fertility study using mature cynomolgus monkeys (Table 10), suggesting that the finding was of low toxicological significance. The

no observed adverse effect level (NOAEL) of lebrikizumab in the 9-month repeated intravenous dose toxicity study was determined to be 25 mg/kg/week.

Table 9. Summary of results of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg)	Main findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkey	i.v.	6 weeks (once weekly)	0,[a] 0.95, 4.90, 22.57	≥4.90: Decreases in thyroid/parathyroid weights (male)	22.57	4.2.3.2.1
	i.v.	13 weeks or 9 months (once weekly)	0,[b] 1, 5, 25	13-week administration: None 9-month administration: ≥1: Decrease in uterine weight (female)	25	4.2.3.2.3
	s.c.	13 weeks (once weekly)	0,[c] 5, 25	None	25	4.2.3.2.2

a) Vehicle, phosphate-buffered solution containing sucrose and polysorbate 80 (pH 7)
b) Vehicle, 0.9% physiological saline
c) Vehicle, 20 mmol/L sodium phosphate buffer containing 0.03% polysorbate 20, 6% sucrose, and 20 mmol/L sodium chloride

5.3 Genotoxicity

Lebrikizumab is a monoclonal antibody consisting of natural amino acids only. It is considered neither to pass through the nuclear or mitochondrial membrane, nor to directly interact with DNA or other chromosomal materials in the nucleus. It is thus considered to pose little genotoxicity concern, and no genotoxicity study was conducted.

5.4 Carcinogenicity

Since lebrikizumab does not bind to rodent IL-13, no carcinogenicity study was conducted.

The applicant's explanation:

On the basis of the following findings, that lebrikizumab is unlikely to have carcinogenic risk associated with the inhibition of IL-13-mediated signal transduction, but the applicant plans to monitor the occurrence of malignant tumour in patients receiving lebrikizumab as part of the post-marketing safety surveillance activities because of the insufficient evidence on the relationship between lebrikizumab and malignant tumour in humans.

- The repeated-dose toxicity study in cynomolgus monkeys showed no proliferative/premalignant lesions suggestive of carcinogenicity [see Section 5.2], and the immunotoxicity assessment did not detect any effect related to immune suppression [see Section 5.9].
- Results of the clinical studies of lebrikizumab did not suggest any increase in the frequency of the occurrence of malignant tumour associated with lebrikizumab [see Section 7.R.3.4].
- Studies in IL-13- or IL-13Rα1-knockout mice suggest the possibility that IL-13 suppression or inhibition promotes tumor development (*Nat Commun.* 2016;7:12080, *J Invest Dermatol.* 2022;142:1565-75). Other studies, in contrast, show that IL-13 and/or IL-13R are expressed at an increased level in various tumors, that IL-13-mediated signal transduction promotes tumorigenesis, and that IL-13 signal transduction inhibition suppresses carcinogenesis (*Drug Saf.* 2018;41:489-509, *Int J Mol Sci.* 2021;22:727, etc.). These findings suggest that IL-13-neutralizing activity is highly likely to suppress tumor growth.
- A safety surveillance study on dupilumab, an anti-IL-4Rα subunit antibody with inhibitory activity against intracellular IL-13 signal transduction, was conducted using the dataset of the World Health

Organization (WHO) global database of individual case safety reports (VigiBase) from 2016 through 2020. Results identified a study which reported a statistical correlation between dupilumab and occurrences of cutaneous T-cell lymphoma but did not observe a correlation with other malignant tumours (*J Am Acad Dermatol.* 2022;86:431-3). The report considers the possibility that the above apparent correlation was due to the misdiagnosis of mycosis fungoides as AD.

5.5 Reproductive and developmental toxicity

Fertility, embryo-fetal development (EFD), and pre- and postnatal developmental (PPND) studies were conducted in cynomolgus monkeys (Table 10). No reproductive or developmental toxicity was detected. In the male fertility study, spots and wheals were observed in the parental animals in the lebrikizumab group, but no related histopathological findings were observed. Increased blood eosinophil count was observed in some animals before lebrikizumab administration. The increased blood globulin and decreased albumin/globulin ratio (A/G ratio) observed in these animals were within the normal range. No other changes related to the above haematological abnormality were observed, from which all the above abnormalities were determined not to be toxic findings. The study on female fertility detected histopathological changes in the thymus, parathyroid, thyroid gland, cervix, and uterus in the lebrikizumab group, but they were considered to be of low toxicological significance, as determined from the following findings: (1) All these findings were common historical findings of cynomolgus monkey (*J Toxicol Pathol.* 2021;34:1S-182S, *Toxicol Pathol.* 2022;50:607-27) and (2) no related abnormalities were observed when lebrikizumab was administered at the same dose in the repeated-dose toxicity study [see Section 5.2]. Polyclonal hyperimmunoglobulinemia in 1 animal in the lebrikizumab group was considered to be associated with lymphocytic plasmacytic enteritis observed in the duodenum and jejunum. It was considered to be an accidental finding and not toxicity because spontaneous inflammation of the small intestine is observed in cynomolgus monkeys (*Toxicol Pathol.* 2010;38:642-57) and no related abnormality was observed when lebrikizumab was administered at the same dose in the repeated-dose toxicity study [see Section 5.2]. The NOAEL on male and female fertility was determined to be 25 mg/kg/week, and the NOAEL on the fertility of the maternal animals, embryo-fetal development, and development of F_1 offspring was determined to be 50 mg/kg/week (initial loading dose 150 mg/kg).

Table 10. Summary of results of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg)	Main findings	NOAEL (mg/kg/week)	Attached document CTD
Fertility study	Male cynomolgus monkey	s.c.	13 weeks (once weekly) + 20-week withdrawal period	0,[a] 5, 25	Parental animals (male) 25: Swelling of administration site, spots/wheal of groin/lower abdomen, increases in blood eosinophil count/globulin level, decrease in A/G ratio Fertility (male) None	Parental animals (general toxicity/ fertility): 25	4.2.3.5.1.2
	Female cynomolgus monkey	i.v.	9 months (once weekly) + 8-month withdrawal period	0,[b] 0.05, 1, 25	Parental animals (female) ≥0.05: Cysts in thymus/parathyroid gland/thyroid gland[c] ≥1: Glandular dilatation/glandular cyst of uterine cervix 25: Polyclonal hyperimmunoglobulinemia, cystic changes in endometrial glands[c] Fertility (female) None	Parental animals (general toxicity/ fertility): 25	4.2.3.5.1.1
EFD study	Female cynomolgus monkey	s.c.	Gestation Day 20 to 48[d] (once weekly)	Loading dose: 0,[e] 15, 45, 150 Maintenance dose: 0,[e] 5, 15, 50	Maternal animals None Embryo-fetal development None	Maternal animals[f]: 150/50 Embryo-fetal development[f]: 150/50	4.2.3.5.2.1
PPND study	Female cynomolgus monkey	s.c.	Maternal animals: From Gestation Day 35 to Delivery or Gestation Day 168[g] (once weekly)	Loading dose: 0,[a] 45, 150 Maintenance dose: 0,[a] 15, 50	Maternal animals None F_1 offspring None	Maternal animals[f]: 150/50 Development of F_1 offspring[f]: 150/50	4.2.3.5.3.1

a) Vehicle, 20 mmol/L histidine acetate buffer containing 175 mmol/L sucrose and 0.03% polysorbate 20 (pH 5.7)
b) Vehicle, 20 mmol/L sodium phosphate buffer containing 6% sucrose, 0.02% polysorbate 80, and 25.3 mmol/L sodium chloride (pH 7.1)
c) Observed in the control group as well.
d) The loading dose was administered on Gestation Day 20, and the maintenance dose was administered from Gestation Day 27 to 48.
e) Vehicle, 20 mmol/L sodium phosphate buffer containing 6% sucrose, 0.03% polysorbate 20, and 20 mmol/L sodium chloride (pH 7.2)
f) Expressed in loading dose/maintenance dose
g) The loading dose was administered on Gestation Day 35, and the maintenance dose was administered from Gestation Day 42 to Delivery or Gestation Day 168.

5.6 Study in juvenile animals

No juvenile animal study on lebrikizumab was conducted. The applicant considers that there is little safety concern in administering lebrikizumab to children aged ≥12 years, concluding from the following:

- The repeated-dose toxicity study of lebrikizumab [see Section 5.2] was conducted using juvenile to sexually matured cynomolgus monkeys. Results showed no findings suggestive of the effect of lebrikizumab on the development of the juvenile animals, including secondary sex characteristics.
- Newborn cynomolgus monkeys exposed to lebrikizumab during the fetal phase, the period when the main immune system undergoes emergence and development in humans and cynomolgus monkeys

(*J Immunotoxicol.* 2005;2:211-6, *J Med Primatol.* 2023;52:64-78) showed no effect on immune function [see Section 5.9].

5.7 Local tolerance

No local irritation was observed at the site of lebrikizumab administration in the repeated subcutaneous and intravenous dose toxicity studies in cynomolgus monkeys [see Section 5.2], from which the applicant considered that lebrikizumab is unlikely to pose safety concern.

5.8 Tissue cross-reactivity

Tissue cross-reactivity studies were conducted using the frozen section of human and monkey normal tissues. No cross-reactivity to human or cynomolgus monkey normal tissues was observed (Table 11).

Table 11. Outline of tissue cross reactivity studies

Test system	Study method	Main findings	Attached document CTD
Human and cynomolgus monkey normal tissues	Frozen sections were treated with lebrikizumab (5, 40 µg/mL) and binding to tissue was detected by enzyme antibody technique.	None	4.2.3.7.7-1 to 4.2.3.7.7-2

5.9 Immunotoxicity assessment

Lebrikizumab administration had no effect on the immune system in the following studies and examinations: (1) Repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2]; (2) haematology in male and female fertility study and EFD study; (3) repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2]; and (4) immunophenotyping of peripheral blood and histopathological findings in lymphoid tissue in the PPND study. T cell-dependent antibody response (TDAR) was conducted on the newborns in the PPND study. Lebrikizumab had no effect on production of keyhole limpet hemocyanin (KLH)-specific IgM or IgG after sensitization with KLH (Table 12).

Table 12. Summary of results of immunotoxicity studies

Study	Test system	Study method	Main findings	Attached document CTD
TDAR	Female cynomolgus monkey	KLH 2 mg/kg was administered to the offspring on Postnatal Day 147, and anti-KLH antibody (IgG and IgM) concentration was measured on Day 7, 14, 21, and 33.	No effect on antibody production	4.2.3.5.3.1

5.R Outline of the review conducted by PMDA

PMDA's view:

No evident safety concerns on the clinical use of lebrikizumab were observed in the results of the toxicity studies submitted. However, the risk of malignant tumour caused by lebrikizumab should be investigated carefully, taking account of the results of the clinical studies, given the following findings: (1) A study administering chemical carcinogens to IL-13-deficient mice suggested the possibility that inhibition of IL-13-mediated signal transduction promotes the development of skin cancer and of the premalignant lesions of colorectal cancer; (2) a statistically correlation was reported between dupilumab administration and incidence of cutaneous T-cell lymphoma although potential influence of the treated

patients is suspected [see Section 5.4]; and (3) the incidence of skin cancer is high in patients with AD (*JAMA Dermatol.* 2020;156:158-71) [see Section 7.R.3.4].

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

6.1 Biopharmaceutic studies and associated analytical methods

The applicant submitted the data of biopharmaceutical studies including absolute bioavailability studies.

Serum lebrikizumab concentration was determined by ELISA (lower limit of quantitation 90 ng/mL). ADA and neutralizing antibody[6)] were measured by ELISA (ADA detection limit 77.6 ng/mL) in the phase II study and by ECL (ADA detection limit 13.8 ng/mL) in the phase III study. Neutralizing antibody was detected by the competitive ligand-binding method.

For the clinical development of lebrikizumab, Formulation A (low concentration phosphate solution [50 mg/2 mL]),[7)] Formulation B (high concentration phosphate solution [125 mg/1 mL),[8)] and Formulation C (high concentration histidine acetate solution [125 mg/1 mL])[9)] were mainly used. Formulation C was used in the phase III study in patients with AD and handled as the proposed commercial formulation.

The dose of the formulation is expressed in the dose of lebrikizumab unless specified otherwise.

6.1.1 Absolute bioavailability study (CTD 5.3.3.1.1, Study J2T-DM-KGBA [[redacted] to [redacted]])

In a randomized, open-label, parallel-group study in non-Japanese healthy subjects, the absolute bioavailability after a single subcutaneous administration of lebrikizumab 1.0 mg/kg was investigated. Table 13 shows pharmacokinetic parameter values following a single subcutaneous or intravenous administration of lebrikizumab.

Table 13. Pharmacokinetic parameter values following a single dose of lebrikizumab 1.0 mg/kg

Route of administration	N	C_{max} (μg/mL)	AUC_{last} (μg▪day/mL)	AUC_{inf} (μg▪day/mL)	t_{max} (day)	$t_{1/2}$ (day)	Absolute bioavailability % [90% CI]
i.v. (Formulation A)	10	20.0 ± 2.54	331 ± 62.5	362 ± 66.5	0.022 [0.021, 0.026]	24.7 ± 5.42	
s.c. (Formulation B)	11	8.69 ± 1.77	268 ± 70.6	315 ± 90.0[a)]	9.96 [6.96, 14.0]	26.0 ± 5.38[b)]	79.9 [66.2, 96.4][c)] 85.3 [69.5, 105][d)]

Mean ± SD; t_{max}, median [range]
a) N = 9, b) N = 10, c) based on AUC_{last}, d) based on AUC_{inf}

6.2 Clinical pharmacology

The applicant submitted evaluation data including those from a clinical study in healthy adults and patients with AD as well as results of the population pharmacokinetic analysis and the exposure-

6) Explanation of the validation of methods for ADA and neutralizing antibody measurement used in the foreign phase I study (Study KGAZ) have not been provided by the applicant.
7) The formulation manufactured by Process 1 and used in the phase I study (Study KGBA) [see Section 2.2.3]
8) The formulation manufactured by Process 2 and used in the phase I study (Study KGBA) [see Section 2.2.3]
9) The formulation manufactured by Process 4 was used in the phase I study (Study KGAZ) and the phase II study (Study KGAF), and the formulation manufactured by the proposed process was used in the phase III studies (Studies KGAA, KGAB, KGAC, KGAD, KGAE, and KGAL) [see Section 2.2.3].

response analysis. The dose of Ebglyss is expressed in the dose of lebrikizumab unless specified otherwise.

6.2.1 Studies in healthy adults

6.2.1.1 Foreign phase I study (CTD 5.3.3.1.2, Study J2T-DM-KGAZ [August 2011 to February 2012])

Table 14 shows the pharmacokinetic parameter values following a single subcutaneous administration of lebrikizumab 125, 250, or 375 mg to Japanese and non-Japanese healthy subjects. In the Japanese subjects, pharmacokinetics showed a linear response over the dose range investigated. In Caucasian subjects, in contrast, AUC_{inf} increased in proportion to dose whereas C_{max} and AUC_{last} increased more than in proportion to dose. No ADA was detected after lebrikizumab administration.

Table 14. Pharmacokinetic parameters following a single subcutaneous administration of lebrikizumab

Dose	Population	N	Body weight (kg)	C_{max} (μg/mL)	AUC_{last} (μg•day/mL)	AUC_{inf} (μg•day/mL)	$t_{1/2}$ (day)	t_{max} (day)	CL/F (mL/day/kg)	V_z/F (mL/kg)
125 mg	Japanese	7	60.7 ± 13.8	15.3 ± 4.37	622 ± 125	643 ± 134	23.1 ± 2.48	4.00 [1.00, 14.0]	3.37 ± 0.63	112 ± 22.7
	Non-Japanese	6	68.2 ± 12.5	14.2 ± 3.85	733 ± 218	802 ± 245	31.6 ± 2.99	7.00 [4.00, 14.0]	2.52 ± 0.51	115 ± 23.6
250 mg	Japanese	7	65.8 ± 13.6	29.0 ± 7.99	1,180 ± 306	1,210 ± 324	21.3 ± 5.61	6.00 [4.00, 14.0]	3.43 ± 1.36	98.0 ± 14.2
	Non-Japanese	7	78.1 ± 16.3	27.9 ± 8.74	1,260 ± 438	1,300 ± 462	22.2 ± 3.37	6.00 [4.00, 14.0]	2.78 ± 0.87	86.9 ± 20.0
375 mg	Japanese	7	69.3 ± 11.5	47.2 ± 8.28	1,760 ± 294	1,790 ± 297	20.4 ± 1.61	6.96 [6.94, 7.95]	3.12 ± 0.34	91.1 ± 8.55
	Non-Japanese	7	70.0 ± 16.2	61.0 ± 11.9	2,430 ± 465	2,550 ± 507	28.3 ± 5.06	6.98 [3.98, 7.19]	2.20 ± 0.13	90.0 ± 17.4

Mean ± SD; t_{max}, median [range]

6.2.2 Studies in patients with AD

6.2.2.1 Foreign phase IIb study (lebrikizumab monotherapy study; CTD 5.3.5.1.3, Study J2T-DM-KGAF [January 2018 to May 2019])

Table 15 shows serum lebrikizumab concentration in non-Japanese adult patients with moderate to severe AD receiving 16-week repeated subcutaneous administration of lebrikizumab according to the following dosage regimens: (1) Lebrikizumab 125 mg (initial dose 250 mg) or 250 mg (initial dose 500 mg) Q4W; or (2) lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W [see Section 7.1.1]. After lebrikizumab administration, ADA was detected in 19 subjects in the 125 mg Q4W group, 19 subjects in the 250 mg Q4W group, and 9 subjects in the 250 mg Q2W group. Among the subjects with ADA, neutralizing antibody was detected in 3 subjects in the 125 mg Q4W group, 2 subjects in the 250 mg Q4W group, and 3 subjects in the 250 mg Q2W group.

Table 15. Change over time in serum lebrikizumab concentration following the repeated subcutaneous administration (μg/mL)

Dose group	Body weight (kg)[a)]	Week 2	Week 4	Week 8	Week 16	Week 24
125 mg Q4W	85.7 ± 24.8	24.5 ± 9.96 (70)	17.0 ± 7.79 (64)	15.5 ± 7.76 (64)	13.2 ± 6.63 (56)	2.71 ± 1.95 (51)
250 mg Q4W	82.6 ± 20.5	44.7 ± 18.8 (77)	30.9 ± 12.7 (72)	30.7 ± 13.9 (64)	31.0 ± 12.8 (61)	4.98 ± 3.55 (49)
250 mg Q2W	78.5 ± 20.6	53.6 ± 16.0 (69)	91.2 ± 32.6 (68)	84.9 ± 33.0 (64)	80.3 ± 34.9 (55)	18.4 ± 12.9 (53)

Mean ± SD (number of subjects)
a) Baseline body weight

6.2.2.2 Foreign phase III studies (lebrikizumab monotherapy study; CTD 5.3.5.1.6, Study J2T-DM-KGAB [September 2019 to May 2022]; CTD 5.3.5.1.7, Study J2T-DM-KGAC [October 2019 to April 2022])

Non-Japanese patients (children aged ≥12 years and adults) with moderate to severe AD received lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) subcutaneously Q2W for 16 weeks, followed by subcutaneous administration of lebrikizumab 250 mg Q2W or Q4W [see Sections 7.2.1 and 7.2.2]. Table 16 shows the serum lebrikizumab concentration. ADA was detected in the following subjects after lebrikizumab administration in Study KGAB: (1) 7 subjects (2.5%) among those who received lebrikizumab during the induction phase (Week 0-16) of Study KGAB; and (2) 8 subjects who, among responders to lebrikizumab at Week 16, received placebo, lebrikizumab 250 mg Q2W or 250 mg Q4W during the double-blind maintenance period (Week 16-52) (2 subjects [6.3%], 4 subjects [6.5%], and 2 subjects [3.3%], respectively).[10)] Neutralizing antibody was positive in these subjects. Also, ADA was detected in the following subjects after lebrikizumab administration in Study KGAC: (1) 2 subjects (0.7%) among those who received lebrikizumab during the induction phase of Study KGAC; and (2) 3 subjects who, among responders to lebrikizumab at Week 16, received placebo or lebrikizumab 250 mg Q2W during the double-blind maintenance period (2 subjects [7.1%] and 1 subject [2.0%], respectively).[10)] Neutralizing antibody was positive in these subjects except 1 subject receiving placebo during the double-blind maintenance period.

Table 16. Change over time in serum lebrikizumab concentration during the repeated subcutaneous administration (μg/mL)

Study code	Dosage regimen	Population	Body weight (kg)[a)]	Week 4	Week 16	Week 32	Week 52
KGAB	250 mg Q2W/Q2W[b)]	Whole population	77.2 ± 19.3 (55)	99.3 ± 28.0 (34)	97.6 ± 32.5 (55)	87.7 ± 31.4 (49)	80.2 ± 30.1 (40)
		12-17 years of age	65.1 ± 10.4 (6)	102 ± 26.3 (4)	133 ± 28.2 (6)	122 ± 28.8 (6)	100 ± 26.6 (5)
		≥18 years of age	78.6 ± 19.7 (49)	99.0 ± 28.6 (30)	93.3 ± 30.5 (49)	82.9 ± 28.8 (43)	77.4 ± 29.8 (35)
	250 mg Q2W/Q4W	Whole population	72.9 ± 19.1 (59)	102 ± 29.7 (39)	104 ± 33.2 (59)	44.3 ± 23.5 (56)	41.7 ± 25.2 (45)
		12-17 years of age	72.1 ± 23.8 (10)	99.9, 116 (2)	107 ± 39.1 (10)	57.0 ± 41.6 (8)	62.4 ± 53.7 (5)
		≥18 years of age	73.1 ± 18.3 (49)	101 ± 30.5 (37)	104 ± 32.3 (49)	42.2 ± 18.9 (48)	39.1 ± 18.9 (40)
KGAC	250 mg Q2W/Q2W[b)]	Whole population	73.0 ± 19.1 (45)	105 ± 29.3 (33)	101 ± 43.6 (44)	91.3 ± 44.9 (41)	90.7 ± 48.9 (40)
		12-17 years of age	47.1 ± 7.13 (5)	118 ± 26.4 (5)	136 ± 40.3 (5)	127 ± 38.7 (5)	115 ± 76.2 (5)
		≥18 years of age	76.3 ± 17.6 (40)	103 ± 29.7 (28)	96.6 ± 42.4 (39)	86.3 ± 43.9 (36)	87.2 ± 44.3 (35)
	250 mg Q2W/Q4W	Whole population	74.9 ± 17.7 (54)	99.1 ± 27.7 (42)	97.3 ± 40.9 (52)	40.7 ± 19.7 (47)	44.5 ± 23.7 (48)
		12-17 years of age	65.0 ± 11.7 (7)	105 ± 24.3 (5)	114 ± 20.9 (6)	41.6 ± 11.1 (6)	51.6 ± 47.7 (3)
		≥18 years of age	76.4 ± 18.0 (47)	98.2 ± 28.3 (37)	95.2 ± 42.5 (46)	40.6 ± 20.8 (41)	44.0 ± 22.2 (45)

Mean ± SD (number of subjects); individual value if n ≤2

a) Baseline body weight

b) Except subjects who proceeded to the maintenance escape period [see Section 7.2.1].

[10)] Includes subjects who were ADA positive at baseline and showed a ≥4-fold increase in antibody titer after baseline.

6.2.2.3 Foreign phase III study (TCS combination therapy study; CTD 5.3.5.1.5, Study J2T-DM-KGAD [February 2020 to September 2021])

Non-Japanese patients (children aged ≥12 years and adults) with moderate to severe AD received lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) subcutaneously Q2W for 16 weeks [see Section 7.2.3]. Table 17 shows serum lebrikizumab concentration. ADA was detected in 5 subjects after lebrikizumab administration. Neutralizing antibody also was positive.

Table 17. Change over time in serum lebrikizumab concentration following the repeated subcutaneous administration (μg/mL)

Dosage regimen	Population	Body weight (kg)[a)]	Week 4	Week 16
250 mg Q2W	Whole population	75.2 ± 23.6 (137)	103 ± 36.6 (115)	86.7 ± 41.2 (124)
	12-17 years of age	58.7 ± 15.2 (29)	133 ± 35.8 (26)	109 ± 43.1 (28)
	≥18 years of age	79.7 ± 23.5 (108)	94.7 ± 32.1 (89)	80.3 ± 38.5 (96)

Mean ± SD (number of subjects)
a) Baseline body weight

6.2.2.4 Japanese phase III study (TCS combination study; CTD 5.3.5.1.4, Study J2T-JE-KGAL [March 2021 to [redacted] 2023 (data cut-off)])

Japanese patients (children aged ≥12 years and adults) with moderate to severe AD received lebrikizumab 250 mg subcutaneously Q2W (500 mg for the initial dose and at Week 2) or Q4W (500 mg for the initial dose) for 16 weeks, followed by subcutaneous administration of 250 mg Q2W or Q4W. Table 18 shows the serum lebrikizumab concentration. ADA was detected after lebrikizumab administration in the following subjects: 3 subjects who received lebrikizumab 250 mg Q2W or Q4W during the induction phase (Week 0-16) (1 subject and 2 subjects, respectively), and 3 subjects who, among responders to lebrikizumab at Week 16, received lebrikizumab 250 mg Q4W during the double-blind maintenance period (Week 16-68). Neutralizing antibody was positive in these subjects.

Table 18. Change over time in serum lebrikizumab concentration following repeated subcutaneous administration (μg/mL)

Dosage regimen	Population	Body weight (kg)[b)]	Week 4	Week 16	Week 24	Week 32	Week 52
250 mg Q2W/Q2W[a)]	Whole population	63.7 ± 10.5 (29)	140 ± 40.1 (29)	90.6 ± 23.4 (29)	92.2 ± 27.9 (29)	92.6 ± 23.9 (29)	107 ± 44.4 (28)
	12-17 years of age	62.3 ± 8.73 (5)	152 ± 38.7 (5)	105 ± 24.2 (5)	108 ± 33.7 (5)	106 ± 17.3 (5)	111 ± 48.8 (5)
	≥18 years of age	64.0 ± 11.0 (24)	138 ± 40.7 (24)	87.6 ± 22.7 (24)	88.9 ± 26.1 (24)	89.8 ± 24.4 (24)	106 ± 44.5 (23)
250 mg Q2W/Q4W	Whole population	62.8 ± 7.95 (30)	131 ± 44.6 (30)	82.0 ± 22.5 (30)	43.8 ± 11.9 (30)	37.9 ± 11.1 (30)	43.8 ± 21.9 (29)
	12-17 years of age	55.8 (1)	179 (1)	97.6 (1)	52.8 (1)	41.5 (1)	90.3 (1)
	≥18 years of age	63.1 ± 7.97 (29)	129 ± 44.5 (29)	81.5 ± 22.7 (29)	43.5 ± 12.0 (29)	37.8 ± 11.3 (29)	42.2 ± 20.3 (28)
250 mg Q4W/Q4W	Whole population	62.4 ± 12.3 (38)	49.8 ± 23.2 (38)	32.1 ± 9.96 (38)	33.3 ± 11.0 (38)	33.6 ± 9.96 (38)	38.6 ± 15.4 (37)
	12-17 years of age	59.8 (1)	90.0 (1)	40.4 (1)	34.8 (1)	42.3 (1)	33.6 (1)
	≥18 years of age	62.5 ± 12.5 (37)	48.7 ± 22.5 (37)	31.9 ± 10.0 (37)	33.3 ± 11.1 (37)	33.3 ± 9.99 (37)	38.7 ± 15.5 (36)

Mean ± SD (number of subjects); individual value if n ≤2
a) Except subjects who proceeded to the maintenance escape period
b) Baseline body weight

6.2.3 Population pharmacokinetics

6.2.3.1 Population pharmacokinetics based on foreign clinical study data (CTD 5.3.3.5.1)

Population pharmacokinetic analysis (US PopPK analysis) was conducted by using the serum lebrikizumab concentration data obtained from 11 foreign clinical studies[11] in healthy adults and patients with AD including children aged ≥12 years and adults (1,607 subjects in total [281 healthy adults, 304 children with AD aged ≥12 years, 1,022 adults with AD], 6,860 measuring points) (NONMEM 7.4.2).

Pharmacokinetics of lebrikizumab was described by a 2-compartment model with the first-order absorption process and linear clearance. The basic model was a model that incorporated body weight into clearance (CL and Q [intercompartmental clearance]) and distribution volume (V2 and V3 [volume of distribution of the peripheral compartment]) using allometric scaling. Since no additional covariates were identified by further exploration of covariates,[12] the basic model was used as the final model. The absolute bioavailability in subcutaneous administration of lebrikizumab was estimated to be 86.1% by the final model.

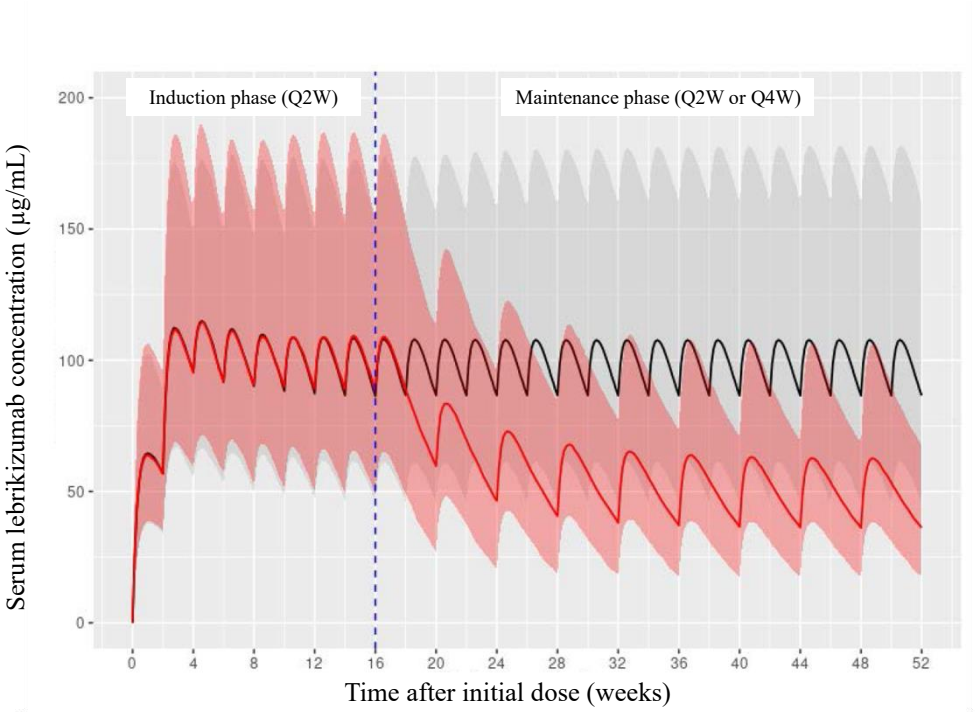
Figure 1 and Table 19 show the results of simulation by the final model of administering lebrikizumab to the subject population of the phase III study using the clinical dosage regimen. The simulation results showed that following the multiple subcutaneous administration of lebrikizumab 250 mg Q2W (500 mg for the initial dose and at Week 2) to the subject population in the phase III study, steady state was reached promptly after the loading dose, and when the lebrikizumab dosing regimen was switched to 250 mg Q4W at Week 16, a new steady state was reached after 12 weeks at the serum lebrikizumab concentration approximately 50% of the level observed in Q2W administration.

