Report on the Deliberation Results

March 8, 2022

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

Brand Name	Mitchga Syringes 60 mg
Non-proprietary Name	Nemolizumab (Genetical Recombination) (JAN*)
Applicant	Maruho Co., Ltd.
Date of Application	July 29, 2020

Results of Deliberation

In its meeting held on March 3, 2022, Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Review Report

February 14, 2002
Pharmaceuticals and Medical Devices Agency

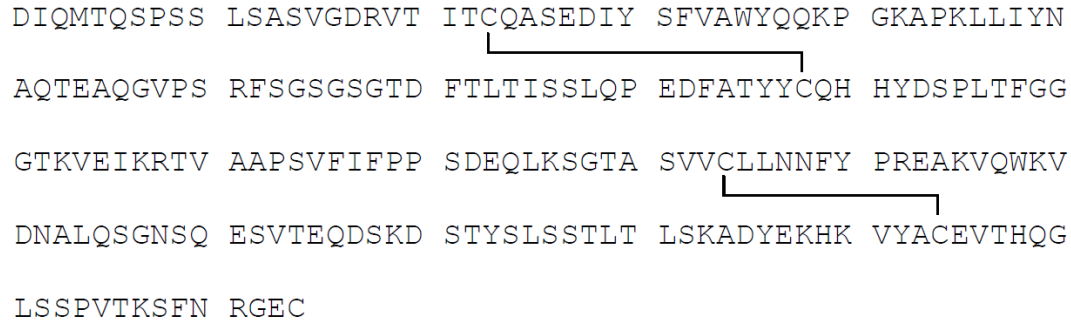
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Mitchga Syringes 60 mg
Non-proprietary Name	Nemolizumab (Genetical Recombination)
Applicant	Maruho Co., Ltd.
Date of Application	July 29, 2020
Dosage Form//Strength	Solution for injection. Each syringe contains 75 mg of nemolizumab (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Nemolizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-31 receptor antibody, human framework regions and human IgG2 constant regions. In the H-chain, amino acid residues at position 135, 137, 141, 142, 223, 268, 355 and 419 are substituted by Ser, Lys, Gly, Gly, Ser, Gln, Gln and Glu, respectively, and Gly and Lys at the C-terminus are deleted. Nemolizumab is produced in Chinese hamster ovary cells. Nemolizumab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ2-chains) consisting of 445 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

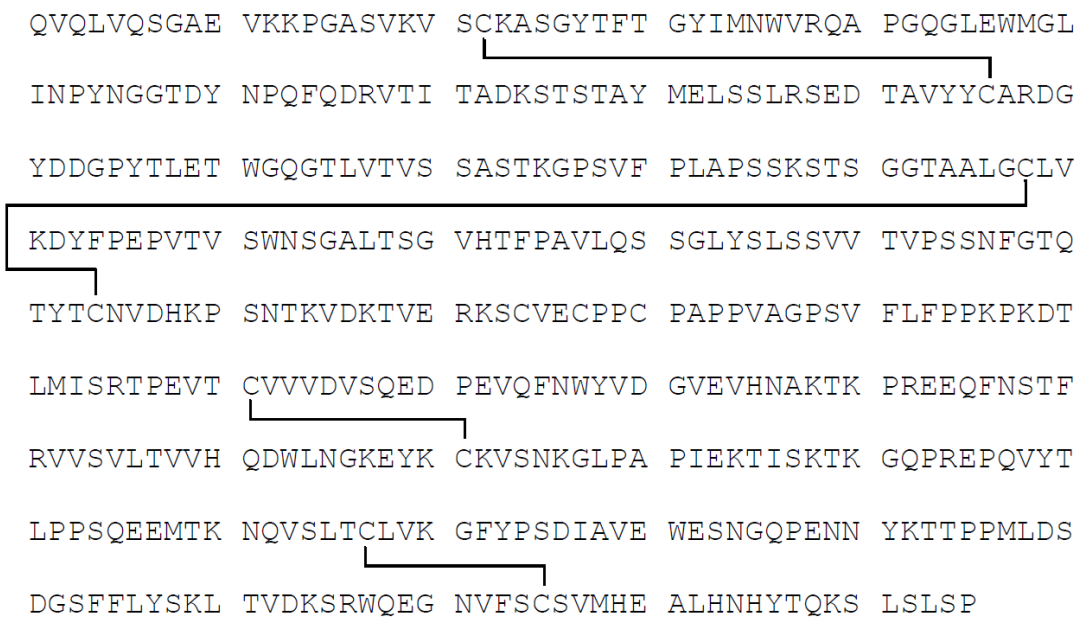
Structure

Amino acid sequence:

L chain



H chain

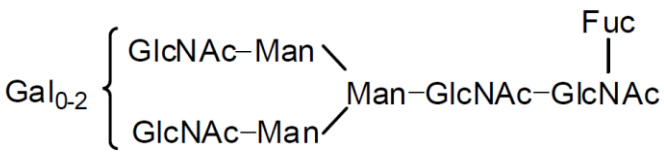


Pyroglutamic acid (partial): H chain Q1. Glycosylation: H chain N297

Intra-chain disulfide bonds: Solid lines in the above figure

Inter-chain disulfide bonds: L chain C214-H chain C224, H chain C227-H chain C227, and H chain C230-H chain C230

Main proposed carbohydrate structure



Molecular formula: $C_{6384}H_{9814}N_{1678}O_{2034}S_{48}$ (protein moiety, 4 chains)

(H chain) $C_{2163}H_{3328}N_{566}O_{679}S_{18}$

(L chain) $C_{1029}H_{1583}N_{273}O_{338}S_{6}$

Molecular weight: 144,153 (protein moiety)

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 pruritus associated with atopic dermatitis (only for patients who are inadequately controlled by conventional treatments), and that the product has acceptable safety in view of its benefit (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 conditions. The safety of the product in clinical practice should be further evaluated.

Indication

Treatment of pruritus associated with atopic dermatitis (only for patients who are inadequately controlled by conventional treatments)

Dosage and Administration

The usual dose for adults and children aged 13 years or older is 60 mg of nemolizumab (genetical recombination) subcutaneously administered once every 4 weeks.

Approval Conditions

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

Attachment

Review Report (1)

April 28, 2021

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	Mitchga Syringes 60 mg
Non-proprietary Name	Nemolizumab (Genetical Recombination)
Applicant	Maruho Co., Ltd.
Date of Application	July 29, 2020
Dosage Form//Strength	Solution for injection. Each syringe contains 75 mg[1)] of nemolizumab (genetical recombination).

Proposed Indication

Treatment of pruritus associated with atopic dermatitis in patients who are inadequately controlled by conventional treatments

Proposed Dosage and Administration

The usual dose for adults and children aged 13 years or older is 60 mg of nemolizumab (genetical recombination) subcutaneously administered once every 4 weeks.

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[1)] With consideration of losses during preparation and administration of the drug solution, one syringe is overfilled to allow for the injection of 60 mg of nemolizumab (genetical recombination).

List of Abbreviations

See Appendix.

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

Nemolizumab (genetical recombination) (nemolizumab), the active ingredient of Mitchga Syringes 60 mg, is a humanized monoclonal antibody against the human Interleukin-31 receptor A (IL-31RA) discovered by Chugai Pharmaceutical Co., Ltd.

Atopic dermatitis (AD) is a chronic pruritic skin disease in which a patient presents with a primary lesion of eczema with repeated exacerbation and remission. Persistent pruritus causes decreases in concentration and sleep disturbance, resulting in a significant reduction in patient quality of life. Scratching associated with pruritus aggravates skin symptoms and further worsens pruritus, which is a vicious cycle (itch-scratch cycle), and also induces complications such as skin infections and ocular symptoms, being involved in the pathogenesis of AD.

The treatment of AD is based on pharmacotherapies, topical therapy/skin care for physiological abnormalities of the skin, exploratory investigation of and measures against aggravating factors, depending on the conditions of patients. Topical anti-inflammatory drugs including topical steroids (topical corticosteroids, TCS) and topical tacrolimus (topical calcineurin inhibitors, TCI) have been recommended to induce remission. For patients who fail to achieve remission with these topical therapies, the use of more potent TCS and the concomitant use of oral ciclosporin and ultraviolet radiation therapy are considered, depending to the severity of skin eruption (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology*. 2018;128:2431-502]). Recently, dupilumab, an anti-IL-4/13 receptor monoclonal antibody, and baricitinib, a Janus kinase (JAK) inhibitor, have been approved for patients with AD who are inadequately controlled by topical anti-inflammatory drugs including TCS and TCI.

Oral antihistamines in combination with TCS or TCI are recommended for the treatment of pruritus associated with AD. However, the effectiveness of antihistamines in relieving pruritus depends on the severity of AD and other clinical features, and the use of oral antihistamines is positioned as an adjuvant therapy. Oral ciclosporin is known to relieve pruritus rapidly after its administration, but the target patient population and treatment duration are limited from the safety point of view. Therefore, there are patients in whom pruritus associated with AD is inadequately controlled with the current therapies, and development of safer and more effective therapies are required.

IL-31, a cytokine produced mainly by activated T cells, is known to be mainly involved in pruritus among AD symptoms (*Nat Immunol*. 2004;5:752-60; *Nat Commun*. 2017;8:13946; *N Engl J Med*. 2017;376:826-35). Since nemolizumab binds to IL-31RA constituting the IL-31 receptor (a heterodimer consisting of IL-31RA and oncostatin M receptor [OSMR]) and inhibits the signal transduction of IL-31, it has been developed with the expectation of offering therapeutic effects for pruritus associated with AD.

The clinical development of nemolizumab began in August 2011. Based on the data including results from Japanese phase III clinical studies, a marketing application for nemolizumab has been filed. Outside Japan, nemolizumab has been developed for the treatment of AD by Galderma Pharma S.A. in Switzerland.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance for nemolizumab is [redacted].

2.1.1 Generation and control of cell substrates

The master cell bank (MCB) and working cell bank (WCB) are prepared and controlled as shown in the Attachment. No viral or non-viral infectious agents were detected in the MCB, WCB, or post process cells (PPCs), other than endogenous retrovirus-like particles commonly observed in cell lines derived from rodents.

2.1.2 Manufacturing process

The manufacturing process is shown in the Attachment.

2.1.3 Safety evaluation of adventitious agents

Except for the host Chinese hamster ovary (CHO) cells, no animal- or human-derived raw materials are used in the manufacturing process of the drug substance.

Purity tests were performed on the MCB, WCB, and PPCs [see Section 2.1.1]. Pre-harvest unprocessed bulk produced at commercial scale was subjected to tests for bioburden, mycoplasma, *in vitro* adventitious viruses, transmission electron microscopy, and minute viruses of mice. None of the tests revealed contamination with viral or nonviral adventitious agents. These tests, except for transmission electron microscopy, are included as in-process controls for unprocessed bulk.

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	Virus reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	SV40
[redacted] chroma-tography	[redacted]	[redacted]	[redacted]
Virus inactivation [redacted]	[redacted]	[redacted]	[redacted]
Viral removal [redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]
Overall reduction factor	≥17.12	≥7.43	≥6.88

2.1.4 Manufacturing process development

The manufacturing process was developed as shown in the Attachment.

2.1.5 Characterization

2.1.5.1 Structure and properties

The drug substance was characterized by the tests shown in Table 2.

Table 2. Characterization parameters

Primary structure/high-order structure	Amino acid sequence, post-translational modifications (oxidation, deamidation, and Asp isomerization), secondary structure, disulfide bond, and free thiol group.
Physicochemical properties	Molecular weight, isoelectric point, molecular weight variant (high molecular weight variant, and low molecular weight variant), and charge variant.
Carbohydrate structure	N-linked carbohydrate
Biological properties	IL-31-dependent cell-growth inhibition
	Binding activities to FcγR (FcγRIa, FcγRIIa [R and H], FcγRIIb, FcγRIIIa [F and V], FcγRIIIb [NA1 and NA2]), FcRn, and C1q, ADCC, and CDC.

The major biological property of nemolizumab is the inhibitory activity against IL-31-dependent proliferation confirmed in the test system using IL-31-dependent [redacted]. As for effector function, the binding activities to Fcγ receptor (FcγR) or complement component 1, q subcomponent (C1q) were confirmed to be comparable or lower than that to the control IgG2 antibody. Nemolizumab was confirmed to show little or no antibody-dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC).

2.1.5.2 Product-related substances/Product-related impurities

No product-related substance has been identified. The results of the characterization described in Section 2.1.5.1 showed that Variant A ([redacted], [redacted]), Variant B ([redacted], [redacted] [[redacted] and [redacted]]), Variant C ([redacted], [redacted]), Variant D [redacted]), Variant E, and Variant F were considered as product-related impurities. Among the product-related impurities, Variant A, [redacted] ([redacted] and [redacted]), and [redacted] are adequately controlled by the drug substance and drug product specifications, respectively, and Variant E is adequately controlled by the in-process control tests for the drug substance. In addition, [redacted] of [redacted] is also controlled by [redacted]. For other product-related impurities, no routine control is specified because their content is constant or small and because no increase is observed in stability studies.

2.1.5.3 Process-related impurities

Impurity A, Impurity B, and Impurity C were identified as process-related impurities. Impurity A is adequately controlled by the in-process control tests. Other process-related impurities have been demonstrated to be adequately removed in the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, appearance, identification (peptide mapping), osmolality, pH, purity (capillary gel electrophoresis with sodium dodecyl sulfate [CE-SDS] [non-reduced], size exclusion chromatography [SEC], and anion exchange chromatography [AEX]), bacterial endotoxins, microbial limits, [redacted], [redacted], potency (IL-31-dependent cell-growth inhibition), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

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

Table 3. Outline of the primary stability studies on the drug substance

Study	Manufacturing method	Number of batches	Storage condition	Duration	Storage package
Long-term testing	Proposed commercial process	3	−50°C ± 10°C	24 months[a)]	EVA bag
Accelerated testing	Proposed commercial process	3	5°C ± 3°C	12 months	EVA bag
Stress testing	Proposed commercial process	3	40°C ± 2°C/75%RH	4 weeks	Polypropylene container

a) The long-term testing is ongoing for up to [redacted] months.

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

The accelerated testing showed [redacted], [redacted] and [redacted], and [redacted] in [redacted], [redacted] and [redacted] in [redacted], [redacted] in [redacted].

Stress testing showed [redacted], [redacted] ([redacted] and [redacted]), and [redacted] in [redacted], [redacted] [redacted] and [redacted] in [redacted], [redacted], [redacted], and [redacted], and reduction in potency in [redacted].

On the basis of the above data, a shelf life of 24 months has been proposed for the drug substance when stored in an ethylene-vinyl acetate (EVA) bag at ≤−50°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized injection containing 75 mg of nemolizumab per syringe.[2)] The excipients used in the drug product include purified sucrose, trometamol, [redacted], L-arginine hydrochloride, and poloxamer 188. The drug product is available as a combination product in a [redacted] rubber-separated, dual-chamber glass syringe with a plunger rod. One chamber is filled with a freeze-dried powder of nemolizumab and excipients, and the other with water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of the following: drug solution preparation; sterile filtration, filling, and partial stoppering of drug solution; lyophilization; filtration of water for injection; sterile filtration, filling, and sealing of water for injection; inspection; assembly; packaging and labelling; and storage and testing.

[redacted], [redacted], and [redacted] have been specified as critical process steps.

The commercial-scale manufacturing process for the drug product has been subjected to process validation.

2) The syringe is overfilled to allow for the injection of 60 mg of nemolizumab, based on the results of the investigation on the extractable volume.

2.2.3 Manufacturing process development

The following are major changes made to the manufacturing process during the development of the drug product (Process 0.1, Process 0.2, Process 0.3, Process 0.4, and the proposed commercial process). The drug products produced in Process 0.3 and Process 0.4 were used in the phase III clinical studies.

- Process 0.1 to Process 0.2: Changes in [redacted] ([redacted]), formulation, etc.
- Process 0.2 to Process 0.3: Changes in [redacted], formulation, etc.
- Process 0.3 to Process 0.4: Changes in [redacted], [redacted], formulation, [redacted] ([redacted]), [redacted], etc.
- Process 0.4 to the proposed commercial process: Changes in formulation, [redacted], [redacted] ([redacted]), etc.

With these changes in manufacturing process, compatibility in quality attributes were evaluated, and comparability between pre- and post-change drug products has been demonstrated.

A quality by design (QbD) approach has been applied to develop the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (peptide mapping), osmolality, pH, purity (CE-SDS [non-reduced], SEC, and AEX), water content, pyrogens, extractable volume, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, [redacted], sterility, potency (IL-31-dependent cell-growth inhibition), assay (ultraviolet-visible spectrophotometry), and [redacted].

2.2.5 Stability of drug product

Table 4 shows the primary stability studies on the drug product.

Table 4. Outline of the primary stability studies on the drug product

Study	Number of batches[a)]	Storage condition	Duration	Storage package[c), d)]
Long-term testing	3	30°C ± 2°C/75% ± 5%RH	[redacted] months[b)]	Dual-chamber borosilicate glass syringe with a [redacted] rubber cap and a plunger
Accelerated testing	4	40°C ± 2°C/75% ± 5%RH	6 months	
Stress testing (heat)	3	50°C ± 2°C/75%RH	12 weeks	
Stress testing (light)	1	Overall illumination of ≥1.20 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

a) The drug substance and the drug product were both produced in the proposed commercial process.
b) The study is ongoing for all batches up to [redacted] months.
c) [redacted] of [redacted] ([redacted])
d) The stress testing (light) was conducted with and without the secondary packaging (paper box).

In the long-term testing, the accelerated testing, and the stress testing (heat), [redacted], [redacted] and [redacted] by [redacted], [redacted] and [redacted] in [redacted], and [redacted] and [redacted] in [redacted] were observed.

At the time of [redacted] for [redacted], insoluble visible particles were detected in some batches in the foreign insoluble matter test. The visible particles were [redacted] or [redacted] (including [redacted]), [redacted], and [redacted]. No clear changes were observed in other test parameters throughout the testing period. The stress testing (light) showed that the drug product is photolabile.

On the basis of the above data, a shelf life of [redacted] months has been proposed for the drug product when stored at room temperature with the use of a dual-chamber syringe consisting of a borosilicate glass syringe as a primary container, a [redacted] rubber cap, and a plunger.

2.3 QbD

A QbD approach has been applied to the development of the drug substance and the drug product, and the quality control strategy was established through the review of the following:

- Identification of critical quality attributes (CQAs)

  The following CQAs have been identified for the quality attributes of product-related impurities, process-related impurities, and drug product formulation, based on the information obtained during the development of nemolizumab and the relevant knowledge.

  CQAs for the drug substance: [redacted], virus, [redacted], mycoplasma, and [redacted].

  CQAs for the drug product: [redacted], sterility, [redacted], and [redacted].

- Characterization of process

  Based on the analyses that determine the effects of each process on CQAs, the acceptable control range was examined for each process parameters.

- Development of control methods

  Based on the process knowledge including the characterization of above processes and risk assessment for the quality attributes, control methods for quality attributes of nemolizumab have been developed by a combination of the process parameters, in-process control, and specifications [for product-related impurities and control of process-related impurities, see Sections 2.1.5.2 and 2.1.5.3, respectively].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled at present, except for the item described in Section 2.R.1. Materials relating to the drug master file (MF) of nemolizumab have been separately submitted by the MF registrant, and the results of the review on the MF by PMDA are shown in Appendix.

2.R.1 Insoluble visible particles found in the drug product

PMDA instructed the applicant to examine the specifications for insoluble visible particles generated during the storage of the drug product [see Section 2.2.5]. The results are described in the Review Report (2).

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

The applicant submitted the results from primary pharmacodynamic studies including *in vitro* studies to determine the binding to IL-31RA and the effects on the signaling by IL-31, and *in vivo* study to determine the effects of nemolizumab in the IL-31-induced pruritus model in monkey. The applicant submitted the results from secondary pharmacodynamic studies to determine the effects of nemolizumab on the signaling by the IL-6 family cytokine, the binding to FcγR and C1q, and the cytotoxic activity. Although no safety pharmacology studies have been conducted, the effects of nemolizumab on the central nervous system, the cardiovascular system, and the respiratory system were evaluated in repeated-dose toxicity studies in cynomolgus monkey [see Section 5.2]. Pharmacological parameters are expressed as the mean, unless otherwise specified.

3.1 Primary pharmacodynamics

3.1.1 Binding of nemolizumab to IL-31RA (CTD 4.2.1.1-1)

With surface plasmon resonance, the K_D of soluble IL-31RA to immobilized nemolizumab in humans and cynomolgus monkey was determined to be 0.374 and 0.191 nmol/L, respectively.

3.1.2 Effects of nemolizumab on the signaling by IL-31 (CTD 4.2.1.1-2 [reference data], 4.2.1.1-3, 4.2.1.1-4 [reference data], and 4.2.1.1-5 [reference data])

In response to the IL-31 stimulation of Ba/F3 cells of a murine pro-B cell line expressing human or cynomolgus monkey IL-31 receptors (IL-31RA or OSMR) (0.3 ng/mL for human and 1 ng/mL for cynomolgus monkey), nemolizumab inhibited cell proliferation in a concentration-dependent manner (0.002 - 100 μg/mL for cells expressing human IL-31 and 0.16 - 20.3 ng/mL for cells expressing cynomolgus monkey IL-31).

In response to the human IL-31 stimulation of A549 cells of a human alveolar epithelial adenocarcinoma cell line (30 ng/mL), nemolizumab inhibited phosphorylation of the signal transducer and activator of transcription 3 (STAT3) in a concentration-dependent manner (0.42 - 101 ng/mL).

In response to the human IL-31 stimulation of HaCaT cells of a human epidermal keratinocyte cell line (50 or 500 ng/mL), nemolizumab inhibited the production of IL-6, MMP-1, and MMP-3 and the activation of caspase 3/7 in a concentration-dependent manner (0.01 - 100 μg/mL) in the presence of human IFN-γ (30 or 100 ng/mL).

3.1.3 Effects of nemolizumab in the IL-31-induced pruritus model in monkeys (CTD 4.2.1.1-11 to 12)

In cynomolgus monkeys, nemolizumab 3 to 100 μg/kg was intravenously administered in a stepwise manner on the day before the administration of IL-31 to examine itching behavior[3)] induced by the administration of IL-31 (1 μg/kg, intravenously). The frequency of itching behavior decreased in the animals receiving nemolizumab at doses of ≥40 μg/kg. In addition, itching behavior was induced by the administration of IL-31 after the subcutaneous administration of nemolizumab (1 mg/kg). The frequency of itching behavior decreased at 28 days after the administration of nemolizumab as compared with the animals receiving no nemolizumab.

3.2 Secondary pharmacodynamics

3.2.1 Effects of nemolizumab on the signaling by the IL-6 family cytokine (CTD 4.2.1.1-6)

Nemolizumab (0.4-250 μg/mL) had no effects on the cell proliferation induced by the stimulation of TF-1 cells of a human leukemia cell line by human IL-6[4)] (10 ng/mL) or human oncostatin M (OSM)[4)] (10 ng/mL).

3.2.2 Effects of nemolizumab on the ADCC activity and CDC activity

3.2.2.1 Binding of nemolizumab to FcγR (CTD 4.2.1.1-7)

Surface plasmon resonance demonstrated that the binding of nemolizumab to human FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb including genetic polymorphism was weaker than that of rituximab, an IgG1 antibody, and comparable to or weaker than that of panitumumab, an IgG2 antibody. In addition, the binding of nemolizumab to cynomolgus monkey FcγRIa, FcγRIIa, FcγRIIb, and FcγRIIIa including genetic polymorphism was comparable to or weaker than that of panitumumab. Meanwhile, the binding of nemolizumab to FcγRIIa and FcγRIIb was comparable to or stronger than that of rituximab, and the binding of nemolizumab to FcγRIa and FcγRIIIa was weaker than that of rituximab.

3.2.2.2 Binding of nemolizumab to C1q (CTD 4.2.1.1-8)

Enzyme-linked immunosorbent assay (ELISA) demonstrated that the binding of nemolizumab to human C1q was weaker than that of rituximab and comparable to that of panitumumab.

3.2.2.3 ADCC activity, CDC activity, and cell-death inducing effect (CTD 4.2.1.1-9)

After incubation of A549 cells overexpressing human IL-31RA with nemolizumab (0.2-200 μg/mL) in the presence or absence of peripheral blood mononuclear cells, no ADCC activity or cell-death inducing effect of nemolizumab was observed. After incubation of A549 cells overexpressing human IL-31RA with nemolizumab (0.2-200 μg/mL) in the presence of human serum, no CDC activity by nemolizumab was observed.

