Report on the Deliberation Results

November 20, 2017

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

Brand Name	Dupixent 300 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	February 21, 2017

Results of Deliberation

In its meeting held on November 6, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Review Report

October 26, 2017
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	Dupixent 300 mg Syringe for S.C. Injection
Non-proprietary name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 21, 2017
Dosage Form/Strength	Injection: Each 2 mL syringe contains 300 mg of Dupilumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Dupilumab is a recombinant human IgG4 monoclonal antibody against human interleukin-4 receptor α subunit, in which amino acid residues at position 233 in the H-chains are substituted by Pro. Dupilumab is produced in Chinese hamster ovary cells. Dupilumab is a glycoprotein (molecular weight: ca. 152,000) composed of 2 H-chains (γ4-chains) consisting of 452 amino acid residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

Structure

Amino acid sequences:

L chain

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DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL YSIGYNYLDW YLQKSGQSPQ
LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGF YYCMQALQTP
YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC
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H chain

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EVQLVESGGG LEQPGGSLRL SCAGSGFTFR DYAMTWVRQA PGKGLEWVSS
ISGSGGNTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKDR
LSITIRPRYY GLDVWGQGTT VTVSSASTKG PSVFPLAPCS RSTSESTAAL
GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS
LGTKTYTCNV DHKPSNTKVD KRVESKYGPP CPPCPAPEFL GGPSVFLFPP
KPKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ
FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE
PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP
PVLDSDGSFF LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL
GK
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Intra-chain disulfide bonds: Solid lines in the figure

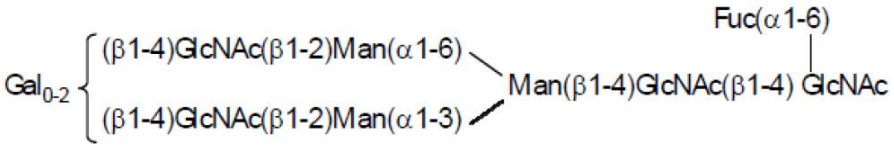
Inter-chain disulfide bonds: C219 in L chain - C139 in H chain, C231 in H chain - C231 in H chain, C234 in H chain - C234 in H chain

H chain

Glycosylation site: N302

Partial processing: K452

Estimated structure of the main carbohydrate chain



Molecular formula: $C_{6524}H_{10090}N_{1734}O_{2054}S_{46}$ (protein moiety composed of 4 chains)

L chain: $C_{1062}H_{1645}N_{279}O_{342}S_7$

H chain: $C_{2200}H_{3404}N_{588}O_{685}S_{16}$

Molecular weight: 147,153.30 (protein moiety composed of 4 chains)
L chain: 24,017.54
H chain: 49,563.14

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 patients with atopic dermatitis that have not responded adequately to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The long-term safety of the product in routine clinical practice, including the occurrences of serious hypersensitivity and aggravation of concurrent allergic diseases, should be further investigated in the post-marketing surveillance, etc., and information thus obtained should be provided to healthcare professionals and patients.

Indication

Atopic dermatitis that have not responded adequately to conventional treatments

Dosage and Administration

The usual initial dose for adults is 600 mg of dupilumab (genetical recombination), followed by 300 mg every 2 weeks, administered by subcutaneous injection.

Approval Conditions

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

Attachment

Review Report (1)

September 20, 2017

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	Dupixent 300 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 21, 2017
Dosage Form/Strength	Injection: Each 2 mL syringe contains 300 mg of Dupilumab (Genetical Recombination).
Proposed Indication	Atopic dermatitis (only in patients with moderate to severe symptoms)

Proposed Dosage and Administration

The usual dose for adults is 600 mg of dupilumab (genetical recombination) once on the first day, followed by 300 mg once every 2 weeks, administered by subcutaneous injection. If 300 mg once every 2 weeks does not demonstrate adequate efficacy, the dosage may be changed to 300 mg once weekly.