Tables 20 and 21 show the estimated pharmacokinetic parameter values by body weight and age, in 16-week multiple subcutaneous administration of lebrikizumab 250 mg Q2W (500 mg for the initial dose and at Week 2) to the subject population of the phase III study, followed by multiple subcutaneous administration of lebrikizumab 250 mg Q2W or Q4W. Whereas the exposure to lebrikizumab tended to be lower in patients of heavy body weight groups, the median $C_{trough,ss}$ was estimated to exceed drug concentration that produces 50% of the maximum effect (EC_{50}) (16.5 μg/mL) derived from the exposure-response analysis using EASI score as the index [see Section 6.2.4], regardless of the dosage regimen and body weight class. Although the exposure to lebrikizumab tended to be higher in children aged ≥12 years compared with the level in adults, the difference in the exposure appears to be mainly due to the difference in the body weight between the groups, as determined from the results of the population pharmacokinetic analysis (mean body weight, 79 kg in adults, 66 kg in children aged ≥12 years). Therefore, the applicant explained that given the results of efficacy [see Table 55] and safety [see Table 67] in the adult population and children aged ≥12 years in the clinical study, the above difference in exposure is not clinically significant.

---

[11] Phase I studies in healthy adults (Studies KGAM, KGAY, KGAZ, and KGBA), phase II studies in patients with AD (Studies KGAF, KGAG, and KGAH), and phase III studies in patients with AD (Studies KGAB, KGAC, KGAD, and KGAE). Only the data during the induction phase were used in Studies KGAB and KGAC.

[12] Effects of the following covariates were investigated: Age, sex, hepatic impairment, renal impairment, race, and disease (AD/healthy adults) for CL; age, body weight, sex, race, disease, and administration site for Ka; age, sex, race, and disease for V2; and administration site for F.



Black/gray, Q2W during maintenance phase; Red, Q4W during maintenance phase
Solid line indicates median serum lebrikizumab concentration at each time point. Shaded area indicates the range that includes 5 to 95 percentile of serum lebrikizumab concentration.

Figure 1. Change in estimated serum lebrikizumab concentration following the administration according to the clinical dosage regimen in the subject population of the phase III studies

Table 19. Estimated pharmacokinetic parameter values following the administration according to the clinical dosage regimen in the subject population of the phase III studies

Dosage regimen	Time	$C_{max,ss}$ (μg/mL)	$C_{avg,ss}$ (μg/mL)	$C_{trough,ss}$ (μg/mL)
250 mg Q2W	Week 16	109 [61.6, 177]	100 [56.3, 167]	86.4 [46.4, 153]
250 mg Q2W/Q2W	Week 52	108 [61.7, 182]	99.9 [56.1, 175]	86.6 [46.0, 159]
250 mg Q2W/Q4W	Week 52	62.6 [38.2, 106]	51.1 [29.4, 86.5]	36.1 [17.6, 67.9]

Median [5 percentile, 95 percentile]

Table 20. Estimated pharmacokinetic parameter values by body weight group, following the administration according to the clinical dosage regimen in the subject population of the phase III studies

Dosage regimen	250 mg Q2W/Q2W				250 mg Q2W/Q4W			
Weight category	First quartile	Second quartile	Third quartile	Fourth quartile	First quartile	Second quartile	Third quartile	Fourth quartile
$C_{max,ss}$ (μg/mL)	143 [97.0, 219]	114 [83.9, 167]	103 [65.3, 146]	81.3 [50.1, 119]	81.4 [56.9, 127]	67.3 [49.4, 96.4]	56.2 [41.0, 80.4]	45.9 [32.7, 63.8]
$C_{avg,ss}$ (μg/mL)	133 [85.1, 208]	106 [76.1, 159]	95.9 [58.1, 138]	75.7 [45.7, 113]	64.9 [38.9, 108]	54.9 [35.7, 83.5]	45.6 [29.6, 70.1]	37.9 [25.3, 54.5]
$C_{trough,ss}$ (μg/mL)	117 [67.8, 191]	93.4 [63.8, 147]	83.7 [47.0, 127]	67.2 [39.0, 103]	43.3 [21.7, 82.1]	39.0 [20.6, 64.3]	32.0 [16.7, 56.3]	26.8 [15.6, 45.2]

Median [5 percentile, 95 percentile]
First quartile, 39.6-58.5 kg; second quartile, 58.5-71.1 kg; third quartile, 71.1-85.1 kg; fourth quartile, 85.1-192 kg

Table 21. Estimated pharmacokinetic parameter values by age group, following the administration according to the clinical dosage regimen in the subject population of the phase III studies

Dosage regimen	250 mg Q2W/Q2W		250 mg Q2W/Q4W	
Subject population	Adults	Children aged ≥12 years	Adults	Children aged ≥12 years
$C_{max,ss}$ (μg/mL)	99.8 [60.1, 174]	121 [70.8, 195]	60.0 [36.0, 91.7]	70.8 [40.8, 109]
$C_{avg,ss}$ (μg/mL)	92.0 [52.6, 164]	111 [63.9, 183]	48.0 [27.4, 76.9]	56.3 [31.9, 92.2]
$C_{trough,ss}$ (μg/mL)	79.0 [43.6, 149]	96.0 [54.0, 165]	33.0 [16.0, 61.1]	37.8 [19.2, 69.8]

Median [5 percentile, 95 percentile]

6.2.3.2 Population pharmacokinetic analysis including the data of Japanese phase III study (CTD 5.3.3.5.2)

Population pharmacokinetic analysis (JP PopPK analysis) was conducted using the data set employed in the population pharmacokinetic analysis based on the foreign clinical study data [see Section 6.2.3.1] together with the data of the plasma lebrikizumab concentration obtained from 12 Japanese and foreign clinical studies[13)] including Japanese patients with AD (children aged ≥12 years and adults) (2,126 subjects in total [281 healthy adults, 354 children with AD aged ≥12 years, 1,491 adults with AD], 9,649 measuring points) (NONMEM 7.5.0).

The final model of the population pharmacokinetic analysis [see Section 6.2.3.1] based on the results of the foreign clinical studies was used as the basic model, and as a result of further covariate exploration,[14)] ethnicity (Japanese/non-Japanese) was incorporated as a covariate for V2. This model was handled as the final model.

Table 22 shows the pharmacokinetic parameters for Japanese and non-Japanese patients with AD estimated by the final model. Table 23 shows the estimates of C_{max} and C_{trough} for subcutaneous administration of lebrikizumab 250 mg Q2W (500 mg for the initial dose and at Week 2) or Q4W (500 mg for the initial dose only) for 16 weeks, followed by a maintenance dose of lebrikizumab 250 mg Q4W for 52 weeks. No significant differences were observed between Japanese and non-Japanese patients.

Table 22. Pharmacokinetic parameters of lebrikizumab estimated from the final model

Ethnicity	N	Body weight (kg)	Ka (1/day)	F	CL (L/day)	V2 (L)	$AUC_{\tau,ss}$ (μg▪day/mL)[a)]	$C_{max,ss}$ (μg/mL)[a)]	$C_{trough,ss}$ (μg/mL)[a)]
Japanese	297	64.3 (19)	0.331 (24)	0.822 (14)	0.140 (28)	2.93 (22)	1,470 (36)	67.7 (34)	33.7 (42)
Non-Japanese	1,829	73.3 (26)	0.328 (22)	0.822 (14)	0.159 (30)	4.16 (27)	1,290 (38)	57.2 (37)	32.0 (43)

Geometric mean (coefficient of variation [CV]%)

a) Pharmacokinetic parameters at steady state following multiple subcutaneous administration of lebrikizumab 250 mg Q4W

Table 23. Estimated C_{max} and C_{trough} following administration of lebrikizumab 250 mg Q2W/Q4W or Q4W/Q4W

Dosage regimen	Ethnicity	C_{max}		C_{trough}	
		Initial dose	Week 48	Week 2 or 4[a)]	Week 52
250 mg Q2W/Q4W	Japanese	70.1	61.1	60.6	30.2
	Non-Japanese	60.6	58.0	55.2	32.6
250 mg Q4W/Q4W	Japanese	72.4	62.2	39.1	30.9
	Non-Japanese	60.4	58.6	37.0	33.8

Median

a) Week 2 for 250 mg Q2W/Q4W administration, Week 4 for 250 mg Q4W/Q4W administration

6.2.4 Exposure-response analysis (CTD 5.3.3.5.3)

An exposure-response analysis was conducted using the change in EASI score from baseline to Week 16 obtained from the foreign clinical studies in pediatric (aged ≥12 years) and adult patients with AD[15)] and empirical Bayes estimate in individual subjects obtained from the preliminary population

13) In addition to the clinical study data used in the population pharmacokinetic analysis based on the results of the foreign clinical studies [Section 6.2.3.1], the data of the maintenance phase of the Japanese phase III study (Study KGAL) and the foreign phase III studies (Studies KGAB and KGAC) were included.

14) Effects of ethnicity (Japanese/non-Japanese) on Ka, F, CL, and V2 were investigated as possible covariates.

15) Only the data of up to Week 16 in the phase II studies (Studies KGAF and KGAG) in patients with AD and in the phase III studies (Studies KGAB, KGAC, and KGAD) in patients with AD were used.

pharmacokinetic analysis. EC_{50} was estimated to be 16.5 μg/mL [95% confidence interval (CI); 9.84, 27.6] from the final model.

Although body weight was identified as a covariate in the population pharmacokinetic analysis [see Section 6.2.3], it was not identified as such in the exposure-response analysis. The applicant therefore explained that the difference in pharmacokinetics due to body weight is not clinically significant from an efficacy perspective.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic difference in the pharmacokinetics of lebrikizumab

On the basis of the data submitted, PMDA has concluded that there is no clinically significant difference in the pharmacokinetics of lebrikizumab between the Japanese and non-Japanese subjects.

6.R.2 ADA

The applicant's explanation about the incidence of ADA in clinical studies,[16)] effects of ADA on the pharmacokinetics, efficacy, and safety of lebrikizumab:

Table 24 shows the incidence of ADA in the pooled population of the phase III studies (Studies KGAB, KGAC, KGAD [including subjects who proceeded from Study KGAD to Study KGAA], and KGAL). Table 25 shows the serum lebrikizumab concentration by expression of ADA, Table 26 shows the results of the efficacy endpoints, and Table 27 shows the incidence of adverse events. As a whole, the incidence rate of ADA and neutralizing antibodies was low. Although the serum lebrikizumab concentration in subjects positive for ADA or neutralizing antibody tended to be lower than in those negative for ADA or neutralizing antibody, the difference was within the variation among negative subjects. There was no clinically significant difference in the efficacy or safety of lebrikizumab between ADA or neutralizing antibody-positive subjects and negative subjects.

Table 24. Incidence of ADA (pooled population of phase III studies)

		Up to Week 16 (induction phase)		Up to Week 52/56/68[a)] (maintenance phase)[b)]			Entire administration period
Antibody expression		250 mg Q2W	250 mg Q4W	250 mg Q2W/Q2W	250 mg Q2W/Q4W	250 mg Q4W/Q4W	All combined[c)]
ADA	Negative	97.7 (799/818)	97.5 (79/81)	95.0 (228/240)	97.2 (173/178)	92.1 (35/38)	94.8 (1,204/1,270)
	Positive	1.8 (15/818)	2.5 (2/81)	4.2 (10/240)	2.2 (4/178)	7.9 (3/38)	3.9 (50/1,270)
Neutralizing antibody	Negative	97.7 (799/818)	97.5 (79/81)	95.0 (228/240)	97.2 (173/178)	92.1 (35/38)	95.1 (1,208/1,270)
	Positive	1.8 (15/818)	2.5 (2/81)	4.2 (10/240)	2.2 (4/178)	7.9 (3/38)	3.6 (46/1,270)

% (number of subjects)

a) Evaluation period for each study: Up to Week 52 in Studies KGAB and KGAC, up to Week 56 in Study KGAD (Study KGAA included), and up to Week 68 in Study KGAL

b) Responders at Week 16 who proceeded to the double-blind maintenance period

c) Subjects receiving at least 1 dose of lebrikizumab 250 mg

16) Subjects available with ADA data at baseline and at 1 or more time points after baseline were evaluated, and subjects who met either of the following definitions were regarded as ADA-positive. Subjects in whom neutralizing antibody was detected at least once during the study period were defined as neutralizing antibody-positive.
(a) Subjects who were ADA-positive at baseline and showed ≥4-fold higher antibody titer than the baseline value.
(b) Subjects who were ADA-negative at baseline and showed antibody titer >2-fold higher than the lower detection limit of immunogenicity assay after baseline

Table 25. Serum trough lebrikizumab concentration by expression of ADA (μg/mL) (pooled phase III studies)

Antibody expression		Week 16 (induction phase)		Week 52/56/68[a] (maintenance phase)[b]		
		250 mg Q2W	250 mg Q4W	250 mg Q2W/Q2W	250 mg Q2W/Q4W	250 mg Q4W/Q4W
ADA	Negative	90.1 ± 36.7 (728)	28.9 ± 12.3 (78)	88.3 ± 58.9 (185)	46.4 ± 31.1 (153)	42.9 ± 15.7 (33)
	Positive	77.7 ± 37.2 (14)	22.0, 25.8 (2)	74.5 ± 45.3 (10)	22.1 ± 9.10 (4)	28.1, 35.0 (2)
Neutralizing antibody	Negative	90.1 ± 36.7 (728)	28.9 ± 12.3 (78)	88.3 ± 58.9 (185)	46.4 ± 31.1 (153)	42.9 ± 15.7 (33)
	Positive	77.7 ± 37.2 (14)	22.0, 25.8 (2)	74.5 ± 45.3 (10)	22.1 ± 9.10 (4)	28.1, 35.0 (2)

Mean ± SD (number of subjects) or individual values

a) Evaluation time point for each study: Week 52 in Studies KGAB and KGAC, Week 44 in Study KGAD (Study KGAA included), and Week 68 in Study KGAL

b) Responders at Week 16 who proceeded to the double-blind maintenance period

Table 26. Efficacy of lebrikizumab by expression of ADA (pooled population of phase III studies)

	Antibody expression		Week 16 (induction phase)		Week 52/56/68[a] (maintenance phase)[b]		
			250 mg Q2W	250 mg Q4W	250 mg Q2W/Q2W	250 mg Q2W/Q4W	250 mg Q4W/Q4W
Percent achieving IGA (0/1)	ADA	Negative	43.0 (288/669)	29.3 (22/75)	82.8 (82/99)	82.7 (67/81)	68.4 (13/19)
		Positive	76.9 (10/13)	50.0 (1/2)	100 (6/6)	100 (4/4)	100 (1/1)
	Neutralizing antibody	Negative	43.0 (288/669)	29.3 (22/75)	82.8 (82/99)	82.7 (67/81)	68.4 (13/19)
		Positive	76.9 (10/13)	50.0 (1/2)	100 (6/6)	100 (4/4)	100 (1/1)
Percent achieving EASI-75	ADA	Negative	66.5 (445/669)	49.3 (37/75)	93.6 (131/140)	91.6 (120/131)	92.9 (26/28)
		Positive	76.9 (10/13)	50.0 (1/2)	100 (7/7)	100 (4/4)	100 (2/2)
	Neutralizing antibody	Negative	66.5 (445/669)	49.3 (37/75)	93.6 (131/140)	91.6 (120/131)	92.9 (26/28)
		Positive	76.9 (10/13)	50.0 (1/2)	100 (7/7)	100 (4/4)	100 (2/2)

% (number of subjects)

a) Evaluation time point for each study: Week 52 in Studies KGAB and KGAC, Week 56 in Study KGAD (Study KGAA included), and Week 68 in Study KGAL

b) Responders at Week 16 who proceeded to the double-blind maintenance period

Table 27. Safety of lebrikizumab by expression of ADA (pooled population of phase III studies)

		ADA		Neutralizing antibody	
		Positive	Negative	Positive	Negative
Subjects receiving lebrikizumab[a]	Number of subjects	50	1,204	46	1,208
	Total exposure period (person-years)	72.8	1,540	69.2	1,543
	All adverse events	37 (74.0) 122	839 (69.7) 131	34 (73.9) 116	842 (69.7) 131
	Hypersensitivity (SMQ)	13 (26.0) 21.4	239 (19.9) 18.1	13 (28.3) 22.7	239 (19.8) 18.1
	Injection site reaction (HLT)	3 (6.0) 4.3	44 (3.7) 2.9	3 (6.5) 4.5	44 (3.6) 2.9

Upper row, Number of subjects (%); Lower row, Number of events per 100 person-years adjusted for the total exposure period [b]

a) Subjects receiving ≥1 dose of lebrikizumab 250 mg

b) Total period up to the first occurrence of events (administration period in subjects without events)

PMDA's view:

Although the information so far available suggests that ADA does not pose clinically significant problems, a tendency of decrease in the exposure to lebrikizumab is observed in subjects with ADA. Immunogenicity should be included in important potential risks of the risk management plan (RMP), and information on the effect of the occurrence of ADA should be collected continuously after the market launch, and when new information become available, the information should be promptly provided to healthcare professionals. Also, information on the incidences of ADA in clinical studies of lebrikizumab should be stated in an appropriate manner in the package insert, etc.

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

The applicant submitted the main efficacy and safety evaluation data from 6 studies shown in Table 28.

Table 28. Main evaluation data on efficacy and safety

Region	Study code	Phase	Study population	No. of subjects enrolled	Dosage regimen	Main endpoints [Primary endpoint]
Foreign	DRM06-AD01 [Study KGAF] (monotherapy)	IIb	Patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or for whom topical drugs are not recommended for safety reason.	(a) 73 (b) 80 (c) 75 (d) 52	(a) Lebrikizumab 125 mg (initial dose 250 mg) Q4W (b) Lebrikizumab 250 mg (initial dose 500 mg) Q4W (c) Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W (d) Placebo Q2W	Efficacy and safety [Percentage change in EASI score from baseline to Week 16]
Foreign	DRM06-AD04 [Study KGAB] (monotherapy)	III	Patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or determination that topical treatments are otherwise medically inadvisable.	(a) 283 (b) 141	(a) Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W (b) Placebo Q2W	Efficacy and safety [Percentage of patients achieving IGA (0/1) and EASI-75 at Week 16]
Foreign	DRM06-AD05 [Study KGAC] (monotherapy)	III	Patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or determination that topical treatments are otherwise medically inadvisable.	(a) 295 (b) 150	(a) Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W (b) Placebo Q2W	
Foreign	DRM06-AD06 [Study KGAD] (TCS combination therapy[a)])	III	Patients with moderate to severe AD who had an inadequate response to topical agents such as TCS.	(a) 153 (b) 75	(a) Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W (b) Placebo Q2W	Efficacy and safety [Percentage of patients achieving IGA (0/1) and EASI-75 at Week 16]
Japan	Study KGAL (TCS combination therapy[b)])	III	Patients with moderate to severe AD who had an inadequate response to topical agents such as TCS.	(a) 81 (b) 123 (c) 82	(a) Lebrikizumab 250 mg (initial dose 500 mg) Q4W (b) Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W (c) Placebo Q2W	Efficacy and safety [Percentage of patients achieving IGA (0/1) and EASI-75 at Week 16]
Foreign	DRM06-AD07 [Study KGAA]	III	Patients with moderate to severe AD (those who completed the preceding study and newly enrolled patients)	(a) 858 (b) 141	(a) Lebrikizumab 250 mg Q2W (b) Lebrikizumab 250 mg Q4W	Safety

a) Medium-potency TCS (triamcinolone acetonide 0.1% cream), low-potency TCS (hydrocortisone 1% cream [use on sensitive skin], or TCI [use on sensitive skin])
b) Medium-potency TCS (hydrocortisone butyrate ointment 0.1% or corresponding TCS), low-potency TCS (prednisolone cream 0.5% or corresponding TCS [use on sensitive skin] or TCI [use on sensitive skin])

7.1 Phase II studies

7.1.1 Foreign clinical studies (lebrikizumab monotherapy study, CTD 5.3.5.1-3; Study J2T-DM-KGAF/DRM06-AD01 [January 2018 to May 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in the US to investigate the safety and efficacy of lebrikizumab and to evaluate the dose-response relationship of

lebrikizumab. The subjects enrolled were patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or for whom topical agents are not recommended for safety reason (Table 29) (target sample size, 275 subjects [75 in each lebrikizumab group, 50 in the placebo group]).

Table 29. Main inclusion/exclusion criteria

Main inclusion criteria 1. Subjects aged ≥18 years. 2. AD according to Hanifin and Rajka Criteria (1980) that has been present for ≥1 year before the screening visit 3. EASI score ≥16 at screening and at baseline. 4. IGA score ≥3 at screening and at baseline. 5. AD involvement on ≥10% of BSA at screening and at baseline. 6. Inadequate response to previous treatment with topical drugs, or determination that topical treatments are medically inadvisable due to significant adverse reactions or safety reasons. 7. Used a stable dose of topical moisturizing agent twice daily for ≥7 days prior to baseline. Main exclusion criteria 1. Has cutaneous comorbidities that may interfere with evaluation of the clinical study. 2. Treatment with the following prior to the baseline visit: B-cell-depleting biologics (e.g., rituximab) within 6 months; other biologics within 5 half-lives or 16 weeks, whichever is longer; dupilumab within 3 months; an investigational drug within 8 weeks or within 5 half-lives, whichever is longer; immunosuppressants/immunomodulators (systemic corticosteroid, cyclosporine, MMF, IFNγ, JAK inhibitor, azathioprine, MTX, etc.) as well as phototherapy and photochemotherapy (PUVA therapy) for AD within past 4 weeks; or TCS or TCI within past 1 week. 3. Regular use of tanning booth/tanning parlor within 4 weeks prior to screening (more than twice a week).

The study drug was administered subcutaneously for 16 weeks according to the following dosage regimen: (1) Lebrikizumab 125 mg (initial dose 250 mg) or 250 mg (initial dose 500 mg) Q4W or (2) lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) or placebo Q2W. A stable dose of topical moisturizing agent was used during the study period. During the study period, concomitant use of therapeutic agents against AD was prohibited, while rescue therapy[17] was allowed if necessary.

All of the 280 subjects who were randomized and received the study drug at least once (73 in the 125 mg Q4W group, 80 in the 250 mg Q4W group, 75 in the 250 mg Q2W group, and 52 in the placebo group) were included in the modified ITT (mITT) population and the safety analysis population, and the mITT population was handled as the efficacy analysis population.

The study was discontinued on or before Week 16 in 20.5% (15 of 73) of subjects in the 125 mg Q4W group, 22.5% (18 of 80) of subjects in the 250 mg Q4W group, 22.7% (17 of 75) of subjects in the 250 mg Q2W group, and in 55.8% (29 of 52) of subjects in the placebo group. The main reasons for the discontinuation was consent withdrawal (8.2% [6 of 73] of subjects in the 125 mg Q4W group, 8.8% [7 of 80] of subjects in the 250 mg Q4W group, 10.7% [8 of 75] of subjects in the 250 mg Q2W group, and 38.5% [20 of 52] of subjects in the placebo group), lost to follow-up (8.2% [6 of 73], 6.3% [5 of 80], 8.0% [6 of 75], 7.7% [4 of 52]), and adverse events (2.7% [2 of 73], 3.8% [3 of 80], 4.0% [3 of 75], 1.9% [1 of 52]), among others.

Table 30 shows the results of the percentage change in EASI score from baseline to Week 16, primary efficacy endpoint.

[17] As the rescue therapy, addition of TCS before the systemic treatment should be considered, and subjects who have received the rescue therapy with TCS were allowed to continue the study, with the TCS as short a period as possible. When a systemic therapy was needed as the rescue therapy, the study was discontinued.

Table 30. Percentage change in EASI score from baseline to Week 16 (mITT population, multiple imputation [MI])

	125 mg Q4W (n = 73)	250 mg Q4W (n = 80)	250 mg Q2W (n = 75)	Placebo Q2W (n = 52)
EASI score at baseline	29.85 ± 13.52 (73)	26.15 ± 10.13 (80)	25.48 ± 11.21 (75)	28.90 ± 11.79 (52)
EASI score at Week 16	11.55 ± 12.73 (59)	7.88 ± 9.42 (62)	6.61 ± 9.46 (59)	13.12 ± 12.88 (24)
Percentage change from baseline[a)]	−62.34 ± 37.27	−69.21 ± 38.28	−72.09 ± 37.23	−41.12 ± 56.50
Difference from placebo [95% CI][a)]	−21.22 [−38.6, −3.9]	−28.09 [−46.0, −10.2]	−30.97 [−48.3, −13.6]	

EASI score: Mean ± SD (number of subjects)
Missing values were imputed using multiple imputation.
a) Least squares mean, analysis of covariance using treatment group and baseline EASI score as covariates

Adverse events were observed in 57.5% (42 of 73) of subjects in the 125 mg Q4W group, 48.8% (39 of 80) of subjects in the 250 mg Q4W group, 61.3% (46 of 75) of subjects in the 250 mg Q2W group, and 46.2% (24 of 52) of subjects in the placebo group. Table 31 shows the main events.

No death occurred.

Serious adverse events were observed in 2.7% (2 of 73) of subjects in the 125 mg Q4W group (hernial eventration and periprosthetic fracture in 1 subject each), 2.7% (2 of 75) of subjects in the 250 mg Q2W group (chest pain and panic attack in 1 subject each), and 3.8% (2 of 52) of subjects in the placebo group (chronic obstructive pulmonary disease/oedema peripheral and pulmonary embolism in 1 subject each). Their causal relationship to the study drug was denied.

Adverse events leading to treatment discontinuation occurred in 2.7% (2 of 73) of subjects in the 125 mg Q4W group, 3.8% (3 of 80) of subjects in the 250 mg Q4W group, 5.3% (4 of 75) of subjects in the 250 mg Q2W group, and 1.9% (1 of 52) of subjects in the placebo group.

Adverse drug reactions occurred in 11.0% (8 of 73) of subjects in the 125 mg Q4W group, 18.8% (15 of 80) of subjects in the 250 mg Q4W group, 20.0% (15 of 75) of subjects in the 250 mg Q2W group, and 5.8% (3 of 52) of subjects in the placebo group.

Table 31. Adverse events reported by ≥2% of subjects in any group (safety analysis population)

Event	125 mg Q4W (n = 73)	250 mg Q4W (n = 80)	250 mg Q2W (n = 75)	Placebo (n = 52)
Upper respiratory tract infection	6 (8.2)	9 (11.3)	2 (2.7)	3 (5.8)
Nasopharyngitis	4 (5.5)	2 (2.5)	9 (12.0)	2 (3.8)
Headache	3 (4.1)	1 (1.3)	4 (5.3)	3 (5.8)
Anxiety	3 (4.1)	0	2 (2.7)	0
Back pain	3 (4.1)	0	1 (1.3)	0
Dermatitis atopic	2 (2.7)	2 (2.5)	0	3 (5.8)
Arthralgia	2 (2.7)	2 (2.5)	0	2 (3.8)
Oropharyngeal pain	2 (2.7)	1 (1.3)	2 (2.7)	0
Hypertension	2 (2.7)	0	1 (1.3)	0
Urinary tract infection	2 (2.7)	1 (1.3)	0	1 (1.9)
Cough	2 (2.7)	0	2 (2.7)	0
Urine leukocyte esterase positive	2 (2.7)	0	0	0
Abdominal pain	2 (2.7)	0	0	0
Bacterial vaginosis	2 (2.7)	0	0	0
ALT increased	1 (1.4)	2 (2.5)	2 (2.7)	0
Sinusitis	1 (1.4)	2 (2.5)	1 (1.3)	1 (1.9)
Oral herpes	1 (1.4)	2 (2.5)	1 (1.3)	0
Vomiting	1 (1.4)	2 (2.5)	0	0
Paraesthesia	1 (1.4)	2 (2.5)	0	0
Pruritus	1 (1.4)	1 (1.3)	2 (2.7)	0
Conjunctivitis	1 (1.4)	1 (1.3)	2 (2.7)	0
Dry eye	1 (1.4)	0	0	2 (3.8)
Fatigue	0	4 (5.0)	0	0
Injection site pain	0	3 (3.8)	4 (5.3)	1 (1.9)
Diarrhoea	0	3 (3.8)	1 (1.3)	0
Injection site erythema	0	2 (2.5)	3 (4.0)	1 (1.9)
Pharyngitis streptococcal	0	2 (2.5)	2 (2.7)	0
Oedema peripheral	0	2 (2.5)	1 (1.3)	1 (1.9)
Herpes zoster	0	2 (2.5)	1 (1.3)	0
Osteoarthritis	0	2 (2.5)	1 (1.3)	0
Rash	0	2 (2.5)	0	0
Dermatitis contact	0	1 (1.3)	3 (4.0)	0
Pyrexia	0	1 (1.3)	2 (2.7)	1 (1.9)
AST increased	0	1 (1.3)	2 (2.7)	0
Gastritis	0	0	2 (2.7)	0
Abdominal pain upper	0	0	2 (2.7)	0
Pain in extremity	0	0	2 (2.7)	0
Cellulitis	0	0	0	2 (3.8)

Number of subjects with events (%)

7.2 Phase III studies

7.2.1 Foreign clinical study (lebrikizumab monotherapy study; CTD 5.3.5.1-6, Study J2T-DM-KGAB/DRM06-AD04 [September 2019 to May 2022])

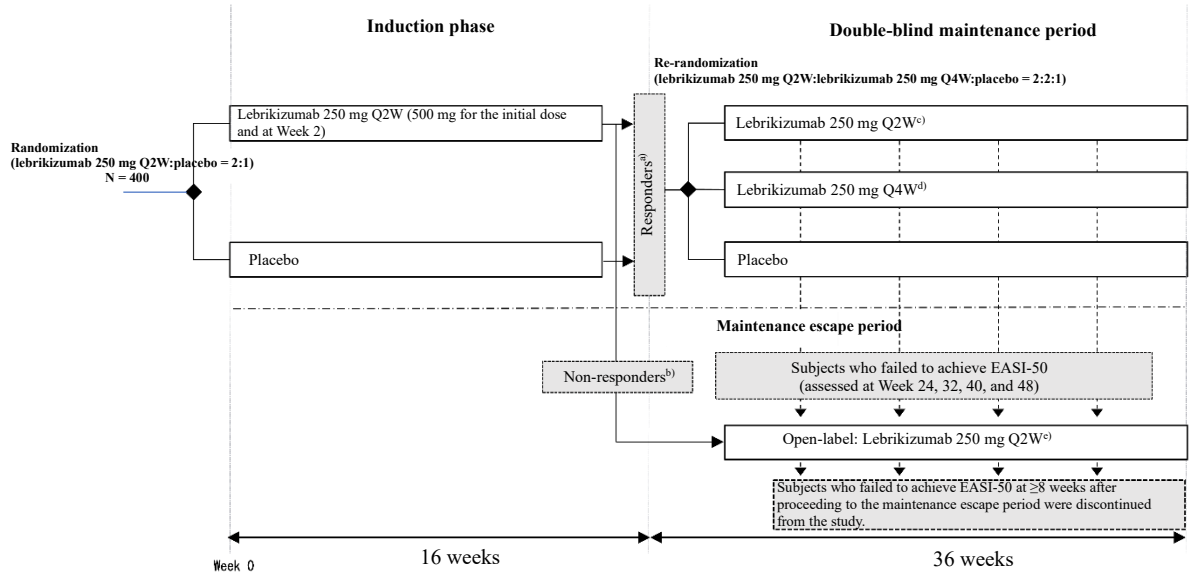
A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 10 countries or regions including the US, Poland, and Australia to investigate the superiority and safety of lebrikizumab monotherapy compared with placebo. The study subjects were patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or for whom topical drug treatment is medically inadvisable (Table 32) (target sample size, 400 subjects[18)] [allocated to the lebrikizumab group and the placebo group at a 2:1 ratio).