3.3 Safety pharmacology (CTD 4.2.3.2-2)

In a 26-week repeated subcutaneous dose toxicity study in cynomolgus monkeys [see Section 5.2], nemolizumab 1 to 25 mg/kg was administered subcutaneously once every 2 weeks, and no changes related to the administration

[3)] Single itching behavior was defined as scratching a part of the body with a forelimb or hindlimb.
[4)] Cytokine consisting of gp130 homologous to IL-31RA as a part of its receptor.

of nemolizumab were observed in the central nervous system (neurobehavioral behavior), the cardiovascular system (electrocardiograms and blood pressure), or the respiratory system (respiratory rate).

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of nemolizumab:

IL-31 is a cytokine produced mainly by Th2 cells. After binding to IL-31RA, IL-31 forms a heterodimer with OSMR, activate downstream JAK/STAT, and transduces signals into the cells (*Eur Cytokine Netw*. 2004;15 291-302). The findings below indicate that IL-31 is considered to be involved in pruritus associated with AD.

- Transgenic mice overexpressing IL-31 or mice treated with IL-31 showed marked scratching behavior (*Nat Immunol.* 2004;5:752-60)
- IL-31 mRNA expression was upregulated in the skin of NC-Nga mice spontaneously developing an AD-like symptoms, indicating positive correlation between expression of IL-31 mRNA and scratching behavior (*Exp Dermatol.* 2006;15:161-7)
- IL-31 mRNA expression is upregulated in the skin of AD patients, and ultraviolet radiation therapy has improved the pruritus score while decreasing IL-31 mRNA expression in the skin (*J Allergy Clin Immunol*. 2006;117:411-17; *J Allergy Clin Immunol*. 2006;117:418-25; and *Br J Dermatol*. 2008;158:1117-20).

Nemolizumab has been demonstrated to inhibit the intracellular signal transduction such as cell proliferation by binding to IL-31RA [see Sections 3.1.1 and 3.1.2] and to reduce itching behavior in a simian pruritus model [see Section 3.1.3]. The above results indicate that nemolizumab is expected to demonstrate efficacy in the treatment of pruritus associated with AD.

PMDA's conclusion:

The submitted data show that nemolizumab blocks the bioactivity of IL-31. Nemolizumab is expected to be effective because IL-31 is considered to be involved in pruritus associated with AD.

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

The applicant submitted data for absorption, distribution, and excretion from studies of nemolizumab intravenously and subcutaneously administered in cynomolgus monkeys and studies of effects on pre- and postnatal development, including maternal function. Nemolizumab or ^{125}I-labeled nemolizumab was used to evaluate pharmacokinetics. Nemolizumab concentrations in plasma and milk were determined by ELISA (lower limit of quantification: 8 or 50 ng/mL), and radioactivity levels in samples were determined by quantitative whole-body autoradiography. Anti-drug antibody (ADA) and neutralizing antibody were determined by electrochemiluminescence immunoassay (ECLIA, detection sensitivity of 50 ng/mL) and ELISA (detection sensitivity of 50 ng/mL), respectively. Since nemolizumab, a monoclonal antibody, is considered to be degraded into peptides and amino acids and to be reused or excreted, no study has been conducted for metabolism or excretion, except for its excretion in milk. Pharmacokinetic parameters are expressed as the mean ± standard deviation unless otherwise specified.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1)

Table 5 shows the pharmacokinetic parameters after intravenous or subcutaneous single dose of nemolizumab in male cynomolgus monkeys. Exposure to nemolizumab was nonlinear between animals receiving nemolizumab 0.04 mg/kg and animals receiving nemolizumab at other doses for both administration routes, except for the doses of 0.2 mg/kg and 1.0 mg/kg, where exposure to nemolizumab generally increased in a dose-proportional manner. Bioavailability after subcutaneous administration ranged from 71.9% to 74.6%. ADA was found in an animal receiving nemolizumab 0.2 mg/kg intravenously, and plasma nemolizumab concentrations slightly decreased in the animal with ADA.

Table 5. Pharmacokinetic parameters after a single dose of nemolizumab in male cynomolgus monkeys

Route	Dose (mg/kg)	N	C_{max} [a)] (μg/mL)	AUC_{inf} (μg·h/mL)	T_{max} (day)	CL_{total} (mL/h/kg)	Vd_{ss} (mL/kg)	$t_{1/2}$ (day)
Intravenous	0.04	3	0.96 ± 0.02	99.1 ± 15.1	—	0.41 ± 0.06	54.4 ± 4.7	3.3 ± 0.5
	0.2	2 [b)] (3)	4.94, 4.70 (4.74 ± 0.18)	1,490, 1,250 (1,130 ± 440)	—	0.13, 0.16 (0.20 ± 0.10)	65.2, 70.0 (64.0 ± 6.6)	14.5, 12.7 (10.8 ± 4.9)
	1.0	3	24.4 ± 2.5	6,890 ± 990	—	0.15 ± 0.02	71.2 ± 6.6	14.9 ± 1.6
Subcutaneous	0.04	3	0.34 ± 0.05	71.5 ± 10.2	4.0 [2.0, 4.0]	—	—	3.1 ± 0.7
	0.2	3	1.97 ± 0.17	985 ± 172	4.0 [4.0, 4.0]	—	—	11.5 ± 1.6
	1.0	3	9.13 ± 1.37	5,140 ± 1,050	4.0 [2.0, 7.0]	—	—	12.8 ± 2.3

Mean ± standard deviation. T_{max}: Median [maximum, minimum]. −: not calculated.
a) Concentration just after the administration in the intravenous administration group.
b) Excluding an animal with ADA (data including the animal with ADA are shown in parentheses).

4.1.2 Repeated-dose studies (toxicokinetics)

4.1.2.1 13-week repeated subcutaneous dose toxicity study (CTD 4.2.3.2-1)

Table 6 shows the pharmacokinetic parameters of nemolizumab in a 13-week repeated subcutaneous dose toxicity study in cynomolgus monkeys [see Section 5.2]. Exposure to nemolizumab generally increased in a dose-proportional manner. ADA was found in a female animal receiving nemolizumab 1 mg/kg and 2 female animals receiving nemolizumab 5 mg/kg, and plasma nemolizumab concentrations decreased in the animals with ADA.

Table 6. Pharmacokinetic parameters after repeated subcutaneous dose of nemolizumab every 2 weeks in cynomolgus monkeys

Dose (mg/kg)	Number of dosing	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}14d}$ (μg·h/mL)	T_{max} (day)
1	Dose 1	Male	4	9.06 ± 1.25	2,290 ± 210	5.5 [4.0, 14.0]
		Female	4	8.67 ± 0.45	2,140 ± 110	3.0 [2.0, 4.0]
	Dose 4	Male	4	17.5 ± 0.8	5,170 ± 480	2.0 [2.0, 7.0]
		Female	3[a)] (4)	11.7 ± 0.5 (10.3 ± 2.8)	3,100 ± 80 (2,450 ± 1,300)	4.0 [4.0, 4.0] (4.0 [2.0, 4.0])
	Dose 6	Male	4	18.9 ± 3.6	5,510 ± 1,270	2.0 [2.0, 4.0]
		Female	3[a)] (4)	14.3 ± 1.2 (10.9 ± 6.9)	3,530 ± 160 (2,660 ± 1,750)	2.0 [2.0, 2.0] (2.0 [2.0, 2.0])
5	Dose 1	Male	4	33.9 ± 5.0	9,410 ± 1,390	5.5 [4.0, 7.0]
		Female	4	34.4 ± 7.2	9,600 ± 2,180	4.0 [2.0, 7.0]
	Dose 4	Male	4	79.4 ± 26.5	20,800 ± 3,900	4.5 [2.0, 7.0]
		Female	3[a)] (4)	52.1 ± 2.2 (42.4 ± 19.4)	14,300 ± 1,600 (11,200 ± 6,400)	4.0 [2.0, 4.0] (3.0 [2.0, 4.0])
	Dose 6	Male	4	90.0 ± 9.2	25,600 ± 3,100	3.0 [2.0, 7.0]
		Female	2[a)] (4)	85.6, 53.7 (49.5 ± 32.5)	22,100, 13,800 (12,200 ± 9,000)	2.0, 2.0 (2.0 [2.0, 2.0])
25	Dose 1	Male	4	187 ± 24	51,400 ± 5,700	3.0 [2.0, 4.0]
		Female	4	179 ± 3	45,800 ± 1,600	2.0 [2.0, 4.0]
	Dose 4	Male	4	353 ± 38	95,300 ± 5,800	2.0 [2.0, 4.0]
		Female	4	321 ± 36	80,400 ± 12,500	4.0 [2.0, 4.0]
	Dose 6	Male	4	430 ± 16	117,000 ± 4,000	2.0 [2.0, 4.0]
		Female	4	400 ± 41	100,000 ± 19,000	2.0 [2.0, 2.0]

Mean ± standard deviation. T_{max}: Median [maximum, minimum].
a) Excluding animals with ADA (data including the animals with ADA are shown in parentheses).

4.1.2.2 26-week repeated subcutaneous dose toxicity study (CTD 4.2.3.2-2)

Table 7 shows the pharmacokinetic parameters of nemolizumab in a 26-week repeated subcutaneous dose toxicity study in cynomolgus monkeys [see Section 5.2]. Exposure to nemolizumab generally increased in a dose-proportional manner. ADA was found in 3 male animals and 1 female animal receiving nemolizumab 1 mg/kg and 1 female animal receiving nemolizumab 25 mg/kg, and plasma nemolizumab concentrations decreased in all of the animals with ADA.

Table 7. Pharmacokinetic parameters after repeated subcutaneous dose of nemolizumab every 2 weeks in cynomolgus monkeys

Dose (mg/kg)	Number of dosing	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}14d}$ (μg·h/mL)	T_{max} (day)
1	Dose 1	Male	4[a)] (5)	9.64 ± 2.82 (9.91 ± 2.52)	2,710 ± 810 (2,640 ± 710)	4.0 [4.0, 4.0] (4.0 [4.0, 4.0])
		Female	5	9.93 ± 2.39	2,620 ± 660	4.0 [2.0, 7.0]
	Dose 6	Male	2[a)] (5)	13.8, 15.9 (9.05 ± 8.24)	3,960, 4,380 (2,450 ± 2,240)	0.3, 2.0 (1.2 [0.3, 2.0])
		Female	4[a)] (5)	14.9 ± 4.5 (11.9 ± 7.7)	3,980 ± 1,100 (3,180 ± 2,020)	3.0 [2.0, 4.0] (2.0 [0.3, 4.0])
	Dose 13	Male	2[a)] (5)	21.0, 22.1 (11.6 ± 10.9)	5,610, 6,460 (3,150 ± 3,050)	4.0, 4.0 (4.0 [4.0, 4.0])
		Female	4[a)] (5)	15.9 ± 4.7 (12.7 ± 8.2)	4,450 ± 1,390 (3,560 ± 2,330)	5.5 [2.0, 7.0] (5.5 [2.0, 7.0])
5	Dose 1	Male	5	52.5 ± 7.1	14,200 ± 2,000	4.0 [4.0, 7.0]
		Female	5	41.6 ± 9.4	11,300 ± 2,400	7.0 [4.0, 7.0]
	Dose 6	Male	5	100 ± 25	26,300 ± 6,200	2.0 [2.0, 4.0]
		Female	5	76.8 ± 12.3	21,100 ± 3,600	2.0 [0.3, 2.0]
	Dose 13	Male	5	94.3 ± 26.2	26,400 ± 7,300	2.0 [0.3, 4.0]
		Female	5	77.1 ± 19.3	22,100 ± 4,800	4.0 [2.0, 7.0]
25	Dose 1	Male	5	187 ± 43	51,400 ± 10,300	4.0 [4.0, 4.0]
		Female	5	230 ± 41	58,600 ± 6,500	4.0 [2.0, 4.0]
	Dose 6	Male	5	334 ± 47	87,700 ± 11,500	2.0 [0.3, 2.0]
		Female	4[a)] (5)	341 ± 76 (299 ± 114)	90,000 ± 24,500 (75,900 ± 37,900)	2.0 [2.0, 2.0] (2.0 [2.0, 4.0])
	Dose 13	Male	5	351 ± 48	101,000 ± 20,000	2.0 [2.0, 4.0]
		Female	4[a)] (5)	317 ± 45 (253 ± 147)	86,800 ± 18,800 (69,400 ± 42,100)	3.0 [2.0, 4.0] (2.0 [2.0, 4.0])

Mean ± standard deviation. T_{max}: Median [maximum, minimum].
a) Excluding animals with ADA (data including the animals with ADA are shown in parentheses).

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.3-1)

Table 8 shows plasma nemolizumab concentrations in dams and neonates on postpartum/postnatal day 7 after subcutaneous dosing of nemolizumab 1 or 25 mg/kg every 2 weeks (up to 12 doses) from gestation day 20 to parturition in a study for effects on prenatal and postnatal development, including maternal function in pregnant cynomolgus monkeys [see Section 5.5]. The results suggest that nemolizumab crossed the placenta into fetuses.

Table 8. Plasma nemolizumab concentrations in dams and neonates on postpartum/postnatal day 7 (μg/mL)

Dose (mg/kg)	Dams	Neonates
1	8.24 ± 3.14 (7)[a)]	7.68 ± 3.59 (8)[a)]
25	136 ± 60 (10)[a)]	177 ± 45 (12)

Mean ± standard deviation (number of animals).
a) Excluding animals with ADA.

4.2.2 Tissue distribution (CTD 4.2.2.3-1)

After subcutaneous administration of ^{125}I-labeled nemolizumab 1 mg/kg in male cynomolgus monkeys (1 animal/time point), the radioactivity levels in tissue measured at 1, 2, 7, 14, and 28 days after the administration reached the maximum on 1 or 2 days after the administration and decreased with time thereafter. The radioactivity, however, was detectable in most tissues even at 28 days after the administration. The radioactivity levels were higher in the thyroid gland and stomach, which were considered to be caused by free iodine. In other tissues, the radioactivity was high in the blood, lungs, liver, kidneys, and spleen, in a descending order.

4.3 Excretion

4.3.1 Excretion in milk (CTD 4.2.3.5.3-1)

Table 9 shows nemolizumab concentrations in plasma and milk in dams in the study for effects on prenatal and postnatal development, including maternal function in pregnant cynomolgus monkeys [see Sections 4.2.1 and 5.5]. The results suggest that nemolizumab was excreted in milk.

Table 9. Nemolizumab concentrations in plasma and milk in dams (μg/mL)

Dose (mg/kg)	Samples	Postpartum Day 7	Postpartum Day 21	Postpartum Day 35	Postpartum Day 63
1	Plasma	8.24 ± 3.14 (7)[a)]	3.86 ± 1.73 (7)[a)]	1.76 ± 1.14 (7)[a)]	0.25 ± 0.30 (7)[a)]
	Milk	0.04 ± 0.03 (7)[a)]	0.008 ± 0.008 (7)[a)]	—[b)]	—[b)]
25	Plasma	136 ± 60 (10)[a)]	60.4 ± 25.2 (9)[a)]	29.8 ± 16.0 (9)[a)]	7.38 ± 4.95 (9)[a)]
	Milk	0.59 ± 0.34 (12)	0.21 ± 0.10 (11)	0.10 ± 0.08 (11)	0.04 ± 0.04 (11)

Mean ± standard deviation (number of animals).
a) Excluding animals with ADA. b) Not calculated because the levels were below the lower limit of quantification in more than half of the animals.

4.R Outline of the review conducted by PMDA

On the basis of the nonclinical pharmacokinetic data submitted, PMDA concluded that the *in vivo* behavior of nemolizumab can be understood to a certain extent and that no particular pharmacokinetic concerns have been suggested for the clinical use of nemolizumab. Since nemolizumab transferred into milk and neonates after administration of nemolizumab in pregnant cynomolgus monkeys, precautionary statement about milk and placental transfer of nemolizumab should be included in the package insert.

In nonclinical pharmacokinetic studies in cynomolgus monkeys, ADA was detected after administration of nemolizumab, and plasma nemolizumab concentrations decreased in animals with ADA. In light of the above findings, PMDA will discuss and make conclusions carefully on the development of ADA and neutralizing antibody, the pharmacokinetics of nemolizumab in the presence of ADA, and its effects on the efficacy and safety after administration of nemolizumab, based on the results of clinical studies [see Section 6.R.1].

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of nemolizumab were conducted: repeated-dose toxicity, reproductive and developmental toxicity, local tolerance, and other toxicity (tissue cross-reactivity and *in vitro* cytokine release) studies. Since nemolizumab binds to cynomolgus monkey IL-31RA [see Section 3.1.1], repeated-dose toxicity and reproductive and developmental toxicity of nemolizumab were evaluated in cynomolgus monkeys.

5.1 Single-dose toxicity

No single-dose toxicity studies have been conducted for nemolizumab. In a 13-week repeated subcutaneous dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2-1), acute toxicity after the initial administration of nemolizumab was evaluated, and no deaths or acute symptoms were observed up to a highest dose of 25 mg/kg [see Section 5.2]. The approximate lethal dose was determined to be >25 mg/kg based on these findings (Table 10).

Table 10. Summary of single-dose toxicity evaluation

Test system	Route	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached CTD
Male and female cynomolgus monkeys	Subcutaneous	0[a], 1, 5, 25	No toxic changes	>25	4.2.3.2-1

a) [redacted] mmol/L tris-hydrochloride buffer containing [redacted] mmol/L arginine (pH [redacted])

5.2 Repeated-dose toxicity

In cynomolgus monkeys, 13-week and 26-week repeated subcutaneous dose toxicity studies were conducted (Table 11).

No signs of systemic toxicity related to nemolizumab were seen. Regarding the effects of local administration, the degree and frequency of infiltration of mononuclear cells of the subcutaneous tissues were slightly higher in animals receiving nemolizumab at 25 mg/kg/2 weeks than in animals receiving a vehicle in the 13-week repeated subcutaneous dose toxicity study [see Section 5.7]. In both of the 13- and 26-week repeated subcutaneous dose toxicity studies, the no-observed-adverse-effect level for systemic toxicity was determined to be 25 mg/kg/2 weeks. The exposure to nemolizumab at the dose ($AUC_{0\text{-}14d}$, 45,800-58,600 μg·h/mL[5]) was approximately 37 to 48 times the exposure after administration of nemolizumab at the proposed dosing regimen in Japanese AD patients[6] ($AUC_{0\text{-}28d}$, 102.30 μg·day/mL).

Table 11. Summary of results of repeated-dose toxicity studies

Test system	Route	Duration of administration	Dose (mg/kg/2 weeks)	Main findings	No-observed-adverse-effect level (mg/kg/2 weeks)	Attached CTD
Male and female cynomolgus monkeys	Subcutaneous	13 weeks (once every 2 weeks)	0[a], 1, 5, 25	25: A tendency toward increased infiltration of mononuclear cells in the subcutaneous tissue at the administration site (male and female animals)	25	4.2.3.2-1
Male and female cynomolgus monkeys	Subcutaneous	26 weeks (once every 2 weeks) + 17-week interval	0[b], 1, 5, 25	None	25	4.2.3.2-2

a) [redacted] mmol/L tris-hydrochloride buffer containing [redacted] mmol/L arginine (pH [redacted])
b) [redacted] mmol/L tris-hydrochloride buffer containing [redacted] mmol/L arginine, [redacted] mmol/L sucrose, and [redacted] mg/mLpoloxamer 188 (pH 7.0)

5.3 Genotoxicity

Since nemolizumab, a monoclonal antibody, does not cross the nuclear membrane and is considered unlikely to act directly on DNA and other chromosomes in the cell, nemolizumab is considered to be associated with low genotoxic concerns, and therefore, no genotoxicity studies have been conducted.

5.4 Carcinogenicity

Although no carcinogenicity studies in rodents have been conducted, the applicant explains that the risk of carcinogenicity related to the inhibitory effects of nemolizumab on IL-31R is low, based on the points presented below. Nemolizumab has been reported not to bind to murine or rat IL-31RA[7].

[5] Minimum and maximum $AUC_{0\text{-}14d}$ in the 13- and 26-week repeated subcutaneous dose toxicity studies after the initial administration of nemolizumab, converted to $AUC_{0\text{-}28d}$ of 3,817 to 4,883 μg· day/mL for comparison with the exposure after the administration of nemolizumab at the recommended human clinical dose.
[6] $AUC_{0\text{-}28d}$ after the initial administration of nemolizumab 60 mg in Study M525101-01 [see Section 7.2.1].
[7] An interaction between immobilized nemolizumab and murine, rat, rabbit, or human IL-31RA was investigated with surface plasmon resonance, and the interaction with nemolizumab was observed only for human IL-31RA (Chugai Pharmaceutical Co., Ltd., Study TOX[redacted]-0198S, 20[redacted]).

- In the 26-week repeated subcutaneous dose toxicity study in cynomolgus monkeys, there were no proliferative or preneoplastic lesions suggestive of carcinogenicity nor findings suggestive of systemic compromised immune function [see Section 5.2].
- In the 26-week repeated subcutaneous dose toxicity study in cynomolgus monkeys and the enhanced study for effects on prenatal and postnatal development, including maternal function, no changes suggestive of endocrine disruption were observed [see Sections 5.2 and 5.5].
- No findings suggestive of carcinogenicity have been reported in IL-31R knock-out mice (*Exp Hematol.* 2007;35:78-86).

5.5 Reproductive and developmental toxicity

An enhanced study for effects on prenatal and postnatal development, including maternal function in cynomolgus monkeys was conducted to evaluate reproductive and developmental toxicity of nemolizumab (Table 12).

No effects of nemolizumab on dams, prenatal development of fetuses, or neonates were observed, and the no-observed-adverse-effect level for them was determined to be 25 mg/kg/2 weeks. The exposure to nemolizumab at the dose ($AUC_{0\text{-}14d}$, 56,000 μg·h/mL[8)]) was approximately 46 times the exposure to nemolizumab at the proposed dosing regimen in Japanese AD patients [see Section 5.2].

Nemolizumab is determined to have little effects on male or female fertility, considering that nemolizumab had no effects on male or female reproductive organs in the 26-week repeated subcutaneous dose toxicity study [see Section 5.2]. Placental transfer of nemolizumab was observed in cynomolgus monkeys [see Section 4.2.1].

Table 12. Summary of results of a reproductive and developmental toxicity study

Study type	Test system	Route	Duration of administration	Dose (mg/kg/2 weeks)	Main findings	No-observed-adverse-effect level (mg/kg/2 weeks)	Attached CTD
Effects on prenatal and postnatal development, including maternal function	Female cynomolgus monkeys	Subcutaneous	Dams: Gestation day 20 to parturition Up to 12 (once every 2 weeks) Neonates: 26 weeks after Postnatal Day 35 (once every 2 weeks)	0[a)], 1, 25	Dams: No findings Neonates: No findings	Dams (general toxicity): 25 Development of F_1 neonates: 25	4.2.3.5.3-1

a) [redacted] mmol/L tris-hydrochloride buffer containing [redacted] mmol/L arginine, [redacted] mmol/L sucrose, and [redacted] mg/mL poloxamer 188 (pH 7.0)

5.6 Juvenile animals

A study on prenatal and postnatal development, including maternal function was conducted in cynomolgus monkey. Nemolizumab was administered to neonates from 35 days after birth for 26 weeks, and no effects of nemolizumab were observed in the neonates [see Section 5.5].

5.7 Local tolerance

A study on local tolerance after single subcutaneous administration of nemolizumab was conducted in New Zealand white (NZW) rabbits. There were no changes relevant to subcutaneous administration in the study,

8) $AUC_{0\text{-}14d}$ after the initial administration of nemolizumab, converted to $AUC_{0\text{-}28d}$ of 4,667 μg· day/mL for comparison with the exposure after the administration of nemolizumab at the recommended human clinical dose.

and nemolizumab was considered to have no local irritant effects when administered subcutaneously (Table 13). A tendency toward increased infiltration of mononuclear cells in the subcutaneous tissue at the administration site was observed in the 13-week repeated subcutaneous dose toxicity study (Table 11). However, in the 26-week repeated subcutaneous dose toxicity study, there were no local changes relevant to the subcutaneous administration of nemolizumab. Therefore, nemolizumab is unlikely to raise safety concerns.

Table 13. Summary of results of the local tolerance study

Test system	Test method	Main findings	Attached CTD
Male rabbits (NZW)	Single subcutaneous dose of 0.9 mL of nemolizumab 100 mg/mL	None	4.2.3.6-1

5.8 Other studies

5.8.1 Tissue cross-reactivity

In a tissue cross-reactivity study with frozen sections of normal human and cynomolgus monkey tissues (Table 14), similar cross-reactivity was observed between human and cynomolgus monkey tissues.