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List of Abbreviations

See Appendix.

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

Dupilumab (genetical recombination) (hereinafter referred to as dupilumab), the active ingredient of "Dupixent 300 mg Syringe for S.C. Injection," is a human immunoglobulin (Ig) G4 monoclonal antibody discovered by Regeneron Pharmaceuticals. It inhibits interleukin (IL)-4 and IL-13 signal transduction pathways through binding to IL-4 receptor α-subunit (IL-4Rα), a component of IL-4 receptor and IL-13 receptor.

Atopic dermatitis is a disease characterized by pruritic eczema with recurrent aggravation and remission. The Japanese clinical practice guidelines state that atopic dermatitis should be treated by the combination of drug therapy, topical therapy, skin care, and search for aggravating factors and taking countermeasures, depending on the symptoms and characteristics of individual patients. For the treatment of atopic dermatitis, the guideline recommends a continued use of a topical skin moisturizer for the improvement and maintenance of dermal barrier function and a concomitant use of anti-inflammatory drugs such as topical corticosteroid (TCS) and topical calcineurin inhibitor (TCI) as a remission-induction therapy for skin inflammation symptoms, together with oral antihistaminic drugs as adjuvant therapy. Patients with an inadequate response to these therapies are treated with intermittent administration of an immunosuppressant oral cyclosporine. Oral corticosteroid is sometimes used during the acute aggravation phase or for remission induction in severe or most severe cases.

It is considered that type 2 inflammatory response (including T-helper type 2 [Th2] response) and Th2 cell activation play important roles in the pathology of atopic dermatitis and related atopic/allergic diseases (Japanese clinical practice guidelines). In atopic dermatitis, it is considered that, in addition to the dermal inflammatory symptoms induced by type 2 inflammatory response, cytokines produced by activated Th2 cells inhibit the differentiation of normal epidermis, thereby inhibiting the expression of proteins in the terminally differentiated epidermis, resulting in the defective skin barrier (*J Allergy Clin Immunol*. 2007;120:150-5, *Clin Immunol*. 2008;26:332-7, etc.). Since IL-4 and IL-13 signal transduction pathways contribute to the type 2 inflammatory response, Th2 cell activation, etc., dupilumab is expected to be effective against atopic dermatitis. Therefore, Dupixent has been developed as a therapeutic agent for atopic dermatitis with an inadequate response to topical anti-inflammatory drugs such as TCS and TCI.

In foreign countries, clinical development of dupilumab for atopic dermatitis was initiated in [redacted] 20[redacted]. It was approved in the US in March 2017 and under review in Europe as of September 2017. In Japan, clinical development was initiated in [redacted] 20[redacted], and a marketing application has now been filed, based on the results of global clinical studies including Japan.

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

[redacted] transgenic mice were immunized with the extracellular domain protein of human IL-4Rα, and B cells producing anti-human IL-4Rα were obtained. Gene fragments encoding the variable regions of the heavy and light chains, prepared from these cells, were inserted into the plasmids containing the constant region of

human IgG heavy and light chains, respectively, to obtain a gene expression construct for dupilumab. This expression construct was introduced into a Chinese hamster ovary (CHO) cell line and, using a clone appropriate for dupilumab production, master cell bank (MCB) and working cell bank (WCB) were prepared.

Characterization and purity test were performed on MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) according to International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH) Q5A (R1), Q5B, and Q5D guidelines. Results demonstrated their genetic stability during the manufacturing period. Except endogenous retrovirus-like particles commonly observed in rodent-derived cell lines, no other viral or non-viral infectious agents were detected within the range of the attributes tested.

MCB and WCB are stored in the gaseous phase of liquid nitrogen. There is no plan to generate MCB, while WCB is generated on an as-needed basis.

2.1.2 Manufacturing process

The manufacturing process of the drug substance comprises expansion culture, manufacturing culture, harvesting, [redacted], [redacted], [redacted], [redacted], [redacted], virus filtration, [redacted], dispensing/storage, and formulation/testing/storage.

[redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

The manufacturing process of the drug substance is subjected to process validation on production scale.

2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, no raw materials of biological origin are used except the host cells which are derived from a CHO cell line. On the other hand, bovine milk-derived N-Z amine is used in the manufacture of [redacted], a component of the culture medium used for MCB and WCB preparation, and an enzyme extracted from porcine pancreas is used for the manufacture of N-Z amine. These raw materials are confirmed to meet the Standards for Biological Ingredients.

MCB, WCB, and CAL have been subjected to purity tests [see Section 2.1.1]. Unpurified bulks before harvest obtained after the commercial manufacturing of culture were subjected to bioburden test, mycoplasma testing, *in vitro* adventitious virus testing, and test for minute virus of mice. Within the range of the attributes tested, no contamination with viral or non-viral adventitious agents was observed. These tests for the unpurified bulk before harvest are defined as in-process control tests.

The purification process was subjected to virus clearance study using model viruses, and results demonstrated a sufficient level of viral-clearance performance (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Viral clearance factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Pseudorabies virus	Reovirus type 3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>18.4	>13.6	>20.5	>13.9

2.1.4 Manufacturing process development

Main changes made to the manufacturing process of the drug substance are as follows (each manufacturing process is abbreviated as Process S1, Process S2, Process S3, and the Proposed Process). The Japanese phase I study, the global phase II study, and main global phase III studies were conducted using the formulation manufactured from the drug substance prepared by the Process S3. The extension/re-administration study of the global phase III study was conducted using the formulation manufactured in and after [redacted] 20[redacted] from the drug substance prepared by the Proposed Process.

- From Manufacturing Process S1 to S2: Changes of [redacted], [redacted], [redacted], etc.
- From Manufacturing Process S2 to S3: Changes of [redacted], [redacted], [redacted], etc.
- From Manufacturing Process S3 to Proposed Process: Addition of [redacted], etc.

With each change of the manufacturing process, the pre-change and post-change drug substances were assessed for comparability of quality attributes. Clinical pharmacology studies were conducted when Process S2 was changed to Process S3, and the results showed that the post-change drug substance was comparable to the pre-change drug substance [see Section 6.1.1].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The drug substance was subjected to characterization tests described in Table 2.

Table 2. Parameters evaluated in characterization tests

Primary/higher order structure	Amino acid sequence, post-translational modification ([redacted]), disulfide bonds, free thiol groups, secondary structure, tertiary structure
Physicochemical properties	Molecular weight, [redacted], size variants, charge variants
Carbohydrate structure	Monosaccharide component, oligosaccharide profile
Biological properties	IL-4Rα binding affinity, complex formation with IL-4Rα
	IL-4 and IL-13 signal inhibitory activity
	ADCC activity, CDC activity

As for biological properties, [redacted] showed that dupilumab and IL-4Rα form complexes mainly at a ratio of [redacted] and [redacted].

Dupilumab was shown to inhibit IL-4-induced increase in cluster of differentiation (CD)23 expression in Burkitt's lymphoma-derived Ramos cells and in human peripheral blood mononuclear cells (PBMC). Also, dupilumab was shown to inhibit IL-4- and IL-13-induced signal transducer and activator of transcription (STAT)6 activation in human embryonic kidney (HEK)293 cells and to inhibit IL-4- and IL-13-induced thymus and activation regulated chemokine (TARC) secretion in human whole blood

[see Section 3.1.2]. On the other hand, dupilumab was shown not to have either antibody dependent cell mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity [see Section 3.1.3].