18) When it is assumed that (1) the expected value of achieving IGA (0/1) at Week 16 ,the primary endpoint, to be 34.7% and 7.7%, respectively, in the 250 mg Q2W group and the placebo group, and that (2) the expected value of achieving EASI-75 at Week 16 to be 48.0% and 11.5%, respectively, in the 250 mg Q2W group and the placebo group, the statistical power in the comparison between the 250 mg Q2W group (96 subjects) and the placebo group (48 subjects) is >95% for both endpoints under the two-sided significance level of 5%. In order to collect sufficient safety information and to ensure a sufficient number of responsive cases, the target sample size was approximately 400.

Table 32. Main inclusion/exclusion criteria

Main inclusion criteria
1. Subjects aged ≥18 years, or subjects aged ≥12 to <18 years weighing ≥40 kg.
2. AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year.
3. History of inadequate response to topical treatment; or determination that topical treatments are otherwise medically inadvisable.
4. Subjects with moderate to severe AD who meet the following criteria:
   - EASI score ≥16 at baseline
   - IGA score ≥3 at baseline
   - AD involvement on ≥10% of BSA at baseline
5. Used a stable dose of topical moisturizing agent at least twice daily or more for ≥7 days prior to baseline.

Main exclusion criteria
1. Has cutaneous comorbidities that may interfere with evaluation of the clinical study.
2. Prior treatment with dupilumab or tralokinumab.
3. Treatment with the following prior to the baseline visit: B-cell-depleting biologics (e.g., rituximab) within 6 months; other biologics within 5 half-lives or 16 weeks, whichever is longer; an investigational drug within 8 weeks or within 5 half-lives, whichever is longer; immunosuppressants/immunomodulators (systemic corticosteroid, cyclosporine, MMF, IFNγ, JAK inhibitor, azathioprine, MTX, etc.) as well as phototherapy and photochemotherapy (PUVA therapy) for AD within 4 weeks; or TCS, TCI, or topical PDE4 inhibitor within 1 week.
4. Regular use of tanning booth/tanning parlor within 4 weeks prior to screening (more than twice a week).



◆: Randomization
a) Subjects who did not receive rescue therapy during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16
b) Subjects who received rescue therapy during the induction phase or failed to achieve neither IGA (0/1) nor EASI-75 at Week 16
c) Only those subjects who were in the placebo group during the induction phase received subcutaneous administration of lebrikizumab 500 mg at Week 16 and Week 18
d) Only those subjects who were in the placebo group during the induction phase received subcutaneous administration of lebrikizumab 500 mg at Week 16
e) Only those subjects who received placebo before proceeding to the maintenance escape period received subcutaneous administration of lebrikizumab 500 mg at the time of and 2 weeks after proceeding to the maintenance escape period

Figure 2. Study design of Studies KGAB and KGAC

The study consisted of the induction phase (Week 0-16) and the double-blind maintenance period (Week 16-52). Subjects who had completed the 52-week administration period were allowed to proceed to the long-term extension study (Study KGAA/DRM06-AD07) for continuous administration (Figure 2).

During the induction phase, lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) or placebo was administered subcutaneously for 16 weeks Q2W. During the double-blind maintenance period, subjects who did not receive rescue therapy during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16 (responders) were re-randomized under blinded conditions to the 250 mg Q2W group, 250 mg Q4W group, or placebo group at a ratio of 2:2:1, and received lebrikizumab 250 mg Q2W,

lebrikizumab 250 mg Q4W, or placebo Q2W subcutaneously up to Week 52.[19] Subjects who failed to maintain EASI-50 at Week 24, 32, 40, or 48 during the double-blind maintenance period proceeded to the maintenance escape period and received subcutaneous administration of lebrikizumab 250 mg Q2W up to Week 52 under unblinded conditions.[20] Subjects who received rescue therapy or achieved neither IGA (0/1) nor EASI-75 (non-responders) at Week 16 proceeded to the maintenance escape period and subcutaneously received lebrikizumab 250 mg Q2W up to Week 52 under unblinded conditions.[20] Subjects who failed to achieve EASI-50 at Week 8 after proceeding to the maintenance escape period were discontinued from the study. During the study period, subjects were to use a stable dose of topical moisturizing agent. Co-administration of therapeutic drugs against AD was prohibited, but rescue therapy[21] was allowed when it was medically necessary, such as for unbearable symptoms, etc.

All of the 424 randomized subjects[22] (283 in the 250 mg Q2W group, 141 in the placebo group) were included in the intention to treat (ITT) population and handled as the efficacy analysis population. The safety analysis population in each phase was defined as follows.

- Induction phase, safety analysis population [induction phase]; 423 subjects (282 in the 250 mg Q2W group, 141 in the placebo group) who were randomized and received at least 1 dose of the study drug during the induction phase
- Entire administration period, entire lebrikizumab safety population; 399 subjects who were randomized and received at least 1 dose of lebrikizumab during the entire administration period

During the induction phase, study discontinuation occurred in 7.1% (20 of 283) of subjects in the 250 mg Q2W group and in 14.9% (21 of 141) of subjects in the placebo group. Main reasons for the discontinuation included protocol deviation (2.1% [6 of 283] of subjects in the 250 mg Q2W group, 3.5% [5 of 141] of subjects in the placebo group), lack of efficacy (0.7% [2 of 283], 5.0% [7 of 141]), and consent withdrawal (1.1% [3 of 283], 4.3% [6 of 141]), among others.

The percentage of patients achieving IGA (0/1) and EASI-75 [see Section 10 for definitions] at Week 16 were used as the coprimary efficacy endpoints. As shown in Table 33, a statistically significant difference was observed in both endpoints in the paired comparison between the placebo group and the 250 mg Q2W group, demonstrating the superiority of lebrikizumab 250 mg Q2W to placebo.

---

19) Subjects who received placebo during the induction phase and were re-randomized to the 250 mg Q2W group or the Q4W group during the double-blind maintenance period received the loading dose according to the re-randomized group (the 250 mg Q2W group, lebrikizumab 500 mg was administered subcutaneously at Week 16 and 18; 250 mg Q4W, lebrikizumab 500 mg was administered subcutaneously at Week 16).

20) Subjects receiving placebo before proceeding to the maintenance escape period received lebrikizumab 500 mg subcutaneously at the time of proceeding and 2 weeks after proceeding as the loading dose.

21) During the induction phase, topical treatment (e.g., medium-potency TCS) was used as the rescue therapy, but study drug was discontinued immediately if systemic rescue therapy (e.g., oral corticoid, phototherapy, cyclosporine) became necessary. Subjects who received systemic rescue therapy before Week 16 underwent a washout period ≥5 times the elimination half-life before proceeding to the maintenance escape period. During the double-blind maintenance period, intermittent use of topical drugs was allowed as a rescue therapy. Subjects requiring rescue therapy with a short-period systemic therapy were evaluated individually, and discussion with the medical expert of the sponsor was required before the start of the treatment. During the maintenance escape period, intermittent use of rescue therapy with a topical medicine was allowed, and subjects requiring a short-term systemic rescue therapy were evaluated individually. For these subjects, discussion with the medical expert of the sponsor was required before the start of the treatment. Subjects requiring a long-term systemic rescue therapy were to be discontinued from the study.

22) Stratified by region (US/EU/other), age (children [≥12 to <18 years]/adults [≥18 years]), and disease severity (IGA score 3/4).

Table 33. Results of primary efficacy endpoints (ITT population, MI)

	250 mg Q2W (n = 283)	Placebo (n = 141)
Percentage of patients achieving IGA (0/1) at Week 16	43.1 (122)	12.7 (18)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	29.7 [21.6, 37.8] <0.001	
Percentage of patients achieving EASI-75 at Week 16	58.8 (166)	16.2 (23)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	42.0 [33.3, 50.6] <0.001	

% (number of subjects). Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

a) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

b) Two-sided significance level of 5%, Cochran-Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors. A graphical approach was used to adjust for multiplicity in hypothesis testing [for details, see Section 10].

During the induction phase, adverse events were observed in 45.7% (129 of 282) of subjects in the 250 mg Q2W group and in 51.8% (73 of 141) of subjects in the placebo group. Table 34 shows the main adverse events.

No death occurred.

Serious adverse events were observed in 2.1% (6 of 282) of subjects in the 250 mg Q2W group (arthralgia, synovitis, myocardial infarction, oedema peripheral, accidental overdose, carpal tunnel syndrome in 1 subject each) and 0.7% (1 of 141) of subjects in the placebo group (cellulitis/sepsis). A causal relationship to the study drug could not be ruled out for arthralgia in 1 subject in the 250 mg Q2W group.

Adverse events leading to treatment discontinuation occurred in 1.1% (3 of 282) of subjects in the 250 mg Q2W group and in 0.7% (1 of 141) of subjects in the placebo group.

Adverse drug reactions were observed in 14.2% (40 of 282) of subjects in the 250 mg Q2W group and in 10.6% (15 of 141) of subjects in the placebo group.

Table 34. Adverse events reported by ≥2% of subjects in either group (safety analysis population [induction phase])

Event name	250 mg Q2W (n = 282)	Placebo (n = 141)
Conjunctivitis	21 (7.4)	4 (2.8)
Dermatitis atopic	16 (5.7)	30 (21.3)
Nasopharyngitis	11 (3.9)	4 (2.8)
Oral herpes	9 (3.2)	5 (3.5)
Headache	9 (3.2)	2 (1.4)
Conjunctivitis allergic	7 (2.5)	1 (0.7)
COVID-19	5 (1.8)	3 (2.1)
Pruritus	3 (1.1)	6 (4.3)
Dysmenorrhoea[a)]	3 (2.1)	0

Number of subjects with events (%)

a) Because of a women-specific event, the percentage was calculated using the number of female subjects as the denominator (141 subjects in the 250 mg Q2W group, 73 subjects in the placebo group)

During the entire administration period, adverse events were observed in 58.1% (232 of 399) of subjects in the entire lebrikizumab safety population. Table 35 shows the main adverse events.

No death occurred.

Serious adverse events were observed in 3.3% (13 of 399) of subjects (micromastia, arthritis, cholecystitis, accidental overdose, oedema peripheral, dysmenorrhoea, thermal burn, arthralgia, myocardial infarction, synovitis, somatic symptom disorder, carpal tunnel syndrome, and COVID-19 in 1 subject each). A causal relationship to the study drug could not be ruled out in 2 subjects (arthritis, arthralgia in 1 subject each).

Adverse events leading to treatment discontinuation occurred in 2.3% (9 of 399) of subjects.

Adverse drug reactions were observed in 20.8% (83 of 399) of subjects.

Table 35. Adverse events reported by ≥2% of subjects (entire administration period, entire lebrikizumab safety population)

Event name	Subjects receiving lebrikizumab (n = 399)
Conjunctivitis	33 (8.3)
Dermatitis atopic	31 (7.8)
Nasopharyngitis	27 (6.8)
COVID-19	24 (6.0)
Conjunctivitis allergic	22 (5.5)
Oral herpes	15 (3.8)
Headache	13 (3.3)
Dysmenorrhoea[a)]	4 (2.0)

Number of subjects with events (%)

a) Because of a women-specific event, the percentage was calculated using the number of female subjects (n = 196) as the denominator.

7.2.2 Foreign clinical study (lebrikizumab monotherapy study; CTD 5.3.5.1-7, Study J2T-DM-KGAC/DRM06-AD05 [October 2019 to April 2022])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 8 countries or regions including the US, Germany, and Taiwan to investigate the superiority and safety of lebrikizumab monotherapy to placebo. The subjects enrolled in the study were patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or for whom topical drug treatment is medically inadvisable (Table 32) (target sample size, 400 subjects[18)])[allocation ratio of lebrikizumab group and placebo group 2:1]).

This study was conducted according to the same study design as that of Study KGAB [see Section 7.2.1].

A total of 445 randomized subjects[22)] (295 in the 250 mg Q2W group, 150 in the placebo group) were included in the ITT population. However, upon identification of non-compliance with Good Clinical Practice (GCP) regarding assessment of baseline AD severity at 1 study site during post-blinding audit, the statistical analysis plan was revised. A total of 427 subjects (281 subjects in the 250 mg Q2W group, 146 subjects in the placebo group) excluding the subjects at the above study site were included in the mITT population, which was handled as the efficacy analysis population. The safety analysis population in each study phase was defined as follows:

- Induction phase, modified safety analysis population; Of 444 randomized subjects who received at least 1 dose of the study drug during the induction phase, 426 subjects (281 subjects in the 250 mg Q2W group, 145 subjects in the placebo group) were detected, excluding those at 1 study site with GCP noncompliance.
- Entire administration period, modified entire lebrikizumab safety analysis population; Of 423 randomized subjects who received at least 1 dose of lebrikizumab during the entire administration period, 407 subjects were detected, excluding those at 1 study site with GCP noncompliance.

During the induction phase, study discontinuation occurred in 7.8% (22 of 281) of subjects in the 250 mg Q2W group and in 11.0% (16 of 146) of subjects in the placebo group. The main reasons for the discontinuation were adverse events (2.1% [6 of 281] of subjects in the 250 mg Q2W group, 2.7% [4 of 146] of subjects in the placebo group), consent withdrawal (1.4% [4 of 281], 3.4% [5 of 146]), and protocol deviation (2.1% [6 of 281], none), among others.

The percentage of patients achieving IGA (0/1) and EASI-75 at Week 16 were used as the co-primary efficacy endpoints. As shown in Table 36, a statistically significant difference was observed in both endpoints in the paired comparison between the placebo group and the 250 mg Q2W group, demonstrating the superiority of lebrikizumab 250 mg Q2W to placebo.

Table 36. Results of primary efficacy endpoints (mITT population, MI)

	250 mg Q2W (n = 281)	Placebo (n = 146)
Percentage of patients achieving IGA (0/1) at Week 16	33.2 (93)	10.8 (16)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	21.9 [14.2, 29.6] <0.001	
Percentage of patients achieving EASI-75 at Week 16	52.1 (146)	18.1 (26)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	33.3 [24.4, 42.2] <0.001	

% (number of subjects). Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

a) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

b) Two-sided significance level of 5%, Cochran-Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors. A graphical approach was used to adjust for multiplicity in hypothesis testing [for details, see Section 10].

During the induction phase, adverse events were observed in 53.4% (150 of 281) of subjects in the 250 mg Q2W group and in 66.2% (96 of 145) of subjects in the placebo group. Table 37 shows the main adverse events.

Death occurred in 0.7% (1 of 145) of subjects in the placebo group (myocardial infarction). Its causal relationship to the study drug was denied.

Serious adverse events were observed in 0.7% (2 of 281) of subjects in the 250 mg Q2W group (cardiac failure/multiple injuries/dermatitis atopic, and large intestine infection/cerebellar syndrome in 1 subject each) and in 2.8% (4 of 145) of subjects in the placebo group (uterine leiomyoma, myocardial infarction,

fibula fracture/tibia fracture, and dermatitis atopic in 1 subject each). A causal relationship to the study drug could not be ruled out for cerebellar syndrome in 1 subject in the 250 mg Q2W group.

Adverse events leading to treatment discontinuation occurred in 3.2% (9 of 281) of subjects in the 250 mg Q2W group and in 2.8% (4 of 145) of subjects in the placebo group.

Adverse drug reactions were observed in 21.4% (60 of 281) of subjects in the 250 mg Q2W group and in 15.2% (22 of 145) of subjects in the placebo group.

Table 37. Adverse events reported by ≥2% of subjects in either group (modified safety analysis population [induction phase])

Event name	250 mg Q2W (n = 281)	Placebo (n = 145)
Dermatitis atopic	28 (10.0)	38 (26.2)
Conjunctivitis	21 (7.5)	3 (2.1)
Headache	14 (5.0)	6 (4.1)
Nasopharyngitis	14 (5.0)	3 (2.1)
Conjunctivitis allergic	7 (2.5)	2 (1.4)
Dry eye	7 (2.5)	0
Oral herpes	4 (1.4)	3 (2.1)
Acne	1 (0.4)	3 (2.1)
Folliculitis	1 (0.4)	3 (2.1)
Impetigo	0	3 (2.1)
Anxiety	0	3 (2.1)

Number of subjects with events (%)

During the entire administration period, adverse events were observed in 67.8% (276 of 407) of subjects in the modified entire lebrikizumab safety population. Table 38 shows the main adverse events.

Death occurred in 0.2% (1 of 407) of subjects (metastases to bone/metastases to liver/pancreatic carcinoma metastatic). A causal relationship to the study drug was denied.

Serious adverse events were observed in 2.7% (11 of 407) of subjects (dermatitis atopic in 3 subjects, hepatic steatosis, rhegmatogenous retinal detachment, pancreatitis, metastases to bone/metastases to liver/pancreatic carcinoma metastatic, humerus fracture/ulna fracture, cardiac failure/multiple injuries/dermatitis atopic/acarodermatitis/erysipelas/spinal osteoarthritis, paternal exposure during pregnancy, and large intestine infection/cerebellar syndrome in 1 subject each). A causal relationship to the study drug could not be ruled out for adverse events in 2 subjects (dermatitis atopic and cerebellar syndrome in 1 subject each).

Adverse events leading to treatment discontinuation occurred in 3.9% (16 of 407) of subjects.

Adverse drug reactions were observed in 28.0% (114 of 407) of subjects.

Table 38. Adverse events reported by ≥2% of subjects (entire administration period, modified entire lebrikizumab safety population)

Event name	Subjects receiving lebrikizumab (n = 407)
Dermatitis atopic	41 (10.1)
Nasopharyngitis	39 (9.6)
Conjunctivitis	33 (8.1)
Conjunctivitis allergic	26 (6.4)
Headache	23 (5.7)
COVID-19	14 (3.4)
Vaccination complication	14 (3.4)
Dry eye	13 (3.2)
Folliculitis	13 (3.2)
Oral herpes	12 (2.9)
Acne	10 (2.5)
Upper respiratory tract infection	8 (2.0)
Urinary tract infection	8 (2.0)
Arthralgia	8 (2.0)

Number of subjects with events (%)

7.2.3 Foreign clinical study (TCS combination study; CTD 5.3.5.1-5, Study J2T-DM-KGAD/DRM06-AD06 [February 2020 to September 2021])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in the US, Poland, Canada, and Germany to investigate the superiority and safety of lebrikizumab to placebo under co-administration with TCS in patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS (Table 39) (target sample size, 225 subjects[23)] [150 in the lebrikizumab group, 75 subjects in the placebo group]).

Table 39. Main inclusion/exclusion criteria

Main inclusion criteria
1. Subjects aged ≥18 years, or subjects aged ≥12 to <18 years weighing ≥40 kg.
2. AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year.
3. History of inadequate response to topical treatment.
4. AD involvement on ≥10% of BSA at baseline.
5. EASI score ≥16 at baseline.
6. IGA score ≥3 at baseline.
7. Used a stable dose of topical moisturizing agent at least twice daily for ≥7 days prior to baseline.

Main exclusion criteria
1. Has cutaneous comorbidities that may interfere with evaluation of the clinical study.
2. Treatment with the following prior to the baseline visit: B-cell-depleting biologics, (e.g., rituximab) within 6 months; other biologics within 5 half-lives or 16 weeks, whichever is longer; an investigational drug within 8 weeks or within 5 half-lives, whichever is longer; dupilumab within 8 weeks; immunosuppressants/immunomodulators (systemic corticosteroid, cyclosporine, MMF, IFNγ, JAK inhibitor, azathioprine, MTX, etc.) as well as phototherapy and photochemotherapy (PUVA therapy) for AD within 4 weeks; or TCS, TCI, or topical PDE4 inhibitor within 1 week.
3. Regular use of tanning booth/tanning parlor within 4 weeks prior to screening (more than twice a week).
4. Have had an important adverse reaction to TCS (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the investigator or attending physician that would prevent further use.

Lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) or placebo was administered subcutaneously Q2W for 16 weeks. Subjects who had completed the 16-week administration period were allowed to continue the administration in the long-term extension study (Study KGAA/DRM06-AD07). During the study period, subjects were to use a stable dose of topical moisturizing agent. TCS

23) When it is assumed that (1) the expected value of achieving IGA (0/1) at Week 16, the primary endpoint, to be 38% and 13%, respectively, in the 250 mg Q2W group and the placebo group, and that (2) the expected value of achieving EASI-75 at Week 16 to be 58% and 20%, respectively, in the 250 mg Q2W group and the placebo group, the statistical power in the comparison between the 250 mg Q2W group (150 subjects) and the placebo group (75 subjects) is >95% under the two-sided significance level of 5%.

therapy was started from baseline, but could be tapered, discontinued, or resumed as necessary.[24] Concomitant use of anti-AD therapy other than permitted topical agents such as TCS was prohibited, but rescue therapy[25] was allowed when it was medically necessary, such as for unbearable symptoms, etc.

A total of 228 randomized subjects[26] (153 in the 250 mg Q2W group, 75 in the placebo group) were included in the ITT population. However, upon identification of non-compliance with GCP regarding baseline AD severity assessment at 1 study site during post-blinding audit, the statistical analysis plan was revised. A total of 211 subjects (145 in the 250 mg Q2W group, 66 in the placebo group) excluding the subjects at the above study site were included in the mITT population, which was handled as the efficacy analysis population. Of 228 subjects who were randomized and received at least 1 dose of the study drug, 211 subjects (145 in the 250 mg Q2W group, 66 in the placebo group) were included in the modified safety analysis population and handled as the safety analysis population. The remaining subjects at 1 study site were excluded due to detection of GCP noncompliance.

Study discontinuation occurred in 7.6% (11 of 145) of subjects in the 250 mg Q2W group and in 12.1% (8 of 66) of subjects in the placebo group. The main reasons for the discontinuation were consent withdrawal (2.1% [3 of 145] of subjects in the 250 mg Q2W group, 6.1% [4 of 66] of subjects in the placebo group), lack of efficacy (2.1% [3 of 145], 1.5% [1 of 66]), and protocol deviation (1.4% [2 of 145], 3.0% [2 of 66]), among others.

The percentages of patients achieving IGA (0/1) and EASI-75 at Week 16 were used as the co-primary efficacy endpoints. As shown in Table 40, a statistically significant difference was observed in both endpoints in the paired comparison between the placebo group and the 250 mg Q2W group, demonstrating the superiority of lebrikizumab 250 mg Q2W to placebo.

Table 40. Results of primary efficacy endpoints (mITT population, MI)

	250 mg Q2W (n = 145)	Placebo (n = 66)
Percentage of patients achieving IGA (0/1) at Week 16	41.2 (60)	22.1 (15)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	18.3 [5.1, 31.5] 0.011	
Percentage of patients achieving EASI-75 at Week 16	69.5 (101)	42.2 (28)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	26.4 [12.1, 40.8] 0.011	

% (number of subjects). Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

a) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

b) Two-sided significance level of 5%, Cochran-Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors. A graphical approach was used to adjust for multiplicity in hypothesis testing [for details, see Section 10].

[24] Medium-potency TCS (triamcinolone acetonide 0.1% cream) was used as the concomitant therapy for the symptoms of AD. Low-potency TCS (hydrocortisone 1% cream) or TCI was to be used only on sensitive skin.

[25] High potency TCS (potency corresponding to very strong class and above according to the Japanese classification) or systemic therapy (oral corticoid, phototherapy, cyclosporin, etc.) was used as the rescue therapy. Lebrikizumab was to be discontinued immediately in subjects requiring systemic rescue therapy.

[26] Stratified by region (US/EU/other), age (children [≥12 to <18 years]/adults [≥18 years]), and disease severity (IGA score 3/4).

Adverse events were observed in 43.4% (63 of 145) of subjects in the 250 mg Q2W group and in 34.8% (23 of 66) of subjects in the placebo group. Table 41 shows the main adverse events.

No death occurred.

Serious adverse events were observed in 1.4% (2 of 145) of subjects in the 250 mg Q2W group (sinus node dysfunction and fall in 1 subject each) and in 1.5% (1 of 66) of subjects in the placebo group (dehydration/acute kidney injury). A causal relationship to the study drug was denied for all of them.

Adverse events leading to treatment discontinuation occurred in 2.1% (3 of 145) of subjects in the 250 mg Q2W group.

Adverse drug reactions were observed in 11.7% (17 of 145) of subjects in the 250 mg Q2W group and in 4.5% (3 of 66) of subjects in the placebo group.

Table 41. Adverse events reported by ≥2% of subjects in either group (modified safety analysis population)

Event name	250 mg Q2W (n = 145)	Placebo (n = 66)
Conjunctivitis	7 (4.8)	0
Headache	7 (4.8)	1 (1.5)
Hypertension	4 (2.8)	1 (1.5)
Nasopharyngitis	3 (2.1)	4 (6.1)
Dermatitis atopic	3 (2.1)	3 (4.5)
Dry eye	3 (2.1)	0
Upper respiratory tract infection	1 (0.7)	2 (3.0)

Number of subjects with events (%)

7.2.4 Japanese clinical study (TCS combination study; CTD 5.3.5.1-4, Study J2T-JE-KGAL [ongoing since March 2021 (data cut-off in ■ 2023)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japan to investigate the superiority and safety of lebrikizumab to placebo under co-administration with TCS in Japanese patients with moderate to severe AD who had an inadequate response to medium or higher potency TCS[27] (Table 42) (target sample size, 280 subjects[28] (80 in the 250 mg Q4W group, 120 in the 250 mg Q2W group, 80 in the placebo group) (Figure 3).

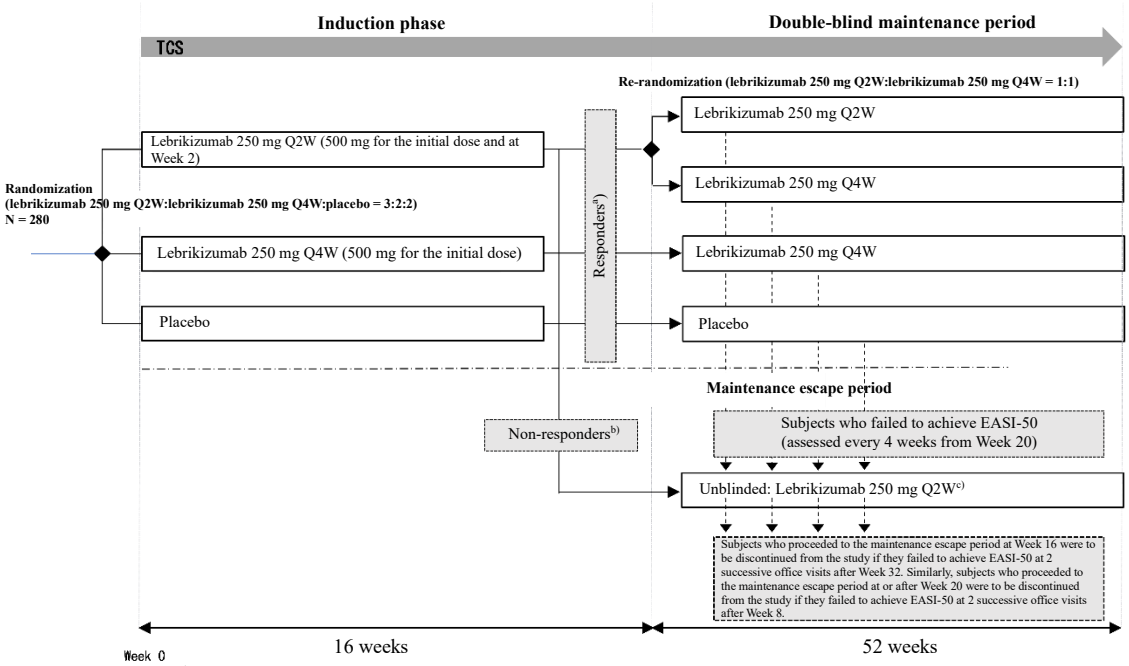
[27] Potency corresponding to medium to strong class and above according to the Japanese classification

[28] When it is assumed that (1) the expected value of achieving IGA (0/1) at Week 16, the primary endpoint, to be 38%, 33%, and 13%, respectively, in the 250 mg Q2W group, the 250 mg Q4W group, and the placebo group, and that (2) the expected value of achieving EASI-75 at Week 16 to be 58%, 53%, and 20%, respectively, in the 250 mg Q2W group, the 250 mg Q4W group, and the placebo group, the statistical power in the comparison between the 250 mg Q2W group (120 subjects) and the placebo group (80 subjects) and between the 250 mg Q4W group (80 subjects) and the placebo group (80 subjects) is >95% and >80%, respectively, under the two-sided significance level of 5%.