Table 14. Summary of results of the tissue cross-reactivity study

Test system	Test methods	Main findings	Attached CTD
Normal human and cynomolgus monkey tissues	Frozen sections were treated with nemolizumab (2 µg/mL or 10 µg/mL), and tissue binding ability was evaluated with immunohistochemical staining.	**Tissues positive for humans and cynomolgus monkeys** Stratified squamous epithelium of the esophagus, epithelium of the lung cells and the bronchioles, epithelium of the salivary glands (duct), stratified squamous epithelium of the skin epidermis/epithelium of the sudoriferous glands, stratified squamous epithelium of the thymic Hassall's corpuscle, stratified squamous epithelium of the tonsillar mucosa and crypts, prostate glandular epithelium/transitional epithelium of the prostatic urethra, transitional epithelium of the ureter, transitional epithelium of the bladder, stratified squamous epithelium of the uterine cervix, musculoskeletal myocytes, periocular myocytes, follicular root sheath, and alveolar macrophage. **Tissues positive for humans only** Stratified squamous epithelium of the cornea of the eye and uterine glandular epithelium of the endometrium **Tissues positive for cynomolgus monkey only** Stratified squamous epithelium of the stomach, epithelium of the uterine tube (oviduct)/ovarian surface, neural network of the spinal cord, and the salivary glands cuboidal epithelium of the tonsil.	4.2.3.7.7-1

5.8.2 *In vitro* cytokine release

An *in vitro* cytokine release study was conducted with whole human blood collected from healthy adults. In high-risk controls (alemtuzumab or TGN1412 [anti-CD28 monoclonal antibody] identical-sequence antibody), the ability of nemolizumab to induce cytokines has been determined to be low under the conditions in which at least one of IL-6, IL-8, or tumor necrosis factor (TNF) is induced (Table 15).

Table 15. *In vitro* cytokine release study

Test system	Test methods	Main findings	Attached CTD
Whole human blood	Nemolizumab was added at a final concentration of 0.1, 1, 10, or 100 µg/mL, and IL-6, IL-8, and TNF were measured 24 hours. Alemtuzumab and TGN1412 identical-sequence antibody were used as high-risk controls.	Nemolizumab: Nemolizumab induced the release of IL-6 in 1 of 10 samples and TNF in 1 of 10 samples. Alemtuzumab: Alemtuzumab induced the release of at least one of IL-6, IL-8, and TNF in 10 of 10 samples. TGN1412 identical-sequence antibody: TGN1412 identical-sequence antibody induced the release of at least one of IL-6, IL-8, and TNF in 5 of 10 samples.	4.2.3.7.7-2

5.R Outline of the review conducted by PMDA

5.R.1 Administration of nemolizumab in adolescent patients

The applicant explained that there are no particular safety concerns about the use of nemolizumab in adolescent patients aged ≥13 years based on the following reasons.

- The ages of the cynomolgus monkeys in the 13- and 26-week repeated subcutaneous dose toxicity studies with nemolizumab were 4 to 7 years and 3 to 6 years, respectively, and nemolizumab was started at the time of the onset of secondary sexual characters to sexual maturity in cynomolgus monkeys. However, no signs of systemic toxicity were observed up to the highest dose of 25 mg/kg/2 weeks.
- IL-31RA knock-out mice has shown no abnormalities in development and no evident abnormal findings in histopathological examinations (*Nat Immunol*. 2004;5:752-60).

PMDA considers that no particular safety concerns have been suggested for the use of nemolizumab in adolescent patients aged ≥13 years in view of the non-clinical safety evaluation. The safety of nemolizumab in adolescent patients is discussed in Section 7.R.5.1 based on the results of clinical studies.

5.R.2 Tissue cross-reactivity

The applicant explained that there are little safety concerns in tissues with positive results from the tissue cross-reactivity study, based on the following reasons.

- The tissues with positive results from the repeated-dose toxicity study showed no abnormal findings associated with nemolizumab [see Section 5.2].
- The incidence of adverse events related to the eye (cornea) and uterus, which are tissues tested positive only in human tissues in the tissue cross-reactivity study, was not higher in the nemolizumab group than the placebo group in clinical studies (the combined group of 1 global and 2 Japanese studies [see Section 7.R.3]). Among these events, a causal relationship to the study drug could not be ruled out for atopic keratoconjunctivitis (1 of 481 patients, 0.2%), endometrial hyperplasia (1 of 481 patients, 0.2%), endometriosis (1 of 481 patients, 0.2%), and menstruation irregular (1 of 481 patients, 0.2%) in the nemolizumab group.

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum nemolizumab concentrations were determined by a sandwich ELISA (lower limit of quantification, 100 ng/mL). Serum ADAs were detected by a bridging ELISA (detection sensitivity, 5.88-19.3 ng/mL), and serum neutralizing anti-drug antibodies were detected by a colorimetric cell viability assay kit (detection sensitivity: 9.11 μg/mL).

6.2 Clinical pharmacology

The applicant submitted the data from a Japanese phase I study in healthy adults and AD patients (Study CIM001JP [CTD 5.3.3.1-1]), a global phase II study in AD patients (Study CIM003JG [CTD 5.3.5.1-1]), and Japanese phase III studies (Studies M525101-01 [CTD 5.3.5.1-2] and M525101-02 [CTD 5.3.5.2-1]), population pharmacokinetic analyses, and exposure-response analyses. Unless otherwise specified, doses are expressed in terms of nemolizumab, and pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation.

6.2.1 Phase I study

6.2.1.1 Japanese study in healthy adults and AD patients (CTD 5.3.3.1-1: Study CIM001JP [August 2011-December 2012])

After a single subcutaneous administration of nemolizumab in healthy adults (0.003-3 mg/kg) and AD patients (0.3-3 mg/kg), serum nemolizumab concentrations in subjects receiving nemolizumab 0.003 or 0.01 mg/kg were below the lower limit of quantification. Table 16 shows pharmacokinetic parameters in subjects receiving nemolizumab 0.03-3 mg/kg. Exposure to nemolizumab (C_{max} and AUC_{inf}) increased in the studied doses in a dose-proportional manner, and no evident differences in pharmacokinetics were observed between the healthy Japanese adults and healthy non-Japanese adults. The exposure to nemolizumab in AD patients tended to be lower than that in healthy adults. No AD patients tested positive for ADAs[9)].

Table 16. Pharmacokinetic parameters after single subcutaneous administration of nemolizumab

Dose (mg/kg)	Subject	N	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	T_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day)	V/F (mL)
0.03	Healthy Japanese adults	6	0.32 ± 0.04	7.01 ± 1.20[a)]	6.5 [4.0, 11.0]	12.7 ± 3.38[a)]	274 ± 35.1[a)]	4,960 ± 1,150[a)]
0.1	Healthy Japanese adults	6	0.78 ± 0.14	19.7 ± 5.16	7.0 [6.0, 10.0]	14.5 ± 4.22	331 ± 122	6,510 ± 1,620
0.3	Healthy Japanese adults	5	2.33 ± 0.49	75.7 ± 12.0	10.0 [4.0, 10.0]	15.1 ± 1.71	264 ± 37.3	5,690 ± 697
	Healthy non-Japanese adults	6	2.28 ± 0.54	79.7 ± 19.5	8.5 [7.0, 14.0]	16.0 ± 2.87	300 ± 117	6,590 ± 1,470
	Japanese AD patients	9	2.20 ± 0.69	49.2 ± 14.3	5.0 [2.0, 14.0]	12.6 ± 4.01	408 ± 141	7,320 ± 3,150
1	Healthy Japanese adults	6	8.82 ± 1.23	226 ± 24.5	4.0 [4.0, 7.0]	15.2 ± 1.81	269 ± 47.7	5,840 ± 842
	Healthy non-Japanese adults	6	8.33 ± 1.57	272 ± 103	6.5 [3.0, 7.0]	16.3 ± 7.20	321 ± 110	6,760 ± 1,150
	Japanese AD patients	9	6.50 ± 1.57	161 ± 25.1	4.2 [2.0, 7.2]	13.2 ± 3.44	368 ± 56.8	6,990 ± 2,160
3	Healthy Japanese adults	6	23.9 ± 3.40	634 ± 199	5.0 [4.0, 6.0]	16.4 ± 3.92	319 ± 75.9	7,250 ± 1,200
	Healthy non-Japanese adults	6	26.0 ± 8.01	777 ± 236	6.0 [2.0, 10.0]	16.5 ± 3.01	337 ± 119	7,700 ± 1,850
	Japanese AD patients	9	19.4 ± 5.85	489 ± 196	4.0 [3.0, 7.0]	14.6 ± 6.18	459 ± 207	8,510 ± 2,050

Mean ± standard deviation. T_{max}, median [maximum, minimum]. a) 5 subjects

6.2.2 Phase II study

6.2.2.1 Global clinical study in AD patients (CTD 5.3.5.1-1: Study CIM003JG [December 2013-June 2016], see Section 7.1.1)

Multiple doses of nemolizumab was subcutaneously administered at 0.1, 0.5, or 2.0 mg/kg every 4 weeks (Q4W) or at 2.0 mg/kg every 8 weeks in patients with moderate to severe AD. Table 17 shows pharmacokinetic parameters after the initial dosing, and Table 18 shows serum nemolizumab concentrations after the multiple dosing. ADAs were positive in 6.4% of patients receiving nemolizumab (16 of 249 patients: 4 patients in the

[9)] In clinical studies of nemolizumab, ADA was determined to be positive in either of the following cases: 1) test results are negative or missing before the start of the study drug and are positive after the start of the study drug; or 2) test results are positive before and after the start of the study drug, and antibody titer after the start of the study drug is 4-times higher than that before the study drug.

0.1 mg/kg group, 8 patients in the 0.5 mg/kg group, 1 patient in the 2.0 mg/kg group, 2 patients in the 2.0 mg/kg once every 8 weeks (Q8W) group, and 1 patient in the placebo to nemolizumab 2.0 mg/kg). Neutralizing antibody was positive at Week 64 and during the follow-up in 1 patient in the nemolizumab 0.1 mg/kg group who did not test positive for ADA.

Table 17. Pharmacokinetic parameters after initial administration

Dose (mg/kg)	Treatment interval	N	C_{max} (μg/mL)	$AUC_{0\text{-}28d}$ (μg·day/mL)	AUC_{last} (μg·day/mL)	T_{max} (day)
0.1	4 weeks	51	1.26 ± 1.19	21.3 ± 14.6[a)]	21.4 ± 24.6	7.0 [5.9, 20.9]
0.5		54	3.45 ± 1.02	64.9 ± 19.1[b)]	62.8 ± 20.1	7.0 [5.8, 21.0]
2.0		52	12.7 ± 3.64	228 ± 65.1[c)]	214 ± 78.6	7.0 [5.0, 29.0]
2.0	8 weeks	51	12.7 ± 4.03	231 ± 76.0[d)]	291 ± 129	6.9 [5.7, 13.9]

Mean ± standard deviation. T_{max}, median [maximum, minimum].
a) 39 patients. b) 46 patients. c) 43 patients. d) 46 patients

Table 18. Serum nemolizumab concentrations after subcutaneous administration of nemolizumab in AD patients (patients receiving nemolizumab in Part A, μg/mL)

	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 64
Nemolizumab 0.1 mg/kg	1.23 ± 1.21 (50)	0.97 ± 1.18 (48)	0.52 ± 0.89 (49)	0.62 ± 0.67 (46)	0.74 ± 0.81 (44)	0.65 ± 0.52 (37)	0.77 ± 0.73 (36)	0.71 ± 0.43 (29)
Nemolizumab 0.5 mg/kg	3.46 ± 1.02 (52)	2.77 ± 0.78 (48)	1.56 ± 0.65 (51)	2.14 ± 0.88 (45)	2.61 ± 1.08 (40)	2.66 ± 1.09 (34)	2.91 ± 1.35 (27)	2.69 ± 1.38 (22)
Nemolizumab 2.0 mg/kg	12.5 ± 3.99 (47)	9.99 ± 3.10 (46)	4.99 ± 2.21 (48)	7.50 ± 3.14 (46)	8.09 ± 2.98 (41)	8.98 ± 3.61 (35)	9.49 ± 3.58 (32)	10.3 ± 3.32 (24)
Nemolizumab 2.0 mg/kg Q8W	12.7 ± 4.07 (50)	9.99 ± 3.27 (42)	5.18 ± 2.09 (44)	1.66 ± 1.18 (39)	6.05 ± 3.49 (34)	1.79 ± 1.17 (31)	1.94 ± 1.36 (23)	2.18 ± 1.02 (17)

Mean ± standard deviation (number of patients)

6.2.3 Phase III studies

6.2.3.1 Japanese study in AD patients (CTD 5.3.5.1-2: Study M525101-01 [October 2017-[redacted] 20[redacted]], see Section 7.2.1)

Nemolizumab 60 mg was subcutaneously administered Q4W in AD patients with moderate to severe pruritus, and Table 19 shows serum nemolizumab concentrations after administration. The pharmacokinetic parameters after first dosing were as follows (143 patients in the nemolizumab group; 124 patients for $AUC_{0\text{-}28d}$ only): C_{max}, 5.74 ± 1.79 μg/mL; $AUC_{0\text{-}28d}$, 102.3 ± 29.4 μg·day/mL; AUC_{last}, 103.6 ± 31.5 μg·day/mL; and T_{max}, 7.0 [5.0, 28.0] days (median [maximum, minimum]). ADAs were positive in 7 of 143 patients in the nemolizumab group and 3 of 67 patients in the placebo to nemolizumab group, and no patients tested positive for neutralizing antibodies. No evident differences in serum nemolizumab concentrations were observed between patients with and without ADAs.

Table 19. Serum nemolizumab concentrations after subcutaneous administration of nemolizumab 60 mg Q4W in AD patients (nemolizumab group, μg/mL)

Week 1	Week 2	Week 4	Week 8	Week 16	Week 32	Week 56	Week 68
5.70 ± 1.83 (143)	4.48 ± 1.43 (142)	2.47 ± 0.94 (142)	3.34 ± 1.46 (140)	3.65 ± 1.77 (140)	3.77 ± 1.86 (137)	3.82 ± 2.04 (133)	4.18 ± 2.17 (130)

Mean ± standard deviation (number of patients)

6.2.3.2 Japanese study in AD patients (CTD 5.3.5.2-1: Study M525101-02 [[redacted] 20[redacted]-[redacted] 20[redacted]], see Section 7.2.2)

Nemolizumab 60 mg was subcutaneously administered Q4W in AD patients with moderate to severe pruritus. Table 20 shows changes in serum nemolizumab concentrations after administration. Pharmacokinetic parameters after first dosing were as follows (88 patients in the overall study population; 71 patients for $AUC_{0\text{-}28d}$ only): C_{max},

5.12 ± 1.55 μg/mL; $AUC_{0\text{-}28d}$, 86.7 ± 26.9 μg·day/mL; AUC_{last}, 87.6 ± 26.7 μg·day/mL; and T_{max}, 7.0 [5.0, 16.0] days (median [maximum, minimum]). ADAs were positive in 9 of 44 patients in the medical professional administration group and 2 of 44 patients in the self-injection group, but no patients tested positive for neutralizing antibodies. No evident differences in serum nemolizumab concentrations were observed between patients with and without ADAs.

Table 20. Serum nemolizumab concentrations after subcutaneous administration of nemolizumab 60 mg Q4W in AD patients (μg/mL)

	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52
Medical professional administration group	4.59 ± 1.71 (44)	3.78 ± 1.44 (44)	2.01 ± 0.88 (44)	2.80 ± 1.22 (44)	3.31 ± 1.42 (43)	3.30 ± 1.59 (44)	3.75 ± 1.61 (40)	3.68 ± 1.89 (41)	4.40 ± 2.32 (41)
Self-injection group	5.22 ± 1.67 (44)	3.91 ± 1.23 (44)	1.93 ± 0.83 (44)	2.64 ± 1.39 (44)	2.97 ± 1.48 (44)	Self-injection			
						3.02 ± 1.47 (44)	3.32 ± 1.47 (42)	3.41 ± 1.85 (39)	3.59 ± 1.67 (37)

Mean ± standard deviation (number of patients)

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis was performed with NONMEM (ver.7.3.0) using the serum nemolizumab concentration data obtained from Studies CIM001JP and CIM003JG in AD patients (238 patients, 1,867 sampling points).

A 1-compartment model with first-order absorption and first-order elimination processes was developed as a basic model. After investigation of covariates[10)], a final model was established with body weight and albumin for the apparent total clearance corrected for bioavailability (CL/F) and body weight for apparent volume of distribution (V/F) as covariates. The population pharmacokinetic parameters [90%CI] of nemolizumab estimated from the final model were 0.327 [0.312, 0.343] for CL/F (L/day), 7.46 [7.12, 7.83] for V/F (L), and 0.514 [0.442, 0.609] for first-order absorption rate constant (day^{-1}).

6.4 Exposure-response analysis (CTD 5.3.3.5-1)

Data on serum nemolizumab concentrations and visual analog scale (VAS) for pruritus from Studies CIM001JP and CIM003JG in AD patients were used to examine an exposure-response relationship. Figure 1 shows the simulation results of percent change from baseline in pruritus VAS after subcutaneous administration of nemolizumab 0.1, 0.5, or 2 mg/kg Q4W. The results suggest that the improvement in pruritus VAS may reach a plateau at doses of 0.5 mg/kg or higher

[10)] Sex, age, body weight, laboratory data (albumin, bilirubin, total protein, IgE, and creatine), and eGFR were examined as covariates.

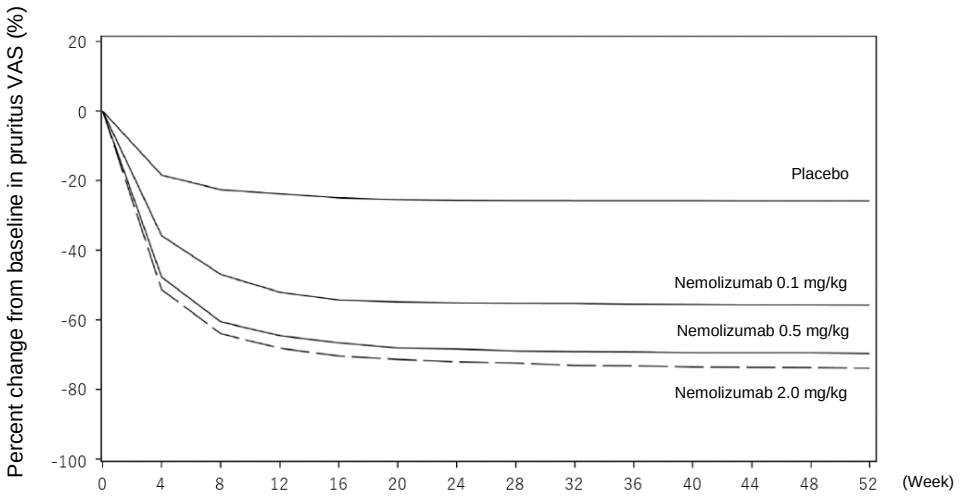

Figure 1. Estimated percent change from baseline in pruritus VAS after subcutaneous administration of nemolizumab Q4W

6.R Outline of the review conducted by PMDA

6.R.1 ADA

The applicant's explanation about the effects of ADAs on the pharmacokinetics, efficacy, and safety of nemolizumab based on data from phase III studies (Studies M525101-01 and M525101-02):

In the phase III studies, 21 subjects were determined to be ADA-positive. However, changes in serum nemolizumab concentrations in these subjects were similar to those in ADA-negative subjects, and the antibody titters were ≤40-fold lower in the majority of subjects (18 subjects). No neutralizing antibodies were detected in ADA-positive subjects.

Efficacy: In 14 subjects, ADAs initially developed at timepoints other than Week 16 or follow-up period. At the time of being assessed as ADA-positive, the percent change from baseline in pruritus VAS worsened from the values immediately before in 4 of 14 subjects, and the changes were approximately <10%.

Safety: In 14 subjects, 30 adverse events were reported at or about the time of the being assessed as ADA-positive (period between the timepoints immediately before and immediately after being assessed as ADA-positive). However, all events were nonserious, and the study drug treatment was continued. The outcome was reported as "resolved" or "resolving" except for irritable bowel syndrome and abdominal discomfort (both events were mild in severity, not resolved).

The above indicates that the development of ADAs is unlikely to affect the efficacy or safety of nemolizumab.

PMDA's view:

Currently available information does not indicate clinical problems associated with the development of ADAs. However, because the number of ADA-positive subjects is limited in the clinical studies, PMDA considers that the applicant should continue to collect information on the effects of the development of ADA and that new information obtained should be promptly communicated to healthcare professionals in clinical practice.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 3 studies shown in Table 21.

Table 21. Main evaluation data

Region	Study	Phase	Study population	No. of subjects	Summary of dosing regimens (Subcutaneous administration)	Main endpoints
Global	CIM003JG	II	AD patients who are inadequately controlled by treatment with potent (classified as medium to very strong in Japan) or more potent TCS or TCI or for whom topical therapies with these drugs is not recommended for safety reasons.	1) 53 2) 54 3) 52 4) 52 5) 53	1) Nemolizumab 0.1 mg/kg Q4W 2) Nemolizumab 0.5 mg/kg Q4W 3) Nemolizumab 2.0 mg/kg Q4W 4) Nemolizumab 2.0 mg/kg Q8W 5) Placebo Q4W[a)]	Efficacy Safety
Japan	M525101-01	III	AD patients with moderate to severe pruritus who are inadequately controlled by treatment with TCS or TCI, that are classified as strong or stronger in Japan, and antihistamines or antiallergics, or for whom treatment with these drugs was not recommended for safety reasons.	1) 143 2) 72	1) Nemolizumab 60 mg Q4W 2) Placebo Q4W[b)]	Efficacy Safety
Japan	M525101-02	III	AD patients with moderate to severe pruritus who are inadequately controlled by treatment with TCS or TCI, that are classified as strong or stronger in Japan, and antihistamines or antiallergics, or for whom treatment with these drugs was not recommended for safety reasons.	1) 44 2) 44	1) and 2) Nemolizumab 60 mg Q4W (Nemolizumab was administered by a healthcare professional at Weeks 0, 4, and 8 and by a healthcare professional [1] or the subject [2] after Week 12.	Safety Efficacy

a) Nemolizumab 0.1, 0.5, or 2.0 mg/kg Q4W after Week 12
b) Nemolizumab 60 mg Q4W after Week 16

7.1 Phase II studies

7.1.1 Global clinical study in patients with moderate to severe AD (CTD 5.3.5.1-1: Study CIM003JG [December 2013-June 2016])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japan, Poland, the U.S., Germany, and the U.K. to evaluate the efficacy and safety of nemolizumab in patients with moderate to severe AD who are inadequately controlled by treatment with potent or more potent[11)] TCS or TCI, or for whom topical therapies with these drugs was not recommended for safety reasons[12)] (target sample size of 250 patients [50 in each group]).

This study consisted of 2 parts: Part A, up to Week 12; and Part B, from Week 12 to Week 64. In Part A, nemolizumab 0.1, 0.5, or 2.0 mg/kg or placebo was subcutaneously administered at Weeks 0, 4, and 8, or nemolizumab 2.0 mg/kg was subcutaneously administered at Weeks 0 and 8. In Part B, subjects who received nemolizumab in Part A continued to receive nemolizumab at the previously assigned dose, and subjects who received placebo in Part A were re-randomized to either subcutaneous administration of nemolizumab 0.1, 0.5, or 2.0 mg/kg every 4 weeks. Concomitant therapies for AD were discontinued 4 weeks before baseline for systemic medications, 2 weeks before the baseline for potent or more potent TCS and TCI, and 1 week before baseline for mild or more potent[13)] TCS, antihistamines, and hypnotics. In Part A, concomitant use of moisturizing agents were allowed. In Part B, concomitant use of moisturizing agents, mild TCS including prednisolone, TCI, and antihistamines other than the first-generation antihistamines (nonselective) were allowed. Patients with little

11) Classified as medium to very strong according to the Japanese classification.
12) AD patients aged ≥18 and ≤65 years meeting all of the following: (1) meeting the Hanifin & Rajka diagnostic criteria for AD; (2) meeting either a or b at screening: a, inadequate response to potent or more potent TCS or TCI for ≥4 weeks or for the longest duration recommended in package inserts (an sIGA score of ≥3); or b, unable to receive standard topical therapy with TCS or TCI due to allergy or contraindication, etc.; (3) an EASI score of ≥10 at screening and randomization; (4) pruritus VAS of ≥50 mm at screening and randomization (for 3 days prior to the date of randomization); and (5) an sIGA score of ≥3 at randomization.
13) TCS classified as mild is not marketed in Japan, but TCS classified as weak or medium in Japan is considered mild or moderately potent.

or no improvement with symptoms[14], a rescue therapy with TCS was allowed after Week 4 at the discretion of a physician[15].