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization in Section 2.1.5.1, non-glycosylated form, charge variants, and oxidized forms were identified as product-related substances, while aggregates and truncated forms were identified as product-related impurities. The levels of aggregates and truncated forms are controlled by the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

[redacted], endotoxin, bioburden, host cell-derived protein, and host cell-derived DNA were identified as process-related impurities. All process-related impurities have been shown to be completely removed during the manufacturing process. Endotoxin is controlled by the specifications for the drug substance and for the drug product, and bioburden by the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (dot blotting and peptide mapping), osmotic pressure, pH, purity (size exclusion chromatography [SEC] and capillary electrophoresis-sodium dodecyl sulfate [CE-SDS] [reduced and non-reduced]), electrical conductivity, charge heterogeneity (capillary isoelectric focusing [cIEF]), bacterial endotoxin, bioburden, potency (IL-4 signal inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

Identification ([redacted]) was added to the specifications during the review process.

2.1.7 Stability of drug substance

Table 3 shows the main stability studies for the drug substance.

Table 3. Outline of main stability studies for drug substance

	Manufacturing process of drug substance	Number of batches	Storage conditions	Test period	Storage form
Long-term testing	Process S3	3	[redacted] ± [redacted]°C	[redacted] months	[redacted]
	Proposed Process	3		[redacted] months[a)]	
Accelerated testing	Process S3	3	[redacted] ± [redacted]°C	[redacted] months	
	Proposed Process	3			
Stress testing	Process S3	1	[redacted] ± [redacted]°C	[redacted] months	
	Proposed Process	1			
Photostability testing	Process S3	1	Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m^2		

a) The stability study (ongoing) is conducted for [redacted] months.

The long-term testing showed no clear change in the quality attributes throughout the test period.

The accelerated testing showed [redacted].

The stress testing showed [redacted] in addition to the changes observed in the accelerated testing.

The photostability testing showed [redacted].

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance when stored [redacted] at [redacted]°C to [redacted]°C in [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a combination product consisting of a glass syringe with needle (2.25 mL) filled with 2 mL solution containing 300 mg of dupilumab. The syringe is equipped with a safety device to prevent a needle-stick accident after injection. The drug product contains, as excipients, L-histidine, L-histidine hydrochloride hydrate, L-arginine hydrochloride, sodium acetate hydrate, glacial acetic acid, sucrose, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product comprises thawing of the drug substance, mixing, pre-filtration, sterile filtration, filling/capping, syringe assembly/labeling, storage/testing, and packaging/labeling/storing/testing processes.

[redacted] and [redacted] are defined as critical steps.

The manufacturing process of the drug product is subjected to process validation on a production scale.

2.2.3 Manufacturing process development

Main changes made to the manufacturing process of the drug product are as follows (each manufacturing process is abbreviated as Process A, Process B, and Proposed Process):

- From Process A to B: Changes of [redacted], etc.
- From Process B to Proposed Process: Changes of [redacted], etc.

With each change of the manufacturing process, pre-change and post- change drug products were assessed for comparability of quality attributes. Clinical pharmacology studies were conducted when Process B was changed to Proposed Process, and the results showed that the post-change drug product was comparable to the pre-change drug product [see Section 6.1.1].

2.2.4 Control of drug product

The proposed specifications for the drug product include content, description, identification (dot blotting), pH, purity (SEC and CE-SDS [reduced and non-reduced]), charge heterogeneity (cIEF), polysorbate 80, bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate

matter, sterility, potency (IL-4 signal inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows the main stability studies for the drug product manufactured by the Proposed Process.

Table 4. Outline of main stability studies for drug product

	Manufacturing process of drug product	Number of batches	Storage conditions	Test period	Storage form
Long-term testing	Proposed Process	7	5 ± 3°C	15 months[a)]	Glass syringe with a bromobutyl plunger stopper
Accelerated testing		7	[redacted] ± [redacted]°C	[redacted] months	
Stress testing		2	[redacted] ± [redacted]°C	[redacted] months	
Stress testing (light)		1	Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m^2		

a) [redacted] months for 1 batch and [redacted] months for 4 batches. The stability study (ongoing) is conducted for [redacted] months.