Table 42. Main inclusion/exclusion criteria

Main inclusion criteria
1. Subjects aged ≥12 years weighing ≥40 kg.
2. AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year.
3. Subjects who meet at least one of the following conditions with documented history by the attending physician and/or the investigator or sub-investigator of an inadequate response to conventional topical medications within 6 months before screening,
   a) Inability to achieve good disease control after use of at least a medium-potency[27)] TCS for at least 4 weeks, or for the maximum duration recommended by the package insert, whichever is shorter (regardless of concomitant use of TCI and/or topical JAK inhibitor)
   b) Not cured by systemic treatment with cyclosporine, MTX, azathioprine, MMF, etc., for the treatment of AD for 6 months before screening:
4. AD involvement on ≥10% of BSA at baseline
5. EASI score ≥16 at baseline
6. IGA score ≥3 at baseline

Main exclusion criteria
1. Has cutaneous comorbidities that may interfere with evaluation of the clinical study.
2. Treatment with the following prior to the baseline visit: B-cell-depleting biologics (e.g., rituximab) within 6 months; other biologics within 5 half-lives or 16 weeks, whichever is longer; an investigational drug within 8 weeks or within 5 half-lives, whichever is longer; dupilumab within 8 weeks; immunosuppressants/immunomodulators (systemic corticosteroid, cyclosporine, MMF, IFNγ, JAK inhibitor, azathioprine, MTX, etc.) as well as phototherapy and photochemotherapy (PUVA therapy) for AD within 4 weeks; or high potency[29)] TCS, topical JAK inhibitor or topical PDE4 inhibitor within 1 week.
3. Regular use of tanning parlor within 4 weeks prior to screening (more than twice a week).
4. Have had an important adverse reaction to TCS (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the investigator or attending physician that would prevent further use.



◆: Randomization
a) Subjects who did not receive rescue therapy during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16
b) Subjects who received rescue therapy during the induction phase or achieved neither of IGA (0/1) and EASI-75 at Week 16
c) Only those subjects who were in the placebo group during the induction phase received subcutaneous administration of lebrikizumab 500 mg at Week 16 and Week 18

Figure 3. Study design of Study KGAL

During the induction phase, lebrikizumab 250 mg (500 mg for the initial dose) Q4W, lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W, or placebo Q2W was administered subcutaneously for 16 weeks. During the double-blind maintenance period, subjects who did not receive

[29)] Potency corresponding to very strong class and above according to the Japanese classification.

rescue therapy[30] during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16 (responders) proceeded to the double-blind maintenance period under blinded conditions. Subjects who were in the 250 mg Q2W group during the induction phase were re-randomized to the 250 mg Q2W group or the 250 mg Q4W group in a 1:1 ratio, and subjects who were in the 250 mg Q4W or in the placebo group continued to receive the same dosage regimen as that in the induction phase. Subjects who received the rescue therapy or failed to achieve neither IGA (0/1) nor EASI-75 at Week 16 (non-responders) and subjects who failed to maintain EASI-50 during the double-blind maintenance period proceeded to the maintenance escape period and received lebrikizumab 250 mg subcutaneously Q2W up to Week 68 under open-label conditions.[31] Subjects who proceeded to the maintenance escape period at Week 16 were to be discontinued from the study if they failed to achieve EASI-50 at 2 successive office visits after Week 32. Similarly, subjects who proceeded to the maintenance escape period at Week 20 were to be discontinued from the study if they failed to achieve EASI-50 at 2 successive office visits at Week ≥8 after proceeding to the maintenance escape period.

A stable dose of topical moisturizing agent and TCS were to be used throughout the study period from ≥7 days before baseline. TCS therapy was allowed to be tapered, discontinued, or resumed as needed.[32] Concomitant use of anti-AD therapy other than permitted topical agents such as TCS was prohibited, but rescue therapy was allowed when it was medically necessary, such as for unbearable symptoms, etc.

All of the 286 randomized[33] subjects (81 in the 250 mg Q4W group, 123 in the 250 mg Q2W group, 82 in the placebo group) were included in the ITT population, which was handled as the efficacy analysis population. A total of 286 subjects (81 in the 250 mg Q4W group, 123 in the 250 mg Q2W group, 82 in the placebo group) who were randomized and received at least one dose of the study drug during the induction phase were included in the safety analysis population (induction phase), and a total of 276 subjects who were randomized and received at least one dose of lebrikizumab during the entire administration period including the induction phase, the double-blind maintenance period, and the maintenance escape period were included in the entire lebrikizumab safety population and handled as the safety analysis population.

During the induction phase, study discontinuation occurred in 1.2% (1 of 81) of subjects in the 250 mg Q4W group and in 2.4% (3 of 123) of subjects in the 250 mg Q2W group. Reasons for the discontinuation were adverse events (1.6% [2 of 123] of subjects in the 250 mg Q2W group) and consent withdrawal (1.2% [1 of 81] of subjects in the 250 mg Q4W group, 0.8% [1 of 123] of subjects in the 250 mg Q2W group).

---

30) In the induction phase, the first step in rescue therapy was treatment with high-potency TCS and, if systemic rescue therapy (oral corticoid, phototherapy, cyclosporin, etc.) became necessary, study drug administration was to be discontinued immediately. Subjects who received systemic rescue therapy before Week 16 were to undergo a withdrawal period lasting ≥5 half-lives of the systemic drug(s) used before proceeding to the maintenance escape period.
Intermittent use of high-potency TCS against AD was permitted as the rescue therapy during the double-blind maintenance period and the maintenance escape period. Subjects requiring a short-term systemic rescue therapy were evaluated individually. For these subjects, discussion with the medical expert of the sponsor was required before the start of the treatment. Subjects requiring a long-term systemic rescue therapy were to be discontinued from the study.

31) Subjects who were in the placebo group during the induction phase and proceeded to the maintenance escape period at Week 16 received lebrikizumab 500 mg subcutaneously at Week 16 and Week 18 as the loading dose.

32) Medium-potency TCS (hydrocortisone butyrate ointment 0.1% or equivalent TCS) was used as the combination therapy for symptoms of AD. Low-potency TCS (prednisolone cream 0.5% or equivalent TCS) or TCI was to be used only on sensitive skin. After baseline, tapering or discontinuation of combination therapy was allowed depending on the therapeutic response. If relapse or flares of AD lesions were observed, the combination therapy could be resumed based on the decision of the subject or investigator.

33) Stratified by age (children [≥12 to <18 years]/ adults [≥18 years]) and disease severity (IGA score 3/4).

The percentage of patients achieving IGA (0/1) and EASI-75 at Week 16 were used as the co-primary efficacy endpoints. As shown in Table 43, a statistically significant difference was observed in both endpoints in the paired comparison between the placebo group and the 250 mg Q4W group and between the placebo group and the 250 mg Q2W group, demonstrating the superiority of lebrikizumab 250 mg Q4W and Q2W to placebo.

Table 43. Results of primary efficacy endpoints (ITT population, MI)

	250 mg Q4W (n = 81)	250 mg Q2W (n = 123)	Placebo (n = 82)
Percentage of patients achieving IGA (0/1) at Week 16	29.1 (24)	33.4 (41)	6.1 (5)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	22.6 [11.6, 33.6] <0.001	27.3 [17.5, 37.0] <0.001	
Percentage of patients achieving EASI-75 at Week 16	47.2 (38)	51.2 (63)	13.4 (11)
Difference from placebo [95% CI][a)] Adjusted *P* value[b)]	33.2 [20.6, 45.8] <0.001	37.6 [26.2, 49.0] <0.001	

% (number of subjects). Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

a) Mantel-Haenszel test with age (≥12 to <18 years/≥18 years) and baseline disease severity (IGA score 3/4) as stratification factors.

b) Two-sided significance level of 5%, Cochran-Mantel-Haenszel test with age (≥12 to <18 years/≥18 years) and baseline disease severity (IGA score 3/4) as stratification factors. A graphical approach was used to adjust for multiplicity in hypothesis testing [for details, see Section 10].

During the induction phase, adverse events were observed in 60.5% (49 of 81) of subjects in the 250 mg Q4W group, 75.6% (93 of 123) of subjects in the 250 mg Q2W group, and 63.4% (52 of 82) of subjects in the placebo group. Table 44 shows the main events observed.

No death occurred.

Serious adverse events were observed in 0.8% (1 of 123) of subjects in the 250 mg Q2W group (cerebral infarction) and in 2.4% (2 of 82) of subjects in the placebo group (COVID-19 and Campylobacter gastroenteritis in 1 subject each). A causal relationship to the study drug was denied for all of them.

Adverse events leading to treatment discontinuation occurred in 1.6% (2 of 123) of subjects in the 250 mg Q2W group.

Adverse drug reactions were observed in 17.3% (14 of 81) of subjects in the 250 mg Q4W group, 25.2% (31 of 123) of subjects in the 250 mg Q2W group, and 13.4% (11 of 82) of subjects in the placebo group.

Table 44. Adverse events reported by ≥2% of subjects in any group (safety analysis population [induction phase])

Event name	250 mg Q4W (n = 81)	250 mg Q2W (n = 123)	Placebo (n = 82)	Event name	250 mg Q4W (n = 81)	250 mg Q2W (n = 123)	Placebo (n = 82)
Pyrexia	15 (18.5)	25 (20.3)	13 (15.9)	Skin infection	1 (1.2)	1 (0.8)	2 (2.4)
Conjunctivitis allergic	10 (12.3)	21 (17.1)	4 (4.9)	Dermatitis atopic	1 (1.2)	0	2 (2.4)
Conjunctivitis	5 (6.2)	12 (9.8)	2 (2.4)	Ligament sprain	1 (1.2)	0	2 (2.4)
Folliculitis	5 (6.2)	7 (5.7)	8 (9.8)	Chloasma[a)]	1 (4.0)	0	0
Nasopharyngitis	5 (6.2)	7 (5.7)	2 (2.4)	Endometriosis[a)]	1 (4.0)	0	0
Headache	3 (3.7)	4 (3.3)	9 (11.0)	Malaise	0	4 (3.3)	2 (2.4)
Vaccination site pain	3 (3.7)	4 (3.3)	4 (4.9)	Pain in extremity	0	4 (3.3)	0
Oral herpes	2 (2.5)	6 (4.9)	2 (2.4)	Injection site reaction	0	3 (2.4)	0
Acne	2 (2.5)	4 (3.3)	5 (6.1)	Rhinitis allergic	0	3 (2.4)	0
Diarrhoea	2 (2.5)	2 (1.6)	2 (2.4)	Dermatitis contact	0	3 (2.4)	0
Back pain	2 (2.5)	2 (1.6)	0	Dysmenorrhoea[a)]	0	2 (4.9)	0
COVID-19	2 (2.5)	1 (0.8)	3 (3.7)	Injection site pain	0	1 (0.8)	2 (2.4)
Urticaria	2 (2.5)	0	2 (2.4)	Skin abrasion	0	1 (0.8)	2 (2.4)
Eczema	2 (2.5)	0	0	Malassezia infection	0	1 (0.8)	2 (2.4)
Conjunctivitis bacterial	2 (2.5)	0	0	Dyslipidaemia	0	1 (0.8)	2 (2.4)
Hyperuricaemia	2 (2.5)	0	0	Cellulitis	0	0	3 (3.7)
Myalgia	1 (1.2)	5 (4.1)	0	Otitis externa	0	0	3 (3.7)
Eye pruritus	1 (1.2)	3 (2.4)	0	ALT increased	0	0	2 (2.4)
Arthralgia	1 (1.2)	3 (2.4)	0	AST increased	0	0	2 (2.4)
Skin papilloma	1 (1.2)	3 (2.4)	0	Vulvovaginal candidiasis[a)]	0	0	1 (4.2)
Dry eye	1 (1.2)	2 (1.6)	2 (2.4)	Menstruation irregular[a)]	0	0	1 (4.2)
Herpes simplex	1 (1.2)	1 (0.8)	2 (2.4)	Premenstrual headache[a)]	0	0	1 (4.2)

Number of subjects with events (%)

a) Because of a women-specific event, the percentage was calculated using the number of female subjects as the denominator (25 subjects in the 250 mg Q4W group, 41 subjects in the 250 mg Q2W group, 24 subjects in the placebo group).

During the entire administration period, adverse events were observed in 91.7% (253 of 276) of subjects in the entire lebrikizumab safety population. Table 45 shows the main adverse events.

No death occurred.

Serious adverse events were observed in 2.9% (8 of 276) of subjects (COVID-19, cerebral infarction, ligament injury, appendicitis, tonsillitis, anaphylactic reaction, tooth extraction, and Hodgkin's disease in 1 subject each). A causal relationship to the study drug could not be ruled out in 2 subjects (tonsillitis and anaphylactic reaction in 1 subject each).

Adverse events leading to treatment discontinuation occurred in 1.4% (4 of 276) of subjects.

Adverse drug reactions were observed in 35.5% (98 of 276) of subjects.

Table 45. Adverse events reported by ≥2% of subjects (entire administration period, entire lebrikizumab safety population)

Event name	Lebrikizumab (n = 276)	Event name	Lebrikizumab (n = 276)
Pyrexia	75 (27.2)	Vaccination site pain	9 (3.3)
Conjunctivitis allergic	58 (21.0)	Furuncle	8 (2.9)
COVID-19	56 (20.3)	Arthralgia	8 (2.9)
Nasopharyngitis	39 (14.1)	Tooth extraction	8 (2.9)
Acne	29 (10.5)	Dry eye	7 (2.5)
Folliculitis	28 (10.1)	Eye pruritus	7 (2.5)
Conjunctivitis	27 (9.8)	Herpes zoster	7 (2.5)
Back pain	22 (8.0)	Upper respiratory tract infection	7 (2.5)
Dental caries	21 (7.6)	Injection site erythema	7 (2.5)
Headache	21 (7.6)	Milia	7 (2.5)
Dysmenorrhoea[a)]	6 (7.0)	Diarrhoea	7 (2.5)
Herpes simplex	19 (6.9)	Ligament sprain	7 (2.5)
Oral herpes	15 (5.4)	Rhinitis allergic	7 (2.5)
Skin papilloma	15 (5.4)	Injection site reaction	6 (2.2)
Myalgia	12 (4.3)	Urticaria	6 (2.2)
Pain in extremity	10 (3.6)	Tenosynovitis	6 (2.2)
Post vaccination syndrome	10 (3.6)	Asthma	6 (2.2)
Malaise	9 (3.3)	Immunisation reaction	6 (2.2)

Number of subjects with events (%)

a) Because of a women-specific event, the percentage was calculated using the number of female subjects (n = 86) as the denominator

7.2.5 Long-term extension study (CTD 5.3.5.2-1; Study J2T-DM-KGAA/DRM06-AD07 [ongoing since June 2020 (data cut-off in [redacted] 20[redacted])])

A 100-week long-term extension study was conducted in 16 countries or regions including the US, Poland, and Canada to investigate the safety and efficacy of long-term treatment with lebrikizumab in patients with AD (target sample size, 1,000 subjects[34)]) including adults and children aged ≥12 years who had completed the preceding 5 studies[35)] (Table 46).

Table 46. Main inclusion/exclusion criteria (new subjects)

Main inclusion criteria
1. Subjects aged ≥18 years, or subjects ≥12 to <18 years weighing ≥40 kg.
2. AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year.
3. AD involvement on ≥10% of BSA at baseline.
4. EASI score ≥16 at baseline.
5. IGA score ≥3 at baseline.
6. History of inadequate response to topical treatment; or determination that topical treatments are medically inadvisable.

Main exclusion criteria
1. Has cutaneous comorbidities that interferes with evaluation of the clinical study.
2. Treatment with the following prior to the baseline visit: B-cell-depleting biologics (e.g., rituximab) within 6 months; an investigational drug or biologic within 8 weeks or within 5 half-lives, whichever is longer; immunosuppressants/immunomodulators (systemic corticosteroid, cyclosporine, MMF, IFNγ, JAK inhibitor, azathioprine, MTX, etc.) as well as phototherapy and photochemotherapy (PUVA therapy) for AD; regular use (more than twice a week) of tanning parlor within 4 weeks; or prescribed topical moisturizing agent, TCS, TCI, or topical PDE4 inhibitor within 1 week.

34) In addition to subjects who had completed the proceeding studies, approximately 100 subjects were newly enrolled.

35) Lebrikizumab monotherapy studies (Studies KGAB and KGAC), a TCS combination study (Study KGAD), an open-label, single-arm study to investigate the safety and efficacy of lebrikizumab in children with AD aged ≥12 years (Study KGAE), and a study to evaluate immune response in vaccinated adult patients with AD (Study KGAK). The data of the interim analysis submitted for the present application do not include those of subjects who proceeded from Study KGAK.

Subjects who proceeded from the preceding study received subcutaneously lebrikizumab 250 mg Q2W or Q4W in accordance with the treatment they had received in the preceding study.[36)] Newly enrolled subjects received subcutaneously lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W under open-label condition. Subjects were to make the study site visit at Weeks 2, 4, 16 and at every 12 weeks thereafter for safety and efficacy evaluation. Subjects unable to achieve EASI-50 at Week 16 of study using the baseline in the preceding study as the starting point of reference, subjects who failed to maintain EASI-50, and subjects determined by the investigator to have not obtained sufficient clinical benefit were discontinued from the study.

During the study period, subjects were to use a stable dose of topical moisturizing agent and were allowed to use TCS, TCI, and topical PDE4-inhibitor intermittently. Among subjects who proceeded from Study KGAD, subjects who used TCS at the end of the preceding study were allowed to taper, discontinue, or resume TCS as needed. Concomitant use of anti-AD therapy other than permitted topical agents such as TCS was prohibited.

A total of 999 subjects assigned to the study (141 in the 250 mg Q4W group, 858 in the 250 mg Q2W group) were included in the ITT population. However, upon identification of non-compliance with GCP regarding baseline AD severity assessment at 1 study site, the statistical analysis plan was revised. A total of 979 subjects (141 in the 250 mg Q4W group, 838 in the 250 mg Q2W group) excluding those at the above study site were included in the mITT population, which was handled as the efficacy analysis population. Of 999 subjects who received at least 1 dose of the study drug, 979 subjects (141 in the 250 mg Q4W group, 838 in the 250 mg Q2W group) were included in the modified safety analysis population and handled as the safety analysis population. The remaining subjects at 1 study site, where GCP noncompliance was detected, were excluded.

Study discontinuation before the cut-off date occurred in 8.5% (12 of 141) of subjects in the 250 mg Q4W group and in 15.6% (131 of 838) of subjects in the 250 mg Q2W group. Reasons for the discontinuation were consent withdrawal (2.8% [4 of 141] of subjects in the 250 mg Q4W group, 6.1% [51 of 838] of subjects in the 250 mg Q2W group) and adverse events (0.7% [1 of 141], 3.3% [28 of 838]), among others.

---

36) [Subjects who proceeded from Study KGAB or KGAC]
Subjects re-randomized to lebrikizumab 250 mg Q2W or Q4W during the double-blind maintenance period of the preceding study continued the treatment at the same dosage regimen as that in the preceding study under blinded conditions. Subjects who received placebo during the double-blind maintenance period of the preceding study received lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W under blinded conditions. Subjects who proceeded to the maintenance escape period in the preceding study continued lebrikizumab 250 mg Q2W under open-label conditions.
[Subjects who proceeded from Study KGAD]
Subjects who were assigned to lebrikizumab 250 mg Q2W group in the preceding study, did not receive rescue therapy up to Week 16, and achieved IGA (0/1) or EASI-75 (responders) were assigned to the 250 mg Q2W group or the 250 mg Q4W group in a ratio of 2:1, and received lebrikizumab according to the respective dosage regimen under blinded conditions. Subjects who achieved neither IGA (0/1) nor EASI-75 at Week 16 (non-responders) and subjects who received rescue therapy before Week 16 received lebrikizumab 250 mg Q2W under blinded conditions. Subjects assigned to the placebo group received lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W under blinded conditions.
[Subjects who proceeded from Study KGAE]
All subjects received lebrikizumab 250 mg Q2W under open-label conditions.
[Subjects who proceeded from Study KGAK]
Subjects who received lebrikizumab 250 mg Q2W in the preceding study continued the treatment at the same dosage regimen under blinded conditions, and subjects who received placebo received lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W under blinded conditions.

Adverse events were observed in 37.6% (53 of 141) of subjects in the 250 mg Q4W group and in 43.3% (363 of 838) of subjects in the 250 mg Q2W group. Table 47 shows the main adverse events.

Death occurred in 0.1% (1 of 838) of subjects in the 250 mg Q2W group (death). Its causal relationship to the study drug was denied.

Serious adverse events were observed in 1.4% (2 of 141) of subjects in the 250 mg Q4W group (hip fracture and depression in 1 subject each) and in 2.5% (21 of 838) of subjects in the 250 mg Q2W group (death, influenza like illness, bacteraemia/small intestinal obstruction, COVID-19, pneumonia, hip fracture, ankle fracture, road traffic accident, subdural haematoma, cervical cord compression, seizure/hypokalaemia, transient ischaemic attack, prostate cancer, endometrial adenocarcinoma, ovarian germ cell teratoma benign, invasive breast carcinoma, neuroendocrine tumour, depression suicidal, cataract/sudden visual loss, blood potassium decreased, and Stevens-Johnson syndrome in 1 subject each). A causal relationship to the study drug could not be ruled out for invasive breast carcinoma in 1 subject in the 250 mg Q2W group.

Adverse events leading to treatment discontinuation were observed in 0.7% (1 of 141) of subjects in the 250 mg Q4W group and in 3.3% (28 of 838) of subjects in the 250 mg Q2W group.

Adverse drug reactions were observed in 7.1% (10 of 141) of subjects in the 250 mg Q4W group and in 7.9% (66 of 838) of subjects in the 250 mg Q2W group.

Table 47. Adverse events reported by ≥1% of subjects in either group (modified safety analysis population)

Event name	250 mg Q4W (n = 141)	250 mg Q2W (n = 838)	Event name	250 mg Q4W (n = 141)	250 mg Q2W (n = 838)
COVID-19	10 (7.1)	64 (7.6)	Vulvovaginal candidiasis[a)]	1 (1.2)	1 (0.2)
Nasopharyngitis	7 (5.0)	41 (4.9)	Dysmenorrhoea[a)]	1 (1.2)	1 (0.2)
Dermatitis atopic	6 (4.3)	22 (2.6)	Vaginal discharge[a)]	1 (1.2)	0
Conjunctivitis	2 (1.4)	22 (2.6)	Upper respiratory tract infection	1 (0.7)	16 (1.9)
Conjunctivitis allergic	2 (1.4)	9 (1.1)	Urinary tract infection	1 (0.7)	11 (1.3)
Headache	2 (1.4)	9 (1.1)	Injection site reaction	1 (0.7)	9 (1.1)
Dermatitis contact	2 (1.4)	3 (0.4)	Oral herpes	0	12 (1.4)
Weight decreased	2 (1.4)	0	Hypertension	0	9 (1.1)
Vaginosis bacterial[a)]	1 (1.2)	1 (0.2)	Arthralgia	0	8 (1.0)

Number of subjects with events (%)

a) Because of a women-specific event, the percentage was calculated using the number of female subjects as the denominator (82 subjects in the 250 mg Q4W group, 418 subjects in the 250 mg Q2W group).

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of lebrikizumab:

It was considered appropriate to evaluate the efficacy and safety of lebrikizumab in Japanese patients with AD based on the clinical data package focused on Study KGAL, the Japanese phase III study investigating the efficacy and safety of lebrikizumab in Japanese patients with moderate to severe AD under co-administration with TCS. Since there is no significant difference in the pathogenesis, pathophysiology, diagnostic criteria, or treatment algorithm for AD between Japan and foreign countries (Clinical Practice Guidelines for AD 2021, *J Am Acad Dermatol.* 2014;70:338-51, *J Eur Acad Dermatol Venereol.* 2018;32:657-82 [published correction appears in *J Eur Acad Dermatol Venereol.*

2019;33:1436]) and there is no clear ethnic difference in the pharmacokinetics of lebrikizumab [see Sections 6.2.1.1 and 6.2.3], results of the foreign phase II study (Study KGAF) and the foreign phase III studies (Studies KGAB, KGAC, KGAD, and KGAA) may be used for interpreting the efficacy and safety of lebrikizumab in Japanese patients with AD.

"Study population," "efficacy endpoint and evaluation time point," "dosage regimen," and "concomitant drugs" in Study KGAL, the Japanese phase III study of lebrikizumab in patients with AD, were defined as shown below.

- Study percentage Taking account of the treatment algorithm for AD, Study KGAL was conducted in patients with AD requiring systemic therapy, i.e., patients with AD who had an inadequate response to topical treatment with TCS or to systemic therapy such as cyclosporin, methotrexate (MTX), azathioprine, and mycophenolate mofetil (MMF) and had a certain level of disease activity (lesion site ≥10% of body surface area [BSA], EASI score ≥16, IGA score ≥3). Since the pathology, clinical symptoms, diagnosis, treatment algorithm, etc., of AD are similar between adult patients and pediatric patients aged ≥12 years (Clinical Practice Guidelines for AD 2018), children aged ≥12 years were included in Study KGAL. On the basis of the results of the simulation using the population pharmacokinetic analysis model (*Pulm Pharmacol Ther.* 2017;46:88-98) constructed by using the serum lebrikizumab concentration data of 2,259 healthy adults and patients with asthma (18-75 years of age [median age 49], body weight 40-141 kg [median weight 79 kg]) available at the time point of the study planning, pediatric patients with AD aged ≥12 years with body weight of ≥40 kg were selected as a population that could be treated with the same dosage regimen as adults.

- Efficacy endpoint and evaluation time point

Since the objective of treatment of AD is to reduce the signs and symptoms of AD (Clinical Practice Guidelines for AD 2018), IGA and EASI, the 2 parameters commonly used in Japan and foreign countries as the indices for assessing skin lesions in the development of agents for AD, were used as the co-primary endpoints, and the evaluation time point was Week 16, as in the preceding phase III studies conducted overseas in advance (Studies KGAB, KGAC, and KGAD). Itch numeric rating scale (NRS) score was also used as the secondary endpoint for assessing itching, an important subjective symptom of AD.

- Dosage regimen

On the basis of the fact that there was no clear ethnic difference in the pharmacokinetics of lebrikizumab in Study KGAZ [see Section 6.2.1.1], the dosage regimen for the Japanese phase III study (Study KGAL) was determined by referring to the dosage regimens of the foreign phase II study (Study KGAF) and the phase III studies (Studies KGAB, KGAC, and KGAD) that had been conducted in advance in foreign countries. The 2 dosage regimens (lebrikizumab 250 mg Q4W [500 mg for the initial dose] and lebrikizumab 250 mg Q2W [500 mg for the initial dose and at Week 2] for which the efficacy was suggested in Study KGAF, were selected as the dosage regimen during the induction phase up to Week 16. In the double-blind maintenance period following the induction phase, subjects continued to receive the study drug according to the dosage regimen in the induction phase and subjects who had been in the 250 mg Q2W group during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16

(responders) were re-randomized to receive lebrikizumab 250 mg Q2W or Q4W to investigate the dosage regimen for maintaining the improving effect obtained in the induction phase. (see Figure 3).

- Concomitant drugs

The basic drug treatment for AD is control of the disease with topical anti-inflammatory drugs such as TCS and TCI with continuous use of topical skin moisturizer, and lebrikizumab is used in combination with these topical drugs in clinical settings as well. The Japanese phase III study (Study KGAL), accordingly, investigated the efficacy and safety of lebrikizumab in combination with TCS. Thus, a stable amount of topical skin moisturizer and TCS were co-administered throughout the study period starting from ≥7 days before baseline, and TCS therapy was allowed to be tapered, discontinued, or resumed as needed.

PMDA accepted the above explanation and concluded that it is acceptable to evaluate the efficacy and safety of lebrikizumab in patients with AD based on the submitted clinical data package, focusing on the results of the Japanese phase III study (Study KGAL).

7.R.2 Efficacy

7.R.2.1 Change in statistical analysis plan of foreign phase III studies (Studies KGAC and KGAD)

The applicant's explanation about the background that led to the change in the statistical analysis plan after unblinding [see Sections 7.2.2 and 7.2.3] in the foreign phase III studies (Studies KGAC and KGAD):

After the data lock and unblinding for the primary analysis at Week 16 in Study KGAD, the data were analyzed individually by multiple unblinded statisticians according to the usual procedures and subjected to data validation to share and confirm the results of the analysis, but IGA score at Week 16 was found to be 1 in all subjects at 1 study site, a statistically unlikely situation. Similar problems did not occur at any other study sites. Blinded review by personnel not involved in the study found that IGA scores were identical at multiple time points for all subjects in Study KGAC and nearly all subjects in Study KGAD, who participated from the study site. Results of the audit of the study site confirmed GCP violation that subjects who failed to meet the inclusion criteria related to baseline IGA score were enrolled in the study. On the basis of the above situation, it was decided by the personnel not involved in the study to exclude all subjects at the pertinent study site from efficacy and safety analysis. The statistical analysis plans of both studies were revised to reflect this decision by independent statistical analysts not involved in the development of lebrikizumab. Before the unblinding of Study KGAA, it was decided that subjects excluded from Studies KGAC and KGAD were to be excluded from the data analysis of Study KGAA as well. The statistical analysis plan was revised to reflect this decision by the statistical analyst of the study.