All randomized 264 patients[16] (53 patients in the nemolizumab 0.1 mg/kg group, 54 patients in the nemolizumab 0.5 mg/kg group, 52 patients in the nemolizumab 2.0 mg/kg group, 52 patients in the nemolizumab 2.0 mg/kg Q8W group, and 53 patients in the placebo group) received ≥1 dose of the study drug, were evaluated for the post-dose efficacy at least once, and were included in the intention-to-treat (ITT) population and the safety analysis population in Part A. In the ITT population, 35 patients who are either withdrawn early or had major protocol deviation[17] (7 patients in the nemolizumab 0.1 mg/kg group, 9 patients in the nemolizumab 0.5 mg/kg group, 5 patients in the nemolizumab 2.0 mg/kg group, 7 patients in the nemolizumab 2.0 mg/kg Q8W group, and 7 patients in the placebo group) were excluded, and the remaining 229 patients (46 patients in the nemolizumab 0.1 mg/kg group, 45 patients in the nemolizumab 0.5 mg/kg group, 47 patients in the nemolizumab 2.0 mg/kg group, 45 patients in the nemolizumab 2.0 mg/kg Q8W group, and 46 patients in the placebo group) were included in the per-protocol set (PPS), and the PPS was the efficacy analysis population. In addition, 249 patients receiving ≥1 dose of nemolizumab in Part A or B (53 patients in the nemolizumab 0.1 mg/kg group, 54 patients in the nemolizumab 0.5 mg/kg group, 52 patients in the nemolizumab 2.0 mg/kg group, 52 patients in the nemolizumab 2.0 mg/kg Q8W group, 13 patients in the placebo to nemolizumab 0.1 mg/kg group, 12 patients in the placebo to nemolizumab 0.5 mg/kg group, and 13 patients in the placebo to nemolizumab 2.0 mg/kg group) were included in the safety analysis population for the entire study period.

In Part A, the study drug was discontinued in 17.0% (9 of 53) of patients in the nemolizumab 0.1 mg/kg group, 16.7% (9 of 54) of patients in the nemolizumab 0.5 mg/kg group, 13.5% (7 of 52) of patients in the nemolizumab 2.0 mg/kg group, 26.9% (14 of 52) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 17.0% (9 of 53) of patients in the placebo group. The main reasons for discontinuation included subject decision (3.8% [2 of 53] of patients in the nemolizumab 0.1 mg/kg group, 11.1% [6 of 54] of patients in the nemolizumab 0.5 mg/kg group, 3.8% [2 of 52] of patients in the nemolizumab 2.0 mg/kg group, 13.5% [7 of 52] of patients in the nemolizumab 2.0 mg/kg Q8W group, and 9.4% [5 of 53] of patients in the placebo group); adverse events (9.4% [5 of 53] of patients in the nemolizumab 0.1 mg/kg group, 3.7% [2 of 54] of patients in the nemolizumab 0.5 mg/kg group, 3.8% [2 of 52] of patients in the nemolizumab 2.0 mg/kg group, 7.7% [4 of 52] of patients in the nemolizumab 2.0 mg/kg Q8W group, and 1.9% [1 of 53] of patients in the placebo group); lack of efficacy (1.9% [1 of 53] of patients in the nemolizumab 0.1 mg/kg group, 1.9% [1 of 54] of patients in the nemolizumab 0.5 mg/kg group, 3.8% [2 of 52] of patients in the nemolizumab 2.0 mg/kg group, 1.9% [1 of 52] of patients in the nemolizumab 2.0 mg/kg Q8W group, and 5.7% [3 of 53] of patients in the placebo group).

[14] A patient was defined as having 'No improvement' if he or she meets all of the following criteria (1) to (4): (1) no improvement in sIGA score from baseline; (2) sIGA score ≥3; (3) <10% improvement in pruritus VAS from baseline (defined as average pruritus VAS for 3 days before baseline [i.e. Day -3 , Day -2, Day -1]); and (4) pruritus VAS ≥50 mm (latest data).

[15] As rescue therapies, patients were allowed to use "potent" TCS in Part A and "potent" or "very potent" TCS in Part B.

[16] Unless otherwise specified, the dosing frequency was Q4W.

[17] Main exclusion criteria included the following: withdrawal before being evaluated for pruritus VAS at Week 8 (5 patients in the nemolizumab 0.1 mg/kg group, 8 patients in the nemolizumab 0.5 mg/kg group, 4 patients in the nemolizumab 2.0 mg/kg group, 6 patients in the nemolizumab 2.0 mg/kg Q8W group, and 6 patients in the placebo group); and inclusion criteria deviation (1 patient in the nemolizumab 0.1 mg/kg group, 1 patient in the nemolizumab 0.5 mg/kg group, 1 patient in the nemolizumab 2.0 mg/kg group, 2 patients in the nemolizumab 2.0 mg/kg Q8W group, and 1 patient in the placebo group).

In the ITT population, 79 patients were Japanese (16 patients in the nemolizumab 0.1 mg/kg group, 16 patients in the nemolizumab 0.5 mg/kg group, 16 patients in the nemolizumab 2.0 mg/kg group, 15 patients in the nemolizumab 2.0 mg/kg Q8W group, and 16 patients in the placebo group). In the Japanese subgroup, the study treatment was discontinued in Part A in 12.5% (2 of 16) of patients in the nemolizumab 0.1 mg/kg group, 25.0% (4 of 16) of patients in the nemolizumab 0.5 mg/kg group, 18.8% (3 of 16) of patients in the nemolizumab 2.0 mg/kg group, 33.3% (5 of 15) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 31.3% (5 of 16) of patients in the placebo group. The main reasons for discontinuation included subject decision (6.3% [1 of 16] of patients in the nemolizumab 0.1 mg/kg group, 18.8% [3 of 16] of patients in the nemolizumab 0.5 mg/kg group, 20.0% [3 of 15] of patients in the nemolizumab 2.0 mg/kg Q8W group, and 25.0% [4 of 16] of patients in the placebo group), lack of efficacy (6.3% [1 of 16] of patients in the nemolizumab 0.1 mg/kg group, 12.5% [2 of 16] of patients in the nemolizumab 2.0 mg/kg group, 6.7% [1 of 15] of patients in the nemolizumab 2.0 mg/kg Q8W group, and 6.3% [1 of 16] of patients in the placebo group). In the PPS, 66 patients were Japanese (15 patients in the nemolizumab 0.1 mg/kg group, 12 patients in the nemolizumab 0.5 mg/kg group, 14 patients in the nemolizumab 2.0 mg/kg group, 13 patients in the nemolizumab 2.0 mg/kg Q8W group, and 12 patients in the placebo group).

Table 22 shows the primary efficacy endpoint, percent change from baseline in pruritus VAS at Week 12, and the secondary efficacy endpoint, percent change from baseline in pruritus VAS at Week 8. Statistically significant differences in the primary endpoint were observed in the comparison between the nemolizumab 0.1 mg/kg group and the placebo group, the nemolizumab 0.5 mg/kg group and the placebo group, and the nemolizumab 2.0 mg/kg group and the placebo group. Data in the Japanese subgroup are shown in Table 23.

Table 22. Results of pruritus VAS (PPS, LOCF)

	Nemolizumab 0.1 mg/kg	Nemolizumab 0.5 mg/kg	Nemolizumab 2.0 mg/kg	Placebo	Nemolizumab 2.0 mg/kg Q8W
Baseline	74.55 ± 12.34 (46)	76.48 ± 13.24 (45)	75.97 ± 11.13 (47)	73.21 ± 10.85 (46)	77.56 ± 12.25 (45)
Week 8	45.92 ± 25.48 (44)	30.02 ± 26.03 (43)	32.06 ± 25.27 (46)	57.47 ± 24.58 (43)	35.14 ± 23.61 (44)
Percent change from baseline[a)]	***−40.25 ± 4.93 (44)***	***−58.81 ± 5.00 (43)***	***−56.71 ± 4.81 (46)***	***−21.16 ± 4.99 (43)***	***−53.62 ± 4.76 (44)***
Difference from placebo[a)] [95% CI]	***−19.09 [−32.93, −5.26]***	***−37.65 [−51.64, −23.67]***	***−35.55 [−49.24, −21.85]***		***−32.04 [−45.63, −18.45]***
Week 12 (*)	44.84 ± 24.63 (44)	28.08 ± 27.41 (43)	29.56 ± 23.96 (46)	58.29 ± 25.15 (43)	30.01 ± 24.37 (44)
Percent change from baseline[a) b)]	***−41.46 ± 4.94 (44)***	***−61.24 ± 5.01 (43)***	***−60.46 ± 4.82 (46)***	***−20.07 ± 5.00 (43)***	***−61.03 ± 5.03 (44)***
Difference from placebo[a)] [95% CI]	***−21.39 [−35.25, −7.53]***	***−41.16 [−55.17, −27.15]***	***−40.39 [−54.11, −26.67]***		***−40.78 [−55.12, −26.44]***
Two-sided p-value[b)]	0.0027	<0.0001	<0.0001		—

Mean ± standard deviation (number of patients). ***Bold italic: least-squares mean [± standard error] (number of patients).*** Percent change, %. *, primary endpoint.

a) ANCOVA with treatment groups and study regions (the U.S., Europe, and Japan) as fixed effects and baseline pruritus VAS as a covariate.

b) A two-sided significance level of 5%. If the comparison between the nemolizumab 2.0 mg/kg group and the placebo group showed a statistically significant difference, it was planned to conduct a comparison between the nemolizumab 0.5 mg/kg group and the placebo group. If the comparison between the nemolizumab 0.5 mg/kg group and the placebo group showed a statistically significant difference, it was planned to conduct a comparison between the nemolizumab 0.1 mg/kg group and the placebo group. No comparison with consideration of the multiplicity adjustment of hypothesis testing was performed between the nemolizumab 2.0 mg/kg Q8W group and the placebo group.

Table 23. Results of pruritus VAS (PPS, LOCF, Japanese subgroup)

	Nemolizumab 0.1 mg/kg	Nemolizumab 0.5 mg/kg	Nemolizumab 2.0 mg/kg	Placebo	Nemolizumab 2.0 mg/kg Q8W
Baseline	78.09 ± 11.64 (15)	77.12 ± 13.78 (12)	80.31 ± 10.38 (14)	76.11 ± 10.82 (12)	78.19 ± 9.20 (13)
Week 8	54.50 ± 27.64 (14)	47.32 ± 31.99 (11)	40.48 ± 18.02 (13)	67.89 ± 20.71 (11)	46.77 ± 22.95 (12)
Percent change from baseline[a)]	***−31.14 ± 8.88 (14)***	***−35.76 ± 10.02 (11)***	***−45.56 ± 9.25 (13)***	***−12.63 ± 10.05 (11)***	***−37.99 ± 8.33 (12)***
Difference from placebo[a)] [95% CI]	***−18.51 [−45.51, 8.49]***	***−23.13 [−51.76, 5.50]***	***−32.93 [−60.54, −5.32]***		***−26.44 [−51.61, −1.27]***
Week 12 (*)	55.30 ± 25.07 (14)	44.14 ± 30.73 (11)	35.51 ± 17.72 (13)	67.71 ± 24.10 (11)	36.03 ± 24.12 (12)
Percent change from baseline[a)]	***−30.24 ± 8.80 (14)***	***−41.00 ± 9.93 (11)***	***−52.32 ± 9.16 (13)***	***−12.35 ± 9.96 (11)***	***−51.75 ± 9.56 (12)***
Difference from placebo[a)] [95% CI]	***−17.89 [−44.64, 8.86]***	***−28.65 [−57.02, −0.29]***	***−39.97 [−67.33, −12.62]***		***−40.05 [−68.93, −11.17]***

Mean ± standard deviation (number of patients). ***Bold italic: least-squares mean [± standard error] (number of patients).*** Percent change, %. *, primary endpoint.
a) ANCOVA with treatment group as fixed effect and baseline pruritus VAS as covariate.

In Part A, adverse events occurred in 71.7% (38 of 53) of patients in the nemolizumab 0.1 mg/kg group, 66.7% (36 of 54) of patients in the nemolizumab 0.5 mg/kg group, 76.9% (40 of 52) of patients in the nemolizumab 2.0 mg/kg group, 71.2% (37 of 52) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 67.9% (36 of 53) of patients in the placebo group, and the main events are shown in Table 24.

No deaths occurred.

Serious adverse events occurred in 1.9% (1 of 53) of patients in the nemolizumab 0.1 mg/kg group, 5.8% (3 of 52) of patients in the nemolizumab 2.0 mg/kg group, 9.6% (5 of 52) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 1.9% (1 of 53) of patients in the placebo group. Among these events, a causal relationship to the study drug could not be ruled out in 2 patients in the nemolizumab 2.0 mg/kg Q4W group (atopic dermatitis and skin infection in 1 patient; lymphadenopathy in 1 patient) and 1 patient in the nemolizumab 2.0 mg/kg Q8W group (dermatitis exfoliative).

Adverse events led to treatment discontinuation in 9.4% (5 of 53) of patients in the nemolizumab 0.1 mg/kg group, 5.6% (3 of 54) of patients in the nemolizumab 0.5 mg/kg group, 7.7% (4 of 52) of patients in the nemolizumab 2.0 mg/kg group, 5.8% (3 of 52) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 1.9% (1 of 53) of patients in the placebo group.

Adverse drug reactions occurred in 24.5% (13 of 53) of patients in the nemolizumab 0.1 mg/kg group, 25.9% (14 of 54) of patients in the nemolizumab 0.5 mg/kg group, 46.2% (24 of 52) of patients in the nemolizumab 2.0 mg/kg group, 28.8% (15 of 52) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 15.1% (8 of 53) of patients in the placebo group.

Table 24. Adverse events occurring in ≥3 patients in any group (Part A, safety analysis population)

Event	Nemolizumab 0.1 mg/kg (n = 53)	Nemolizumab 0.5 mg/kg (n = 54)	Nemolizumab 2.0 mg/kg (n = 52)	Nemolizumab 2.0 mg/kg Q8W (n = 52)	Placebo (n = 53)
Atopic dermatitis	11 (20.8)	10 (18.5)	11 (21.2)	9 (17.3)	7 (13.2)
Nasopharyngitis	9 (17.0)	6 (11.1)	5 (9.6)	7 (13.5)	8 (15.1)
Upper respiratory tract infection	4 (7.5)	1 (1.9)	4 (7.7)	5 (9.6)	6 (11.3)
Impetigo	4 (7.5)	0	0	0	0
Headache	3 (5.7)	2 (3.7)	3 (5.8)	1 (1.9)	0
Oedema peripheral	2 (3.8)	3 (5.6)	5 (9.6)	2 (3.8)	0
Blood CPK increased	2 (3.8)	2 (3.7)	4 (7.7)	3 (5.8)	3 (5.7)
Lymphadenopathy	2 (3.8)	1 (1.9)	1 (1.9)	1 (1.9)	3 (5.7)
Folliculitis	0	0	0	1 (1.9)	3 (5.7)

Number of patients (%)

In the Japanese subgroup in Part A, adverse events occurred in 62.5% (10 of 16) of patients in the nemolizumab 0.1 mg/kg group, 56.3% (9 of 16) of patients in the nemolizumab 0.5 mg/kg group, 68.8% (11 of 16) of patients in the nemolizumab 2.0 mg/kg group, 46.7% (7 of 15) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 50.0% (8 of 16) of patients in the placebo group, and the main events are shown in Table 25.

No deaths occurred.

Serious adverse events occurred in 6.3% (1 of 16) of patients in the nemolizumab 0.1 mg/kg group, 6.3% (1 of 16) of patients in the nemolizumab 2.0 mg/kg group, 6.7% (1 of 15) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 6.3% (1 of 16) of patients in the placebo group, and a causal relationship to the study drug was denied in all events.

Adverse events led to treatment discontinuation in 12.5% (2 of 16) of patients in the nemolizumab 0.5 mg/kg group, 6.3% (1 of 16) of patients in the nemolizumab 2.0 mg/kg group, and 6.7% (1 of 15) of patients in the nemolizumab 2.0 mg/kg Q8W group.

Adverse drug reactions occurred in 25.0% (4 of 16) of patients in the nemolizumab 0.1 mg/kg group, 18.8% (3 of 16) of patients in the nemolizumab 0.5 mg/kg group, 31.3% (5 of 16) of patients in the nemolizumab 2.0 mg/kg group, and 6.7% (1 of 15) of patients in the nemolizumab 2.0 mg/kg Q8W group.

Table 25. Adverse events occurring in ≥2 patients in any group (Part A, Japanese subgroup, safety analysis population)

Event	Nemolizumab 0.1 mg/kg (n = 16)	Nemolizumab 0.5 mg/kg (n = 16)	Nemolizumab 2.0 mg/kg (n = 16)	Nemolizumab 2.0 mg/kg Q8W (n = 15)	Placebo (n = 16)
Atopic dermatitis	6 (37.5)	3 (18.8)	4 (25.0)	2 (13.3)	1 (6.3)
Nasopharyngitis	3 (18.8)	2 (12.5)	1 (6.3)	1 (6.7)	1 (6.3)
Impetigo	3 (18.8)	0	0	0	0
Pyrexia	2 (12.5)	0	1 (6.3)	1 (6.7)	0
Headache	2 (12.5)	0	1 (6.3)	0	0
Blood CPK increased	2 (12.5)	0	1 (6.3)	0	0
Hepatic function abnormal	0	0	2 (12.5)	0	0
Folliculitis	0	0	0	0	2 (12.5)

Number of patients (%)

In Part B, adverse events occurred in 82.9% (34 of 41) of patients in the nemolizumab 0.1 mg/kg group, 73.7% (28 of 38) of patients in the nemolizumab 0.5 mg/kg group, 71.8% (28 of 39) of patients in the nemolizumab 2.0 mg/kg group, 74.3% (26 of 35) of patients in the nemolizumab 2.0 mg/kg Q8W group, 69.2% (9 of 13) of

patients in the placebo to nemolizumab 0.1 mg/kg group, 66.7% (8 of 12) of patients in the placebo to nemolizumab 0.5 mg/kg group, and 92.3% (12 of 13) of patients in the placebo to nemolizumab 2.0 mg/kg group, and the main adverse events are shown in Table 26.

No deaths occurred.

Serious adverse events occurred in 4.9% (2 of 41) of patients in the nemolizumab 0.1 mg/kg group, 5.3% (2 of 38) of patients in the nemolizumab 0.5 mg/kg group, 2.6% (1 of 39) of patients in the nemolizumab 2.0 mg/kg group, 14.3% (5 of 35) of patients in the nemolizumab 2.0 mg/kg Q8W group, and 7.7% (1 of 13) of patients in the placebo to nemolizumab 2.0 mg/kg group. Among these events, a causal relationship to the study drug could not be ruled out in 2 patients in the nemolizumab 2.0 mg/kg Q8W group (pyelonephritis in 1 patient; cataract in 1 patient) and 1 patient in the placebo to nemolizumab 2.0 mg/kg group (diverticulitis).

Adverse events led to treatment discontinuation in 4.9% (2 of 41) of patients in the nemolizumab 0.1 mg/kg group, 2.6% (1 of 39) of patients in the nemolizumab 2.0 mg/kg group, 8.6% (3 of 35) of patients in the nemolizumab 2.0 mg/kg Q8W group, 7.7% (1 of 13) of patients in the placebo to nemolizumab 0.1 mg/kg group, and 7.7% (1 of 13) of patients in the placebo to nemolizumab 2.0 mg/kg group.

Adverse drug reactions occurred in 24.4% (10 of 41) of patients in the nemolizumab 0.1 mg/kg group, 26.3% (10 of 38) of patients in the nemolizumab 0.5 mg/kg group, 17.9% (7 of 39) of patients in the nemolizumab 2.0 mg/kg group, 28.6% (10 of 35) of patients in the nemolizumab 2.0 mg/kg Q8W group, 30.8% (4 of 13) of patients in the placebo to nemolizumab 0.1 mg/kg group, 8.3% (1 of 12) of patients in the placebo to nemolizumab 0.5 mg/kg group, and 30.8% (4 of 13) of patients in the placebo to nemolizumab 2.0 mg/kg group.

Table 26. Adverse events occurring in ≥3 patients in any group (Part B, safety analysis population)

Event	Nemolizumab 0.1 mg/kg (n = 41)	Nemolizumab 0.5 mg/kg (n = 38)	Nemolizumab 2.0 mg/kg (n = 39)	Nemolizumab 2.0 mg/kg Q8W (n = 35)	Placebo to nemolizumab 0.1 mg/kg (n = 13)	Placebo to nemolizumab 0.5 mg/kg (n = 12)	Placebo to nemolizumab 2.0 mg/kg (n = 13)
Nasopharyngitis	10 (24.4)	11 (28.9)	12 (30.8)	7 (20.0)	2 (15.4)	3 (25.0)	4 (30.8)
Atopic dermatitis	7 (17.1)	3 (7.9)	3 (7.7)	2 (5.7)	2 (15.4)	3 (25.0)	1 (7.7)
Influenza	5 (12.2)	1 (2.6)	2 (5.1)	0	0	0	0
Blood CPK increased	4 (9.8)	3 (7.9)	7 (17.9)	3 (8.6)	2 (15.4)	1 (8.3)	2 (15.4)
Upper respiratory tract infection	3 (7.3)	3 (7.9)	3 (7.7)	2 (5.7)	0	0	1 (7.7)
Impetigo	3 (7.3)	3 (7.9)	0	3 (8.6)	1 (7.7)	1 (8.3)	0
Headache	1 (2.4)	4 (10.5)	2 (5.1)	1 (2.9)	2 (15.4)	1 (8.3)	1 (7.7)
Cystitis	1 (2.4)	3 (7.9)	1 (2.6)	1 (2.9)	1 (7.7)	0	0

Number of patients (%)

In the Japanese subgroup in Part B, adverse events occurred in 78.6% (11 of 14) of patients in the nemolizumab 0.1 mg/kg group, 55.6% (5 of 9) of patients in the nemolizumab 0.5 mg/kg group, 60.0% (6 of 10) of patients in the nemolizumab 2.0 mg/kg group, 77.8% (7 of 9) of patients in the nemolizumab 2.0 mg/kg Q8W group, 25.0% (1 of 4) of patients in the placebo to nemolizumab 0.1 mg/kg group, 66.7% (2 of 3) of patients in the placebo to nemolizumab 0.5 mg/kg group, and 100% (4 of 4) of patients in the placebo to nemolizumab 2.0 mg/kg group, and the main events are shown in Table 27.

No deaths occurred.

Serious adverse events occurred in 7.1% (1 of 14) of patients in the nemolizumab 0.1 mg/kg group and 11.1% (1 of 9) of patients in the nemolizumab 2.0 mg/kg Q8W group. Among these events, a causal relationship to the study drug could not be ruled out in 1 patient in the nemolizumab 2.0 mg/kg Q8W group (cataract).

Adverse events led to treatment discontinuation in 7.1% (1 of 14) of patients in the nemolizumab 0.1 mg/kg group and 11.1% (1 of 9) of patients in the nemolizumab 2.0 mg/kg Q8W group.

Adverse drug reactions occurred in 7.1% (1 of 14) of patients in the nemolizumab 0.1 mg/kg group, 22.2% (2 of 9) of patients in the nemolizumab 0.5 mg/kg group, 10.0% (1 of 10) of patients in the nemolizumab 2.0 mg/kg group, and 33.3% (3 of 9) of patients in the nemolizumab 2.0 mg/kg Q8W group.

Table 27. Adverse events occurring in ≥2 patients in any group (Part B, Japanese subgroup, safety analysis population)

Event	Nemolizumab 0.1 mg/kg (n = 14)	Nemolizumab 0.5 mg/kg (n = 9)	Nemolizumab 2.0 mg/kg (n = 10)	Nemolizumab 2.0 mg/kg Q8W (n = 9)	Placebo to nemolizumab 0.1 mg/kg (n = 4)	Placebo to nemolizumab 0.5 mg/kg (n = 3)	Placebo to nemolizumab 2.0 mg/kg (n = 4)
Nasopharyngitis	4 (28.6)	3 (33.3)	3 (30.0)	2 (22.2)	0	1 (33.3)	1 (25.0)
Impetigo	2 (14.3)	3 (33.3)	0	1 (11.1)	0	1 (33.3)	0
Influenza	2 (14.3)	1 (11.1)	0	0	0	0	0
Atopic dermatitis	2 (14.3)	0	0	0	0	2 (66.7)	0
Blood CPK increased	1 (7.1)	0	0	0	0	0	2 (50.0)
Herpes zoster	0	2 (22.2)	0	0	0	0	0
Folliculitis	0	0	0	2 (22.2)	0	0	0

Number of patients (%)

7.2 Phase III studies[18)]

7.2.1 Japanese study in AD patients with moderate to severe pruritus[19)] (CTD 5.3.5.1-2: Study M525101-01 [October 2017-[redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy and safety of nemolizumab in AD patients with moderate to severe pruritus who inadequately responded to strong or stronger class TCS or TCI and antihistamines or antiallergics or for whom these drugs were not recommended for safety reasons[20)] (target sample size of 204 subjects[21)] [136 subjects in the nemolizumab group and 68 subjects in the placebo group]).