The long-term testing showed no clear change in the quality attributes throughout the test period.

The accelerated testing showed [redacted].

The stress testing showed [redacted] in addition to the changes observed in the accelerated testing.

The photostability testing showed that the drug product is unstable to light.

Based on the above, a shelf life of 15 months has been proposed for the drug product when filled in a glass syringe with a bromobutyl plunger stopper and stored at 2°C to 8°C in a paper box protected from light.

2.R Outline of the review conducted by PMDA

Based on the reviews on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

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

The applicant submitted the results from the following primary pharmacodynamic studies of dupilumab: Binding affinity to IL-4Rα, effect on the binding of IL-4 to IL-4Rα, effect on IL-4 and IL-13 signal transduction, effect on *Il4ra*$^{hu/hu}$*Il4*$^{hu/hu}$ mice, a mouse model of type 2 inflammation, and effect on a hapten-induced contact hypersensitivity type 2 dermatitis model. No safety pharmacology study was conducted. Instead, the effect on the central nervous system, cardiovascular system, and respiratory system was investigated in repeated-dose toxicity studies using cynomolgus monkeys and mice. During the early stage of the development, the drug substance manufactured by a manufacturing process prior to Process S1 [see Section 2.1.4] was used.

In this section, human IL-4, human IL-13, and human IL-4Rα are expressed simply as IL-4, IL-13, and IL-4Rα, respectively. Pharmacodynamic parameters are expressed in mean values.

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to IL-4Rα and effect of binding of IL-4 to IL-4Rα (CTD 4.2.1.1-1, 4.2.1.1-2, and 4.2.1.1-3)

The affinity of dupilumab to the monomer and dimer of the extracellular domain of IL-4Rα of humans and other animals was investigated by surface plasmon resonance. Dupilumab bound to IL-4Rα monomer (equilibrium dissociation constant [K_D], 33.1 pmol/L) and dimer (11.9 pmol/L), cynomolgus monkey IL-4Rα monomer (832 nmol/L) and dimer (5.30 nmol/L), rhesus monkey IL-4Rα monomer (576 nmol/L), and common marmoset IL-4Rα monomer (1.19 μmol/L), but not to mouse IL-4Rα monomer up to 800 nmol/L.

Binding of dupilumab (1 μg/L) to IL-4Rα on the surface of peripheral lymphocytes from humans, cynomolgus monkeys, rhesus monkeys, and common marmosets was investigated by flow cytometry. Results showed that dupilumab bound only to human peripheral lymphocytes.

The effect of dupilumab on the binding of IL-4 to IL-4Rα was investigated by surface plasmon resonance. When a mixture of dupilumab (333 nmol/L) and IL-4 (25 nmol/L) was added to IL-4Rα on the surface of a sensor chip, binding of IL-4 to IL-4Rα was not observed.

3.1.2 Effect on IL-4 and IL-13 signal transduction (CTD 4.2.1.1-3)

The effect of dupilumab on IL-4 and IL-13 signal transduction was investigated in various test systems. Table 5 shows the results.

Table 5. Effect of dupilumab on IL-4 and IL-13 signal transductions in various test systems

Test system	Endpoint	Results
HEK293 cells	Effect on IL-4 (10 pmol/L)- and IL-13 (40 pmol/L)-induced STAT6 activation	IC_{50} for inhibition of IL-4-induced STAT6 activation, 20 pmol/L IC_{50} for inhibition of IL-13-induced STAT6 activation, 12 pmol/L
Burkitt's lymphoma-derived Ramos cells	Effect on IL-4 (1 nmol/L)-induced increase in CD23 expression	Increase in CD23 expression suppressed by ≥25 nmol/L of dupilumab
Human PBMC	Effect on IL-4 (0.14 nmol/L)-induced increase in CD23 expression	IC_{50}, 34-157 pmol/L
Human whole blood	Effect on IL-4 (0.5 nmol/L)- and IL-13 (1 nmol/L)-induced TARC secretion	IC_{50} for inhibition of IL-4-induced TARC secretion, 0.24-0.52 nmol/L IC_{50} for inhibition of IL-13-induced TARC secretion, 0.26-0.27 nmol/L