As mentioned above, given that exhaustive data validation has identified facilities with GCP violation, it is considered appropriate to evaluate the efficacy of lebrikizumab in patients with AD based on the results of the mITT population, which excludes cases from facilities with GCP violations, as the efficacy analysis population. Table 48 shows the results for the ITT population based on the original statistical analysis plan for Studies KGAC and KGAD. Although no statistically significant difference was

detected in the percentage of patients achieving IGA (0/1) in Study KGAD, other endpoints were generally consistent with the mITT population results after the change in statistical analysis plan (Tables 36 and 40).

Table 48. Results of primary endpoints before change in statistical analysis plan (ITT population, MI)

Study KGAC (foreign study, lebrikizumab alone)	250 mg Q2W (n = 295)	Placebo (n = 150)
Percentage of patients achieving IGA (0/1) at Week 16	34.7 (102)	12.7 (19)
Difference from placebo [95% CI],[a] *P* value[b]	21.6 [13.8, 29.4], *P* < 0.001	
Percentage of patients achieving EASI-75 at Week 16	54.4 (160)	19.7 (30)
Difference from placebo [95% CI],[a] *P* value[b]	34.2 [25.4, 43.1], *P* < 0.001	
Study KGAD (foreign study, combination with TCS)	250 mg Q2W (n = 153)	Placebo (n = 75)
Percentage of patients achieving IGA (0/1) at Week 16	44.3 (68)	32.1 (24)
Difference from placebo [95% CI],[a] *P* value[b]	11.3 [−2.4, 25.0], *P* = 0.110	
Percentage of patients achieving EASI-75 at Week 16	71.2 (109)	49.8 (37)
Difference from placebo [95% CI],[a] *P* value[b]	21.0 [7.5, 28.6], —[c]	

% (number of subjects). Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

a) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

b) Two-sided significance level of 5%, Cochran-Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

c) In Study KGAD, no statistically significant difference was observed in the percentage of patients achieving IGA (0/1) at Week 16. Accordingly, no formal hypothesis testing was conducted on the percentage of patients achieving EASI-75 at Week 16.

PMDA's view:

Changes in statistical analysis plan after unblinding raise questions about interpretation of results. However, given that exhaustive data validation identified sites with GCP violation, and that it is understandable to exclude unreliable data confirmed by facility audits from the analysis, the mITT population can be used for the analysis of efficacy of lebrikizumab in patients with AD in Studies KGAC and KGAD.

7.R.2.2 Efficacy of lebrikizumab

The applicant's explanation about the efficacy of lebrikizumab against AD:

In Study KGAL investigating the efficacy and safety of lebrikizumab in combination with TCS in Japanese patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS [see Section 7.2.4], statistically significant differences were observed between the placebo group and the 250 mg Q2W and between the placebo group and 250 mg Q4W groups in each pairwise comparison of the percentage of patients achieving IGA (0/1) and EASI-75 at Week 16, co-primary endpoints, demonstrating the superiority of both lebrikizumab 250 mg Q2W and 250 mg Q4W to placebo (Table 43). The foreign Study KGAD conducted in combination with TCS also demonstrated the superiority of lebrikizumab 250 mg Q2W to placebo (Table 40). Results of analysis based on the non-responder imputation (NRI) method, which was conducted to assess the effect of the difference in the method for imputing missing values on the efficacy evaluation, provided results similar to those of the main analyses in both studies (Table 49). Results of other main efficacy endpoints in the 250 mg Q2W and 250 mg Q4W groups showed a trend toward improvement over the placebo group in all endpoints and at all time points evaluated (Table 50).

Table 49. Results of supplementary analysis of primary endpoints (TCS combination study, ITT population/mITT population,[a] NRI)

	250 mg Q4W	250 mg Q2W	Placebo
Study KGAL (Japanese study)			
Percentage of patients achieving IGA (0/1) at Week 16	28.4 (23/81)	32.5 (40/123)	6.1 (5/82)
Difference from placebo [95% CI][b]	21.9 [11.0, 32.8]	26.4 [16.7, 36.0]	
Percentage of patients achieving EASI-75 at Week 16	46.9 (38/81)	50.4 (62/123)	13.4 (11/82)
Difference from placebo [95% CI][b]	32.9 [20.3, 45.5]	36.8 [25.5, 48.1]	
Study KGAD (foreign study)			
Percentage of patients achieving IGA (0/1) at Week 16		39.3 (57/145)	19.7 (13/66)
Difference from placebo [95% CI][c]		18.8 [6.7, 30.9]	
Percentage of patients achieving EASI-75 at Week 16		66.9 (97/145)	39.4 (26/66)
Difference from placebo [95% CI][c]		26.6 [12.9, 40.4]	

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, or had missing data.

a) ITT population in Study KGAL and mITT population in Study KGAD were handled as the population for analysis.

b) Mantel-Haenszel test with age (≥12 to <18 years/≥18 years) and baseline disease severity (IGA score 3/4) as stratification factors.

c) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

Table 50. Main efficacy endpoints (TCS combination study, ITT population/mITT population,[a] NRI)

		Study KGAL (Japanese study)			Study KGAD (foreign study)	
Endpoint	Week	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q2W	Placebo
Percentage of patients achieving IGA (0/1)	2	4.9 (4/81)	2.4 (3/123)	0 (0/82)	1.4 (2/145)	6.1 (4/66)
	4	7.4 (6/81)	8.9 (11/123)	3.7 (3/82)	11.7 (17/145)	6.1 (4/66)
	8	16.0 (13/81)	19.5 (24/123)	4.9 (4/82)	29.0 (42/145)	7.6 (5/66)
	16	28.4 (23/81)	32.5 (40/123)	6.1 (5/82)	39.3 (57/145)	19.7 (13/66)
Percentage of patients achieving EASI-75	2	7.4 (6/81)	8.9 (11/123)	4.9 (4/82)	8.3 (12/145)	6.1 (4/66)
	4	28.4 (23/81)	21.1 (26/123)	14.6 (12/82)	23.4 (34/145)	9.1 (6/66)
	8	38.3 (31/81)	43.9 (54/123)	15.9 (13/82)	55.2 (80/145)	24.2 (16/66)
	16	46.9 (38/81)	50.4 (62/123)	13.4 (11/82)	66.9 (97/145)	39.4 (26/66)
Percentage of patients achieving EASI-50	2	32.1 (26/81)	27.6 (34/123)	15.9 (13/82)	29.0 (42/145)	19.7 (13/66)
	4	53.1 (43/81)	59.3 (73/123)	24.4 (20/82)	53.1 (77/145)	34.8 (23/66)
	8	66.7 (54/81)	74.8 (92/123)	24.4 (20/82)	75.9 (110/145)	47.0 (31/66)
	16	75.3 (61/81)	80.5 (99/123)	31.7 (26/82)	80.0 (116/145)	56.1 (37/66)
Percentage of patients achieving EASI-90	2	2.5 (2/81)	1.6 (2/123)	1.2 (1/82)	2.8 (4/145)	4.5 (3/66)
	4	8.6 (7/81)	6.5 (8/123)	4.9 (4/82)	10.3 (15/145)	6.1 (4/66)
	8	17.3 (14/81)	22.0 (27/123)	8.5 (7/82)	26.9 (39/145)	10.6 (7/66)
	16	28.4 (23/81)	34.1 (42/123)	9.8 (8/82)	39.3 (57/145)	19.7 (13/66)
Percentage of patients with pruritus NRS ≥4-points improvement[b]	2	1.7 (1/59)	3.8 (3/80)	0 (0/60)	8.5 (11/130)	7.0 (4/57)
	4	8.5 (5/59)	16.3 (13/80)	0 (0/60)	22.3 (29/130)	8.8 (5/57)
	8	11.9 (7/59)	31.3 (25/80)	1.7 (1/60)	34.6 (45/130)	17.5 (10/57)
	16	23.7 (14/59)	32.5 (26/80)	3.3 (2/60)	45.4 (59/130)	26.3 (15/57)

% (number of subjects), Shaded area indicates data at the main evaluation point.
Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, or had missing data.

a) ITT population in Study KGAL and mITT population in Study KGAD were handled as the population for analysis.

b) Subjects with baseline pruritus NRS score of ≥4 were included in the evaluation.

In addition, in Studies KGAB and KGAC [see Sections 7.2.1 and 7.2.2] which investigated the efficacy and safety of lebrikizumab monotherapy in non-Japanese patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS or for whom topical agents are not recommended for safety reason, superiority of lebrikizumab 250 mg Q2W to placebo was confirmed (Tables 33 and 36). Results of analysis based on the NRI method, which was conducted to assess the effect of the difference in the imputing method for missing values on the efficacy evaluation, provided results similar to those of the main analyses in both studies (Table 51). Results of other main efficacy

endpoints also showed a tendency of improvement in the 250 mg Q2W group over the placebo group (Table 52).

Table 51. Results of complementary analysis of primary endpoints (lebrikizumab monotherapy study, ITT population/mITT population,[a] NRI)

	250 mg Q2W	Placebo
Study KGAB (foreign study)		
Percentage of patients achieving IGA (0/1) at Week 16	41.0 (116/283)	11.3 (16/141)
Difference from placebo [95% CI][b]	29.0 [21.5, 36.5]	
Percentage of patients achieving EASI-75 at Week 16	56.5 (160/283)	14.2 (20/141)
Difference from placebo [95% CI][b]	41.7 [33.7, 49.7]	
Study KGAC (foreign study)		
Percentage of patients achieving IGA (0/1) at Week 16	31.3 (88/281)	9.6 (14/146)
Difference from placebo [95% CI][b]	21.3 [13.9, 28.6]	
Percentage of patients achieving EASI-75 at Week 16	50.2 (141/281)	17.1 (25/146)
Difference from placebo [95% CI][b]	32.4 [23.7, 41.0]	

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, or had missing data.

a) ITT population in Study KGAB and mITT population in Study KGAC were handled as the populations for analysis.

b) Mantel-Haenszel test with region (US/EU/other), age (≥12 to <18 years/≥18 years), and baseline disease severity (IGA score 3/4) as stratification factors.

Table 52. Main efficacy endpoints (lebrikizumab monotherapy study, ITT population/mITT population,[a] NRI)

		Study KGAB (foreign study)		Study KGAC (foreign study)	
Endpoint	Week	250 mg Q2W	Placebo	250 mg Q2W	Placebo
Percentage of patients achieving IGA (0/1)	2	2.5 (7/283)	0.7 (1/141)	0.7 (2/281)	0 (0/146)
	4	10.2 (29/283)	0.7 (1/141)	8.5 (24/281)	1.4 (2/146)
	8	26.9 (76/283)	1.4 (2/141)	20.6 (58/281)	3.4 (5/146)
	16	41.0 (116/283)	11.3 (16/141)	31.3 (88/281)	9.6 (14/146)
Percentage of patients achieving EASI-75	2	11.7 (33/283)	5.0 (7/141)	2.1 (6/281)	2.1 (3/146)
	4	25.8 (73/283)	6.4 (9/141)	17.1 (48/281)	5.5 (8/146)
	8	45.6 (129/283)	11.3 (16/141)	35.2 (99/281)	8.2 (12/146)
	16	56.5 (160/283)	14.2 (20/141)	50.2 (141/281)	17.1 (25/146)
Percentage of patients achieving EASI-50	2	27.6 (78/283)	10.6 (15/141)	22.8 (64/281)	8.2 (12/146)
	4	53.4 (151/283)	18.4 (26/141)	42.0 (118/281)	12.3 (18/146)
	8	66.4 (188/283)	26.2 (37/141)	57.7 (162/281)	24.0 (35/146)
	16	68.6 (194/283)	29.8 (42/141)	65.8 (185/281)	29.5 (43/146)
Percentage of patients achieving EASI-90	2	3.5 (10/283)	0.7 (1/141)	0.4 (1/281)	0 (0/146)
	4	12.0 (34/266)	1.4 (2/141)	6.0 (17/281)	1.4 (2/146)
	8	26.5 (75/283)	0.7 (1/141)	14.2 (40/281)	2.7 (4/146)
	16	36.7 (104/283)	7.8 (11/141)	29.5 (83/281)	8.9 (13/146)
Percentage of patients with pruritus NRS ≥4-point improvement[b]	2	6.1 (16/263)	0.8 (1/130)	3.6 (9/253)	0.7 (1/134)
	4	20.5 (54/263)	2.3 (3/130)	16.6 (42/253)	3.0 (4/134)
	8	33.5 (88/263)	3.8 (5/130)	28.5 (72/253)	7.5 (10/134)
	16	42.6 (112/263)	11.5 (15/130)	37.9 (96/253)	9.7 (13/134)

% (number of subjects), Shaded area indicates data at the main evaluation point.

Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, or had missing data.

a) ITT population in Study KGAB and mITT population in Study KGAC were handled as the populations for analysis.

b) Subjects with baseline pruritus NRS score of ≥4 were included in the evaluation.

Table 53 shows the results of the efficacy in long-term treatment in subjects who were responders to lebrikizumab at Week 16 in Japanese and foreign phase III studies (Studies KGAL, KGAD/KGAA, KGAB, and KGAC) and received lebrikizumab 250 mg Q2W or Q4W thereafter. Results showed that the effect was maintained at a certain level with continued administration of lebrikizumab. Also, Table 54 shows the results of administration of lebrikizumab 250 mg Q2W to non-responders, namely subjects

who received the rescue therapy during the induction phase, or achieved neither IGA (0/1) nor EASI-75 at Week 16 in Studies KGAL, KGAB, or KGAC. Regardless of use or non-use of concomitant TCS, a certain level of therapeutic response was obtained with continued lebrikizumab administration even after proceeding to the maintenance escape period.

Table 53. Long-term efficacy[a)] in subjects who were responders at Week 16 (NRI)

Study	Week	250 mg Q4W/Q4W		250 mg Q2W/Q4W		250 mg Q2W/Q2W	
		Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75	Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75	Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75
KGAL (combination with TCS)	16	60.5 (23/38)	100 (38/38)	48.5 (16/33)	100 (33/33)	75.0 (24/32)	90.6 (29/32)
	24	50.0 (19/38)	86.8 (33/38)	51.5 (17/33)	93.9 (31/33)	59.4 (19/32)	87.5 (28/32)
	32	34.2 (13/38)	89.5 (34/38)	48.5 (16/33)	81.8 (27/33)	59.4 (19/32)	84.4 (27/32)
	40	36.8 (14/38)	81.6 (31/38)	51.5 (17/33)	84.8 (28/33)	65.6 (21/32)	87.5 (28/32)
	52	44.7 (17/38)	81.6 (31/38)	48.5 (16/33)	72.7 (24/33)	59.4 (19/32)	87.5 (28/32)
	68	42.1 (16/38)	73.7 (28/38)	45.5 (15/33)	75.8 (25/33)	68.8 (22/32)	78.1 (25/32)
KGAD/KGAA (combination with TCS)	16			55.2 (16/29)	100 (29/29)	64.9 (37/57)	98.2 (56/57)
	32			51.7 (15/29)	89.7 (26/29)	63.2 (36/57)	94.7 (54/57)
	44			58.6 (17/29)	86.2 (25/29)	66.7 (38/57)	84.2 (48/57)
	56			58.6 (17/29)	72.4 (21/29)	64.9 (37/57)	78.9 (45/57)
KGAB (lebrikizumab monotherapy)	16			71.4 (45/63)	98.4 (62/63)	72.6 (45/62)	98.4 (61/62)
	24			71.4 (45/63)	84.1 (53/63)	64.5 (40/62)	87.1 (54/62)
	32			57.1 (36/63)	82.5 (52/63)	64.5 (40/62)	79.0 (49/62)
	40			57.1 (36/63)	76.2 (48/63)	59.7 (37/62)	72.6 (45/62)
	52			55.6 (35/63)	66.7 (42/63)	51.6 (32/62)	66.1 (41/62)
KGAC (lebrikizumab monotherapy)	16			58.2 (32/55)	96.4 (53/55)	62.7 (32/51)	100 (51/51)
	24			54.5 (30/55)	81.8 (45/55)	58.8 (30/51)	86.3 (44/51)
	32			52.7 (29/55)	76.4 (42/55)	56.9 (29/51)	82.4 (42/51)
	40			61.8 (34/55)	78.2 (43/55)	52.9 (27/51)	72.5 (37/51)
	52			54.5 (30/55)	72.7 (40/55)	51.0 (26/51)	64.7 (33/51)

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, proceeded to the maintenance escape period, or had missing data

a) Results obtained by administering lebrikizumab 250 mg Q2W or Q4W to subjects who had achieved IGA (0/1) or EASI-75 at Week 16.

Table 54. Long-term efficacy[a)] in subjects who were non-responders at Week 16 and proceeded to the maintenance escape period (NRI)

Study[b)]	Week	250 mg Q4W/Q2W		250 mg Q2W/Q2W		Placebo/250 mg Q2W	
		Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75	Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75	Percentage of patients achieving IGA (0/1)	Percentage of patients achieving EASI-75
KGAL (combination with TCS)	16	0 (0/42)	0 (0/42)	0 (0/55)	0 (0/55)	0 (0/71)	0 (0/71)
	24	14.3 (6/42)	42.9 (18/42)	20.0 (11/55)	52.7 (29/55)	25.4 (18/71)	47.9 (34/71)
	32	26.2 (11/42)	57.1 (24/42)	27.3 (15/55)	54.5 (30/55)	25.4 (18/71)	56.3 (40/71)
	40	26.2 (11/42)	54.8 (23/42)	21.8 (12/55)	47.3 (26/55)	26.8 (19/71)	59.2 (42/71)
	52	21.4 (9/42)	64.3 (27/42)	23.6 (13/55)	50.9 (28/55)	23.9 (17/71)	53.5 (38/71)
	68	26.2 (11/42)	52.4 (22/42)	25.5 (14/55)	56.4 (31/55)	26.8 (19/71)	47.9 (34/71)
KGAB (lebrikizumab monotherapy)	16			2.8 (3/106)	5.7 (6/106)	0 (0/96)	0 (0/96)
	24			21.7 (23/106)	47.2 (50/106)	20.8 (20/96)	40.6 (39/96)
	32			23.6 (25/106)	49.1 (52/106)	27.1 (26/96)	45.8 (44/96)
	40			27.4 (29/106)	48.1 (51/106)	25.0 (24/96)	46.9 (45/96)
	52			24.5 (26/106)	47.2 (50/106)	31.3 (30/96)	42.7 (41/96)
KGAC (lebrikizumab monotherapy)	16			6.4 (8/125)	8.0 (10/125)	0.9 (1/108)	3.7 (4/108)
	24			20.8 (26/125)	47.2 (59/125)	25.0 (27/108)	43.5 (47/108)
	32			18.4 (23/125)	38.4 (48/125)	29.6 (32/108)	40.7 (44/108)
	40			18.4 (23/125)	38.4 (48/125)	28.7 (31/108)	46.3 (50/108)
	52			18.4 (23/125)	32.8 (41/125)	26.9 (29/108)	39.8 (43/108)

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, or had missing data

a) Results obtained by administering lebrikizumab 250 mg Q2W to subjects who had received rescue therapy during the induction phase or achieved neither IGA (0/1) nor EASI-75 at Week 16.

Table 55 shows the primary endpoint outcomes of Study KGAL by subject baseline characteristics. In all subgroups of lebrikizumab 250 mg Q2W, the results tended to exceed those in the placebo group. In the lebrikizumab 250 mg Q4W group, results in all subgroups other than the pediatric patient population aged ≥12 to <18 years tended to exceed those in the placebo group. In the pediatric patients aged ≥12 to <18 years, the percentage of patients achieving IGA (0/1) was similar between the lebrikizumab 250 mg Q4W group and the placebo group. The cause of this outcome could not be identified despite the exhaustive investigation of other baseline characteristics, suggesting that the small number of subjects in both groups (4 and 7 cases, respectively) may be the main cause. In addition to the percentage of patients achieving EASI-75 (Table 55), the other primary endpoint, the percentage of patients achieving EASI-90 and the percentage of patients with pruritus NRS ≥4-point improvement (% [95% CI], [number of subjects]) were numerically higher in the lebrikizumab 250 mg Q4W group than in the placebo group (25.0 [0.0, 67.4] (n = 4) in the lebrikizumab 250 mg Q4W group and 0 [0.0, 0.0] (n = 7) in the placebo group for both percentages). Thus, the applicant considers that results suggest the efficacy of lebrikizumab 250 mg Q4W administration to the pediatric patient population aged ≥12 to <18 years.

Table 55. Subgroup analysis (Study KGAL, MI)

Efficacy endpoint			Percentage of patients achieving IGA (0/1)			Percentage of patients achieving EASI-75		
Baseline characteristics/ treatment group			250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Placebo
Age	12-18 years		0 [0.0, 0.0] (4)	60.0 [29.6, 90.4] (10)	0 [0.0, 0.0] (7)	25.0 [0.0, 67.4] (4)	70.0 [41.6, 98.4] (10)	14.3 [0.0, 40.2] (7)
	≥18 years		30.6 [20.3, 41.0] (77)	31.1 [22.5, 39.7] (113)	6.7 [1.0, 12.3] (75)	48.4 [37.1, 59.6] (77)	49.5 [40.2, 58.8] (113)	13.3 [5.6, 21.0] (75)
Sex	Male		25.0 [13.7, 36.3] (56)	31.7 [21.6, 41.8] (82)	5.2 [0.0, 10.9] (58)	41.1 [28.2, 54.0] (56)	50.0 [39.2, 60.8] (82)	10.3 [2.5, 18.2] (58)
	Female		38.4 [18.9, 57.9] (25)	36.9 [21.8, 51.9] (41)	8.3 [0.0 19.4] (24)	61.0 [41.5, 80.4] (25)	53.6 [37.9, 69.2] (41)	20.8 [4.6, 37.1] (24)
Body weight	<60 kg		36.6 [18.7, 54.4] (29)	38.0 [24.1, 52.0] (47)	6.9 [0.0, 16.1] (29)	66.3 [48.9, 83.8] (29)	47.9 [33.5, 62.4] (47)	10.3 [0.0, 21.4] (29)
	60-<100 kg		25.5 [13.5, 37.5] (51)	30.6 [20.2, 41.0] (76)	5.7 [0.0, 11.9] (53)	37.3 [24.0, 50.5] (51)	53.2 [41.9, 64.5] (76)	15.1 [5.5, 24.7] (53)
AD duration	2-<5 years		40.0 [−12.9, 92.9] (4)	33.3 [0.0, 71.1] (6)	0 [0.0, 0.0] (2)	31.0 [−18.3, 80.3] (4)	50.0 [10.0, 90.0] (6)	0 [0.0, 0.0] (2)
	5-<10 years		50.0 [10.0, 90.0] (6)	75.0 [32.6, 100.0] (4)	0 [0.0, 0.0] (2)	50.0 [10.0, 90.0] (6)	50.0 [1.0, 99.0] (4)	50.0 [0.0, 100] (2)
	10-<20 years		45.5 [16.0, 74.9] (11)	44.5 [23.9, 65.2] (23)	9.5 [0.0, 22.1] (21)	72.7 [46.4, 99.0] (11)	58.4 [37.8, 79.0] (23)	19.0 [2.3, 35.8] (21)
	≥20 years		23.3 [12.6, 34.0] (60)	29.1 [19.6, 38.5] (89)	5.3 [0.0, 11.1] (57)	43.3 [30.8, 55.9] (60)	50.0 [39.6, 60.5] (89)	10.5 [2.6, 18.5] (57)
IGA score	3		35.6 [22.9, 48.4] (55)	39.1 [28.7, 49.6] (84)	9.1 [1.5, 16.7] (55)	58.6 [45.5, 71.7] (55)	56.6 [45.9, 67.2] (84)	20.0 [9.4, 30.6] (55)
	4		15.4 [1.5, 29.3] (26)	21.1 [8.1, 34.1] (39)	0 [0.0, 0.0] (27)	23.1 [6.9, 39.3] (26)	39.6 [24.0, 55.2] (39)	0 [0.0, 0.0] (27)
EASI score	16-≤21		46.7 [21.4, 71.9] (15)	52.9 [34.9, 70.9] (30)	7.7 [0.0, 22.2] (13)	60.0 [35.2, 84.8] (15)	61.7 [44.0, 79.4] (30)	23.1 [0.2, 46.0] (13)
	21-≤50		27.4 [15.7, 39.1] (57)	30.3 [20.2, 40.4] (80)	6.3 [0.3, 12.2] (64)	49.5 [36.5, 62.6] (57)	53.1 [42.0, 64.1] (80)	12.5 [4.4, 20.6] (64)
	50-≤72		11.1 [0.0, 31.6] (9)	7.7 [0.0, 22.2] (13)	0 [0.0, 0.0] (5)	11.1 [0.0, 31.6] (9)	15.4 [0.0, 35.0] (13)	0 [0.0, 0.0] (5)
Pruritus NRS score	<4		40.9 [20.4, 61.5] (22)	41.9 [27.1, 56.6] (43)	9.5 [0.0, 22.1] (21)	50.0 [29.1, 70.9] (22)	55.8 [41.0, 70.7] (43)	23.8 [5.6, 42.0] (21)
	≥4		24.7 [13.6, 35.9] (59)	28.9 [18.9, 38.9] (80)	5.0 [0.0, 10.5] (60)	46.2 [33.4, 59.0] (59)	48.7 [37.6, 59.8] (80)	10.0 [2.4, 17.6] (60)
Prior treatment	Systemic therapy	Yes	30.4 [17.1, 43.7] (46)	29.5 [18.1, 41.0] (61)	2.3 [0.0, 6.7] (44)	47.8 [33.4, 62.3] (46)	57.4 [45.0, 69.8] (61)	6.8 [0.0, 14.3] (44)
		No	27.4 [12.4, 42.5] (35)	37.3 [25.1, 49.5] (62)	10.5 [0.8, 20.3] (38)	46.4 [29.7, 63.1] (35)	45.1 [32.5, 57.7] (62)	21.1 [8.1, 34.0] (38)
	Cyclosporine	Yes	16.7 [0.0, 37.8] (12)	27.8 [7.1, 48.5] (18)	0 [0.0, 0.0] (12)	25.0 [0.5, 49.5] (12)	66.7 [44.9, 88.4] (18)	0 [0.0, 0.0] (12)
		No	31.3 [20.3, 42.3] (69)	34.4 [25.2, 43.6] (105)	7.1 [1.1, 13.2] (70)	51.1 [39.2, 62.9] (69)	48.5 [38.9, 58.2] (105)	15.7 [7.2, 24.2] (70)
	Systemic corticoid	Yes	27.6 [11.3, 43.9] (29)	35.7 [21.2, 50.2] (42)	2.9 [0.0, 8.4] (35)	48.3 [30.1, 66.5] (29)	59.5 [44.7, 74.4] (42)	5.7 [0.0, 13.4] (35)
		No	30.0 [17.4, 42.6] (52)	32.2 [22.0, 42.5] (81)	8.5 [0.5, 16.5] (47)	46.6 [33.0, 60.3] (52)	46.9 [35.9, 57.9] (81)	19.1 [7.9, 30.4] (47)
	Topical JAK inhibitor	Yes	34.5 [14.2, 54.9] (22)	27.6 [11.3, 43.9] (29)	10.5 [0.0, 24.3] (19)	55.6 [34.5, 76.8] (22)	55.2 [37.1, 73.3] (29)	10.5 [0.0, 24.3] (19)
		No	27.1 [15.8, 38.5] (59)	35.2 [25.5, 45.0] (94)	4.8 [0.0, 10.0] (63)	44.1 [31.4, 56.7] (59)	50.0 [39.7, 60.2] (94)	14.3 [5.6, 22.9] (63)

% [95% CI] (number of subjects), Data of subjects who received rescue therapy or discontinued the treatment due to the lack of efficacy were imputed by baseline data up to Week 16. Treatment discontinuation for other reasons was handled as missing data and, together with other missing data, imputed using multiple imputation.

PMDA's view:

In Study KGAL investigating the efficacy and safety of lebrikizumab in combination with TCS in Japanese patients with moderate to severe AD who had an inadequate response to treatment with topical agents such as TCS, the percentage of patients achieving IGA (0/1) and the percentage of patients achieving EASI-75 at Week 16, co-primary endpoints, were confirmed to be higher in the lebrikizumab 250 mg Q2W group and the 250 mg Q4W group than in the placebo group, demonstrating the superiority of lebrikizumab over placebo. Results of other efficacy endpoints in the lebrikizumab 250 mg Q2W group and the 250 mg Q4W group exceeded those of the placebo group, and a certain level of efficacy was observed in continued administration. Results of the primary endpoints by baseline characteristics

of patients also demonstrated generally superior results with lebrikizumab 250 mg Q2W and Q4W administration to those with placebo. Similar results were obtained in foreign phase III studies as in the Japanese study. All of these results suggest the efficacy of lebrikizumab in Japanese patients with AD.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of lebrikizumab in patients with AD, based on the results of the pooled population of the Japanese and foreign clinical studies shown in Table 56.

Table 56. Definition of pooled population used for safety studies

Pooled population	Studies included (target period)
Placebo-controlled pooled population	5 Clinical studies in patients with AD: Studies KGAF, KGAB, KGAC, KGAD, and KGAL (up to primary endpoint assessment at Week 16)
Pooled population of 9 studies	9 Clinical studies in patients with AD: Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAE, and KGAL (entire administration period in each study) and Study KGAA (data cut-off on [redacted], 20[redacted])

7.R.3.1 Safety summary

Table 57 shows the summary of safety of lebrikizumab in each pooled population.

There were no obvious differences in the incidence of adverse events between the lebrikizumab group and the placebo group except that the incidence of adverse drug reactions was slightly higher in the lebrikizumab group compared with the placebo group in the whole population in the placebo-controlled pooled population. In the placebo-controlled pooled population and the pooled population of 9 studies, the incidences of adverse events and adverse drug reactions tended to be higher in the Japanese subpopulation than in the whole population. However, the incidence of serious adverse events was low, and no obvious difference was observed in the safety profile between the whole population and the Japanese subpopulation.