[18)] The Japanese classification is used for TCS in this section.

[19)] It indicates the extent of the itch scores [see Section 10].

[20)] AD patients aged ≥13 years meeting all of the following criteria: (1) Diagnosed as AD according to the Hanifin & Rajka diagnostic criteria for AD; (2) meeting either a or b at the time of informed consent: a, History of persisted pruritus (itch scale of ≥3 determined by a physician) to strong or stronger class TCS or TCI for ≥4 consecutive weeks; or b, History of inability to receive topical therapies with TCS or TCI due to hypersensitivity or contraindication, etc.; (3) meeting either a or b at the time of informed consent: a, History of inadequate response of pruritus (itch scale of ≥3 determined by a physician) to antihistamines or antiallergics for ≥2 consecutive weeks; or b, History of inability to receive oral therapies with antihistamines or antiallergics (due to hypersensitivity or contraindication, etc.); (4) Pruritus VAS ≥50 on all of 3 days during 2 days prior to the day of randomization and the day of enrollment; (5) Itch score ≥3 on the day of enrollment; (6) Itch score ≥2 on all of 3 days during 2 days prior to the day of randomization, and itch score ≥3 on ≥2 days during these 3 days; and (7) EASI score of ≥10 on the day of randomization (only for Study M525101-01). For Study M525101-02, "the day of enrollment" and "randomization" in the above criteria of (4) to (6) should be read as "on the day of screening" and "the start of treatment with nemolizumab," respectively.

[21)] By referring to the results from a phase II study (Study CIM003JG), the primary endpoint of the expected percent change from baseline in pruritus VAS at Week 16 was assumed to be -53% in the nemolizumab group and -36% in the placebo group, and the standard deviation in percent change in each group was assumed to be 35%. With these assumptions, the two-sided significance level was specified as 5%, and the number of subjects required for a comparison with a detection power of 90% is determined as 204 subjects (136 subjects in the nemolizumab group and 68 subjects in the placebo group).

This study consisted of 2 parts: Part A (up to Week 16) and Part B (from Week 16 to Week 68). In Part A, nemolizumab 60 mg or placebo was subcutaneously administered every 4 weeks, and in Part B, nemolizumab 60 mg was subcutaneously administered every 4 weeks. As for concomitant therapies for AD, systemic medications and very strong class or stronger class TCS were discontinued 4 weeks before the baseline, and hypnotics were discontinued 2 weeks before the baseline. Patients were not allowed to newly initiate concomitant use of antihistamines or antiallergics for atopic dermatitis, change the medications or the dosing regimen within 2 weeks before the baseline. Strong class TCS or TCI were concomitantly used from ≥4 weeks before the baseline to Part A[22)]. If adverse event occurred after the date of randomization and worsened AD, rescue therapy with very strong class or stronger class TCS was allowed to be concomitantly used at the discretion of a physician. In Part B, the concomitant use of topical therapies, antihistamines, antiallergics, and hypnotics was not restricted.

All 215 randomized patients (143 patients in the nemolizumab group and 72 patients in the placebo group) received ≥1 dose of the study drug and were evaluated for efficacy after randomization at least once. All patients were included in the full analysis set (FAS) and safety analysis population, and the FAS was regarded as the efficacy analysis population.

In Part A, the study treatment was discontinued in 2.8% (4 of 143) of patients in the nemolizumab group and 6.9% (5 of 72) of patients in the placebo group. The main reasons for discontinuation included violation of the inclusion criteria (0.7% [1 of 143] of patients in the nemolizumab group and 4.2% [3 of 72] of patients in the placebo group), subject decision (0.7% [1 of 143] of patients in the nemolizumab group and 2.8% [2 of 72] of patients in the placebo group).

Table 28 shows percent change from baseline in pruritus VAS at Week 16, the primary efficacy endpoint. Statistically significant differences were observed in the pairwise comparison of the placebo group and the nemolizumab group, demonstrating the superiority of nemolizumab to placebo.

Table 28. Results of pruritus VAS (FAS, OC)

	Nemolizumab	Placebo
Baseline	74.92 ± 10.48 (143)	75.30 ± 10.46 (72)
Week 16	39.91 ± 21.24 (116)	56.76 ± 21.42 (55)
Percent change from baseline[a)]	***−42.84 ± 2.57***	***−21.39 ± 3.61***
Difference from placebo[a)] [95% CI] Two-sided p-value[b)]	***−21.45 [−30.19, −12.71]*** <0.0001	

Mean ± standard deviation (number of patients). ***Bold italic: least-squares mean [± standard error].*** Percent change, %.
a) Mixed effect model for repeated measures (MMRM) assuming unstructured covariance structure with treatment group, evaluation points, and interaction between treatment group and evaluation points as fixed effects and baseline pruritus VAS as a covariate.
b) Two-sided significance level of 5%

In Part A, adverse events occurred in 70.6% (101 of 143) of patients in the nemolizumab group and 70.8% (51 of 72) of patients in the placebo group, and the main events are shown in Table 29.

[22)] After randomization, dose reduction (e.g., a longer dosing interval, reduced daily dose frequency, etc.)/discontinuation and dose reduction/dose increase after discontinuation/resumption (up to the dosing regimen at the time of randomization) were allowed. The concomitant use of moisturizing agents or medium class or weaker TCS was also allowed.

No deaths occurred.

Serious adverse events occurred in 2.1% (3 of 143) of patients in the nemolizumab group and 2.8% (2 of 72) of patients in the placebo group. Among these events, a causal relationship to the study drug could not be ruled out in 2 patients in the nemolizumab group (bacteraemia, alopecia areata/Meniere's disease).

Adverse events led to treatment discontinuation in 2.1% (3 of 143) of patients in the nemolizumab group.

Adverse drug reactions occurred in 37.1% (53 of 143) of patients in the nemolizumab group and 22.2% (16 of 72) of patients in the placebo group.

Table 29. Adverse events occurring with an incidence of ≥2% in either group (Part A, safety analysis population)

Event	Nemolizumab (N = 143)	Placebo (N = 72)	Event	Nemolizumab (N = 143)	Placebo (N = 72)
Atopic dermatitis	33 (23.1)	15 (20.8)	Contusion	3 (2.1)	0
Nasopharyngitis	18 (12.6)	11 (15.3)	Blood uric acid increased	3 (2.1)	0
Cytokine abnormal	10 (7.0)	0	Eosinophil count increased	3 (2.1)	0
Blood CPK increased	5 (3.5)	1 (1.4)	Dyshidrotic eczema	3 (2.1)	0
Pyrexia	4 (2.8)	2 (2.8)	Urticaria	3 (2.1)	0
Influenza	4 (2.8)	2 (2.8)	Acne	2 (1.4)	3 (4.2)
Upper respiratory tract inflammation	4 (2.8)	2 (2.8)	Cellulitis	2 (1.4)	2 (2.8)
Malaise	4 (2.8)	1 (1.4)	Abdominal discomfort	1 (0.7)	2 (2.8)
Headache	4 (2.8)	1 (1.4)	Constipation	1 (0.7)	2 (2.8)
Oedema peripheral	4 (2.8)	0	Seasonal allergy	0	2 (2.8)
Dermatitis contact	4 (2.8)	0	Paronychia	0	2 (2.8)
Diarrhoea	3 (2.1)	2 (2.8)	Spinal osteoarthritis	0	2 (2.8)
Dental caries	3 (2.1)	0			

Number of patients (%)

The incidence of adverse events in patients receiving nemolizumab during the overall treatment period was 96.2% (202 of 210) of patients, and the main events are shown in Table 30.

No deaths occurred.

Serious adverse events occurred in 8.6% (18 of 210) of patients. Among these events, a causal relationship to the study drug could not be ruled out in 6 patients (bacteraemia, Kaposi's varicelliform eruption/bacteraemia, pneumonia, alopecia areata/Meniere's disease, dermatitis exfoliative, and cellulitis).

Adverse events led to treatment discontinuation in 10.5% (22 of 210) of patients, and adverse drug reactions occurred in 58.1% (122 of 210) of patients.

Table 30. Adverse events occurring with an incidence of ≥5% (overall treatment period, safety analysis population)

Event	Nemolizumab (n = 210)	Event	Nemolizumab (n = 210)
Nasopharyngitis	70 (33.3)	Upper respiratory tract inflammation	15 (7.1)
Atopic dermatitis	52 (24.8)	Dermatitis contact	15 (7.1)
Blood CPK increased	22 (10.5)	Headache	13 (6.2)
Acne	20 (9.5)	Pyrexia	13 (6.2)
Urticaria	20 (9.5)	Cytokine abnormal	12 (5.7)
Influenza	17 (8.1)	Diarrhoea	12 (5.7)
Dental caries	16 (7.6)	Contusion	11 (5.2)
Gastroenteritis	15 (7.1)	Cellulitis	11 (5.2)

Number of patients (%)

7.2.2 Japanese study in AD patients with moderate to severe pruritus (CTD 5.3.5.2-1: Study M525101-02 [[redacted]])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of nemolizumab in AD patients with moderate to severe pruritus who inadequately responded to strong or stronger class TCS or TCI and antihistamines or antiallergics or for whom treatment with these drugs was not recommended for safety reasons[20] (target sample size of 80 patients [40 patients in the medical professional administration group and 40 patients in the self-injection group]).

Nemolizumab 60 mg was subcutaneously administered Q4W for 52 weeks. Nemolizumab was administered by healthcare professionals at Weeks 0, 4, and 8 in both groups and by patients after Week 12 in the self-injection group. As for concomitant therapies for AD, systemic medications were discontinued 4 weeks before the start of treatment with nemolizumab, but there was no restriction on the use of topical drugs, antihistamines, antiallergics, and hypnotics.

All 88 enrolled patients (44 patients in the medical professional administration group and 44 patients in the self-injection group) received ≥1 dose of the study drug, were evaluated for efficacy at least once, and were included in the FAS and the safety analysis population, and the FAS was regarded as the efficacy analysis population.

The study drug was discontinued in 6.8% (3 of 44) of patients in the medical professional administration group and 15.9% (7 of 44) of patients in the self-injection group. The reasons for discontinuation included adverse events (2.3% [1 of 44] of patients in the medical professional administration group and 9.1% [4 of 44] of patients in the self-injection group]), subject decision (4.5% [2 of 44] of patients in the medical professional administration group and 4.5% [2 of 44] of patients in the self-injection group), and lack of efficacy (2.3% [1 of 44] of patients in the self-injection group).

Adverse events occurred in 86.4% (38 of 44) of patients in the medical professional administration group and 93.2% (41 of 44) of patients in the self-injection group, and the main events are shown in Table 31.

No deaths occurred.

Serious adverse events[23] occurred in 6.8% (3 of 44) of patients in the medical professional administration group and 15.9% (7 of 44) of patients in the self-injection group. Among these events, a causal relationship to the study drug could not be ruled out in 2 patients in the medical professional administration group (optic neuritis in 1 patient and impetigo in 1 patient) and 3 patients in the self-injection group (cellulitis in 1 patient, viral infection in 1 patient, and extranodal marginal zone B-cell lymphoma [MALT type] in 1 patient).

Adverse events led to treatment discontinuation in 4.5% (2 of 44) of patients in the medical professional administration group and 11.4% (5 of 44) of patients in the self-injection group.

Adverse drug reactions occurred in 59.1% (26 of 44) of patients in the medical professional administration group and 54.5% (24 of 44) of patients in the self-injection group.

Table 31. Adverse events occurring in ≥3 patients in the combined group (safety analysis population)

Event	Medical professional administration (n = 44)	Self-injection (n = 44)	Event	Medical professional administration (n = 44)	Self-injection (n = 44)
Nasopharyngitis	14 (31.8)	17 (38.6)	Vertigo	2 (4.5)	1 (2.3)
Atopic dermatitis	10 (22.7)	13 (29.5)	Dental caries	2 (4.5)	1 (2.3)
Dermatitis contact	6 (13.6)	5 (11.4)	Herpes zoster	2 (4.5)	1 (2.3)
Influenza	6 (13.6)	3 (6.8)	Toxic skin eruption	1 (2.3)	3 (6.8)
Cough	5 (11.4)	3 (6.8)	Kaposi's varicelliform eruption	1 (2.3)	3 (6.8)
Cellulitis	3 (6.8)	7 (15.9)	Pain	1 (2.3)	2 (4.5)
Headache	3 (6.8)	5 (11.4)	Arthralgia	1 (2.3)	2 (4.5)
Blood CPK increased	2 (4.5)	3 (6.8)	Dermatitis	1 (2.3)	2 (4.5)
Pharyngitis	2 (4.5)	3 (6.8)	Bronchitis	0	4 (9.1)
Impetigo	2 (4.5)	2 (4.5)	Skin infection	0	3 (6.8)
Upper respiratory tract inflammation	2 (4.5)	2 (4.5)	Gastrooesophageal reflux disease	0	3 (6.8)
Urticaria	2 (4.5)	2 (4.5)	Folliculitis	0	3 (6.8)
Otitis externa	2 (4.5)	1 (2.3)	Dermal cyst	0	3 (6.8)

Number of patients (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation:

On the basis of the current status of treatment for pruritus associated with AD, the applicant specified "study population," "efficacy endpoint," "dosing regimen," and "concomitant drugs" in the Japanese phase III clinical studies in AD patients with pruritus as shown below.

- **Study population**

Topical anti-inflammatory drugs such as TCS are the basic pharmacotherapy for AD. It is important to select TCS of the appropriate rank for the severity of rash (TCI should be added if necessary) and to use them appropriately at the necessary dose for the necessary duration, under the continuous use of topical moisturizing agents. In cases of inadequate response to these therapies, systemic therapy with oral medications such as ciclosporin should be considered. In addition, the use of oral antihistamines as an adjunct therapy for topical therapy is recommended for pruritus associated with AD (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology*. 2018;128:2431-502]). In view of the above, patients meeting the following criteria were

[23] One patient in the medical professional administration group (ophthalmic herpes simplex) was hospitalized after the database lock, and the event was considered serious. A causal relationship to the study drug could not be ruled out.

considered eligible for the phase III studies: AD patients with a history of inadequate response to ≥2 weeks of treatment with antihistamines or antiallergics for pruritis (itch score ≥3) and with persistent pruritus despite of ≥4 weeks of topical therapy (with strong or stronger class TCS or TCI) in combination with antihistamines/antiallergics (pruritus VAS ≥50 and itch score ≥3). In patients who were unsuitable for treatment with TCS, TCI, antihistamines, or antiallergics due to hypersensitivity, contraindication, or other reasons, such treatment was unnecessary.

- **Efficacy endpoint**

For evaluation of pruritus, pruritus VAS, which is described as useful in the Guidelines for the Management of Atopic Dermatitis 2018 (*The Japanese Journal of Dermatology*. 2018;128:2431-502), was specified as the primary endpoint in the phase III studies. Since it is recommended to evaluate pruritus with multiple rating scales (*Acta Derm Venereol*. 2012;92:502-7), the numerical rating scale (NRS) for pruritus and itch scores were specified as other endpoints. Furthermore, since persistent pruritus in AD significantly impairs the quality of life (QOL) due to difficulty with concentration and sleep disorder (*Arch Pediatr Adolesc Med*. 2005;159:745-50; *J Dermatol*. 2018;45:390-6), the dermatology life quality index (DLQI) (the children's dermatology life quality life [CDLQI] for subjects aged <16 years), a rating index for QOL in skin diseases, and the insomnia severity index (ISI), an index for evaluation of the severity of insomnia, were specified as secondary endpoints. Since AD is characterized by a vicious cycle, also known as an itch-scratch cycle, in which the worsening of skin symptoms due to scratching associated with pruritus leads to an intensification of pruritus, the eczema area and severity index (EASI) score (as a secondary endpoint) and the static investigator's global assessment (sIGA) score (as another endpoint) were also included for evaluation of skin symptoms.

- **Dosing regimen**

In the phase II study conducted in patients with moderate to severe AD who inadequately responded to topical therapy or for whom topical therapy was not recommended for safety reasons [see Section 7.1.1], the serum trough concentrations of nemolizumab increased in a dose-dependent manner in the nemolizumab group [see Section 6.2.2.1], but the percent changes from baseline in pruritus VAS at Week 12, the primary endpoint, were similar between the nemolizumab 0.5 mg/kg and 2.0 mg/kg groups. Based on the results of exposure-response analyses on serum nemolizumab concentrations and pruritus VAS available from the phase I and II studies, the improvement in pruritus was assumed to reach a plateau at doses of ≥0.5 mg/kg [see Section 6.4].

In light of the convenience in clinical practice, a fixed dose independent of body weight was used for the dosing regimen in the phase III studies. The dosing regimen of "nemolizumab 60 mg Q4W," equivalent to a dose of 0.5 to 2.0 mg/kg for AD patients weighing 30 to 120 kg, was chosen by taking account of above clinical study results and average weight distribution of the Japanese population aged ≥13 years (47.6-71.3 kg for males and 46.1-55.5 kg for females, the National Health and Nutrition Survey Report 2015).

- **Concomitant drugs**

As mentioned above, the basic pharmacotherapy for AD consists of topical moisturizing agents and topical anti-inflammatory drugs, and oral medications such as antihistamines are used to treat pruritus. Nemolizumab is thus

expected to be used in combination with topical anti-inflammatory drugs and antihistamines/antiallergics in clinical practice. In view of the above, concomitant use of TCS or TCI with nemolizumab was allowed in the phase III studies, and as needed use of antihistamines and antiallergics were also allowed.

PMDA accepted the applicant's explanation and has concluded that the efficacy and safety of nemolizumab in AD patients with pruritus can be evaluated based on the submitted clinical data package, focusing on the Japanese phase III studies.

7.R.2 Efficacy

The applicant's explanation about the efficacy of nemolizumab:

In Study M525101-01, the Japanese phase III study in AD patients with moderate to severe pruritus, the percent change from baseline in pruritus VAS at Week 16 was specified as the primary endpoint, which is shown in Table 28. Pairwise comparison showed statistically significant differences in the primary endpoint between the placebo and the nemolizumab groups, demonstrating the superiority of nemolizumab to placebo. Table 32 shows the results of the main efficacy endpoints for pruritis in Study M525101-01 and Study M525101-02, a Japanese open-label study. In Study M525101-01, nemolizumab tended to be superior to placebo for all endpoints in Part A, and the efficacy of nemolizumab tended to increase and be maintained during other periods.

Table 32. Results of main efficacy endpoints for pruritus

	Time of assessment	Study M525101-01			Study M525101-02
		Nemolizumab	Placebo	Placebo to nemolizumab	Nemolizumab
Pruritus VAS (mean ± standard deviation [number of subjects], OC)					
Percent change from baseline	Week 4	−33.11 ± 26.02 (134)	−13.38 ± 17.89 (67)	—	−32.17 ± 25.76 (88)
	Week 8	−38.40 ± 28.94 (125)	−18.33 ± 21.80 (65)	—	−40.27 ± 27.55 (88)
	Week 16	−45.38 ± 29.32 (115)	−24.13 ± 27.55 (55)	—	−47.48 ± 26.50 (87)
	Week 32	−58.37 ± 27.09 (114)	—	−54.55 ± 27.95 (55)	−57.94 ± 28.07 (82)
	Week 52	−64.31 ± 25.26 (112)	—	−65.12 ± 24.41 (52)	−60.61 ± 29.83 (78)
	Week 68	−65.87 ± 25.61 (109)	—	−69.46 ± 22.93 (52)	—
Pruritus VAS (% [number of subjects], NRI)					
Proportion of subjects with improvement by ≥50%	Week 4	23.7 (33/139)	4.5 (3/67)	—	26.1 (23/88)
	Week 8	31.7 (44/139)	9.0 (6/67)	—	36.4 (32/88)
	Week 16	34.5 (48/139)	14.9 (10/67)	—	45.5 (40/88)
	Week 32	48.9 (68/139)	—	50.7 (34/67)	52.3 (46/88)
	Week 52	56.8 (79/139)	—	62.7 (42/67)	55.7 (49/88)
	Week 68	59.0 (82/139)	—	62.7 (42/67)	—
Proportion of subjects with improvement by ≥75%	Week 4	8.6 (12/139)	0 (0/67)	—	5.7 (5/88)
	Week 8	10.8 (15/139)	1.5 (1/67)	—	13.6 (12/88)
	Week 16	15.1 (21/139)	4.5 (3/67)	—	14.8 (13/88)
	Week 32	26.6 (37/139)	—	23.9 (16/67)	33.0 (29/88)
	Week 52	33.1 (46/139)	—	32.8 (22/67)	34.1 (30/88)
	Week 68	33.1 (46/139)	—	37.3 (25/67)	—
Proportion of subjects with improvement by ≥90%	Week 4	1.4 (2/139)	0 (0/67)	—	0 (0/88)
	Week 8	3.6 (5/139)	0 (0/67)	—	3.4 (3/88)
	Week 16	6.5 (9/139)	3.0 (2/67)	—	4.5 (4/88)
	Week 32	8.6 (12/139)	—	6.0 (4/67)	12.5 (11/88)
	Week 52	14.4 (20/139)	—	7.5 (5/67)	20.5 (18/88)
	Week 68	14.4 (20/139)	—	14.9 (10/67)	—
Itch scores (% [number of subjects], NRI)					
Proportion of subjects achieving a score of ≤1	Week 4	10.1 (14/139)	0 (0/67)	—	6.8 (6/88)
	Week 8	15.1 (21/139)	3.0 (2/67)	—	13.6 (12/88)
	Week 16	17.3 (24/139)	6.0 (4/67)	—	20.5 (18/88)
	Week 32	33.1 (46/139)	—	25.4 (17/67)	34.1 (30/88)
	Week 52	40.3 (56/139)	—	37.3 (25/67)	36.4 (32/88)
	Week 68	39.6 (55/139)	—	43.3 (29/67)	—
Pruritus NRS (% [number of subjects], NRI)					
Proportion of subjects with improvement by ≥4 points	Week 4	19.4 (27/139)	1.5 (1/67)	—	25.0 (22/88)
	Week 8	28.8 (40/139)	6.0 (4/67)	—	34.1 (30/88)
	Week 16	32.4 (45/139)	13.4 (9/67)	—	44.3 (39/88)
	Week 32	46.8 (65/139)	—	47.8 (32/67)	53.4 (47/88)
	Week 52	49.6 (69/139)	—	55.2 (37/67)	55.7 (49/88)
	Week 68	51.1 (71/139)	—	61.2 (41/67)	—

—: Not applicable

For Study M525101-01, data for the FAS for overall period are shown (FAS subjects excluding 9 subjects who did not enter Part B [4 subjects in the nemolizumab group and 5 subjects in the placebo group]: 139 subjects in the nemolizumab group and 67 subjects in the placebo group). For Study M525101-02, data for the FAS are shown.

Table 33 shows the results of the subgroup analyses by patient characteristics in Study M525101-01, and no evident differences were seen in the efficacy of nemolizumab among individual subgroups.

Table 33. Percent change from baseline in pruritus VAS at Week 16 by patient characteristics (Study M525101-01, FAS)

		Nemolizumab	Placebo
Sex	Male	−43.08 ± 3.07 (93)	−17.24 ± 4.27 (48)
	Female	−36.57 ± 4.18 (50)	−25.96 ± 6.04 (24)
Age	≥13 and <30 years	−39.89 ± 4.48 (43)	−18.39 ± 6.92 (18)
	≥30 and <50 years	−40.86 ± 3.37 (76)	−27.07 ± 4.59 (41)
	≥50 years	−42.25 ± 5.99 (24)	−0.75 ± 8.14 (13)
Body weight	<60 kg	−37.65 ± 3.80 (61)	−17.91 ± 5.94 (25)
	≥60 kg	−43.15 ± 3.28 (82)	−21.33 ± 4.33 (47)
Pruritus VAS at baseline	<70	−34.88 ± 4.62 (41)	−25.61 ± 6.45 (21)
	≥70	−43.19 ± 2.93 (102)	−17.90 ± 4.14 (51)
EASI score at baseline	≤21	−35.85 ± 3.94 (57)	−21.78 ± 5.52 (29)
	>21 and ≤50	−43.75 ± 3.45 (74)	−19.58 ± 4.76 (39)
	>50	−46.16 ± 8.58 (12)	−13.77 ± 14.86 (4)
sIGA score at baseline	≤3	−37.50 ± 3.27 (82)	−21.69 ± 4.41 (45)
	≥4	−45.24 ± 3.79 (61)	−17.57 ± 5.70 (27)
TARC levels at the start of treatment[a)]	<500 ng/L	−48.48 ± 35.77 (19)	−31.67 ± 35.82 (9)
	≥500 and <2,000 ng/L	−48.65 ± 27.87 (55)	−24.38 ± 28.04 (32)
	≥2,000 and <5,000 ng/L	−43.96 ± 27.75 (20)	−17.56 ± 22.70 (9)
	≥5,000 ng/L	−36.89 ± 28.07 (22)	−20.75 ± 17.74 (5)

Least squares mean ± standard error (number of subjects). ANCOVA with missing values imputed by the last observation carried forward (LOCF) and the interaction between treatment group, subgroup parameters, and interaction between treatment group and subgroup parameters as the fixed effect. a) Mean ± standard deviation (number of subjects), OC.