3.1.3 Study on effector function (CTD 4.2.1.1-4)

ADCC and CDC activities of dupilumab were investigated. Dupilumab did not show ADCC activity (dupilumab concentration 3.3 pmol/L to 200 nmol/L) or CDC activity (dupilumab concentration 3.2 pmol/L to 188 nmol/L) in any of the cells with different IL-4Rα expression levels (CHO-K1, HEK293, Burkitt's lymphoma-derived Ramos cells).

3.1.4 Effect in mouse type 2 inflammation model (CTD 4.2.1.1-3 and 4.2.1.1-5)

Il4ra$^{hu/hu}$*Il4*$^{hu/hu}$ mice were prepared by substituting genes encoding mouse IL-4 and the extracellular domain protein of mouse IL-4Rα with corresponding human gene sequences, and the effect of dupilumab on type 2 cytokine response was investigated using these animals. IL-25 expression by hydrodynamic DNA delivery resulted in metaplasia of goblet cells in the airway epithelium and increase in total IgE concentration in blood caused by IL-4 and IL-13 induction, while administration of dupilumab suppressed the increase in IgE concentration at 5 mg/kg and goblet cell metaplasia at 25 mg/kg.

3.1.5 Effect of mouse homologous antibody on IL-4 and IL-13 signal transduction and in hapten-induced contact hypersensitivity type 2 dermatitis model (CTD 4.2.1.1-7a and 4.2.1.1-8)

Since the binding of dupilumab to mouse IL-4Rα was not observed up to 800 nmol/L [see Section 3.1.1], 2 types of dupilumab homologous antibody against mouse IL-4Rα (M2M1869N, REGN1103; mouse homologous antibodies) were prepared. These homologous antibodies bound to mouse IL-4Rα (K_D, 640 pmol/L and 86.7 pmol/L; surface plasmon resonance).

The effect of REGN1103 on mouse IL-4 and IL-13 signal transduction was investigated. REGN1103 suppressed HT-2 cell proliferation stimulated by mouse IL-4 (1 nmol/L) and suppressed B9 cell proliferation induced by mouse IL-13 (100 pmol/L) (half maximal inhibitory concentration [IC_{50}] 1.9 nmol/L and 11 pmol/L, respectively).

The effect of M2M1869N in the hapten-induced contact hypersensitivity model of female BALB/c mice was investigated. Administration of the mouse homologous antibody (20 mg/kg) tended to suppress auricular swelling.

3.1.6 Effect of monkey homologous antibody on IL-4 and IL-13 signal transduction (CTD 4.2.1.1-2)

Since dupilumab up to 1 μmol/L did not bind to IL-4Rα on the surface of lymphocytes in peripheral blood from cynomolgus monkey [see Section 3.1.1], dupilumab homologous antibody against IL-4Rα of cynomolgus monkeys (monkey homologous antibody) was prepared. The monkey homologous antibody bound to the monomer and dimer of cynomolgus monkey IL-4Rα (K_D, 2.5 nmol/L and 31 pmol/L, respectively, by surface plasmon resonance). Also, the monkey homologous antibody (333 nmol/L) inhibited the binding of IL-4 and cynomolgus monkey IL-4 (both 25 nmol/L) to cynomolgus monkey IL-4Rα. In addition, a flow cytometric study showed that the monkey homologous antibody bound to IL-4Rα on the surface of lymphocytes in peripheral blood of cynomolgus monkeys.

The effect of monkey homologous antibody on IL-4 and IL-13 signal transduction was investigated in various test systems. Table 6 shows the results.