Table 57. Outline of safety of lebrikizumab (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure period	46.5	270.6	139.0	355.5	1,724.4	2,186.1
All adverse events	84 (52.2) 282.2	477 (52.6) 269.1	267 (54.9) 306.1	220 (61.3) 118.4	1,101 (68.6) 146.7	1,386 (69.4) 147.3
Serious adverse events	0	11 (1.2) 4.1	10 (2.1) 7.3	8 (2.2) 2.3	58 (3.6) 3.4	72 (3.6) 3.3
Adverse events leading to treatment discontinuation	3 (1.9) 6.5	20 (2.2) 7.5	6 (1.2) 4.3	6 (1.7) 1.7	70 (4.4) 4.1	81 (4.1) 3.7
Adverse drug reactions	29 (18.0) 70.5	162 (17.9) 67.9	53 (10.9) 41.3	75 (20.9) 24.9	386 (24.1) 27.8	479 (24.0) 27.3
Death	0	0	1 (0.2) 0.7	0	4 (0.2) 0.2	4 (0.2) 0.2
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure period	24.6	37.3	25.2	92.5	233.1	325.6
All adverse events	49 (60.5) 337.9	93 (75.6) 471.3	52 (63.4) 347.7	85 (74.6) 238.8	213 (89.9) 336.4	253 (91.7) 316.0
Serious adverse events	0	1 (0.8) 2.7	2 (2.4) 8.0	1 (0.9) 1.1	7 (3.0) 3.0	8 (2.9) 2.5
Adverse events leading to treatment discontinuation	0	2 (1.6) 5.4	0	0	4 (1.7) 1.7	4 (1.4) 1.2
Adverse drug reactions	14 (17.3) 63.0	31 (25.2) 97.1	11 (13.4) 47.5	30 (26.3) 41.5	77 (32.5) 43.7	98 (35.5) 41.4
Death	0	0	0	0	0	0

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

Tables 58 and 59 show the main adverse events in the placebo-controlled pooled population and in the pooled population of 9 studies.

Pyrexia and allergic conjunctivitis tended to occur at a higher incidence in the Japanese subpopulation than in the whole population, most of pyrexia in the Japanese subpopulation occurred immediately after administration of anti-COVID-19 vaccine, and a causal relationship to the study drug was denied. All cases of allergic conjunctivitis observed in the Japanese subpopulation were non-serious and did not lead to discontinuation of the study drug administration.

Table 58. Adverse events reported by ≥2% of subjects in any group (placebo-controlled pooled population, safety analysis population)

	Whole population			Japanese subpopulation		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Placebo
Number of subjects	161	906	486	81	123	82
Pyrexia	16 (9.9)	27 (3.0)	14 (2.9)	15 (18.5)	25 (20.3)	13 (15.9)
Conjunctivitis allergic	11 (6.8)	35 (3.9)	7 (1.4)	10 (12.3)	21 (17.1)	4 (4.9)
Nasopharyngitis	7 (4.3)	41 (4.5)	15 (3.1)	5 (6.2)	7 (5.7)	2 (2.4)
Conjunctivitis	6 (3.7)	63 (7.0)	9 (1.9)	5 (6.2)	12 (9.8)	2 (2.4)
Folliculitis	6 (3.7)	12 (1.3)	13 (2.7)	5 (6.2)	7 (5.7)	8 (9.8)
Upper respiratory tract infection	6 (3.7)	5 (0.6)	7 (1.4)	0	2 (1.6)	0
Diarrhoea	5 (3.1)	6 (0.7)	3 (0.6)	2 (2.5)	2 (1.6)	2 (2.4)
Headache	4 (2.5)	38 (4.2)	21 (4.3)	3 (3.7)	4 (3.3)	9 (11.0)
Oral herpes	4 (2.5)	21 (2.3)	11 (2.3)	2 (2.5)	6 (4.9)	2 (2.4)
Arthralgia	4 (2.5)	9 (1.0)	3 (0.6)	1 (1.2)	3 (2.4)	0
Fatigue	4 (2.5)	5 (0.6)	3 (0.6)	0	0	0
Injection site pain	3 (1.9)	8 (0.9)	6 (1.2)	0	1 (0.8)	2 (2.4)
Vaccination site pain	3 (1.9)	5 (0.6)	5 (1.0)	3 (3.7)	4 (3.3)	4 (4.9)
Dermatitis atopic	2 (1.2)	47 (5.2)	76 (15.6)	1 (1.2)	0	2 (2.4)
COVID-19	2 (1.2)	10 (1.1)	8 (1.6)	2 (2.5)	1 (0.8)	3 (3.7)
Acne	2 (1.2)	6 (0.7)	8 (1.6)	2 (2.5)	4 (3.3)	5 (6.1)
Eye pruritus	2 (1.2)	5 (0.6)	0	1 (1.2)	3 (2.4)	0
Skin infection	2 (1.2)	4 (0.4)	5 (1.0)	1 (1.2)	1 (0.8)	2 (2.4)
Back pain	2 (1.2)	4 (0.4)	2 (0.4)	2 (2.5)	2 (1.6)	0
Urticaria	2 (1.2)	3 (0.3)	5 (1.0)	2 (2.5)	0	2 (2.4)
Eczema	2 (1.2)	3 (0.3)	2 (0.4)	2 (2.5)	0	0
ALT increased	2 (1.2)	3 (0.3)	2 (0.4)	0	0	2 (2.4)
Conjunctivitis bacterial	2 (1.2)	3 (0.3)	0	2 (2.5)	0	0
Ligament sprain	2 (1.2)	2 (0.2)	3 (0.6)	1 (1.2)	0	2 (2.4)
Hyperuricaemia	2 (1.2)	0	0	2 (2.5)	0	0
Dry eye	1 (0.6)	13 (1.4)	6 (1.2)	1 (1.2)	2 (1.6)	2 (2.4)
Rhinitis allergic	0	11 (1.2)	1 (0.2)	0	3 (2.4)	0
Cellulitis	0	1 (0.1)	7 (1.4)	0	0	3 (3.7)

Number of subjects with events (%)

Table 59. Adverse events reported by ≥2% of subjects in any group (pooled population of 9 studies, safety analysis population)

	Whole population			Japanese subpopulation		
	250 mg Q4W	250 mg Q2W	Lebrikizumab	250 mg Q4W	250 mg Q2W	Lebrikizumab
Number of subjects	359	1,604	1,996	114	237	276
COVID-19	45 (12.5)	185 (11.5)	229 (11.5)	16 (14.0)	41 (17.3)	56 (20.3)
Nasopharyngitis	29 (8.1)	154 (9.6)	204 (10.2)	8 (7.0)	31 (13.1)	39 (14.1)
Pyrexia	27 (7.5)	63 (3.9)	87 (4.4)	25 (21.9)	53 (22.4)	75 (27.2)
Conjunctivitis allergic	26 (7.2)	99 (6.2)	132 (6.6)	16 (14.0)	42 (17.7)	58 (21.0)
Headache	18 (5.0)	79 (4.9)	104 (5.2)	10 (8.8)	15 (6.3)	21 (7.6)
Dermatitis atopic	16 (4.5)	118 (7.4)	138 (6.9)	1 (0.9)	2 (0.8)	3 (1.1)
Conjunctivitis	15 (4.2)	128 (8.0)	147 (7.4)	5 (4.4)	23 (9.7)	27 (9.8)
Folliculitis	13 (3.6)	40 (2.5)	52 (2.6)	9 (7.9)	21 (8.9)	28 (10.1)
Oral herpes	12 (3.3)	57 (3.6)	66 (3.3)	4 (3.5)	11 (4.6)	15 (5.4)
Acne	12 (3.3)	48 (3.0)	60 (3.0)	9 (7.9)	22 (9.3)	29 (10.5)
Upper respiratory tract infection	11 (3.1)	48 (3.0)	77 (3.9)	1 (0.9)	6 (2.5)	7 (2.5)
Diarrhoea	8 (2.2)	24 (1.5)	37 (1.9)	4 (3.5)	5 (2.1)	7 (2.5)
Dental caries	8 (2.2)	21 (1.3)	29 (1.5)	7 (6.1)	14 (5.9)	21 (7.6)
Arthralgia	7 (1.9)	24 (1.5)	35 (1.8)	3 (2.6)	5 (2.1)	8 (2.9)
Herpes simplex	7 (1.9)	24 (1.5)	32 (1.6)	7 (6.1)	14 (5.9)	19 (6.9)
Ligament sprain	7 (1.9)	13 (0.8)	21 (1.1)	4 (3.5)	3 (1.3)	7 (2.5)
Back pain	6 (1.7)	32 (2.0)	41 (2.1)	4 (3.5)	18 (7.6)	22 (8.0)
Urinary tract infection	5 (1.4)	32 (2.0)	39 (2.0)	1 (0.9)	1 (0.4)	2 (0.7)
Vaccination site pain	5 (1.4)	20 (1.2)	25 (1.3)	3 (2.6)	6 (2.5)	9 (3.3)
Myalgia	4 (1.1)	18 (1.1)	24 (1.2)	3 (2.6)	11 (4.6)	12 (4.3)
Eye pruritus	4 (1.1)	17 (1.1)	23 (1.2)	1 (0.9)	6 (2.5)	7 (2.5)
Injection site erythema	4 (1.1)	15 (0.9)	19 (1.0)	2 (1.8)	6 (2.5)	7 (2.5)
Skin papilloma	3 (0.8)	23 (1.4)	26 (1.3)	3 (2.6)	12 (5.1)	15 (5.4)
Injection site reaction	3 (0.8)	23 (1.4)	26 (1.3)	2 (1.8)	5 (2.1)	6 (2.2)
Urticaria	3 (0.8)	19 (1.2)	22 (1.1)	2 (1.8)	5 (2.1)	6 (2.2)
Herpes zoster	3 (0.8)	16 (1.0)	21 (1.1)	1 (0.9)	6 (2.5)	7 (2.5)
Dry eye	2 (0.6)	25 (1.6)	32 (1.6)	1 (0.9)	6 (2.5)	7 (2.5)
Pain in extremity	2 (0.6)	16 (1.0)	20 (1.0)	2 (1.8)	8 (3.4)	10 (3.6)
Asthma	1 (0.3)	22 (1.4)	28 (1.4)	0	6 (2.5)	6 (2.2)
Rhinitis allergic	0	24 (1.5)	25 (1.3)	0	7 (3.0)	7 (2.5)

Number of subjects with events (%)

Death occurred in 0.2% (4 of 1,996) of subjects receiving lebrikizumab in the pooled population of 9 studies (metastases to bone/metastases to liver/pancreatic carcinoma metastatic, death, pancreatic carcinoma metastatic, and cardiac arrest in 1 subject each). A causal relationship to the study drug was denied for all events.

Serious adverse events were observed in 3.6% (72 of 1,996) of subjects receiving lebrikizumab, which were dermatitis atopic and COVID-19 in 3 subjects each, hip fracture in 2 subjects, ankle fracture, rotator cuff syndrome, blood potassium decreased, Stevens-Johnson syndrome, influenza like illness, attention deficit hyperactivity disorder, neuroendocrine tumour, arthritis, subdural haematoma, prostate cancer, cervical cord compression, endometrial adenocarcinoma, cholecystitis, accidental overdose, oedema peripheral, small intestinal obstruction/bacteraemia, dysmenorrhoea, micromastia, thermal burn, arthralgia, myocardial infarction, synovitis, somatic symptom disorder, carpal tunnel syndrome, hypokalaemia/seizure/depression, hepatic steatosis, pancreatitis, metastases to bone/metastases to liver/pancreatic carcinoma metastatic, prostate cancer/hiatus hernia, invasive breast carcinoma, humerus fracture/ulna fracture, depression suicidal, vulval abscess, pulmonary embolism, cardiac failure/multiple injuries/dermatitis atopic/acarodermatitis/erysipelas/spinal osteoarthritis, rhegmatogenous retinal detachment, ovarian germ cell teratoma benign, paternal exposure during pregnancy, large intestine

infection/cerebellar syndrome, cellulitis, sinus node dysfunction, road traffic accident, depression, fall/death, pancreatic carcinoma metastatic, pneumonia, sudden visual loss/cataract, multiple injuries, conjunctivitis allergic, testicular torsion, bile duct stone, cardiac arrest, periprosthetic fracture, dizziness/sensory loss/diplopia/hypoaesthesia/multiple sclerosis, inguinal hernia, cyst, myopathy, nephrolithiasis, cerebral infarction, ligament injury, appendicitis, anaphylactic reaction, tooth extraction, tonsillitis, and Hodgkin's disease in 1 subject each. A causal relationship to the study drug could not be ruled out in 9 subjects (dermatitis atopic, arthritis, arthralgia, invasive breast carcinoma, cerebellar syndrome, conjunctivitis allergic, myopathy, anaphylactic reaction, and tonsillitis in 1 subject each).

PMDA reviewed adverse events that may be related to the administration of lebrikizumab in the following sections based on the incidences of adverse events of special interest associated with lebrikizumab administration, taking account of the following: (1) Pharmacological action of lebrikizumab, (2) incidence of adverse events in clinical studies, and (3) safety information reported with approved therapeutic agents (including drugs in the same class) against AD.

7.R.3.2 Anaphylaxis/hypersensitivity-related events and injection site reaction

The applicant's explanation about the incidence of anaphylaxis/hypersensitivity-related events and injection site reaction:

Table 60 shows the incidence of anaphylaxis/hypersensitivity-related events and injection site reaction in each pooled population.

In the whole population of the placebo-controlled pooled population, the incidence of anaphylaxis/hypersensitivity-related events was lower in each of lebrikizumab groups of the pooled population than in the corresponding placebo group. Both in the placebo-controlled pooled population and in the pooled population of 9 studies, the incidence of anaphylaxis/hypersensitivity-related events tended to be higher in the Japanese subpopulation than in the whole population. In contrast, the incidence of serious events was similar between the Japanese subpopulation and the whole population. Serious anaphylaxis/hypersensitivity-related events were observed in 6 subjects receiving lebrikizumab of the pooled population of 9 studies (dermatitis atopic in 3 subjects, Stevens-Johnson syndrome, conjunctivitis allergic, and anaphylactic reaction[37)] in 1 subject each). A causal relationship to the study drug could not be ruled out for the events in 3 subjects (dermatitis atopic, conjunctivitis allergic, and anaphylactic reaction[37)] in 1 subject each). All of these serious anaphylaxis/hypersensitivity-related events were delayed events that occurred on or later than the day after the lebrikizumab administration.

The incidence of injection site reaction was similar between the placebo group and each of the lebrikizumab groups, both in the whole population and the Japanese subpopulation of the placebo-controlled pooled population. Both in the placebo-controlled pooled group and in the pooled population of 9 studies, the incidence of injection site reaction tended to be higher in the Japanese subpopulation than in the whole population. All injection site reactions observed in the Japanese subpopulation were non-serious.

37) This event occurred after ingesting [redacted] on the day following lebrikizumab administration. The subject was hospitalized but recovered on the same day. The subject was diagnosed with [redacted] allergy. However, since taking [redacted] does not always induce anaphylactic reaction, the investigator concluded that a causal relationship to the study drug could not be ruled out.

On the basis of the above, the applicant considers that no clear relationship exists between lebrikizumab and occurrence of anaphylactic reaction/serious hypersensitivity-related events, and that it is unnecessary to call attention to these events as clinically significant adverse reactions. Injection site reactions should be alerted in the Other Adverse Reactions section of the package insert.

Table 60. Incidence of anaphylaxis/hypersensitivity-related events and injection site reactions (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
Anaphylaxis/hypersensitivity-related events[a)]	17 (10.6) 39.1	119 (13.1) 47.8	97 (20.0) 80.8	52 (14.5) 16.2	301 (18.8) 20.3	368 (18.4) 19.5
Serious events	0	1 (0.1) 0.4	1 (0.2) 0.7	2 (0.6) 0.6	4 (0.2) 0.2	6 (0.3) 0.3
Injection site reaction	4 (2.5) 8.8	27 (3.0) 10.2	10 (2.1) 7.3	11 (3.1) 3.2	61 (3.8) 3.6	73 (3.7) 3.4
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
Anaphylaxis/hypersensitivity-related events	13 (16.0) 58.2	24 (19.5) 72.3	8 (9.8) 33.3	20 (17.5) 24.7	57 (24.1) 29.5	76 (27.5) 29.3
Serious events	0	0	0	1 (0.9) 1.1	0	1 (0.4) 0.3
Injection site reaction	0	7 (5.7) 19.3	4 (4.9) 16.5	5 (4.4) 5.7	16 (6.8) 7.3	19 (6.9) 6.2

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[b)]

a) Include events that occurred after placebo administration in 1 subject of Study KGAG in the pooled population of 9 studies.
b) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

PMDA's view:

In general, drug products containing protein as active ingredients, such as antibody drugs, may cause serious hypersensitivity, and serious anaphylactic reactions, etc., were observed in clinical studies of lebrikizumab. The applicant should therefore take the following measures: (1) Serious hypersensitivity such as anaphylaxis should be alerted in the Clinically Significant Adverse Reactions section of the package insert; (2) anaphylaxis should be included as an important identified risk of RMP; and (3) information should be collected continuously in the post-marketing surveillance, etc., and provided to healthcare professionals in an appropriate manner.

7.R.3.3 Infection

The applicant's explanation about the incidences of infection following the administration of lebrikizumab:

Table 61 shows the incidence of infection in each pooled population.

In the whole population of the placebo-controlled pooled population, infection occurred in a certain percentage of subjects receiving lebrikizumab, but the incidence was similar to, or lower than, the incidence in the placebo group. The tendency was similar in the Japanese subpopulation as well. The incidence of herpes zoster tended to be higher in the lebrikizumab group than in the placebo group. In

the pooled population of 9 studies, serious infection was observed in 11 subjects receiving lebrikizumab (COVID-19 in 3 subjects, bacteraemia, vulval abscess, acarodermatitis/erysipelas, large intestine infection, cellulitis, pneumonia, appendicitis, and tonsillitis in 1 subject each). A causal relationship to the study drug could not be ruled out for tonsillitis in 1 subject.

While definitions and methods of tallying adverse events of special interest vary, limiting comparisons between clinical studies, the incidence of infection and serious infection in lebrikizumab-treated subjects in the pooled population of 9 studies (53.1 and 0.5 cases, respectively, per 100 person-years) was not significantly different from that observed in lebrikizumab-treated subjects in the pooled data of clinical studies in patients with AD receiving drugs in the same class (dupilumab,[38)] 119.1 and 0.8 cases per 100 person-years, respectively; tralokinumab,[39)] 62.4 and 1.3 cases per 100 person-years, respectively).

As for events related to parasite infection, patients with a high risk of active internal parasitic infection or related infection were excluded from the clinical studies of lebrikizumab. However, such an infection was observed in 1 subject receiving lebrikizumab 250 mg Q4W among those in the pooled population of 9 studies (ascariasis/helminthiasis). Although causal relation of the event to the study drug could not be ruled out, the event was non-serious and did not result in discontinuation of the study drug.

Thus, the results so far available do not suggest a clear relationship between lebrikizumab and occurrence of infection and infestation.

38) Pooled data of 8 Japanese and foreign studies (Review report of "Dupixent 300 mg Syringe for S.C. Injection" dated October 26, 2017)
39) Pooled data of 7 AD studies (Review report of "Adtralza S.C. Injection 150 mg Syringe" dated November 8, 2022)

Table 61. Incidence of infection (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
Infection	38 (23.6) 97.4	203 (22.4) 86.6	105 (21.6) 86.9	133 (37.0) 50.2	645 (40.2) 52.2	818 (41.0) 53.1
Serious events	0	1 (0.1) 0.4	3 (0.6) 2.2	1 (0.3) 0.3	10 (0.6) 0.6	11 (0.6) 0.5
Opportunistic infection (broad)	3 (1.9) 6.6	10 (1.1) 3.7	6 (1.2) 4.3	11 (3.1) 3.1	49 (3.1) 2.9	62 (3.1) 2.9
Opportunistic infection (narrow)	1 (0.6) 2.2	6 (0.7) 2.2	1 (0.2) 0.7	3 (0.8) 0.8	19 (1.2) 1.1	24 (1.2) 1.1
Skin infection	9 (5.6) 20.0	26 (2.9) 9.8	38 (7.8) 28.6	20 (5.6) 5.8	82 (5.1) 4.9	109 (5.5) 5.2
Herpes zoster	1 (0.6) 2.2	5 (0.6) 1.9	1 (0.2) 0.7	3 (0.8) 0.8	18 (1.1) 1.1	23 (1.2) 1.1
Herpes simplex virus infection	2 (1.2) 4.4	4 (0.4) 1.5	5 (1.0) 3.6	8 (2.2) 2.3	32 (2.0) 1.9	41 (2.1) 1.9
Infection parasitic	0	0	0	1 (0.3) 0.3	0	1 (0.1) 0.05
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
Infection	21 (25.9) 102.7	37 (30.1) 118.7	28 (34.1) 135.4	48 (42.1) 71.4	134 (56.5) 91.8	165 (59.8) 82.8
Serious events	0	0	2 (2.4) 8.0	0	3 (1.3) 1.3	3 (1.1) 0.9
Opportunistic infection (broad)	2 (2.5) 8.3	2 (1.6) 5.4	3 (3.7) 12.0	9 (7.9) 10.2	23 (9.7) 10.4	30 (10.9) 9.8
Opportunistic infection (narrow)	0	1 (0.8) 2.7	1 (1.2) 4.0	1 (0.9) 1.1	7 (3.0) 3.0	8 (2.9) 2.5
Skin infection	7 (8.6) 29.8	9 (7.3) 25.1	14 (17.1) 59.7	12 (10.5) 14.1	29 (12.2) 13.6	39 (14.1) 13.3
Herpes zoster	0	0	1 (1.2) 4.0	1 (0.9) 1.1	6 (2.5) 2.6	7 (2.5) 2.2
Herpes simplex virus infection	2 (2.5) 8.3	1 (0.8) 2.7	2 (2.4) 8.0	8 (7.0) 9.0	17 (7.2) 7.6	23 (8.3) 7.4
Infection parasitic	0	0	0	0	0	0

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

PMDA's view:

At present, no data have been obtained that strongly suggest a risk of developing serious infections due to administration of lebrikizumab. However, given the pharmacological effects of lebrikizumab, the risk of developing infections due to administration of lebrikizumab cannot be ruled out. Serious infection occurred in subjects receiving lebrikizumab in clinical studies and herpes zoster, albeit non-serious, tended to occur at a higher rate in the lebrikizumab group than in the placebo group. In addition, serious infections occur in patients treated with drugs with pharmacological action similar to that of lebrikizumab. Serious infection should therefore be included in important potential risk of RMP, and information should be collected continuously in the post-marketing surveillance, etc., and provided to healthcare professionals in an appropriate manner. Furthermore, while no clear association has been identified between the administration of lebrikizumab and parasitic infections at present, lebrikizumab may attenuate type 2 immune responses by inhibiting IL-13-mediated signal transduction, thereby compromising the body's defenses against parasitic infections. In the "Precautions Concerning Patients

with Specific Backgrounds" section of the package insert, caution should be provided to patients with parasitic infections, as is the case with drugs in the same class.

7.R.3.4 Malignant tumour

The applicant's explanation about the risk of lebrikizumab-induced malignant tumour:
Table 62 shows the incidence of malignant tumour in each pooled population.

In the placebo-controlled pooled population, the incidence of malignant tumour did not significantly differ between the placebo group and each of lebrikizumab groups. In the pooled population of 9 studies, non-melanoma skin cancer (NMSC) was observed in 5 lebrikizumab-treated subjects (penile squamous cell carcinoma, Bowen's disease, squamous cell carcinoma/squamous cell carcinoma of skin, keratoacanthoma, and basal cell carcinoma in 1 subject each). All were non-serious and their causal relationship to the study drug was denied. Malignant tumour other than NMSC was observed in 10 subjects (prostate cancer, cutaneous T-cell lymphoma in 2 subjects each, neuroendocrine tumour, endometrial adenocarcinoma, metastases to bone/metastases to liver/pancreatic carcinoma metastatic, invasive breast carcinoma, pancreatic carcinoma metastatic, and Hodgkin's disease in 1 subject each). A causal relationship to the study drug could not be ruled out for invasive breast carcinoma in 1 subject.

Despite the limitations to comparison among clinical studies due to differences in definitions or aggregation methods, etc. of adverse events of special interest, the incidence of NMSC and malignant tumour other than NMSC among subjects receiving lebrikizumab in the pooled population of 9 studies (0.2 and 0.5 cases per 100 person-years) was similar to that in the lebrikizumab-treated subjects in the pooled data of clinical studies on tralokinumab in patients with AD[39] (0.6 and 0.3 cases per 100 person-years).

The above results demonstrate that the incidence of malignant tumour in the lebrikizumab group does not exceed that of the placebo group in clinical studies, suggesting that lebrikizumab is unlikely to cause malignant tumour.

Table 62. Incidence of malignant tumour (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
NMSC	0	2 (0.2) 0.7	2 (0.4) 1.4	0	5 (0.3) 0.3	5 (0.3) 0.2
Malignant tumour other than NMSC	0	0	0	0	10 (0.6) 0.6	10 (0.5) 0.5
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
NMSC	0	0	0	0	0	0
Malignant tumour other than NMSC	0	0	0	0	1 (0.4) 0.4	1 (0.4) 0.3

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]
a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

PMDA's view:
It is difficult to conclude the risk of developing malignant tumour with lebrikizumab due to the limited number of subjects and duration of administration based on the clinical studies obtained to date. However, given the pharmacological action of lebrikizumab, the possibility that the malignant tumour-suppressive mechanism of lebrikizumab is affected by the immunomodulatory action of lebrikizumab cannot be ruled out. Taking into account the occurrence of malignant tumours in clinical studies on lebrikizumab and in patients treated with drugs in the same class, the applicant should include malignant tumour as an important potential risk of RMP, collect information including published reports after the marketing, and provide the information obtained to healthcare professionals in an appropriate manner.

7.R.3.5 Conjunctivitis/keratitis

The applicant's explanation about the incidences of conjunctivitis-related events and keratitis-related events associated with lebrikizumab:
Conjunctivitis- and keratitis-related events may be associated with the mechanism of action of lebrikizumab. Dupilumab and tralokinumab, which are biologics with a similar mechanism of action to lebrikizumab, have been reported to have a higher risk of developing conjunctivitis in clinical studies targeting patients with AD compared with the placebo groups (*Br J Dermatol.* 2022;186:453-65, *Br J Dermatol.* 2020;182:1120-35).

Table 63 shows the incidences of conjunctivitis- and keratitis-related events in each pooled population.

All of the conjunctivitis-related events in the placebo-controlled pooled population were non-serious, but tended to occur at a higher incidence in the lebrikizumab group than in the placebo group. A serious conjunctivitis-related event (conjunctivitis allergic) occurred in 1 subject receiving lebrikizumab in the pooled population of 9 studies, its causal relationship to the study drug could not be ruled out. In both pooled populations, the incidence of conjunctivitis-related events tended to be higher in the Japanese subpopulation than in the whole population, but all of the events observed in the Japanese subpopulation were non-serious and did not result in the discontinuation of the study drug.

On the basis of the above, the risk of conjunctivitis- and keratitis-related events associated with lebrikizumab will be listed in the "Other Adverse Reactions" section of the package insert to urge caution.

Table 63. Incidences of conjunctivitis- and keratitis-related events (safety analysis populations)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
Conjunctivitis-related events	17 (10.6) 39.2	99 (10.9) 39.2	16 (3.3) 11.7	41 (11.4) 12.5	227 (14.2) 14.7	278 (13.9) 14.3
Keratitis-related events	0	5 (0.6) 1.9	1 (0.2) 0.7	1 (0.3) 0.3	12 (0.7) 0.7	12 (0.6) 0.6
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
Conjunctivitis-related events	15 (18.5) 68.4	32 (26.0) 99.9	6 (7.3) 24.6	21 (18.4) 26.2	65 (27.4) 35.2	84 (30.4) 34.0
Keratitis-related events	0	0	0	0	1 (0.4) 0.4	1 (0.4) 0.3

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

PMDA's view:

PMDA accepts the applicant's explanation to provide cautionary statements regarding the risk of conjunctivitis- and keratitis-related events during administration of lebrikizumab in the "Other Adverse Reactions" section of the package insert to urge caution. Considering that although the occurrence of conjunctivitis is observed relatively frequently after the administration of lebrikizumab, many of the events are non-serious, it is deemed unnecessary at the moment to include conjunctivitis- and keratitis-related events in safety specification of RMP. Nevertheless, post-marketing information, including published literature, should be collected continuously, and if new information such as factors related to the risk of conjunctivitis- or keratitis-related events becomes available, it should be provided to healthcare professionals appropriately.

7.R.3.6 Eosinophilia

The applicant's explanation about the risk of eosinophilia after lebrikizumab administration:

Table 64 shows the incidence of eosinophilia in each pooled population.

The percentage of subjects whose blood eosinophil count category[40)] became higher than baseline at any time point after the start of lebrikizumab during the induction phase of Study KGAL was higher in the 250 mg Q4W group (40.7% [33 of 81 subjects]) and in the 250 mg Q2W group (32.5% [40 of 123 subjects]) than in the placebo group (26.8% [22 of 82 subjects]), whereas mean change [range] from baseline in eosinophil count at the last evaluation time point of the induction phase was small in all of the groups; i.e., 0.187 [−2.36, 2.47] × 10^9/L in the 250 mg Q4W group, 0.128 [−1.43, 2.27] × 10^9/L in the 250 mg Q2W group, and −0.08 [−1.48, 0.98] × 10^9/L in the placebo group.

In the placebo-controlled pooled population, the incidence of eosinophilia did not significantly differ between the lebrikizumab group and the placebo group. In the pooled population of 9 studies, eosinophilia was observed in 28 subjects in the lebrikizumab group, but the event was non-serious in all of them.

40) Normal, <500/mL; mild, ≥500/mL and <1,500/mL; moderate, ≥1,500/mL and <5,000/mL; severe, ≥5,000/mL.

Diseases with eosinophilia, including eosinophilic polyangiitis granulomatosis, were not observed.

Thus, while serious eosinophilia with clinical symptoms has not been observed, the possibility of an increase in blood eosinophil count due to lebrikizumab administration cannot be ruled out. The risk of eosinophilia will be listed in the "Other Adverse Reactions" section of the package insert to urge caution.