Table 34 shows the results of the main QOL-related efficacy endpoints in Study M525101-01. The results in the nemolizumab group tended to be superior to those in the placebo group, and the efficacy of nemolizumab was maintained throughout the treatment period.

Table 34. Results of main QOL-related efficacy endpoints (Study M525101-01, FAS for overall period)

	Time of assessment	Nemolizumab	Placebo	Placebo to nemolizumab
DLQI (OC) (≥16 years old)	Baseline	12.4 ± 5.4 (132)	12.2 ± 5.5 (65)	—
	Week 4	7.4 ± 5.5 (134)	9.8 ± 6.0 (65)	—
	Week 8	7.4 ± 5.2 (134)	9.7 ± 5.6 (65)	—
	Week 16	6.6 ± 4.9 (134)	8.9 ± 5.8 (65)	—
	Week 32	4.7 ± 3.8 (128)	—	5.7 ± 4.9 (64)
	Week 44	4.6 ± 4.0 (129)	—	4.7 ± 3.9 (62)
	Week 68	3.9 ± 3.6 (128)	—	4.4 ± 3.8 (62)
Proportion of subjects achieving a score of ≤4 (NRI) (Subjects with baseline DLQI of ≥5)	Week 4	33.6 (42/125)	17.5 (11/63)	—
	Week 8	32.8 (41/125)	17.5 (11/63)	—
	Week 16	40.0 (50/125)	23.8 (15/63)	—
	Week 32	53.6 (67/125)	—	49.2 (31/63)
	Week 44	54.4 (68/125)	—	54.0 (34/63)
	Week 68	64.8 (81/125)	—	55.6 (35/63)
Proportion of subjects with improvement of ≥4 points (NRI) (Subjects with baseline DLQI of ≥4)	Week 4	64.3 (83/129)	40.6 (26/64)	—
	Week 8	62.8 (81/129)	42.2 (27/64)	—
	Week 16	68.2 (88/129)	53.1 (34/64)	—
	Week 32	75.2 (97/129)	—	71.9 (46/64)
	Week 44	72.1 (93/129)	—	82.8 (53/64)
	Week 68	79.8 (103/129)	—	76.6 (49/64)
CDLQI (OC) (<16 years old)	Baseline	11.2 ± 6.6 (5)	3, 6 (2)	—
	Week 4	5.2 ± 3.0 (5)	6, 7 (2)	—
	Week 8	4.6 ± 3.0 (5)	6, 12 (2)	—
	Week 16	4.2 ± 4.2 (5)	9, 10 (2)	—
	Week 32	2.5 ± 2.1 (4)	—	4, 4 (2)
	Week 44	1.5 ± 1.9 (4)	—	5, 5 (2)
	Week 68	1.0 ± 1.4 (4)	—	2, 6 (2)
Proportion of subjects achieving ISI of ≤7 (NRI) (Subjects with baseline ISI of ≥8)	Week 4	41.0 (43/105)	17.3 (9/52)	—
	Week 8	44.8 (47/105)	13.5 (7/52)	—
	Week 16	56.2 (59/105)	21.2 (11/52)	—
	Week 32	57.1 (60/105)	—	42.3 (22/52)
	Week 44	56.2 (59/105)	—	53.8 (28/52)
	Week 68	61.0 (64/105)	—	55.8 (29/52)

Mean ± standard deviation (number of subjects) (observed values are shown in the case of 2 subjects) or % (number of subjects). —: Not applicable.

As shown above, the efficacy of nemolizumab for pruritus associated with AD has been demonstrated.

Table 35 shows the results of the main efficacy endpoints for skin symptoms.

Table 35. Results of main efficacy endpoints for skin symptoms (Study M525101-01, FAS for overall period)

	Time of assessment	Nemolizumab	Placebo	Placebo to nemolizumab
EASI score (OC)	Baseline	27.28 ± 13.30 (139)	26.53 ± 11.93 (67)	—
	Week 4	17.42 ± 12.69 (139)	19.58 ± 11.57 (67)	—
	Week 8	17.46 ± 12.91 (139)	19.47 ± 12.67 (67)	—
	Week 16	14.71 ± 11.72 (139)	18.49 ± 14.48 (67)	—
	Week 32	8.72 ± 9.38 (137)	—	12.04 ± 10.35 (66)
	Week 52	6.61 ± 8.20 (133)	—	6.65 ± 6.06 (64)
	Week 68	5.57 ± 7.52 (131)	—	6.29 ± 6.63 (64)
Proportion of subjects achieving EASI-75 (NRI)	Week 4	12.9 (18/139)	7.5 (5/67)	—
	Week 8	15.8 (22/139)	9.0 (6/67)	—
	Week 16	25.9 (36/139)	17.9 (12/67)	—
	Week 32	46.8 (65/139)	—	34.3 (23/67)
	Week 52	61.9 (86/139)	—	59.7 (40/67)
	Week 68	68.3 (95/139)	—	64.2 (43/67)
Proportion of subjects achieving sIGA of 0 or 1 and ≥2 level improvement of score (NRI)	Week 4	1.4 (2/139)	0 (0/67)	—
	Week 8	0.7 (1/139)	3.0 (2/67)	—
	Week 16	5.8 (8/139)	6.0 (4/67)	—
	Week 32	9.4 (13/139)	—	9.0 (6/67)
	Week 52	23.0 (32/139)	—	14.9 (10/67)
	Week 68	29.5 (41/139)	—	17.9 (12/67)

Mean ± standard deviation (number of subjects) or % (number of subjects). —: Not applicable

PMDA's view:

Study M525101-01 has demonstrated the superiority of nemolizumab to placebo with respect to the primary endpoint of percent change from baseline in pruritus VAS at Week 16 in AD patients with moderate to severe pruritus. Nemolizumab tended to be superior to placebo also for other parameters of pruritis. The efficacy of nemolizumab for pruritus associated with AD has been demonstrated.

The above conclusions made by PMDA will be further discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant described the safety of nemolizumab based on data from the placebo-controlled period (Part A) in the Japanese phase III study (Study M525101-01), pooled data for the entire study period in 2 Japanese phase III studies (Studies M525101-01 and M525101-02) (hereinafter referred to as "the combined group of 2 Japanese studies"), pooled data for the placebo-controlled period (Part A) in the global phase II study (Study CIM003JG) and the Japanese phase III study (Study M525101-01) (hereinafter referred to as "the combined placebo-controlled group of phase II/III studies"), and pooled data for the entire study period in the global phase II study (Study CIM003JG) and 2 Japanese phase III studies (Studies M525101-01 and M525101-02) (hereinafter referred to as "the combined group of 1 global and 2 Japanese studies").

Table 36 shows the summary of safety of nemolizumab in each group, and Table 37 shows the main adverse events, indicating no evident differences among the groups. While no evident differences were seen in the incidence of all adverse events or serious adverse events among the groups, adverse events leading to treatment discontinuation and adverse drug reactions occurred more frequently in the nemolizumab group than in the placebo group. In the combined placebo-controlled group of phase II/III studies, adverse events leading to

treatment discontinuation occurring in ≥2 subjects were atopic dermatitis in 9 subjects and skin infection in 2 subjects, and all were reported in the nemolizumab group. Table 38 shows the main adverse drug reactions in each group.

Table 36. Summary of safety of nemolizumab (safety analysis population)

	Japanese studies			Combined placebo-controlled group of phase II/III studies		Combined group of 1 global and 2 Japanese studies
	Study M525101-01 Part A		Combined group of 2 Japanese studies			
	Nemolizumab	Placebo	Nemolizumab	Nemolizumab[a)]	Placebo[b)]	Nemolizumab[a)]
Number of subjects	143	72	298	301	112	481
Total exposure duration (person-year)	43.5	21.2	328.3	78.1	29.7	470.7
All adverse events	101 (70.6) 526.3	51 (70.8) 423.6	281 (94.3) 410.7	215 (71.4) 646.2	79 (70.5) 596.1	435 (90.4) 433.4
Serious adverse events	3 (2.1) 9.2	2 (2.8) 9.4	28 (9.4) 10.7	10 (3.3) 15.4	3 (2.7) 10.1	45 (9.4) 12.1
Death	0 0	0 0	0 0	0 0	0 0	0 0
Adverse events leading to treatment discontinuation[c)]	6 (4.2) 18.4	2 (2.8) 9.4	33 (11.1) 14.3	19 (6.3) 34.6	2 (1.8) 6.7	59 (12.3) 17.2
Adverse drug reactions	53 (37.1) 245.9	16 (22.2) 94.1	172 (57.7) 131.0	107 (35.5) 253.4	22 (19.6) 131.3	241 (50.1) 123.9

Upper: number of subjects (%). Lower: Number of events per 100 person-year adjusted with total exposure duration.
a) Subjects in the nemolizumab 0.1 mg/kg group and the placebo to nemolizumab 0.1 mg/kg group in Study CIM003JG are excluded (the same applies for the tables below).
b) Subjects in the placebo to nemolizumab 0.1 mg/kg group in Study CIM003JG are excluded (the same applies for the tables below).
c) Treatment interruption and dose reduction are included.

Table 37. Main adverse events (safety analysis population)

Events (Events with an incidence of ≥2% in either group)	Combined placebo-controlled group of phase II/III studies		Events (Events with an incidence of ≥5% in either group)	Combined group of 2 Japanese studies	Combined group of 1 global and 2 Japanese studies
	Nemolizumab (n = 301)	Placebo (n = 112)		Nemolizumab (n = 298)	Nemolizumab (n = 481)
Atopic dermatitis	63 (20.9)	21 (18.8)	Nasopharyngitis	101 (33.9)	149 (31.0)
Nasopharyngitis	37 (12.3)	18 (16.1)	Atopic dermatitis	75 (25.2)	117 (24.3)
Blood CPK increased	14 (4.7)	3 (2.7)	Blood CPK increased	27 (9.1)	48 (10.0)
Oedema peripheral	14 (4.7)	0	Dermatitis contact	26 (8.7)	30 (6.2)
Headache	10 (3.3)	1 (0.9)	Influenza	26 (8.7)	29 (6.0)
Cytokine abnormal	10 (3.3)	0	Urticaria	24 (8.1)	29 (6.0)
Upper respiratory tract infection	9 (3.0)	5 (4.5)	Acne	22 (7.4)	24 (5.0)
Pyrexia	7 (2.3)	2 (1.8)	Headache	21 (7.0)	36 (7.5)
Acne	2 (0.7)	3 (2.7)	Cellulitis	21 (7.0)	23 (4.8)
Folliculitis	2 (0.7)	3 (2.7)	Upper respiratory tract inflammation	19 (6.4)	20 (4.2)
Number of subjects (%)			Dental caries	19 (6.4)	20 (4.2)
			Gastroenteritis	17 (5.7)	21 (4.4)

Table 38. Main adverse drug reactions (safety analysis population)

Events (Events with an incidence of ≥1% in either group)	Combined placebo-controlled group of phase II/III studies		Events (Events with an incidence of ≥2% in either group)	Combined group of 2 Japanese studies	Combined group of 1 global and 2 Japanese studies
	Nemolizumab (n = 301)	Placebo (n = 112)		Nemolizumab (n = 298)	Nemolizumab (n = 481)
Atopic dermatitis	37 (12.3)	5 (4.5)	Atopic dermatitis	55 (18.5)	69 (14.3)
Cytokine abnormal	10 (3.3)	0	Cytokine abnormal	13 (4.4)	13 (2.7)
Oedema peripheral	7 (2.3)	0	Cellulitis	12 (4.0)	14 (2.9)
Upper respiratory tract infection	5 (1.7)	1 (0.9)	Urticaria	9 (3.0)	12 (2.5)
Injection site reaction	5 (1.7)	0	Nasopharyngitis	8 (2.7)	16 (3.3)
Nasopharyngitis	4 (1.3)	1 (0.9)	Erythema	8 (2.7)	9 (1.9)
Urticaria	4 (1.3)	0	Eosinophil count increased	8 (2.7)	8 (1.7)
Cellulitis	2 (0.7)	2 (1.8)	Toxic skin eruption	8 (2.7)	8 (1.7)
Lymphadenopathy	1 (0.3)	2 (1.8)	Impetigo	8 (2.7)	8 (1.7)
Number of subjects (%)			Headache	7 (2.3)	9 (1.9)
			Oedema peripheral	6 (2.0)	11 (2.3)
			Kaposi's varicelliform eruption	6 (2.0)	6 (1.2)

No deaths occurred in any group.

Serious adverse events occurred in 9.4% (45 of 481) of subjects in the combined group of 1 global and 2 Japanese studies. Serious adverse events occurring in ≥2 subjects were atopic dermatitis (1.0% [5 of 481] of subjects); cellulitis (0.6% [3 of 481] of subjects); bacteraemia, optic neuritis, bladder cancer, dermatitis exfoliative, and infection (0.4% [2 of 481] of subjects each). Serious adverse events occurring in the combined group of 2 Japanese studies were cellulitis (1.0% [3 of 298] of subjects); optic neuritis (0.7% [2 of 298] of subjects); bacteraemia, bladder cancer, dermatitis exfoliative, viral infection, bacteraemia/Kaposi's varicelliform eruption, angina pectoris/chondrocalcinosis pyrophosphate, alopecia areata/Meniere's disease, loss of consciousness, asthenopia, investigation/2 events of pancreatitis acute, primary hyperaldosteronism, haemorrhoids, decreased appetite, extranodal marginal zone B-cell lymphoma (MALT type), cellulitis of male external genital organ, wisdom teeth removal, intervertebral disc protrusion, impetigo, pneumonia, bladder cancer/lung adenocarcinoma stage III, 2 cataract operations, skin bacterial infection, and nasal septum deviation (0.3% [1 of 298] of subjects each). Among these events, a causal relationship to nemolizumab could not be ruled out for cellulitis in 2 subjects, bacteraemia, bacteraemia/Kaposi's varicelliform eruption, pneumonia, alopecia areata/Meniere's disease, dermatitis exfoliative, viral infection, extranodal marginal zone B-cell lymphoma (MALT type), optic neuritis, and impetigo in 1 subject each.

Considering the pharmacological actions of nemolizumab and disease characteristics in AD patients, PMDA focused its safety review on the following events as adverse events of special interest.

Adverse events of special interest in the clinical studies of nemolizumab are summarized in Table 39.

Table 39. Summary of adverse events of special interest (safety analysis population)

	Japanese study			Combined placebo-controlled group of phase II/III studies		Combined group of 1 global and 2 Japanese studies
	Study M525101-01 Part A		Combined group of 2 Japanese studies			
	Nemolizumab	Placebo	Nemolizumab	Nemolizumab	Placebo	Nemolizumab
Number of subjects	143	72	298	301	112	481
Total exposure duration (person-year)	43.5	21.2	328.3	78.1	29.7	470.7
Infectious diseases (excluding skin infections)	30 (21.0) 82.7	18 (25.0) 89.4	160 (53.7) 89.0	78 (25.9) 125.4	34 (30.4) 128.0	251 (52.2) 105.2
Skin infections	13 (9.1) 29.9	9 (12.5) 42.4	88 (29.5) 43.0	32 (10.6) 40.9	12 (10.7) 40.4	128 (26.6) 42.3
Serious infections	1 (0.7) 2.3	0 0	10 (3.4) 3.4	4 (1.3) 5.1	0 0	17 (3.5) 3.8
Tuberculosis	0 0	0 0	0 0	0 0	0 0	0 0
Virus reactivation	0 0	0 0	0 0	0 0	0 0	0 0
Worsening of AD	34 (23.8) 89.6	15 (20.8) 70.6	77 (25.8) 30.8	64 (21.3) 93.4	21 (18.8) 74.1	119 (24.7) 32.1
Cytokine abnormal (PT)	10 (7.0) 23.0	0 0	14 (4.7) 4.3	10 (3.3) 12.8	0 0	14 (2.9) 3.0
Hypersensitivity-related events	13 (9.1) 34.5	2 (2.8) 9.4	81 (27.2) 35.3	24 (8.0) 38.4	7 (6.3) 30.3	109 (22.7) 33.1
Serious hypersensitivity	0 0	0 0	1 (0.3) 0.3	1 (0.3) 1.3	0 0	4 (0.8) 0.8
Anaphylactic reaction	0 0	0 0	1 (0.3) 0.3	0 0	0 0	1 (0.2) 0.2
Injection-related reactions	12 (8.4) 48.3	2 (2.8) 9.4	22 (7.4) 12.5	20 (6.6) 38.4	3 (2.7) 10.1	32 (6.7) 11.0
Ophthalmic complications of AD[a)]	5 (3.5) 11.5	4 (5.6) 18.8	30 (10.1) 10.7	8 (2.7) 10.2	7 (6.3) 23.6	39 (8.1) 10.0
Asthma	0 0	0 0	7 (2.3) 2.4	1 (0.3) 1.3	1 (0.9) 6.7	12 (2.5) 2.8
Oedema peripheral (PT)	4 (2.8) 9.2	0 0	8 (2.7) 2.7	14 (4.7) 20.5	0 0	21 (4.4) 5.7
Blood CPK increased	4 (2.8) 9.2	1 (1.4) 4.7	28 (9.4) 8.8	13 (4.3) 16.6	3 (2.7) 10.1	48 (10.0) 11.9
Depression and suicide/self-injury (SMQ/narrow)	1 (0.7) 2.3	0 0	3 (1.0) 0.9	1 (0.3) 1.3	0 0	3 (0.6) 0.6
Malignant tumors (SMQ)	0 0	0 0	3 (1.0) 1.2	0 0	0 0	3 (0.6) 0.8
Interstitial lung disease (SMQ/narrow)	0 0	0 0	0 0	0 0	0 0	0 0
Cardiovascular event	0 0	1 (1.4) 9.4	3 (1.0) 0.9	4 (1.3) 5.1	1 (0.9) 6.7	9 (1.9) 1.9

Upper: number of subjects (%). Lower: Number of events per 100 person-year adjusted with total exposure duration. See Section 10 for definition of events.
a) Dermatitis eyelid, keratoconjunctivitis, keratoconus, cataract, and retinal detachment.

7.R.3.2 Infectious diseases

The applicant's explanation about the occurrence of infectious diseases during treatment with nemolizumab:

In Part A of Study M525101-01 and the combined placebo-controlled group of phase II/III studies, the incidence of infectious diseases (excluding skin infections) and skin infections was similar between the nemolizumab group and the placebo group (Table 39). In the combined group of 1 global and 2 Japanese studies, serious infections occurred in 17 subjects. Among these events, a causal relationship to nemolizumab could not be ruled out for cellulitis (2 subjects), bacteraemia, diverticulitis, impetigo, pneumonia, pyelonephritis, skin infection, viral infection, bacteraemia/Kaposi's varicelliform eruption, cellulitis of male external genital organ, and skin bacterial infection (1 subject each), but the outcome was "resolved" or "resolving" for all events. In light of the fact that the majority of infectious disease-related adverse events were mild in severity, the risk of developing or exacerbation of infectious diseases with nemolizumab treatment is not considered high. However, AD patients

are prone to bacterial, fungal, and viral infections due to a decreased skin barrier function and reduced skin immune activity (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology.* 2018;128:2431-502]). The possibility that nemolizumab may affect the immune response system and increase the risk of the development of infectious diseases or make infectious diseases serious cannot be ruled out. In addition, serious infections have been reported for which a causal relationship with nemolizumab could not be ruled out. In consideration of them, it is planned that serious infections are specified as an important potential risk and that a precautionary statement for infectious diseases is included in the package insert.

PMDA's view:

In light of the fact that serious infections were reported only in patients receiving nemolizumab in clinical studies, serious infections should be specified as an important identified risk to call attention in the package insert, and the applicant as a marketing authorization holder should take necessary measures including early detection of infectious diseases. Although no tuberculosis or virus reactivation has been reported in clinical studies of nemolizumab, patients infected with tuberculosis, hepatitis B, or hepatitis C virus were excluded from the clinical studies, and sufficient information on the effects of nemolizumab on the activation of tuberculosis or reactivation of hepatitis B or C has not been obtained. Therefore, information collected in post-marketing surveillance or other settings should be closely examined, and measures should be considered as needed.

7.R.3.3 Worsening of AD

The applicant's explanation about the worsening of AD during nemolizumab treatment:

No distinct differences in the incidence of adverse events related to worsening of AD were observed between the nemolizumab group and the placebo group in Part A of Study M525101-01 and the combined placebo-controlled group of phase II/III studies (Table 39). No marked differences were observed between the nemolizumab group and the placebo group for the details of worsening of AD (severity, outcome, and time from the onset to resolution) in Part A of phase III Study M525101-01 (Table 40), and most events were mild to moderate skin symptoms that resolved with very strong class or stronger TCS. In the meantime, events (adverse drug reactions) related to worsening of AD for which a causal relationship to the study drug could not be ruled out occurred more frequently in the nemolizumab group than in the placebo group (Table 40), and those characterized by "new onset of erythema or papules at the site where no (or almost no) erythema or papules had developed" or "exacerbation of desquamation at the site of skin eruption (excluding that with dryness alone)" were more common in the nemolizumab group (Table 41). These findings suggest that nemolizumab may cause new skin symptoms in addition to the worsening of the underlying disease[24)].

[24)] In the clinical studies, skin-related adverse events of special interest other than worsening of AD, were collected as "other cutaneous disorders." "Other cutaneous disorders" were defined as dyshidrotic eczema, eczema nummular, erythema, eczema, blister, toxic skin eruption, dermatitis exfoliative, skin erosion, dermatitis, or skin exfoliation (PT) and reported in 4.3% (13 of 301) of subjects in the nemolizumab group and 2.7% (3 of 112) of subjects in the placebo group in the combined placebo-controlled group of phase II/III studies. Among these events, a causal relationship to the study drug could not be ruled out in 3.0% (9 of 301) of subjects in the nemolizumab group only. The details were dyshidrotic eczema, toxic skin eruption, dermatitis exfoliative, and skin exfoliation in 2 subjects each; erythema and dermatitis in 1 subject each.

Table 40. Adverse events related to worsening of AD (Part A of Study M525101-01, safety analysis population)

	Adverse events		Adverse drug reactions	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Total exposure duration (person-year)	43.5	21.2	43.5	21.2
Worsening of AD	39 89.6	15 70.6	28 64.4	4 18.9
Severity				
Mild	19 (48.7)	7 (46.7)	14 (50.0)	2 (50.0)
Moderate	19 (48.7)	8 (53.3)	14 (50.0)	2 (50.0)
Severe	1 (2.6)	0	0	0
Outcome				
Recovered	37 (94.9)	14 (93.3)	28 (100)	3 (75.0)
Recovering	1 (2.6)	1 (6.7)	0	1 (25.0)
Not recovered	1 (2.6)	0	0	0
Time from the onset to resolution				
≤28 days	4 (10.3)	0	1 (3.6)	0
≥29 and ≤56 days	6 (15.4)	1 (6.7)	6 (21.4)	0
≥57 and ≤84 days	5 (12.8)	6 (40.0)	2 (7.1)	1 (25.0)
≥85 days	22 (56.4)	7 (46.7)	19 (67.9)	2 (50.0)

Upper: number of subjects (%). Lower: Number of events per 100 person-year adjusted with total exposure duration.
Number of events (Percentage to the number of worsening of AD [%])

Table 41. Details of adverse events related to worsening of AD (Part A of Study M525101-01, safety analysis population)

Skin symptoms	Occurrence	Nemolizumab group	Placebo
Expansion or new formation of skin eruption	Yes	30/35 (85.7)	12/15 (80.0)
	No	2/35 (5.7)	1/15 (6.7)
	Unknown	3/35 (8.6)	2/15 (13.3)
Among those who answered "Yes" to expansion or new formation of skin eruption, new onset of erythema or papules occurred at the site where no (or almost no) erythema or papules had developed	Yes	21/30 (70.0)	4/12 (33.3)
	No	8/30 (26.7)	8/12 (66.7)
	Unknown	1/30 (3.3)	0
New formation or increase of infiltrative or edematous erythema	Yes	24/35 (68.6)	9/15 (60.0)
	No	8/35 (22.9)	3/15 (20.0)
	Unknown	3/35 (8.6)	3/15 (20.0)
Increased weeping at the site of skin eruption (excluding that with dryness alone)	Yes	10/35 (28.6)	3/15 (20.0)
	No	22/35 (62.9)	10/15 (66.7)
	Unknown	3/35 (8.6)	2/15 (13.3)
Exacerbation of desquamation at the site of skin eruption (excluding that with dryness alone)	Yes	23/35 (65.7)	4/15 (26.7)
	No	10/35 (28.6)	8/15 (53.3)
	Unknown	2/35 (5.7)	3/15 (20.0)
Exacerbation of dryness at sites without skin eruption	Yes	11/35 (31.4)	3/15 (20.0)
	No	20/35 (57.1)	9/15 (60.0)
	Unknown	4/35 (11.4)	3/15 (20.0)

Number of cases (%)
The study protocol was revised on September 6, 2018, and details of adverse events related to worsening of AD were counted for events reported in the case report forms.

On the basis of the above, the applicant plans to include a precautionary statement about worsening of skin symptoms, including worsening of AD, in the package insert to call attention, specify the symptoms as important potential risks, and to conduct pharmacovigilance activities, such as a specified drug use-results survey, and risk minimization activities, such as developing and distributing information materials for healthcare professionals and patients.

PMDA's view:

Since most of the events observed in clinical studies were mild to moderate skin symptoms with the outcome of resolved or resolving, events related to worsening of skin symptoms can be managed with the use of TCS of an appropriate rank. However, there were cases of worsening of skin symptoms, such as expansion, new formation, and changes in the nature of skin eruption, which suggested events other than the worsening of underlying diseases. The general skin condition should be carefully monitored during treatment with nemolizumab, and appropriate measures including administration of topical anti-inflammatory drugs and discontinuation

of nemolizumab should be taken in a case of worsening of skin symptoms. These precautionary statements should be included in the package insert, information materials for healthcare professionals and patients, and other materials to call attention. Information on the occurrence of events related to the worsening of skin symptoms in association with treatment with nemolizumab should be continuously collected in post-marketing surveillance and other studies, and information obtained from these activities should be promptly communicated to healthcare professionals in clinical practice.

7.R.3.4 Cytokine abnormal (elevated serum TARC levels)

The applicant's explanation about the occurrence of abnormal cytokine during treatment with nemolizumab:
In the combined group of 1 global and 2 Japanese studies, all adverse events reported as cytokine abnormal were increased levels of the serum thymus and activation-regulated chemokine (TARC), with an incidence of 2.9% (14 of 481 subjects) (Table 39). In addition, in Part A of Study M525101-01 and the combined placebo-controlled group of phase II/III studies, cytokine abnormal occurred only in the nemolizumab group.

Table 42 shows the occurrence of adverse events according to elevated serum TARC levels by Week 16 in the combined group of Studies M525101-01 and M525101-02, and no evident differences were observed in the occurrence of adverse events, except for asthma in the nemolizumab group, according to elevated serum TARC levels. In 5 of the 6 subjects who developed asthma, asthma occurred several months after the serum TARC levels had elevated. Therefore, elevated serum TARC levels were considered unlikely to be related to asthmatic attacks. In the placebo group, worsening of AD occurred more frequently in subjects with elevated serum TARC levels than in those without elevated serum TARC levels, which is consistent with the fact that serum TARC levels are regarded as a short-term marker of pathological conditions of AD (described below). However, in the nemolizumab group, there were no evident effects of presence or absence of elevated serum TARC levels on the occurrence of events related to worsening of AD. In addition, the incidence of serious adverse events was higher in the subjects with elevated serum TARC levels than those without elevated serum TARC levels. Of these events, a causal relationship to nemolizumab could not be ruled out in 9 subjects with elevated serum TARC levels alone: Bacteraemia, viral infection, Kaposi's varicelliform eruption/bacteraemia, alopecia areata/Meniere's disease, optic neuritis, extranodal marginal zone B-cell lymphoma (MALT type), impetigo, pneumonia, and cellulitis in 1 subject each. However, most of the events had the outcome of resolved or resolving or did not occur during the elevation of serum TARC levels. The above findings suggest that elevated serum TARC levels have no effect on the safety of nemolizumab.

Table 42. Occurrence of adverse events according to elevated serum TARC levels (combined Studies M525101-01/02, safety analysis population)

Elevated serum TARC levels by ≥1.5 times		Nemolizumab (entire treatment period)		Placebo (up to Week 16)	
		Yes (n = 185)	No (n = 46)	Yes (n = 23)	No (n = 49)
All adverse events		177 (95.7)	40 (87.0)	18 (78.3)	33 (67.3)
	Mild adverse events	166 (89.7)	39 (84.8)	15 (65.2)	30 (61.2)
	Moderate adverse events	72 (38.9)	14 (30.4)	5 (21.7)	9 (18.4)
	Severe adverse events	8 (4.3)	3 (6.5)	0	0
Serious adverse events		19 (10.3)	3 (6.5)	0	2 (4.1)
Adverse events of special interest					
Infectious diseases (excluding skin infections)		102 (55.1)	24 (52.2)	2 (8.7)	16 (32.7)
Skin infections		57 (30.8)	15 (32.6)	3 (13.0)	6 (12.2)
Worsening of AD		51 (27.6)	13 (28.3)	7 (30.4)	8 (16.3)
Injection-related reactions		14 (7.6)	5 (10.9)	0	2 (4.1)
Asthma		6 (3.2)	0	0	0
Blood CPK increased		17 (9.2)	3 (6.5)	0	1 (2.0)

Number of subjects (%)
A subject with at least a serum TARC level of ≥1.5 times baseline by Week 16 was considered to have an "increased" level.

TARC is a chemokine produced by dendritic or other cells and causes migration of Th2 cells, and serum TARC levels correlates with the severity of AD and are thus used as an indicator when treatment strategy is considered (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology*. 2018;128:2431-502]). Therefore, the safety of nemolizumab and the appropriateness of the use of serum TARC levels as a short-term marker of pathological conditions of AD were examined for the elevation in serum TARC levels during treatment with nemolizumab.

Figure 2 shows the changes over time in serum TARC levels, and Table 35 shows percent change from baseline in EASI scores in the nemolizumab group in Study M525101-01. While the EASI scores tended to decrease after administration of nemolizumab, serum TARC levels transiently increased after the start of administration of nemolizumab, showing different changes over time from those of the EASI scores. A similar trend to that observed in the nemolizumab group was also seen after the switching to nemolizumab in the placebo to nemolizumab group. Therefore, it is planned to include a precautionary statement in the package insert stating that serum TARC levels cannot be used as a short-term marker of the pathological conditions of AD for a certain period of time after the start of nemolizumab treatment and to provide information on changes in serum TARC levels in clinical studies.

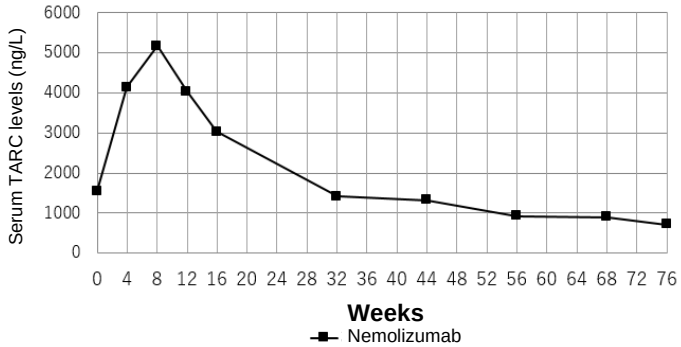

Figure 2. Changes over time in serum TARC levels (Study M525101-01)

PMDA's view:
Since a transient elevation in serum TARC levels unrelated to worsening or relief of AD was seen after

administration of nemolizumab in clinical studies, it is necessary, as the applicant describes, to include a precautionary statement in the package insert that serum TARC levels cannot be used as a short-term marker of the pathological conditions of AD for a certain period of time after the start of nemolizumab treatment and to provide information on changes in serum TARC levels in clinical studies. Furthermore, physicians should carefully determine, based on the circumstances of individual patients with reference to the information, whether to use serum TARC levels as a short-term marker of pathological conditions of AD after a certain period of time after the start of treatment with nemolizumab.

In addition, no definitive relationship has been suggested between the elevation in serum TARC levels and the occurrence of adverse events at present. However, information should be continuously collected in post-marketing surveillance and other studies, and the mechanism of the elevation in serum TARC levels should be investigated continuously. Information obtained from these activities should be promptly communicated to healthcare professionals in clinical practice.

7.R.3.5. Hypersensitivity-related events and injection-related reactions

The applicant's explanation about the occurrence of hypersensitivity-related events and injection-related reactions with the administration of nemolizumab:

Table 39 shows the incidence of hypersensitivity-related events and injection-related reactions in Part A of Study M525101-01 and the combined placebo-controlled group of phase II/III studies, showing that these events and reactions occurred more frequently in the nemolizumab group than in the placebo group.

In the combined group of 1 global and 2 Japanese studies, serious hypersensitivity occurred in 4 patients (dermatitis exfoliative in 2 subjects; rash and urticaria in 1 subject each). Among these events, a causal relationship to nemolizumab could not be ruled out for dermatitis exfoliative in 2 subjects. An anaphylactic reaction occurred in 1 subject (anaphylactic reaction). However, the event developed 28 days after the most recent administration of nemolizumab and was caused by the ingestion of chocolate. A causal relationship to nemolizumab was thus denied, and the outcome was resolved.

In the combined group of 1 global and 2 Japanese studies, the main events of injection-related reactions were injection site reaction (in 7 subjects); injection site bruising and malaise (in 4 subjects each). All of the events were mild in severity, except for the event of injection site reaction in 1 subject (moderate), and did not lead to treatment discontinuation.

PMDA's view:

Hypersensitivity-related events and injection-related reactions occurred more frequently in the nemolizumab group than in the placebo group, and serious hypersensitivity for which a causal relationship to nemolizumab could not be ruled out has been reported also. Therefore, PMDA considers that precautionary statements for the occurrence of serious hypersensitivity should be included in the package insert. In addition, information should be continuously collected on the occurrence of hypersensitivity-related events and injection-related reactions in the post-marketing setting, and information obtained from these activities should be promptly

communicated to healthcare professionals in clinical practice.

7.R.3.6 Oedema peripheral

The applicant's explanation about the occurrence of oedema peripheral with the administration of nemolizumab:
Table 39 shows the incidence of oedema peripheral in Part A of Study M525101-01 and in the combined placebo-controlled group of phase II/III studies, demonstrating that oedema peripheral occurred only in patients receiving nemolizumab. In the combined group of 1 global and 2 Japanese studies, 27 oedema peripheral occurred in 21 subjects. All events were nonserious, and the outcome was resolved for all, except for 1 case of fall in the workplace, for which a causal relationship to nemolizumab was denied. Oedema peripheral commonly occurred at the lower extremities. Oedema peripheral occurred at the time of worsening of AD in 6 subjects and just after the resolution of dermatitis exfoliative in 1 subject. With regard to adverse events related to cardiac, hepatic, or renal functions at the time of onset of oedema peripheral, fibrin D-dimer increased in 2 subjects, but CT images, etc. suggested no thrombus formation, and no abnormalities in cardiac, hepatic, or renal functions were observed.

PMDA's view:
Since oedema peripheral occurred only in subjects receiving nemolizumab in the clinical studies, a precautionary statement for the occurrence of oedema peripheral should be included in the package insert. In addition, oedema may be caused by intense inflammatory reactions or allergy, multiple subjects experienced worsening of AD and oedema peripheral over the same period of time, and some patients experienced worsening of AD for which a causal relationship to nemolizumab could not be ruled out [see Section 7.R.3.3]. In light of the above, the occurrence of oedema peripheral, including a relationship with the occurrence of other adverse events, should be continuously investigated in post-marketing surveillance or other settings, and information obtained should be promptly communicated to healthcare professionals in clinical practice.

7.R.3.7 Depression and suicide/self-injury

The applicant's explanation about the occurrence of depression and suicide/self-injury with the administration of nemolizumab:
Reportedly, mental and psychogenic stress is involved in the triggering and worsening of scratching behaviors for AD (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology*. 2018;128:2431-502]), and AD patients have a higher prevalence of depression, anxiety, and suicidal ideation (*J Am Acad Dermatol*. 2019;80:402-10).

In clinical studies, events related to depression or suicide/self-injury occurred only in patients receiving nemolizumab (Table 39). The event occurring in all of the 3 subjects in the combined group of 1 global and 2 Japanese studies was depression, and a causal relationship to nemolizumab was denied in 2 of the 3 subjects. In the remaining 1 subject, the study treatment was discontinued due to multiple adverse events, and depression occurred 76 days after the discontinuation of nemolizumab due to the persistent adverse events during the follow-up period. In light of the above, nemolizumab is not suggested to worsen mental status such as depressive symptoms.

PMDA's view:

There are no results available from the clinical studies that suggest a relationship between the administration of nemolizumab and the occurrence of depression or suicide/self-injury. However, based on the high prevalence of depression, anxiety, and suicidal ideation in AD patients, information on the effects of nemolizumab on the occurrence of depression and suicide/self-injury, including published literature, should be continuously collected after its market launch, and obtained information should be appropriately communicated to healthcare professionals in clinical practice.

7.R.3.8 Malignant tumors

The applicant's explanation about the occurrence of malignant tumors with the administration of nemolizumab:

In the clinical studies, no malignant tumors have been reported in Part A of Study M525101-01 or the combined placebo-controlled group of phase II/III studies (Table 39). In the combined group of 1 global and 2 Japanese studies, malignant tumors occurred in 3 subjects, but a causal relationship to nemolizumab was denied in 2 of the 3 subjects. The remaining 1 subject had an event of extranodal marginal zone B-cell lymphoma (MALT type), but the event was considered unrelated to nemolizumab because findings suggestive of the event were observed only 2 weeks after the start of the administration of nemolizumab and because no changes were seen in the speed of aggravation. On the basis of the above and given the fact that non-clinical studies suggest no carcinogenic risk with nemolizumab [see Section 5.4], the risk was considered low that the treatment with nemolizumab would increase the incidence of malignant tumors or aggravate malignant tumors.

PMDA's view:

Currently available data do not evidently indicate a causal relationship between treatment with nemolizumab and the occurrence of malignant tumor. However, malignant tumor should be specified as an important potential risk, and the occurrence of malignant tumor during treatment with nemolizumab should be continuously investigated in the post-marketing settings because the possibility cannot be ruled out that the mechanism of inhibition of malignant tumors may be affected by immunosuppressive effects in light of the pharmacological effects of nemolizumab and because malignant tumors occurred in the clinical studies.

7.R.3.9 Other events

The applicant's explanation:

Table 35 shows the incidences of ophthalmic complications of AD (dermatitis eyelid, keratoconjunctivitis, keratoconus, cataract, and retinal detachment), asthma, and blood CPK increased in Part A of Study M525101-01 and the combined placebo-controlled group of phase II/III studies.

No tendency was seen for ophthalmic complications of AD (dermatitis eyelid, keratoconjunctivitis, keratoconus, cataract, and retinal detachment) that the incidence of these events was higher in the nemolizumab group than in the placebo group. The main events of ophthalmic complications of AD in the combined group of 1 global and 2 Japanese studies were conjunctivitis allergic (12 subjects), conjunctivitis (9 subjects), and dry eye (5 subjects), and all events related to conjunctivitis were nonserious.

No asthma occurred in any treatment groups in Part A of Study M525101-01, and the incidence of asthma was similar between the nemolizumab group and the placebo group in the combined placebo-controlled group of phase II/III studies. In the combined group of 1 global and 2 Japanese studies, 13 cases of asthma were reported in 12 subjects and all these events were nonserious.

There was no clear difference in the incidence of blood CPK increased between the nemolizumab group and the placebo group. Most cases of blood CPK increased in the clinical studies were not accompanied by clinical symptoms and were considered to be transient increases due to excessive exercise or other factors.

PMDA's view:
At present, there have been no clinical study data suggesting a relationship between the administration of nemolizumab and the occurrence of these events. However, the applicant should continue to collect information on the effects of nemolizumab on these events, including published literature, after its market launch. Obtained information should be appropriately communicated to healthcare professionals in clinical practice.

PMDA's view on the safety of nemolizumab based on the review in the above sections of 7.R.3.1 to 9:
The submitted clinical study results suggest no serious safety concerns for nemolizumab in AD patients with pruritus and indicate that the observed adverse events can be managed by taking appropriate safety measures. However, serious events including serious infections and serious hypersensitivity have been reported in clinical studies. Nemolizumab is expected to be used for a long period of time, but the risk of the occurrence of infectious diseases by suppressing the IL-31 signaling for a long period of time has not been clarified at present. Therefore, the conditions of patients should be carefully monitored during the treatment with nemolizumab. In addition, as described in Section 7.R.3.3, new skin symptoms may occur with the administration of nemolizumab. In light of the above, information on the long-term safety of nemolizumab, including the worsening of skin symptoms, should be collected in post-marketing surveillance and other studies.

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

7.R.4 Clinical positioning and indications

7.R.4.1 Clinical positioning

The applicant's explanation about the clinical positioning of nemolizumab:
Topical anti-inflammatory drugs such as TCS and TCI are used under the continuous use of topical moisturizing agents in the pharmacological treatment of AD. Patients who are inadequately controlled by these topical therapies are treated with oral ciclosporin and dupilumab depending on the severity of skin eruption, and oral steroids are also considered during acute exacerbation or induction of remission in severe or most severe cases. Oral antihistamines are recommended as an adjunctive therapy in combination with TCS and TCI for pruritus associated with AD (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology.* 2018;128:2431-502.]). However, the effectiveness of antihistamines in relieving pruritus depends on the severity and pathological conditions of AD, and in some patients, pruritus associated with AD cannot be adequately controlled. The efficacy and safety of nemolizumab have been confirmed in clinical trials conducted

in AD patients with moderate to severe pruritus, even though treated with conventional therapies (TCS or TCI and antihistamines or antiallergics) [see Sections 7.R.2 and 7.R.3]. Therefore, nemolizumab is considered to be positioned as a new therapeutic option for AD patients in whom pruritus cannot be adequately controlled even with appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI, and antihistamines.

PMDA's view:
AD is a disease mainly characterized by eczema with pruritus, and pruritus can cause a reduction in QOL and exacerbation of skin symptoms due to scratching behaviors and may trigger skin infections or complications such as ocular symptoms, in addition to disease progression. Therefore, the control of pruritus is important in its therapeutic management (Guidelines for the Management of Atopic Dermatitis 2018 [*The Japanese Journal of Dermatology*. 2018;128:2431-502]). In light of the submitted data of clinical studies and the latest treatment regimens for AD, nemolizumab is considered to be a new treatment option for pruritus in patients with AD not adequately controlled even by treatment with TCS or TCI and antihistamines. However, precautionary statements should be included in the package insert, stating that nemolizumab is for the treatment of pruritus in AD and that treatment of skin symptoms should be continued even during the nemolizumab treatment so that compliance and adherence to the treatment of skin symptoms do not decrease as pruritus improves with nemolizumab treatment. In the clinical studies of nemolizumab, the use of biological products, oral immunosuppressants such as ciclosporin, oral steroids, oral JAK inhibitors, or phototherapy was prohibited, and data on the concomitant use of nemolizumab and these drugs/therapies are not available. Therefore, the specifications of the concomitant drugs in clinical studies should be provided so that physicians who intend to use nemolizumab can appropriately select concomitant drugs and therapies.

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

7.R.4.2 Indication

In light of the submitted data and the reviews in Sections 7.R.2, 7.R.3, and 7.R.4.1, PMDA considers that nemolizumab should be indicated for "pruritus associated with atopic dermatitis (only for patients who are inadequately controlled by conventional treatments)" and that the following precautionary statements should be included in the Precautions Concerning Indication section of the package insert.

- Nemolizumab is used for patients in whom pruritus cannot be adequately controlled even after a certain period of appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI, and antihistamines or antiallergics.
- As a general rule, topical anti-inflammatory drug should be used concomitantly with nemolizumab, according to the conditions of AD lesions.
- The use of topical moisturizing agents should be continued during treatment with nemolizumab.

In addition to the above precautionary statements, information on the inclusion criteria in clinical studies should be provided in the package insert to communicate the intended severity of pruritus. Furthermore, precautionary statements should be provided to the effect that nemolizumab should be used by a physician who is familiar with

the diagnosis and treatment of AD to ensure the appropriate diagnosis, appropriate selection, and proper use in intended patients for treatment with nemolizumab.

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

7.R.5 Dosage regimens

7.R.5.1 Efficacy and safety of nemolizumab in adolescent patients

The applicant's explanation about the efficacy and safety of nemolizumab in adolescent patients:

In Studies M525101-01 and M525101-02, patients aged ≥13 years were eligible, and the proportion of adolescent subjects (aged ≥13 years and ≤17 years) was 4.6% (14 of 303 subjects): in Study M525101-01, 4.9% [7 of 143] of subjects in the nemolizumab group and 5.6% [4 of 72] of subjects in the placebo group: and in Study M525101-02, 3.4% [3 of 88] of subjects).

The percent change from baseline in pruritus VAS in adolescent subjects in Studies M525101-01 and M525101-02 are shown in Table 43 and, despite the limited number of subjects, indicate a tendency toward improvement similar to the percent change from baseline in pruritus VAS in the overall study population (Table 32).

As shown above, nemolizumab is expected to show efficacy in adolescent patients as in adult patients.

Table 43. Percent change from baseline in pruritus VAS in adolescent subjects (FAS)

Sex/age	Body weight (kg)	Percent change from baseline in pruritus VAS (%)		
		Week 16	Week 32	Week 52
Study M525101-01				
Nemolizumab				
Male, age 1[redacted][a)]	4[redacted].4	−33.2	−74.0	−75.0
Female, age 1[redacted]	4[redacted].6	−48.2	−45.7	−42.8
Male, age 1[redacted]	7[redacted].2	−100.0	−100.0	−100.0
Female, age 1[redacted][a)]	4[redacted].6	−61.5	−83.1	−84.1
Male, age 1[redacted]	6[redacted].2	−70.1	−40.3	−65.4
Male, age 1[redacted]	4[redacted].4	−100.0	−100.0	−100.0
Male, age 1[redacted][a)]	4[redacted].5	0.5	—	—
Placebo to nemolizumab[b)]				
Male, age 1[redacted]	7[redacted].6	−9.5	−35.8	−55.4
Male, age 1[redacted]	5[redacted].8	−1.7	−32.8	−37.1
Male, age 1[redacted]	9[redacted].8	−25.6	−35.5	−69.0
Female, age 1[redacted][c)]	5[redacted]	—	—	—

Sex/age	Body weight (kg)	Percent change from baseline in pruritus VAS (%)		
		Week 16	Week 32	Week 52
Study M525101-02				
Nemolizumab				
Male, age 1[redacted]	4[redacted].3	−58.0	−53.8	−51.6
Male, age 1[redacted]	6[redacted].1	−45.2	−95.0	−91.2
Male, age 1[redacted]	6[redacted].1	−50.4	−56.4	—

—: No data.
a) Including data after rescue remedy.
b) Placebo was administered up to Week 16.
c) The study drug was discontinued after its first administration.

A total of 100 adverse events occurred in all 13 adolescent subjects who received ≥1 dose of nemolizumab in Studies M525101-01 and M525101-02. A causal relationship to the study drug could not be ruled out for 29 adverse events (or adverse drug reactions): (atopic dermatitis [4 events], urticaria, headache [3 events each], gastroenteritis [2 events], bacteraemia, pyrexia, upper respiratory tract inflammation, contusion, cellulitis, face oedema, erythema, pain in extremity, hypoaesthesia, acne, eczema, skin exfoliation, toxic skin eruption, eosinophil count increased, cytokine abnormal, cough, and acne pustular [1 event each]). Among these events, face oedema, pain in extremity, hypoaesthesia, and acne pustular were adverse drug reactions not reported in subjects aged ≥18 years. However, these adverse events were all mild in severity and had resolved without discontinuation of the study drug. A serious adverse event was 1 event of bacteraemia, which resolved without

discontinuation of the study drug. In the ongoing clinical study in pediatric AC patients aged ≥6 years and ≤12 years, no particular safety concerns have been raised to date.