Table 64. Incidence of eosinophilia (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
Eosinophilia	0	5 (0.6) 1.9	3 (0.6) 2.2	1 (0.3) 0.3	22 (1.4) 1.3	28 (1.4) 1.3
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
Eosinophilia	0	0	0	0	0	0

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

PMDA's view:

PMDA accepts the applicant's explanation to provide cautionary statements regarding the risk of eosinophilia in the "Other Adverse Reactions" section of the package insert to urge caution. Considering that severe eosinophilia with clinical symptoms was not observed in clinical studies in patients with AD, it is considered unnecessary to include eosinophilia as a safety specification in RMP at present. Post-marketing information, including published literature, should be collected continuously, and if new information such as the mechanism of onset of eosinophilia becomes available, it should be provided to healthcare professionals appropriately.

7.R.3.7 CPK increased/muscle disorder

The applicant's explanation about the risk of creatine phosphokinase (CPK) increased/muscle disorder:

Table 65 shows the incidence of CPK increased/muscle disorder in each pooled population.

Table 65. Incidence of CPK increased/muscle disorder (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
CPK increased/muscle disorder	2 (1.2) 4.3	7 (0.8) 2.6	2 (0.4) 1.4	5 (1.4) 1.4	25 (1.6) 1.5	36 (1.8) 1.7
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
CPK increased/muscle disorder	2 (2.5) 8.2	5 (4.1) 13.7	0	4 (3.5) 4.4	12 (5.1) 5.4	14 (5.1) 4.5

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

In the placebo-controlled pooled population, the incidence was numerically higher in the 250 mg Q4W group and in the 250 mg Q2W group than in the placebo group, whereas all of the events observed in the 250 mg Q4W group or in the 250 mg Q2W group (myalgia in 7 subjects, muscle spasms in 1 subject, blood CPK increased in 1 subject) were non-serious and mild in severity except moderately severe muscle spasms in 1 subject. A causal relationship to the study drug could not be ruled out for muscle spasms in 1 subject, but the event resolved without lebrikizumab discontinuation. Among 7 events of myalgia observed, 6 occurred after COVID-19 vaccination. In the pooled population of 9 studies, the incidence of CPK increased/muscle disorder showed no tendency of increase.

In Study KGAG, serious myopathy not corresponding to CPK increased/muscle disorder occurred. Although its causal relationship to the study drug could not be ruled out, the subject had a history of myalgia and generalized skin pain, and no distinct abnormality was observed in CPK or creatine level.

In Study KGAL which measured CPK, 59 patients showed high CPK levels, including those measured at baseline. Most of the levels were common terminology criteria for adverse events (CTCAE) Grade 1 or 2. High CPK level of CTCAE Grade 3 was observed in 2 subjects, both of which resolved without discontinuation of lebrikizumab.

These results suggest that there is no clear relationship between lebrikizumab administration and CPK increased/muscle disorder.

PMDA's view:

PMDA accepts the applicant's explanation that results of the clinical studies so far obtained do not show a clear relationship between lebrikizumab administration and CPK increased/muscle disorder. However, the incidence of CPK increased/muscle disorder tended to be higher in the lebrikizumab group than in the placebo group. Post-marketing information on the risk of lebrikizumab-induced CPK increased/muscle disorder, including published literature, should be collected continuously, and if new information becomes available, it should be provided to healthcare professionals appropriately.

7.R.3.8 Other events

The applicant's explanation about the risk of depression/suicide related events, latent major adverse cardiovascular event (MACE), and hepatic dysfunction:

Table 66 shows the incidences of depression/suicide-related events, latent MACE, and hepatic dysfunction in each pooled population.

Table 66. Incidences of depression/suicide related events, latent MACE, and hepatic dysfunction (safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Whole population						
Number of subjects	161	906	486	359	1,604	1,996
Total exposure	46.5	270.6	139.0	355.5	1,724.4	2,186.1
Depression/suicide related events	1 (0.6) 2.2	7 (0.8) 2.6	3 (0.6) 2.2	3 (0.8) 0.8	24 (1.5) 1.4	28 (1.4) 1.3
Latent MACE	2 (1.2) 4.3	8 (0.9) 3.0	7 (1.4) 5.1	2 (0.6) 0.6	19 (1.2) 1.1	28 (1.4) 1.3
Hepatic dysfunction	4 (2.5) 8.7	9 (1.0) 3.3	3 (0.6) 2.2	12 (3.3) 3.4	48 (3.0) 2.8	64 (3.2) 3.0
Japanese subpopulation						
Number of subjects	81	123	82	114	237	276
Total exposure	24.6	37.3	25.2	92.5	233.1	325.6
Depression/suicide related events	0	1 (0.8) 2.7	0	0	1 (0.4) 0.4	1 (0.4) 0.3
Latent MACE	0	2 (1.6) 5.4	1 (1.2) 4.0	0	3 (1.3) 1.3	3 (1.1) 0.9
Hepatic dysfunction	0	1 (0.8) 2.7	3 (3.7) 12.2	1 (0.9) 1.1	8 (3.4) 3.5	9 (3.3) 2.8

Upper row, Number of subjects with events (%);. Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]

a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

In the placebo-controlled pooled population, the incidence of depression/suicide related events was similar in all groups. In the pooled population of 9 studies, depression/suicide related events occurred in 28 subjects in the lebrikizumab group. Serious events were observed in 3 subjects (depression in 2 subjects, depression suicidal in 1 subject). Their causal relationship to the study drug was denied.

In the placebo-controlled pooled population, the incidence of latent MACE was similar among all groups. In the pooled population of 9 studies, latent MACE occurred in 28 subjects in the lebrikizumab group, and the event was serious in 4 subjects (myocardial infarction, cardiac arrest, hypoaesthesia, and cerebral infarction in 1 subject each). A causal relationship to the study drug was denied in all of them.

In the placebo-controlled pooled population, the incidence of hepatic dysfunction was higher in the 250 mg Q4W group than in the placebo group but similar between the 250 mg Q2W group and the placebo group, showing no consistent tendency. In the pooled population of 9 studies, hepatic dysfunction was observed in 64 subjects in the lebrikizumab group, and the event was serious in 1 subject (hepatic steatosis), but its causal relationship to the study drug was denied. A causal relationship to the study drug could not be ruled out in 14 subjects, but all of them had risk factors (overweight, obesity, concomitant drugs, etc.).

On the basis of the above, the applicant considers that there are no particular concerns regarding the risk of depression/suicide-related events, latent MACE, or hepatic dysfunction associated with the administration of lebrikizumab at present.

PMDA's view:
Clinical study data available to date show no clear association between lebrikizumab administration and depression/suicide related events, latent MACE, or hepatic dysfunction. Post-marketing information on the risk of lebrikizumab-induced these events, including published literature, should be collected continuously, and if new information becomes available, it should be provided to healthcare professionals appropriately.

7.R.3.9 Safety in children

The applicant's explanation about the safety of lebrikizumab in pediatric patients with AD aged ≥12 to <18 years weighing ≥40 kg:
Table 67 shows the outline of safety of lebrikizumab in the adult subpopulation and the pediatric subpopulation in each pooled population. No clear difference in safety profile was observed between the adult and pediatric subpopulations although results should be interpreted with caution due to the limited number of pediatric subjects compared with adult subjects.

Table 67. Safety summary of lebrikizumab
(adult subpopulation/pediatric subpopulation, safety analysis population)

	Placebo-controlled pooled population			Pooled population of 9 studies		
	250 mg Q4W	250 mg Q2W	Placebo	250 mg Q4W	250 mg Q2W	Lebrikizumab
Adult subpopulation (≥18 years of age)						
Number of subjects	157	790	432	324	1,216	1,606
Total exposure	45.2	238.0	122.5	311.8	1,264.3	1,682.3
All adverse events	82 (52.2) 282.9	439 (54.9) 290.1	237 (54.9) 308.6	203 (62.7) 128.9	858 (70.6) 164.4	1,131 (70.4) 164.3
Serious adverse events	0	10 (1.3) 4.2	10 (2.3) 8.3	7 (2.2) 2.3	49 (4.0) 3.9	62 (3.9) 3.8
Adverse events leading to treatment discontinuation	3 (1.9) 6.7	20 (2.5) 8.5	6 (1.4) 4.9	5 (1.5) 1.6	58 (4.8) 4.6	68 (4.2) 4.1
Adverse drug reactions	29 (18.5) 72.7	151 (18.9) 72.7	47 (10.9) 41.6	71 (21.9) 27.0	305 (25.1) 30.0	395 (24.6) 29.5
Death	0	0	1 (0.2) 0.8	0	3 (0.2) 0.2	3 (0.2) 0.2
Pediatric subpopulation (≥12 to <18 years weighing ≥40 kg)						
Number of subjects	4	107	54	35	388	390
Total exposure	1.2	32.6	16.5	43.7	460.1	503.8
All adverse events	2 (50.0) 255.4	38 (35.5) 146.7	30 (55.6) 287.4	17 (48.6) 59.8	243 (62.6) 106.4	255 (65.4) 100.9
Serious adverse events	0	1 (0.9) 3.1	0	1 (2.9) 2.3	9 (2.3) 2.0	10 (2.6) 2.0
Adverse events leading to treatment discontinuation	0	0	0	1 (2.9) 2.3	12 (3.1) 2.6	13 (3.3) 2.6
Adverse drug reactions	0	11 (10.3) 35.9	6 (11.1) 39.1	4 (11.4) 10.3	81 (20.9) 21.7	84 (21.5) 20.4
Death	0	0	0	0	1 (0.3) 0.2	1 (0.3) 0.2

Upper row, Number of subjects with events (%); Lower row, Number of subjects with adverse events per 100 person-years, adjusted for exposure period[a)]
a) Sum of the period to the occurrence of the first event (treatment period in subjects without event)

In the placebo-controlled pooled population, no significant differences were observed in the tendency of the occurrence of adverse events between the adult and pediatric subpopulations. Among the events investigated in Sections 7.R.3.2 through 7.R.3.7, eosinophilia tended to occur more frequently in the pediatric subpopulation (3.1% [12 of 390] of subjects receiving lebrikizumab) than in the adult subpopulation (1.0% [16 of 1,606] of subjects receiving lebrikizumab). All of them were non-serious, and none resulted in discontinuation of the study drug.

On the basis of the above, the applicant considers that there are no specific safety concerns for pediatric patients with AD associated with the administration of lebrikizumab.

PMDA's view:
The clinical study results obtained to date do not suggest any safety concerns specific to pediatric patients with AD with the administration of lebrikizumab. However, because of the limited analysis of safety study in Japanese pediatric patients with AD in clinical studies, post-marketing information on the safety of lebrikizumab in pediatric patients with AD should be collected continuously, and the obtained information should be provided to healthcare professionals appropriately.

PMDA's view on the safety of lebrikizumab based on the review in Sections 7.R.3.1 through 7.R.3.9:
The submitted clinical study data suggest neither serious safety concern of lebrikizumab in patients with AD nor events specific to Japanese patients with AD at present. Adverse events observed are manageable with the implementation of appropriate safety measures.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the expected clinical positioning of lebrikizumab in the treatment of AD:
On the basis of the efficacy and safety results obtained from the TCS combination studies (Studies KGAL and KGAD) and the lebrikizumab monotherapy studies (Studies KGAB and KGAC) and on the current treatment algorithm in Japan (see Section 1, Clinical Practice Guidelines for AD 2021), similar to the drugs used in already approved systemic therapies, lebrikizumab is qualified as a treatment option for patients with AD who have an inadequate response to appropriate treatment with topical anti-inflammatory drugs such as TCS.

Taking account of the recommendation of the most current Guidelines, clinical study results of lebrikizumab, specifications in the clinical studies, etc., the package insert for lebrikizumab will include the following precautionary statements: (1) Continuous use of topical moisturizing agents is necessary and (2) anti-inflammatory topical drugs should be used in combination depending on the condition of the AD lesion site, as a general rule.

PMDA's view:
Given the clinical study data submitted and the most current treatment algorithm for AD, lebrikizumab can be qualified as an option for the treatment of AD that have an inadequate response to conventional

treatments, as are the cases with approved biological products and oral JAK inhibitors, etc., that are used for systemic treatment of AD.

As for concomitant drugs, given the recommendations in the most current guidelines, clinical study data of lebrikizumab, specifications in the clinical studies, etc., lebrikizumab should be used with continuous use of topical moisturizing agents in combination with anti-inflammatory topical agents, as a rule. In the clinical studies of lebrikizumab, co-administration of the following treatments was prohibited, and there are no data available on the co-administration of these treatments with lebrikizumab: Biological drugs, oral immunosuppressants such as cyclosporine, oral corticosteroid, oral JAK inhibitors, and phototherapy. Information on the specifications regarding concomitant drugs in clinical studies should be provided so that physicians planning to use lebrikizumab can appropriately select concomitant drugs and therapy.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Indication

On the basis of the submitted documents and on the reviews in Sections 7.R.2, 7.R.3, and 7.R.4, PMDA considers that the indication for lebrikizumab should be "atopic dermatitis not responding adequately to conventional treatments," as proposed.

The following precautions should be provided in the package insert, as is the case with approved biological products and oral JAK inhibitors used for AD:

- Lebrikizumab should be used in patients with wide-spread, severe inflammatory rash who have an inadequate response even after a certain period of appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI.
- As a general rule, lebrikizumab should be administered in combination with topical anti-inflammatory drugs according to the conditions of the site affected by AD.
- A topical moisturizing agent should be used continuously during the treatment with lebrikizumab.

Information on the inclusion criteria in clinical studies should be provided as reference information for selecting subjects eligible for treatment with lebrikizumab. Also, caution should be provided that physicians well versed in the diagnosis and treatment of AD should use lebrikizumab to facilitate appropriate diagnosis and selection of patients treatable with lebrikizumab and proper use of lebrikizumab.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation:

In light of the results described in Sections 7.R.2 and 7.R.3 as well as from the point of view of the efficacy described below, the dosage regimen should be changed from the proposed one to the new regimen described below. The initially proposed treatment option of lebrikizumab 250 mg Q8W from Week 16 was deleted from the dosage regimen because of the infeasibility.

The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals, administered by subcutaneous injection. After the therapeutic effect is achieved, the maintenance dose of 250 mg is administered subcutaneously at 4-week intervals.
After proceeding to the maintenance dose, the 250 mg dosing interval may be changed to 2 weeks as appropriate according to the patient's condition.

Dosage regimen from the induction phase until therapeutic effects are achieved:

For the following reasons, it is considered appropriate to start treatment with lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) Q2W.

- In Study KGAL, a statistically significant difference was observed in both of the percentage of patients achieving IGA (0/1) and EASI-75 at Week 16, the co-primary endpoints, by each paired comparison between the placebo group and the lebrikizumab 250 mg Q2W group and between the placebo group and the lebrikizumab 250 mg Q4W group, establishing the superiority of both lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W to placebo (Table 43).
- Table 50 shows the results of main efficacy endpoints in Study KGAL, which showed a trend of improvement in the 250 mg Q2W group and the 250 mg Q4W group over the placebo group. All endpoints tended to be numerically greater in the 250 mg Q2W group than in the 250 mg Q4W group. In particular, the indices related to itching which significantly affect the QOL of patients with AD tended to improve more rapidly (at Week 4) in the 250 mg Q2W group than in the 250 mg Q4W group.
- Table 54 shows the results obtained by administering lebrikizumab 250 mg Q2W to subjects who had received the rescue therapy during the induction phase of the pivotal phase III study or subjects who had failed to achieve IGA (0/1) and EASI-75 at Week 16. A certain level of therapeutic response was obtained with continued administration of lebrikizumab even after transition to the maintenance escape period, regardless of concomitant use of TCS.

Maintenance dose after achievement of treatment effect:

For the following reasons, it is considered possible to maintain a therapeutic effect similar to that of continued lebrikizumab 250 mg Q2W administration by switching the dosing interval to Q4W at an arbitrary time point and continuing the administration in patients who have achieved adequate therapeutic effects with 250 mg Q2W.

- Table 53 shows the results obtained in subjects who received lebrikizumab 250 mg Q2W or Q4W after achieving IGA (0/1) or EASI-75 at Week 16 in the pivotal phase III study. The treatment efficacy of lebrikizumab tended to be maintained both in subjects receiving 250 mg Q2W/Q4W group and in subjects receiving 250 mg Q4W/Q4W, as demonstrated by both endpoints. The above findings suggest that the treatment efficacy is maintained by 250 mg Q4W administration once an adequate treatment efficacy has been achieved in the induction phase, regardless of the dosage regimen during the phase.
- Table 68 shows the percentages of patients achieving EASI-75 or EASI-90 at Week 52 after administration of lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo after Week 16 in patients who had achieved EASI-75 at Week 16, estimated from the exposure-response model [see

Section 6.2.4] constructed by using EASI scores during the induction phase in children aged ≥12 years and adults with AD obtained from 5 foreign clinical studies in patients with AD.[15)] Results suggest that similar efficacy is achieved by both of the dosage regimens 250 mg Q2W and 250 mg Q4W.

Table 68. Results of simulation based on the exposure-response model associated with percentage of patients achieving EASI-75 or EASI-90 at Week 52 after administration of lebrikizumab or placebo after Week 16 in subjects who had achieved EASI-75 at Week 16

Dosage regimen	Percentage of patients achieving EASI-75	Percentage of patients achieving EASI-90
250 mg Q2W	88 [81, 95]	60 [49, 70]
250 mg Q4W	80 [72, 88]	48 [38, 58]
250 mg Q8W	73 [63, 82]	41 [30, 51]
Placebo	48 [38, 59]	22 [14, 32]

% [95% CI]

- Given the superiority of lebrikizumab 250 mg Q4W (500 mg for the initial dose) to placebo demonstrated in Study KGAL (Table 43), efficacy can be expected even after switching from Q2W to Q4W administration before Week 16 if an adequate therapeutic effect has been achieved with Q2W administration, although there are no study results of switching to 250 mg Q4W after the loading dose of 500 mg of lebrikizumab at the initial and Week 2 in clinical studies of lebrikizumab.

It is considered appropriate to specify a dosage regimen that uniformly switches the dosing interval to Q4W for patients who have achieved adequate therapeutic effects with 250 mg Q2W administration because this will obliterate unnecessary continued Q2W administration and thereby reduce patient burden and improve the treatment adherence. Among subjects receiving 250 mg Q2W/Q4W in the pivotal phase III study, most of those who failed to maintain EASI-50 and proceeded to the maintenance escape period and received 250 mg Q2W administration showed a tendency of symptom improvement,[41)] suggesting that it is acceptable to change the dosage regimen to 250 mg Q2W according to the patient conditions after proceeding to the maintenance dose phase.

PMDA's view:

With regard to the maintenance dose after an adequate therapeutic effect is achieved, the applicant's explanation that the same level of the therapeutic effect can be maintained in both the 250 mg Q2W dosing and 250 mg Q4W dosing is understandable based on the clinical study results presented by the applicant. On the other hand, for subjects who achieved IGA (0/1) or EASI-75 at Week 16 in Study KGAL, results of the percentage of subjects who maintained IGA (0/1) or EASI-75 in the double-blind maintenance period (Table 69) showed a trend toward a lower percentage of IGA (0/1) achievement in the 250 mg Q4W/Q4W and 250 mg Q2W/Q4W groups compared with the 250 mg Q2W/Q2W group, thus, the 250 mg Q2W dosing may have a higher therapeutic effect even in patients who have achieved an adequate therapeutic effect. The incidence of adverse events showed no significant difference

41) Among subjects receiving 250 mg Q2W/Q4W in Study KGAL, all 3 subjects who failed to maintain EASI-50 showed improvement in the EASI score from immediately after proceeding to the maintenance escape period and receiving 250 mg Q2W administration. The pooled data of Studies KGAB and KGAC showed that, in 3 of 5 subjects in the 250 mg Q2W/Q4W group who had failed to maintain EASI-50, improvement of EASI score was observed from immediately after receiving 250 mg Q2W upon proceeding to the maintenance escape period.

between the subjects receiving 250 mg Q2W and 250 mg Q4W [see Section 7.R.3], and the results do not suggest that the 250 mg Q4W dosing should be more recommended from a safety perspective.

On the basis of the above, there is little need to uniformly administer 250 mg Q4W as the maintenance dose after an adequate therapeutic effect has been achieved, as proposed by the applicant. Taking into consideration the patient's conditions and the therapeutic effect of lebrikizumab in clinical settings, it is determined whether the dosing interval of Q2W or Q4W is appropriate and the dosage regimen of lebrikizumab should be specified.

Table 69. Efficacy of long-term treatment in subjects achieving IGA (0/1) or EASI-75 at Week 16 (Study KGAL, NRI)

Week	Percentage of subjects who maintained IGA (0/1) among those who achieved IGA (0/1) at Week 16			Percentage of subjects who maintained EASI-75 among those who achieved EASI-75 at Week 16		
	250 mg Q4W/Q4W	250 mg Q2W/Q4W	250 mg Q2W/Q2W	250 mg Q4W/Q4W	250 mg Q2W/Q4W	250 mg Q2W/Q2W
16	100 (23/23)	100 (16/16)	100 (24/24)	100 (38/38)	100 (33/33)	100 (29/29)
24	73.9 (17/23)	75.0 (12/16)	75.0 (18/24)	86.8 (33/38)	93.9 (31/33)	89.7 (26/29)
32	52.2 (12/23)	68.8 (11/16)	75.0 (18/24)	89.5 (34/38)	81.8 (27/33)	86.2 (25/29)
40	52.2 (12/23)	62.5 (10/16)	79.2 (19/24)	81.6 (31/38)	84.8 (28/33)	89.7 (26/29)
52	69.6 (16/23)	50.0 (8/16)	66.7 (16/24)	81.6 (31/38)	72.7 (24/33)	89.7 (26/29)
68	60.9 (14/23)	56.3 (9/16)	70.8 (17/24)	73.7 (28/38)	75.8 (25/33)	79.3 (23/29)

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, proceeded to the maintenance escape period, or had missing data

Regarding the timing of switching to Q4W, given that the superior results with 250 mg Q4W to placebo in the primary endpoints of Study KGAL has been demonstrated, and that, in subjects who have achieved IGA (0/1) or EASI-75 at Week 16, it is possible to maintain the efficacy by lebrikizumab 250 mg Q4W regardless of the dosage regimen during the induction phase, 250 mg Q4W may be selected at an appropriate timing in patients who have achieved an adequate treatment effect after the end of administration of the loading dose.

On the basis of the above, for patients who have achieved an adequate therapeutic effect after completion of the loading dose, the following "Dosage and Administration" that includes an option of administering 250 mg Q4W at any time depending on the patient's conditions should be specified.

Dosage and administration: The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals after Week 4, administered by subcutaneous injection. After Week 4, the 250 mg may be administered subcutaneously at 4-week intervals, according to the patient's condition.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.7 Self-injection

The applicant's explanation about the safety and efficacy of lebrikizumab self-injection, based on the results of Study KGAL:

In Study KGAL, self-injection[42)] was recommended during the double-blind maintenance period and the maintenance escape period. Among 103 subjects (38 receiving 250 mg Q4W/Q4W, 33 receiving 250 mg Q2W/Q4W, 32 receiving 250 mg Q2W/Q2W) who were responders at Week 16 and enrolled in the double-blind maintenance period, 72 subjects (25 receiving 250 mg Q4W/Q4W, 27 receiving 250 mg Q2W/Q4W, 20 receiving 250 mg Q2W/Q2W) self-injected lebrikizumab. In subjects who self-injected lebrikizumab, the number of self-injections (mean ± SD) was 21.3 ± 8.20 doses.

Table 70 shows the results of efficacy evaluation in the subject population who were responders at Week 16 and in the self-injection sub-population among this population. No significant difference in the efficacy was observed between the self-injection subpopulation and the whole population.

Table 70. Comparison of efficacy at Week 68 between the entire 16-week responder population[a)] and the self-injection subpopulation (Study KGAL, NRI)

	Subject population who were responders at Week 16			Self-injection subpopulation[b)]		
Endpoint	250 mg Q4W/Q4W	250 mg Q2W/Q4W	250 mg Q2W/Q2W	250 mg Q4W/Q4W	250 mg Q2W/Q4W	250 mg Q2W/Q2W
Percentage of patients achieving IGA (0/1)	60.9 (14/23)	56.3 (9/16)	70.8 (17/24)	52.9 (9/17)	58.3 (7/12)	75.0 (12/16)
Percentage of patients achieving EASI-75	73.7 (28/38)	75.8 (25/33)	79.3 (23/29)	68.0 (17/25)	74.1 (20/27)	84.2 (16/19)

% (number of subjects). Treatment was regarded as ineffective in subjects who received rescue therapy, discontinued the treatment, proceeded to the maintenance escape period, or had missing data

a) The percentage of patients achieving IGA (0/1) is the percentage among subjects who had achieved IGA (0/1) at Week 16, and the percentage of patients achieving EASI-75 is the percentage among subjects who had achieved EASI-75 at Week 16.

b) Subjects who self-injected lebrikizumab at least once among the subject population who had been responders at Week 16

Table 71 shows the safety summary in the responders at Week 16 and in the self-injection subpopulation among them. The incidence of injection site reaction in the self-injection subpopulation (9.7% [7 of 72 subjects]) was numerically higher than the incidence in the whole population of responders at Week 16 (7.8% [8 of 103 subjects]), but all of the observed events were non-serious, posing no safety concern.

42) The study drug was injected by a healthcare professional during the induction phase and by the subject under the supervision of a healthcare professional at Week 16 and Week 18. Thereafter, self-injection was recommended at home. If the subject was unable to self-inject the study drug, it could be administered by a caregiver.

Table 71. Safety summary in Week 16 responder population[a)] and the self-injection subpopulation (Study KGAL)

	All subjects receiving lebrikizumab	250 mg Q4W/Q4W	250 mg Q2W/Q4W	250 mg Q2W/Q2W
Subject population who were responders at Week 16				
Adverse events	82.5 (85/103)	81.6 (31/38)	75.8 (25/33)	90.6 (29/32)
Serious adverse events	1.9 (2/103)	2.6 (1/38)	0	3.1 (1/32)
Adverse events leading to discontinuation	0	0	0	0
Adverse drug reactions	25.2 (26/103)	21.1 (8/38)	27.3 (9/33)	28.1 (9/32)
Death	0	0	0	0
Injection site reaction	7.8 (8/103)	5.3 (2/38)	9.1 (3/33)	9.4 (3/32)
Self-injection subpopulation[b)]				
Adverse events	81.9 (59/72)	84.0 (21/25)	74.1 (20/27)	90.0 (18/20)
Serious adverse events	2.8 (2/72)	4.0 (1/25)	0	5.0 (1/20)
Adverse events leading to discontinuation	0	0	0	0
Adverse drug reactions	27.8 (20/72)	28.0 (7/25)	25.9 (7/27)	30.0 (6/20)
Death	0	0	0	0
Injection site reaction	9.7 (7/72)	4.0 (1/25)	11.1 (3/27)	15.0 (3/20)

% (number of subjects)

a) The percentage of patients achieving IGA (0/1) is the percentage among subjects who had achieved IGA (0/1) at Week 16, and the percentage of patients achieving EASI-75 is the percentage among subjects who had achieved EASI-75 at Week 16.

b) Subjects who self-injected lebrikizumab at least once among the subject population who had been responders at Week 16

PMDA's view:

Results of clinical studies so far do not suggest any particular problems on the efficacy and safety of lebrikizumab self-injection. Physicians should carefully consider the necessity of self-injection, provide education and training to ensure that patients are able to self-inject lebrikizumab, and instruct self-injection only after confirming that patients have learned lebrikizumab-related risks (and how to manage them). If adverse drug reactions of lebrikizumab such as anaphylaxis/hypersensitivity-related events are suspected, or if the situation becomes difficult to continue self-injection, the patient should be cautioned to immediately discontinue self-injection and take appropriate measures such as careful observation under a physician's supervision.

7.R.8 Post-marketing investigations and safety measures

The applicant plans to conduct a use-result survey in patients with AD newly treated with lebrikizumab to confirm the safety in long-term treatment of lebrikizumab in clinical use after the market launch.

PMDA's view:

As reviewed in Section 7.R.3, the safety of lebrikizumab is acceptable based on the clinical study data. Since lebrikizumab is expected to be administered for a long period of time, the applicant should conduct post-marketing surveillances to investigate (1) the risk of developing serious infections and malignancies by suppressing the IL-13 signaling pathway for a long period of time and (2) the safety of long-term treatment of lebrikizumab, then provide the information thus obtained to healthcare professionals as appropriate. Lebrikizumab should be used by physicians with sufficient knowledge on lebrikizumab and with adequate knowledge and experience in the treatment of AD.

The above conclusions of PMDA and the necessity of additional safety measures will be discussed at the Expert Discussion.

7.R.9 Development of lebrikizumab for children

The applicant is currently conducting a clinical study in pediatric patients with moderate to severe AD who are ≥6 months to <12 years and those with ≥12 to <18 years weighing <40 kg.

PMDA's view on lebrikizumab development in children:

Given the morbidity, etc., of pediatric AD, it is of clinical significance to develop lebrikizumab for patients with moderate to severe AD who are ≥6 months to <12 years and those with ≥12 to <18 years weighing <40 kg, and the applicant's policy of conducting a clinical study targeting the above patients is appropriate.

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

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

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

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

The new drug application data (CTD 5.3.5.1.4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that lebrikizumab has efficacy in the treatment of AD not responding adequately to conventional treatments, and that lebrikizumab has acceptable safety in view of its benefits. Lebrikizumab is clinically meaningful because it offers a new treatment option for patients with AD not responding adequately to conventional treatments. The safety of lebrikizumab in clinical use, including long-term treatment should be further evaluated in post-marketing surveillance.

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

10. Other

Methods for efficacy evaluation and definitions of endpoints in clinical studies of lebrikizumab are as shown below.