As shown above, no events specific to adolescent subjects were identified in the clinical studies, and the safety of nemolizumab in adolescent patients is thus considered acceptable.

PMDA accepted the applicant's explanation and considers that nemolizumab is expected to be effective also in adolescent patients as in adult patients and that the safety of nemolizumab is acceptable. However, because the number of adolescent subjects in clinical studies is limited, the applicant should continue to collect information in post-marketing surveillance and other studies, and obtained information should be promptly communicated to healthcare professionals in clinical practice.

7.R.5.2 Dosage regimens

In light of the submitted data and the reviews in Sections 7.R.2, 7.R.3, and 7.R.5.1, the efficacy and safety of nemolizumab in AD patients with pruritus have been demonstrated at the dosage regimens specified in Study M525101-01, and PMDA thus has concluded that nemolizumab can be approved for the proposed dosage regimen of "The usual dose for adults and children aged 13 years or older is 60 mg of nemolizumab (genetical recombination) subcutaneously administered once every 4 weeks."

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

7.R.6 Self-injection

The applicant's explanation about the efficacy and safety of nemolizumab administered via self-injection based on the results of Study M525101-02:

In Study M525101-02, nemolizumab was administered by medical professionals at Weeks 0, 4, and 8 in all subjects and by subjects themselves from Week 12 in the self-injection group [see Section 7.2.2].

Table 44 shows changes in percent change from baseline in pruritus VAS and shows no evident effects on the efficacy of self-injection.

Table 44. Results of pruritus VAS (Study M525101-02, FAS, OC)

	Medical professional administration (n = 44)			Self-injection (n = 44)		
	Administration performed by	Pruritus VAS	Percent change from baseline	Administration performed by	Pruritus VAS	Percent change from baseline
Baseline		77.25 ± 11.87 (44)			79.53 ± 10.26 (44)	
Week 4	Medical professionals	51.22 ± 19.34 (44)	−32.86 ± 25.67 (44)	Medical professionals	55.16 ± 23.20 (44)	−31.49 ± 26.13 (44)
Week 8		45.44 ± 18.36 (44)	−40.21 ± 24.22 (44)		48.18 ± 26.18 (44)	−40.34 ± 30.80 (44)
Week 12		43.28 ± 18.79 (43)	−42.99 ± 24.60 (43)		45.95 ± 25.64 (44)	−43.49 ± 29.32 (44)
Week 24		35.75 ± 19.63 (41)	−52.74 ± 26.14 (41)	Self-injection	38.96 ± 25.52 (42)	−52.01 ± 30.53 (42)
Week 36		32.54 ± 21.41 (41)	−57.13 ± 27.56 (41)		32.89 ± 23.78 (39)	−58.88 ± 29.22 (39)
Week 52		30.93 ± 22.48 (41)	−59.42 ± 28.44 (41)		31.03 ± 26.11 (37)	−61.94 ± 31.63 (37)

Mean ± standard deviation (number of subjects). Percent change from baseline: %.

Table 45 shows the occurrence of adverse events by treatment period. Serious adverse events and adverse events leading to treatment discontinuation occurred slightly more frequently in the self-injection group. However,

among serious adverse events, events for which a causal relationship could not be ruled out occurred only in 1 subject after the administration by medical professionals (optic neuritis in the medical professional administration group [up to Day 85]) and 1 subject after the self-injection (extranodal marginal zone B-cell lymphoma [MALT type] in the self-injection group [Days 170 to 253]). Adverse events led to treatment discontinuation in 6 subjects after the administration by medical professionals and 5 subjects after self-injection. In addition, no injection-related reactions occurred during self-injection. These results suggest that self-injection has no evident effects on the safety of nemolizumab.

The results presented above suggest that there are no particular problems with the efficacy and safety of self-injected nemolizumab.

Table 45. Occurrence of adverse events by duration of treatment (Study M525101-02, safety analysis population)

	Medical professional administration (n = 44)					Self-injection (n = 44)				
	Administration by medical professionals					Administration by medical professionals	Self-injection			
Duration (day)	-85	86-169	170-253	254-337	338-	-85	86-169	170-253	254-337	338-
Number of patients	44	44	41	41	41	44	44	42	40	37
Summary of safety										
All adverse events	25 (56.8)	6 (13.6)	5 (12.2)	2 (4.9)	0	28 (63.6)	11 (25.0)	0	1 (2.5)	0
Serious adverse events	2 (4.5)	0	0	0	0	0	1 (2.3)	3 (7.1)	1 (2.5)	0
Deaths	0	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation[a)]	4 (9.1)	0	0	0	0	2 (4.5)	2 (4.5)	3 (7.1)	0	0
adverse drug reactions	19 (43.2)	3 (6.8)	2 (4.9)	2 (4.9)	0	12 (27.3)	9 (20.5)	1 (2.4)	1 (2.5)	1 (2.7)
Adverse events of special interest										
Infections (excluding skin infections)	6 (13.6)	7 (15.9)	7 (17.1)	1 (2.4)	0	9 (20.5)	7 (15.9)	6 (14.3)	3 (7.5)	1 (2.7)
Skin infections	5 (11.4)	3 (6.8)	0	3 (7.3)	0	9 (20.5)	2 (4.5)	2 (4.8)	0	0
Worsening of AD	8 (18.2)	1 (2.3)	1 (2.4)	0	0	6 (13.6)	5 (11.4)	1 (2.4)	1 (2.5)	0
Injection-related reactions	2 (4.5)	1 (2.3)	0	0	0	0	0	0	0	0
Asthma	1 (2.3)	0	1 (2.4)	0	0	0	0	0	0	0
Blood CPK increased	0	0	1 (2.4)	0	0	1 (2.3)	1 (2.3)	0	1 (2.5)	0

Number of patients (%)
a) Including treatment discontinuation and dose reduction.

PMDA's view:

The clinical study results suggest that there are no particular problems with the efficacy and safety of self-administered nemolizumab. However, whether to allow patients to self-administer nemolizumab should be determined carefully by the physician. Self-injection will be allowed only in patients who have received adequate education and training, have sufficiently learned nemolizumab-related risks (and how to manage them), and are able to reliably perform self-injection. If adverse drug reactions of nemolizumab, such as infection, are suspected after self-injection, or patients have difficulty in continuation of self-injection, physicians should take appropriate measures by instructing patients to discontinue self-injection immediately and closely monitoring the patients. In addition, the applicant should conduct safety measures by preparing and distributing informative materials with reference to other approved biological products.

7.R.7 Post-marketing safety measures

The applicant plans to conduct a specified drug use-results survey in AD patients newly treated with nemolizumab to collect information on the occurrence of worsening of skin symptoms and others, in addition to the routine pharmacovigilance activities to confirm the safety of nemolizumab in post-marketing clinical practice.

PMDA's view:

As discussed in Section 7.R.3, the safety of nemolizumab was demonstrated in the clinical studies and is acceptable. However, serious events (e.g., infection and hypersensitivity) and worsening of skin symptoms were observed in clinical studies, and nemolizumab is expected to be administered for a long period. Therefore, it is appropriate to conduct post-marketing surveillance and other studies to examine the long-term safety and efficacy of nemolizumab, including the risk of infection in association with the long-term suppression of the IL-31 signaling pathway.

Furthermore, nemolizumab should be used by physicians with sufficient knowledge of nemolizumab and sufficient expertise and experience in the treatment of AD, and adverse drug reactions such as serious infections should be managed in cooperation with other department/medical institutions as needed. In order to promote the proper use of nemolizumab, the applicant should develop informative materials for healthcare professionals (e.g., physicians) and a patient information leaflet that explains the risks associated with nemolizumab.

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

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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 5.3.5.1-2 and CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that nemolizumab has efficacy in the treatment of pruritus associated with AD in patients who are inadequately controlled by conventional treatments, and that nemolizumab has acceptable safety in view of its benefit. PMDA considers that nemolizumab has clinical

significance because nemolizumab has a new mechanism of action and offers a new therapeutic option for pruritus associated with AD. In addition, the safety and other information of nemolizumab in routine clinical practice should be further investigated in post-marketing surveillance and other studies.

PMDA has concluded that nemolizumab may be approved if nemolizumab is not considered to have any particular problems based on comments from the Expert Discussion, and if appropriate actions are taken for insoluble visible particles generated during the storage of the drug product [see Section 2.2.5].

10. Others

The definitions of the efficacy endpoints in clinical studies of nemolizumab are shown in the table below.

<table>
<tr><th>Endpoints</th><th>Definition</th></tr>
<tr><td>Pruritus VAS</td><td>A score of the mean pruritus intensity in the last 24 hours assessed by the subject on a straight line.
The left end of the straight line is “0: no itch” and the right end “100: worst imaginable itch.”</td></tr>
<tr><td>Itch scores</td><td>A score on a 5-point scale assessed by the subject for the pruritus intensity in the last 24 hours (daytime/nighttime).
If the scores differ between daytime and nighttime, the higher score is chosen.
<table>
<tr><th>Score</th><th>Intensity</th><th>Daytime</th><th>Nighttime</th></tr>
<tr><td>0</td><td>None</td><td>Almost no itch</td><td>Almost no itch</td></tr>
<tr><td>1</td><td>Slight</td><td>Sometimes itching, but not itching to scratch</td><td>Can sleep without scratching</td></tr>
<tr><td>2</td><td>Mild</td><td>Sometimes scratch slightly with hand</td><td>Can sleep with scratching</td></tr>
<tr><td>3</td><td>Moderate</td><td>Scratch even in public with substantial itching</td><td>Wake up with itching</td></tr>
<tr><td>4</td><td>Severe</td><td>Unbearable itching</td><td>Hardly sleep with itching</td></tr>
</table></td></tr>
<tr><td>Pruritus NRS</td><td>Score of mean itching in the last 24 hours by the subject on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).</td></tr>
<tr><td>DLQI</td><td>A dermatology-specific quality of life (QOL) instrument, consisting of 10 questions. A total score (range: 0-30) is calculated by summing the scores of all questions for which the subject answers on a 4-point scale (range: 0-3) based on the QOL in the last 1 week.
The higher the total DLQI score is, the greater the impairment of QOL is.</td></tr>
<tr><td>CDLQI</td><td>Modified DLQI questionnaire to fit the life of children <16 years.</td></tr>
<tr><td>ISI</td><td>A score (range: 0-20) calculated from the answers to 5 questions about the severity of insomnia in the last 2 weeks. The higher the score is, the more severe insomnia is.</td></tr>
<tr><td>EASI</td><td>A total score (range: 0-72) of the severity (0 = clear/none, 1 = mild, 2 = moderate, and 3 = severe) of 4 skin eruption components (erythema, infiltration/papule, scratching scar, and lichenification) for the 4 body regions (head/neck, trunk, upper extremities, and lower extremities) which is multiplied by an area score based on the percentage of involved skin (0 = 0%, 1 = 1-9%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89%, and 6 = 90-100%) and is then multiplied by a multiplier for each body site (head/neck = 0.1, trunk = 0.3, upper limbs = 0.2, or lower limbs = 0.4).
EASI score interpretation is as follows: 0 clear, 0.1-1.0 almost clear, 1.1-7.0 mild, 7.1-21.0 moderate, 21.1-50.0 severe, and 50.1-72.0 very severe.</td></tr>
<tr><td>Proportion of subjects achieving EASI-75</td><td>Proportion of patients with reduction in the EASI score by ≥75% from baseline</td></tr>
<tr><td>sIGA</td><td>A score determined by a physician to assess severity of all lesions in patients by 6-level scale in view of erythema, induration/papulation, and oozing/crusting of atopic dermatitis.
<table>
<tr><th>Score</th><th>Severity</th><th>Conditions of skin eruption</th></tr>
<tr><td>0</td><td>No symptoms</td><td>Slight discoloration with no erythema, induration/papulation, or oozing/crusting</td></tr>
<tr><td>1</td><td>Almost no symptoms</td><td>Slight pale pink erythema with almost no induration/papulation or oozing/crusting</td></tr>
<tr><td>2</td><td>Mild</td><td>Pale pink erythema and slightly raised induration/papulation with no oozing/crusting</td></tr>
<tr><td>3</td><td>Moderate</td><td>Pink to red erythema and evidently raised partial induration/papulation with slight oozing/crusting</td></tr>
<tr><td>4</td><td>Severe</td><td>Dark-red erythema and remarkably and extensively raised induration/papulation with oozing/crusting</td></tr>
<tr><td>5</td><td>Most severe</td><td>Dark-red erythema and remarkably and extensively raised and fused induration/papulation with oozing/crusting</td></tr>
</table></td></tr>
</table>

Definition of adverse events shown in Table 39

Definition of events
Infections (excluding skin infections): PTs under infections and infestations (SOC), excluding skin infections, including food poisoning (PT)
Skin infections: Skin and subcutaneous tissue infections and infestations (HLGT), Skin structures and soft tissue infections (HLT), and PTs defined by the applicant as skin infections.
Serious infections: Infections (excluding skin infections) or defined skin infections assessed as serious
Tuberculosis: Tuberculous infections (HLT)
Virus reactivation: Symptoms or events determined by the applicant as hepatitis B virus or related to hepatitis B according to the guidance for use of biological products for psoriasis.
Worsening of AD: Study CIM003JG: Atopic dermatitis (PT) Studies M525101-01 and M525101-02: Determined based on the description in the case report form (CRF).
Hypersensitivity-related events: Hypersensitivity (SMQ, narrow) and anaphylactic reaction (SMQ), Anaphylactic/anaphylactoid shock conditions (SMQ, narrow) (Excluding skin infections and atopic dermatitis [PT])
Serious hypersensitivity: Serious events of hypersensitivity (SMQ, narrow) (excluding skin infections and atopic dermatitis [PT])
Anaphylactic reaction: Anaphylactic reaction (SMQ) and anaphylactic/anaphylactoid shock conditions (SMQ, narrow)
Injection-related reactions: Events defined by the applicant as injection-related reactions
Ocular complication of AD: Lid, lash and lacrimal infections, irritations and inflammations (HLT), conjunctival disorders (SMQ), keratoconus (PT), PTs containing the term of cataract selected by the applicant, and LLTs containing the term of retinal detachment selected by the applicant.
Asthma: Study CIM003JG: Events selected by the applicant from asthma/bronchospasm (SMQ). Studies M525101-01 and M525101-02: Determined based on the description in the CRF.
Blood CPK increased: Study CIM003JG: Events of grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) (2.5-fold the upper limit of the reference range) Studies M525101-01 and M525101-02: Determined based on the description in the CRF.
Cardiovascular events: Cardiac arrhythmias (HLGT), coronary artery disorders (HLGT), and central nervous system haemorrhages and cerebrovascular conditions (SMQ, broad)

Review Report (2)

May 31, 2021

Product Submitted for Approval

Brand Name	Mitchga Syringes 60 mg
Non-proprietary Name	Nemolizumab (Genetical Recombination)
Applicant	Maruho Co., Ltd.
Date of Application	July 29, 2020

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, and post-marketing safety measures

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, safety, clinical positioning, indication, dosage regimen, and post-marketing safety measures for nemolizumab described in the Review Report (1) and made the following comments.

- Nemolizumab is expected to be useful for patients with AD in whom conventional AD therapies improved skin eruption but not pruritus and whose daily life is disturbed by pruritus.
- Nemolizumab should be used with caution in adolescent patients weighing <40 kg because there are no clinical study data on such patient population, and information should be collected in post-marketing surveillance and other studies.
- It is recommended to discuss the changes in patterns of serum TARC level and their contributing factors based on the information obtained from post-marketing surveillance and other studies.

In view of the discussions presented in Section "7.R.7 Post-marketing safety measures" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA concluded that the current risk management plan (draft) for nemolizumab should include the safety specification presented in Table 46 and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 47. PMDA instructed the applicant to conduct post-marketing surveillance and

other studies where these can be examined. PMDA also instructed the applicant to provide information on the proper use of nemolizumab in adolescent patients through materials and collect information on adolescent patients as much as possible in post-marketing surveillance and other studies. The applicant answered that it would take appropriate actions.

Table 46. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infections • Serious hypersensitivity	• Worsening of skin symptoms • Malignant tumors • Immunogenicity	None
Efficacy specification		
None		

Table 47. 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 drug use-results survey	None	• Disseminate information gathered during early post-marketing phase vigilance • Organize and disseminate information on the proper use to healthcare professionals • Organize and disseminate information materials for patients (For users of Mitchga) • Ensure that information on the proper use is provided before the delivery of Mitchga.

The applicant explained to conduct a specified drug use-results survey in AD patients with pruritus who are inadequately controlled by conventional treatments to evaluate the safety of nemolizumab in clinical practice as shown in Table 48.

Table 48. Outline of specified drug use-results survey (draft)

Objective	To collect and evaluate information on the safety of the treatment with nemolizumab in clinical practice
Survey method	Central registration
Population	AD patients with pruritus who are inadequately controlled by conventional treatments
Observation period	76 weeks
Planned sample size	300 patients
Main survey items	• Safety specification: Worsening of skin symptoms • Patient characteristics • Information on treatment with nemolizumab • Concomitant drugs/concomitant therapies • Laboratory data (including serum TARC levels) • Adverse events (Details of worsening of skin symptoms [e.g., pruritus NRS and EASI] are to bel collected)

PMDA accepted these actions and considers that collected information should be appropriately and promptly communicated to healthcare professionals.

1.2 Insoluble visible particles found in the drug product

Since the applicant continues to investigate this issue at the time of preparing the Review Report (2), the results of the investigation will be described in the Review Report (3).

2. Overall Evaluation during Preparation of the Review Report (2)

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below with the following approval conditions, provided that appropriate measures are taken for the insoluble visible particles generated during storage of the drug product.

Indication

Treatment of pruritus associated with atopic dermatitis ~~in patients who are inadequately controlled by conventional treatment~~ (only for patients who are inadequately controlled by conventional treatments)

(Strikethrough denotes deletions. Uunderline denotes additions to the proposed indication.)

Dosage and Administration

The usual dose for adults and children aged 13 years or older is 60 mg of nemolizumab (genetical recombination) subcutaneously administered once every 4 weeks.

(No change)

Approval Conditions

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

Review Report (3)

February 10, 2022

Product Submitted for Approval

Brand Name	Mitchga Syringes 60 mg
Non-proprietary Name	Nemolizumab (Genetical Recombination)
Applicant	Maruho Co., Ltd.
Date of Application	July 29, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

1.1 Insoluble visible particles found in the drug product

The applicant's explanation about insoluble visible particles found at [redacted] under the long-term testing conditions:

1) Identification and origin of insoluble visible particles
   The insoluble visible particles were identified as particles from silicone oil [redacted], such as [redacted]-related cellulose fibers, protein-silicone complex [redacted], and protein alone.
2) Measures to control the generation of insoluble visible particles
   [redacted] will be taken for [redacted]-related cellulose fibers and others. It is inevitable to prevent the generation of particles from silicone oil [redacted]. The causes of generating the protein-silicone complex and protein alone has not been elucidated. A longer time of shaking, etc. at the preparation of solutions tends to suppress the frequency of generating the insoluble visible particles. However, it is difficult to completely prevent the generation of insoluble visible particles.
3) Control of the drug product
   "Readily" detectable, insoluble visible particles have not been identified at the release testing by the foreign insoluble matter test for injections in the General Tests, Processes and Apparatus, the Japanese Pharmacopoeia. At the time of release, the drug product will be managed by conforming to the Method 2 for the foreign insoluble matter test for injections in the General Tests, Processes and Apparatus, the Japanese Pharmacopoeia. However, insoluble visible particles have been found in some batches in the long-term testing. Although the incidence of having such particles suggests that the particles were likely to exist in the study drug used in clinical studies, no evident safety concerns attributable to the particles have been raised in the clinical studies.

   On the basis of the above, precautionary statements will be included in the package insert, stating that the use of drug product should be avoided if insoluble matter is found in the drug product. In addition, the drug

product is to be controlled according to the following specifications on the assumption that insoluble visible particles are generated during storage.

- If insoluble visible particles are detected in the foreign insoluble matter tests, [redacted] is used to determine [redacted] For [redacted], [redacted] should be confirmed by [redacted].
- Taking into account of the previous cases, if [redacted], it is deemed to conform.

PMDA's view:

It is unknown whether insoluble visible particles were present in the study drug used in clinical studies, and it is difficult to specify adverse events caused by insoluble visible particles. However, the currently available results suggest no serious safety concerns for nemolizumab in AD patients with pruritus, and observed adverse events can be controlled with appropriate safety measures [see Section 7.R.3]. In light of the above, the proposed management of foreign insoluble matter tests for the drug products is acceptable, provided that the following measures are appropriately conducted in addition to the measures taken by the applicant.

- Since the frequency of the generation of insoluble visible particles in nemolizumab varies depending on the dissolution methods used in the preparation, precautionary statements on the proper dissolution method of nemolizumab should be included in the package insert or information materials to prevent the generation of insoluble visible particles caused by inappropriate dissolution methods.

The presence of insoluble visible particles may be a potential risk of hypersensitivity or other conditions. Therefore, the applicant should continue to investigate the causes of insoluble visible particles and to examine the measures to prevent the generation and should take appropriate measures including changes in formulation and containers. In the meantime, the applicant should monitor the stability of nemolizumab for all manufactured batches in the post-marketing setting to evaluate the frequency of the generation of insoluble visible particles.

The applicant answered that it would take appropriate actions, and PMDA accepted the applicant's response.

1.2 Shelf-life of the drug product

Data from the 24-month long-term testing of the drug product were submitted. There were no particular problems, including insoluble visible particles, provided that the drug product would be managed with the measures described in the Section 1.1 above. As a result, PMDA concluded that the shelf-life of 24 months for the drug product is acceptable when stored in a primary container of a dual-chamber borosilicate glass syringe with [redacted] rubber cap and a plunger in a light-shielded paper box at room temperature.

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration with approval conditions shown in the Overall Evaluation prepared in the Review Report (2). Because 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. The drug product and its drug substance are both classified as powerful drugs.

Appendix

List of Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AEX	Anion exchange chromatography
Alemtuzumab	Alemtuzumab (Genetical Recombination)
ANCOVA	Analysis of covariance
$AUC_{0\text{-}X}$	Area under the plasma concentration−time curve from time zero to X
AUC_{inf}	Area under the concentration−time curve from time zero extrapolated to infinite time
AUC_{last}	Area under the concentration− time curve from 0 to the last measurable concentration
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CDLQI	Children's dermatology life quality index
CDR	Complementarity determining region
CE-SDS	Capillary gel electrophoresis with sodium dodecyl sulfate
CHO	Chinese hamster ovary
CI	Confidence interval
CL/F	Apparent total clearance corrected for bioavailability
CL_{total}	Total body clearance
C_{max}	Maximum serum concentration
CPK	Creatine phosphokinase
CQA	Critical quality attribute
CT	Computed tomography
C1q	Complement component 1, q subcomponent
DLQI	Dermatology life quality index
DNA	Deoxyribonucleic acid
EASI	Eczema area and severity index
ECLIA	Electrochemiluminescence immunoassay
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EVA	Ethylene-vinyl acetate
FAS	Full analysis set
FcγR	Fcγ receptor
gp130	Glycoprotein 130
HCP	Host cell protein
HLGT	High level group terms
HLT	High level terms
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IL-31RA	Interleukin-31 receptor A
ISI	Insomnia severity index
ITT	Intention to treat
JAK	Janus kinase
K_D	Equilibrium dissociation constant

LLT	Lowest level terms
LOCF	Last observation carried forward
MALT	Mucosa associated lymphoid tissue
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
MF	Drug master file
MMP	Matrix metalloproteinase
MMRM	Mixed effect model for repeated measures
mRNA	Messenger RNA
Nemolizumab	Nemolizumab (Genetical Recombination)
NRI	Non-responder imputation
NRS	Numerical rating scale
OC	Observed cases
OSM	Oncostatin M
OSMR	Oncostatin M receptor
Panitumumab	Panitumumab (Genetical Recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
PPC	Post process cells
PPS	Per protocol set
Product (the)	Mitchga Syringes 60 mg
PT	Preferred term
QbD	Quality by design
QOL	Quality of life
QxW	Once every x weeks
RH	Relative humidity
Rituximab	Rituximab (Genetical Recombination)
RNA	Ribonucleic acid
SEC	Size exclusion chromatography
sIGA	Static investigator's global assessment
SMQ	Standardized MedDRA Query
SOC	System organ class
STAT	Signal transducer and activator of transcription
$t_{1/2}$	Elimination half-life
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th2	T-helper type 2
T_{max}	Time to reach maximum serum concentration
TNF	Tumor necrosis factor
VAS	Visual analog scale
Vd_{ss}	Distribution volume in a steady state
V/F	Apparent volume of distribution
WCB	Working cell bank