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>IGA score</td><td>Physician’s general assessment of rash, with a 5-point evaluation score based on the following criteria:
<table>
<tr><th>Score</th><th>Grade</th><th>Definition</th></tr>
<tr><td>0</td><td>Clear</td><td>Minor, residual discoloration; no erythema or induration/papulation; no oozing/crusting; no oedema</td></tr>
<tr><td>1</td><td>Almost clear</td><td>Trace, faint pink erythema with barely perceptible induration/papulation and no oozing/crusting; no oedema</td></tr>
<tr><td>2</td><td>Mild</td><td>Faint-pink erythema with papulation and edema perceptible upon palpation and no oozing/crusting; minimal induration.</td></tr>
<tr><td>3</td><td>Moderate</td><td>Pink to red erythema with definite edema of skin papules and plaques; there may be some oozing/crusting; palpable induration.</td></tr>
<tr><td>4</td><td>Severe</td><td>Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration.</td></tr>
</table></td></tr>
<tr><td>EASI score</td><td>For each of the 4 body regions (head and neck, trunk, upper limbs, and lower limbs), the severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) of the 4 rash elements (erythema, edema/papulation, excoriation, and lichenification) is summed, multiplied by the region score (0 = 0%, 1 = 1-9% , 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89%, 6 = 90-100%) based on the extent of eczema area, multiplied by the coefficient (0.1 = head and neck, 0.2 = upper limbs, 0.3 = trunk, 0.4 = lower limbs) for each body region, and the resulting score is summed. Minimum value 0, maximum value 72.</td></tr>
<tr><td>Pruritus NRS score</td><td>A patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no itch” and 10 representing “worst itch imaginable.” The score is obtained by choosing the number that best represents the worst degree of itching within 24 hours.</td></tr>
<tr><td>Percentage of patients achieving IGA (0/1)</td><td>Percentage of patients with an IGA score of 0 or 1 and an improvement of ≥2 points from baseline</td></tr>
<tr><td>Percentage of patients achieving EASI-50/75/90</td><td>Percentage of patients whose EASI score decreased by ≥50%, ≥75% or ≥90% from baseline</td></tr>
<tr><td>Percentage of patients with pruritus NRS ≥4-points improvement</td><td>Percentage of patients who achieved an improvement of ≥4 points from baseline at a given time point among subjects with an NRS score of ≥4 points at baseline</td></tr>
</table>

Definitions of events described in Section 7.R.3 are as shown below.

Term	Definition
Anaphylaxis/hypersensitivity-related events	SMQ: Anaphylactic reaction (narrow), hypersensitivity (narrow), angioedema (narrow)
Injection site reaction	HLT: Injection site reaction other than PTs listed below: PT: Injection site joint discomfort, injection site joint effusion, injection site joint erythema, injection site joint infection, injection site joint inflammation, injection site joint movement impairment, injection site joint pain, injection site joint swelling, injection site joint warmth
Infection	SOC: Infections and infestations
Opportunistic infection (narrow)	PT: Aspergillosis oral, cerebral aspergillosis, disseminated aspergillosis, meningitis aspergillus, oro-pharyngeal aspergillosis, bacillary angiomatosis, peliosis hepatis, splenic peliosis, systemic bartonellosis, trench fever, blastomycosis, cutaneous blastomycosis, disseminated blastomycosis, epididymitis blastomyces, osteomyelitis blastomyces, pulmonary blastomycosis, Campylobacter sepsis, Candida endophthalmitis, Candida osteomyelitis, Candida pneumonia, Candida retinitis, Candida sepsis, cerebral candidiasis, endocarditis candida, fungal oesophagitis, gastrointestinal candidiasis, hepatic candidiasis, hepatosplenic candidiasis, meningitis candida, oesophageal candidiasis, oral candidiasis, oral fungal infection, oropharyngeal candidiasis, peritoneal candidiasis, splenic candidiasis, systemic candida, coccidioides encephalitis, coccidioidomycosis, cutaneous coccidioidomycosis, disseminated coccidioidomycosis, meningitis coccidioides, cryptococcal cutaneous infection, cryptococcal fungaemia,

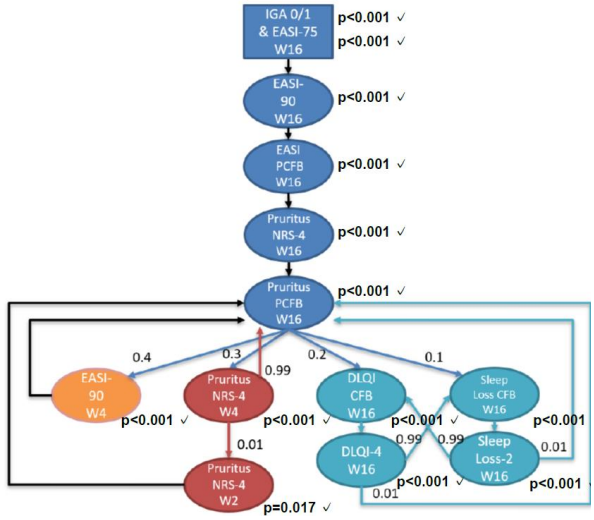
	cryptococcal meningoencephalitis, cryptococcosis, disseminated cryptococcosis, gastroenteritis cryptococcal, laryngeal cryptococcosis, meningitis cryptococcal, neurocryptococcosis, osseous cryptococcosis, pneumonia cryptococcal, biliary tract infection cryptosporidial, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus duodenitis, cytomegalovirus enteritis, cytomegalovirus enterocolitis, cytomegalovirus gastritis, cytomegalovirus gastroenteritis, cytomegalovirus gastrointestinal infection, cytomegalovirus gastrointestinal ulcer, cytomegalovirus hepatitis, cytomegalovirus infection, cytomegalovirus mononucleosis, cytomegalovirus mucocutaneous ulcer, cytomegalovirus myelomeningoradiculitis, cytomegalovirus myocarditis, cytomegalovirus nephritis, cytomegalovirus oesophagitis, cytomegalovirus pancreatitis, cytomegalovirus pericarditis, cytomegalovirus syndrome, cytomegalovirus urinary tract infection, cytomegalovirus viraemia, disseminated cytomegaloviral infection, encephalitis cytomegalovirus, pneumonia cytomegaloviral, cytomegalovirus infection reactivation, hepatitis B reactivation, varicella encephalitis, varicella meningitis, Elsberg syndrome, colitis herpes, gastritis herpes, herpes oesophagitis, herpes sepsis, herpes simplex bronchitis, herpes simplex colitis, herpes simplex encephalitis, herpes simplex gastritis, herpes simplex hepatitis, herpes simplex meningitis, herpes simplex meningoencephalitis, herpes simplex meningomyelitis, herpes simplex necrotising retinopathy, herpes simplex oesophagitis, herpes simplex pneumonia, herpes simplex sepsis, herpes simplex viraemia, herpes simplex visceral, meningitis herpes, meningoencephalitis herpetic, meningomyelitis herpes, pneumonia herpes viral, oral herpes zoster, disseminated varicella, disseminated varicella zoster virus infection, disseminated varicella zoster vaccine virus infection, encephalitis post varicella, genital herpes zoster, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, herpes zoster reactivation, necrotising herpetic retinopathy, ophthalmic herpes zoster, varicella keratitis, varicella zoster sepsis, pulmonary histoplasmosis, acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, endocarditis histoplasma, histoplasmosis, histoplasmosis cutaneous, histoplasmosis disseminated, meningitis histoplasma, pericarditis histoplasma, retinitis histoplasma, JC virus granule cell neuronopathy, polyomavirus-associated nephropathy, progressive multifocal leukoencephalopathy, WU virus infection, Legionella infection, pneumonia legionella, Pontiac fever, disseminated leishmaniasis, visceral leishmaniasis, cutaneous listeriosis, Listeria encephalitis, Listeria sepsis, meningitis listeria, microsporidia infection, cerebral nocardiosis, cutaneous nocardiosis, Nocardia sepsis, nocardiosis, pulmonary nocardiosis, atypical mycobacterial lower respiratory tract infection, atypical mycobacterial lymphadenitis, atypical mycobacterial pneumonia, atypical mycobacterium pericarditis, borderline leprosy, bovine tuberculosis, disseminated mycobacterium avium complex infection, indeterminate leprosy, lepromatous leprosy, leprosy, mycobacterial peritonitis, mycobacterium avium complex immune restoration disease, tuberculoid leprosy, type 1 lepra reaction, type 2 lepra reaction, phaeohyphomycotic brain abscess, pseudallescheria sepsis, disseminated mucormycosis, pulmonary mucormycosis, rhinocerebral mucormycosis, disseminated paracoccidioidomycosis, paracoccidioides infection, pulmonary paracoccidioidomycosis, Penicillium infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Epstein Barr virus positive mucocutaneous ulcer, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, post transplant lymphoproliferative disorder, aortitis salmonella, arthritis salmonella, meningitis salmonella, osteomyelitis salmonella, paratyphoid fever, pneumonia salmonella, Salmonella bacteraemia, Salmonella sepsis, typhoid fever, Shigella sepsis, cutaneous sporotrichosis, disseminated sporotrichosis, pulmonary sporotrichosis, sporotrichosis, disseminated strongyloidiasis, cerebral toxoplasmosis, disseminated toxoplasmosis, eye infection toxoplasmal, meningitis toxoplasmal, myocarditis toxoplasmal, pneumonia toxoplasmal, Chagas' cardiomyopathy, meningitis trypanosomal, tuberculosis of uterine cervix, tuberculous pelvic inflammatory disease, adrenal gland tuberculosis, bone tuberculosis, choroid tubercles, conjunctivitis tuberculous, cutaneous tuberculosis, disseminated Bacillus Calmette-Guerin infection, disseminated tuberculosis, ear tuberculosis, epididymitis tuberculous, extrapulmonary tuberculosis, immune reconstitution inflammatory syndrome associated tuberculosis, intestinal tuberculosis, joint tuberculosis, lymph node tuberculosis, male genital tract tuberculosis, meningitis tuberculous, oesophageal tuberculosis, oral tuberculosis, pericarditis tuberculous, peritoneal tuberculosis, prostatitis tuberculous, pulmonary tuberculoma, pulmonary tuberculosis, renal tuberculosis, salpingitis tuberculous, silicotuberculosis, spleen tuberculosis, thyroid tuberculosis, tuberculid, tuberculoma of central nervous system, tuberculosis, tuberculosis bladder, tuberculosis gastrointestinal, tuberculosis liver, tuberculosis of central nervous system, tuberculosis of eye,

	tuberculosis of genitourinary system, tuberculosis of intrathoracic lymph nodes, tuberculosis of peripheral lymph nodes, tuberculosis ureter, tuberculous abscess central nervous system, tuberculous endometritis, tuberculous laryngitis, tuberculous pleurisy, tuberculous tenosynovitis
Opportunistic infection (broad)	Opportunistic infection (narrow) and the following PTs: PT: Aspergillus infection, Aspergillus test, Aspergillus test positive, bronchopulmonary aspergillosis, sinusitis aspergillus, Bartonella test, Bartonella test positive, bartonellosis, Campylobacter infection, Campylobacter test positive, Candida infection, Candida test, Candida test positive, mucocutaneous candidiasis, respiratory moniliasis, urinary tract candidiasis, Cryptococcus test, Cryptococcus test positive, Cryptosporidiosis infection, gastroenteritis cryptosporidial, Cytomegalovirus test, Cytomegalovirus test positive, asymptomatic viral hepatitis, chronic hepatitis B, HBV-DNA polymerase increased, hepatitis B, hepatitis B antigen, hepatitis B antigen positive, hepatitis B core antigen, hepatitis B core antigen positive, hepatitis B DNA assay, hepatitis B DNA assay positive, hepatitis B DNA increased, hepatitis B e antigen, hepatitis B e antigen positive, hepatitis B surface antigen, hepatitis B surface antigen positive, hepatitis B virus test, hepatitis B virus test positive, hepatitis A, hepatitis post transfusion, hepatitis viral, withdrawal hepatitis, chronic hepatitis C, hepatitis C, hepatitis C RNA, hepatitis C RNA fluctuation, hepatitis C RNA increased, hepatitis C RNA positive, hepatitis C virus core antigen, hepatitis C virus test, hepatitis C virus test positive, eczema herpeticum, herpes ophthalmic, herpes simplex, herpes simplex test positive, herpes simplex reactivation, herpes virus infection, herpes virus test abnormal, ophthalmic herpes simplex, varicella virus test, varicella virus test positive, varicella zoster virus infection, presumed ocular histoplasmosis syndrome, BK polyomavirus test positive, JC polyomavirus test positive, JC virus CSF test positive, anti-JC virus antibody index, BK virus infection, human polyomavirus infection, JC virus infection, JC polyomavirus test, polyomavirus test, polyomavirus test positive, polyomavirus viraemia, Legionella test, Legionella test positive, leishmaniasis, listeraemia, Listeria test, Listeria test positive, listeriosis, Nocardia test positive, septic cardiomyopathy, abscess fungal, Alternaria infection, arthritis fungal, biliary tract infection fungal, central nervous system fungal infection, cerebral fungal infection, encephalitis fungal, erythema induratum, eye infection fungal, fungaemia, fungal abscess central nervous system, fungal endocarditis, fungal labyrinthitis, fungal myositis, fungal peritonitis, fungal pharyngitis, fungal retinitis, fungal sepsis, hepatic infection fungal, mastoiditis fungal, meningitis fungal, mycotic endophthalmitis, myocarditis mycotic, oropharyngitis fungal, osteomyelitis fungal, otitis media fungal, pancreatitis fungal, parasitic pneumonia, pericarditis fungal, phaeohyphomycosis, pneumonia fungal, pulmonary trichosporonosis, sinusitis fungal, splenic infection fungal, systemic mycosis, atypical mycobacterial infection, atypical mycobacterium test positive, mycobacterial disease carrier, mycobacterial infection, Mycobacterium abscessus infection, Mycobacterium avium complex infection, Mycobacterium chelonae infection, Mycobacterium fortuitum infection, Mycobacterium haemophilum infection, Mycobacterium kansasii infection, Mycobacterium leprae test positive, Mycobacterium marinum infection, Mycobacterium test, Mycobacterium test positive, Mycobacterium ulcerans infection, superinfection mycobacterial, allescheriosis, Fusarium infection, mucormycosis, Pseudallescheria infection, Scedosporium infection, penicillium test positive, blood beta-D-glucan, blood beta-D-glucan abnormal, blood beta-D-glucan increased, lung diffusion test, lung diffusion test decreased, Gomori methenamine silver stain, Pneumocystis test positive, Epstein-Barr viraemia, Epstein-Barr virus infection, lymphoproliferative disorder, lymphoproliferative disorder in remission, oral hairy leukoplakia, Salmonella test positive, salmonellosis, Shigella infection, Shigella test positive, strongyloidiasis, Toxoplasma serology, Toxoplasma serology positive, toxoplasmosis, American trypanosomiasis, Trypanosoma serology positive, trypanosomiasis, interferon gamma release assay, interferon gamma release assay positive, Mycobacterium tuberculosis complex test, Mycobacterium tuberculosis complex test positive, tuberculin test, tuberculin test false negative, tuberculin test positive, Vibrio test positive, Vibrio vulnificus infection
Skin infection	HLT: Skin structures and soft tissue infections PT: Cellulitis, eczema impetiginous, folliculitis, staphylococcal skin infection, cellulitis staphylococcal, furuncle, erysipelas, fungal skin infection
Herpes zoster	PT: Oral herpes zoster, disseminated varicella, disseminated varicella zoster virus infection, disseminated varicella zoster vaccine virus infection, encephalitis post varicella, genital herpes zoster, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, herpes zoster reactivation, necrotising herpetic retinopathy, ophthalmic herpes zoster, varicella keratitis, varicella zoster sepsis

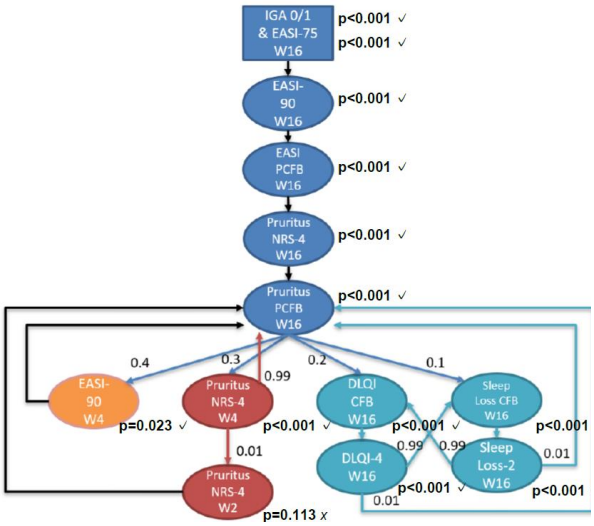
Herpes simplex virus infection	PT: Varicella encephalitis, varicella meningitis, Elsberg syndrome, colitis herpes, gastritis herpes, herpes oesophagitis, herpes sepsis, herpes simplex bronchitis, herpes simplex colitis, herpes simplex encephalitis, herpes simplex gastritis, herpes simplex hepatitis, herpes simplex meningitis, herpes simplex meningoencephalitis, herpes simplex meningomyelitis, herpes simplex necrotising retinopathy, herpes simplex oesophagitis, herpes simplex pneumonia, herpes simplex sepsis, herpes simplex viraemia, herpes simplex visceral, meningitis herpes, meningoencephalitis herpetic, meningomyelitis herpes, pneumonia herpes viral, eczema herpeticum, herpes ophthalmic, herpes simplex, herpes simplex test positive, herpes simplex reactivation, herpes virus infection, herpes virus test abnormal, ophthalmic herpes simplex
Infection parasitic	HLT: Cestode infection, helminthic infection NEC, nematode infection, trematode infection
Malignant tumour	SMQ: Malignant tumours
NMSC	PT: Squamous cell carcinoma of skin, Bowen's disease, basal cell carcinoma, basosquamous carcinoma, basosquamous carcinoma of skin, squamous cell carcinoma, skin cancer, carcinoma in situ of skin, keratoacanthoma, skin squamous cell carcinoma recurrent, lip squamous cell carcinoma, skin squamous cell carcinoma metastatic, penile squamous cell carcinoma
Malignant tumours other than NMSC	Malignant tumours other than NMSC
Conjunctivitis-related events	PT: Conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, giant papillary conjunctivitis
Keratitis-related events	PT: Keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, vernal keratoconjunctivitis
Eosinophilia	PT: Eosinophilia, allergic eosinophilia, eosinophil count abnormal, eosinophil count increased, eosinophil percentage increased
Depression/suicide-related events	SMQ: Suicide/self-injury SMQ: Depression (excl suicide and self-injury)
Latent MACE	SMQ: Myocardial infarction (narrow) HLT: Ventricular arrhythmias and cardiac arrest, coronary artery disorders NEC, ischaemic coronary artery disorders, central nervous system vascular disorders NEC, central nervous system haemorrhages and cerebrovascular accidents, transient cerebrovascular accident, speech and language abnormalities, paraesthesias and dysaesthesias, disturbances in consciousness NEC PT: Sudden cardiac death, sudden death
Hepatic dysfunction	SMQ: Liver related investigations, signs and symptoms (broad), cholestasis and jaundice of hepatic origin (broad), hepatitis, non-infectious (broad), hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (broad), liver-related coagulation and bleeding disturbances (narrow)
CPK increased/muscle disorders	PT: Blood creatine phosphokinase abnormal, blood creatine phosphokinase increased, myositis, muscle contusion, muscle injury, myalgia, muscle disorder, muscle spasms, musculoskeletal pain

For the analysis of the primary and secondary endpoints in the clinical studies, a multiplicity-adjusted analysis was performed using a graphical approach. Details of the graphical approach are shown in the figure below.

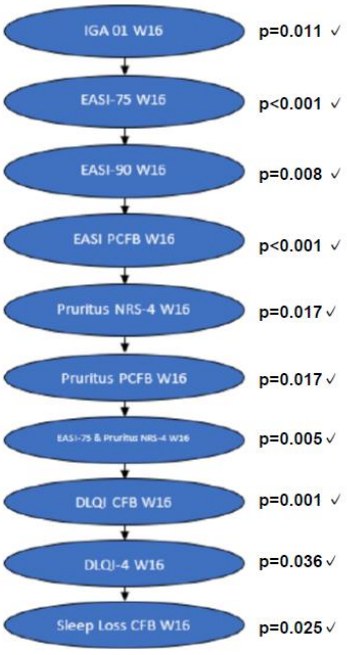
Study KGAB



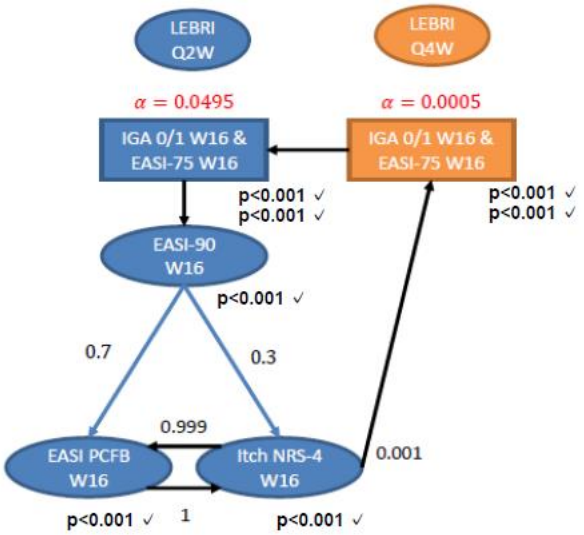
Study KGAC



Study KGAD



Study KGAL



CFB = change from Baseline; DLQI = Dermatology Life Quality Index; DLQI-4 = 4 point or greater improvement in DLQI, among participants with a Baseline score of at least 4; EASI = Eczema Area and Severity Index; EASI-75 = 75% decrease from Baseline in EASI; EASI-90 = 90% decrease from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0/1 = IGA score of 0 or 1 with a 2-point or greater reduction from Baseline; NRS = numeric rating scale; PCFB = percentage change from Baseline; Pruritus NRS-4 = 4 point or greater improvement in Pruritus NRS, among participants with a Baseline score of at least 4; Sleep Loss-2 = 2 point or greater improvement in Sleep-Loss, among participants with a Baseline score of at least 2; W = week.

Black arrows and subscripts indicate the proportion of significance levels to be allocated. A check mark indicates that the endpoint was statistically significant in the graphical approach. A stop symbol indicates that the endpoint is not statistically significant and hypothesis testing using the graphical approach has been stopped.

Review Report (2)

November 15, 2023

Product Submitted for Approval

Brand Name	Ebglyss Subcutaneous Injection 250 mg Autoinjectors Ebglyss Subcutaneous Injection 250 mg Syringes
Non-proprietary Name	Lebrikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	March 3, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy, safety, clinical positioning, indication, dosage and administration, post-marketing investigations, safety measures, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on efficacy, safety, clinical positioning, indication, dosage and administration, post-marketing investigations, and safety measures described in the Review Report (1), with the following comments:

- The dosage regimen proposed by PMDA is appropriate, based on the following: (1) Although no significant difference in the efficacy was observed between lebrikizumab 250 mg Q2W and 250 mg Q4W, maintenance of long-term efficacy tended to be better with 250 mg Q2W in Study KGAL; and (2) in clinical settings, the appropriate dosage regimen should be selected according to the patient's condition.
- Taking into account the safety profile of lebrikizumab, post-marketing surveillance should be conducted and safety measures taken, as are the cases with approved biological drugs for AD.

In view of the discussion at the Expert Discussion, PMDA has concluded that the dosage regimen for lebrikizumab should be "The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals after Week 4, administered by subcutaneous injection. After Week 4, the 250 mg subcutaneous dosing interval may be changed to 4 weeks according to the patient's condition."

In view of the review in Section "7.R.8 Post-marketing investigations and safety measures" in the Review Report (1) and the discussion at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for lebrikizumab should include the safety specifications presented in Table 72, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 73. PMDA instructed the applicant to conduct post-marketing surveillances, etc., that allow investigations of these items.

Table 72. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity	• Serious infection • Immunogenicity • Malignant tumour	None
Efficacy specification		
None		

Table 73. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance

The applicant explained the plan to conduct a specified use-results survey in patients with AD not responding adequately to conventional treatments to evaluate the safety and efficacy of lebrikizumab in long-term use under clinical settings.

Table 74. Outline of specified use-results survey (draft)

Objective	To confirm the safety and efficacy of lebrikizumab in clinical settings
Survey method	Central registry system
Population	Patients with AD not responding adequately to conventional treatments
Observation period	Up to 104 weeks from the initial dose of lebrikizumab
Planned sample size	400 (safety analysis population)
Main survey items	• Safety specification: Serious hypersensitivity, serious infection, malignant tumour • Patient characteristics (age, body weight, severity of AD, time of diagnosis, history/complication[s], etc.) • Use of lebrikizumab • Prior treatment for AD • Concomitant drugs, concomitant therapies • Laboratory tests • Adverse events • Efficacy evaluation

PMDA accepted the above response of the applicant. The information thus obtained should be provided appropriately and promptly to healthcare professionals, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and the dosage and administration as shown below, with the following approval condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. Both the drug product and its drug substance are classified as powerful drugs.

Indication

Atopic dermatitis not responding adequately to conventional treatments

(No change from the proposed text)

Dosage and Administration

The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 500 mg of lebrikizumab (genetical recombination) at Week 0 and Week 2, followed by 250 mg at 2-week intervals ~~from~~ after Week 4 ~~to 16~~, administered by subcutaneous injection. After Week 4, ~~Thereafter,~~ the ~~maintenance dose of~~ 250 mg may be ~~is~~ administered subcutaneously at 4-week intervals, according to the patient's condition. ~~After Week 16 , the 250 mg dosing interval may be changed to 2 weeks or 8 weeks as appropriate, according to the patient's condition.~~

(The underline denotes additions, and strikethrough denotes deletion from the proposed text.)

Approval Condition

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

Appendix

List of Abbreviations

250 mg Q2W group	The group receiving lebrikizumab 250 mg (500 mg for the initial dose and at Week 2) subcutaneously Q2W for 16 weeks during the induction phase
250 mg Q2W/Q2W group	The population of subjects who, after participating in the 250 mg Q2W group, received lebrikizumab 250 mg subcutaneously Q2W during the double-blind maintenance period or maintenance escape period
250 mg Q2W/Q4W group	The population of subjects who, after participating in the 250 mg Q2W group, received lebrikizumab 250 mg subcutaneously Q4W during the double-blind maintenance period (those who proceeded to the maintenance escape period received lebrikizumab 250 mg subcutaneously Q2W)
250 mg Q4W group	The group receiving lebrikizumab 250 mg (500 mg for the initial dose) subcutaneously Q4W for 16 weeks during the induction phase
250 mg Q4W/Q4W group	The population of subjects who, after participating in 250 mg Q4W group, received lebrikizumab 250 mg subcutaneously Q4W during the double-blind maintenance period (those who proceeded to the maintenance escape period received lebrikizumab 250 mg subcutaneously Q2W)
A/G ratio	Albumin/globulin ratio
AD	Atopic dermatitis
ADA	Anti-drug antibody
AI	Autoinjector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the time-serum concentration curve
$AUC_{0\text{-}14\ day}$	AUC from time 0 to day 14
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last observed concentration
$AUC_{\tau,ss}$	AUC over a dosing interval at steady-state
BMI	Body mass index
BSA	Body surface area
C1q	Complement component 1, q subcomponent
CAL	Cells at the limit of in vitro cell age
$C_{avg,ss}$	Average concentration at steady state
CDR	Complementarity determining region
CE-SDS	Capillary electrophoresis-sodium dodecyl sulphate
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL	Clearance
CL/F	Apparent clearance
Clinical Practice Guidelines for AD 2018/2021	Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018/2021, edited by Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis, the Japanese Dermatological Association/Japanese Society for Allergology
C_{max}	Maximum serum concentration
$C_{max,ss}$	Cmax at steady state
CPK	Creatine phosphokinase
CQA	Critical quality attribute
CTCAE	Common terminology criteria for adverse events
C_{trough}	Minimum concentration over a dosing interval

$C_{trough,ss}$	C_{trough} at steady state
CV	Coefficient of variation
Ebglyss	Ebglyss Subcutaneous Injection 250 mg Autoinjectors, Ebglyss Subcutaneous Injection 250 mg Syringes
EC_{50}	Drug concentration that produces 50% of maximum effect
EFD study	Embryo-fetal development study
ELISA	Enzyme-linked immunosorbent assay
F	Bioavailability
FcRn	Neonatal Fc receptor
GCP	Good Clinical Practice
HCP	Host cell protein
hERG	Human *ether-a-go-go* rerated gene
HLT	High level term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) Guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guideline	Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D Guideline	"Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IL-13Rα1/α2	IL-13 receptor α1/α2
IL-4Rα1	IL-4 receptor α
ITT	Intention to treat
JAK	Janus kinase
Ka	Absorption rate constant
KLH	Keyhole limpet hemocyanin
Lebrikizumab	Lebrikizumab (genetical recombination)
MACE	Major adverse cardiovascular event
MCB	Master cell bank
MI	Multiple imputation
mITT	Modified ITT
MMF	Mycophenolate mofetil
MTX	Methotrexate
NMSC	Non-melanoma skin cancer
Non-responders	Subjects who received rescue therapy during the induction phase or achieved neither of IGA (0/1) and EASI-75 at Week 16
NRI	Non-responder imputation
NRS	Numeric rating scale
PDE4	Phosphodiesterase 4
PMDA	Pharmaceuticals and Medical Devices Agency
PPND study	Pre- and postnatal developmental study
PT	Preferred term
PUVA	Psoralen ultraviolet A
QxW	X-week interval
Responders	Subjects who did not receive rescue therapy during the induction phase and achieved IGA (0/1) or EASI-75 at Week 16
RMP	Risk management plan

SEC	Size exclusion chromatography
SMQ	Standardized MedDRA query
SOC	System organ class
SPR	Surface plasmon resonance
Subjects receiving placebo/250 mg Q2W	The population of subjects who, after receiving placebo during the induction phase, received lebrikizumab 250 mg subcutaneously Q2W during the double-blind maintenance period or maintenance escape period
$t_{1/2}$	Elimination half life
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TGF	Transforming growth factor
t_{max}	Time to maximum concentration
V2	Volume of distribution of the central compartment
V_d	Volume of distribution
V_z/F	Apparent volume of distribution at the terminal phase after SC administration
WCB	Working cell bank

* For the non-proprietary names of biological products, the term "(genetical recombinant)" is omitted.