Table 6. Effect of monkey homologous antibody on IL-4 and IL-13 signal transduction in various test systems

Test system	Endpoint	Results
HEK293 cells	Effect on cynomolgus monkey IL-4 (0.3 pmol/L)- and cynomolgus monkey IL-13 (10 pmol/L)-induced STAT6 activation	IC_{50} for inhibition of IL-4-induced STAT6 activation, 116 pmol/L IC_{50} for inhibition of IL-13-induced STAT6 activation, 447 pmol/L
Whole blood of cynomolgus monkeys	Effect on IL-4 (0.5 nmol/L)- and IL-13 (1 mmol/L)-induced TARC secretion	IC_{50} for inhibition of IL-4-induced TARC secretion, N.D. to 37.8 nmol/L IC_{50} for inhibition of IL-13-induced TARC secretion, N.D. to 50.5 nmol/L

3.2 Safety pharmacology (CTD 4.2.3.2.3 to 4.2.3.2.5)

Parameters of safety pharmacology were investigated in 5-week, 13-week, and 6-month repeated-dose toxicity studies using cynomolgus monkeys. The monkey homologous antibody was administered to cynomolgus monkeys intravenously at 1, 5, 25, or 100 mg/kg once every week for 5 weeks, subcutaneously at 1, 5, 25, or 100 mg/kg once every week for 13 weeks, intravenously at 25 mg/kg once every week for 6 months, or subcutaneously at 25 or 100 mg/kg once every week for 6 months. As a result, no monkey homologous antibody-related effect was observed in clinical signs, body temperature, heart rate, blood pressure, electrocardiographic parameters, or respiratory conditions.

3.R Outline of the review conducted by PMDA

The applicant discussed the function of IL-4 and IL-13 in the pathology of atopic dermatitis and the mechanism of action of dupilumab as follows:

Many patients with atopic dermatitis show increased blood IgE concentration, increases in eosinophils, basophils, type 2 innate lymphoid cells, and mast cells, as well as increases in multiple type 2 cytokines/chemokines (e.g., thymic stromal lymphopoietin, TARC, IL-4, IL-5, IL-13) (*J Allergy Clin Immunol*. 2014;134:1293-300, *Allergy.* 2015;70:887-96).

IL-4 and IL-13 are suggested to be potent mediators of type 2 immunoreaction both during the inflammation induction phase and during the manifestation phase. It is reported that activation of IL-4 signal transduction pathway triggers and enhances the class switching of B cell immunoglobulin to IgE production (*J Exp Med.* 1988;168:2385-9, *Science.* 1991;254:707-10, etc.). It is also reported that IL-4 and IL-13 activate eosinophils by acting on epithelial cells, etc., thereby enhancing the migration of effector cells to the site of inflammation (*J Immunol*. 1998;160:60-8, *J Allergy Clin Immunol*. 2007;119:1303-10). Furthermore, IL-4 and IL-13 are also reported to be involved in the prolonged inflammatory reaction in atopic dermatitis (*J Allergy Clin Immunol.* 2007;120:150-5, *Clin Immunol.* 2008;126:332-7).

These findings suggest the involvement of IL-4 and IL-13 signal transduction pathways in the pathology of atopic dermatitis. Therefore, dupilumab is expected to be effective against atopic dermatitis by inhibiting IL-4 and IL-13 signal transduction pathways through binding to IL-4Rα.

PMDA concluded that the submitted data demonstrate the suppressive effect of dupilumab against the biological activities of IL-4 and IL-13 mediated by binding to IL-4Rα, and that, from the pharmacological point of view, dupilumab is expected to be effective against atopic dermatitis for which IL-4 and IL-13 are involved in the pathogenesis.

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

The applicant submitted results of studies on intravenous and subcutaneous administration of dupilumab or the monkey homologous antibody in rats and cynomolgus monkeys as data on the absorption and distribution. Serum concentrations of dupilumab and the monkey homologous antibody were measured by enzyme-linked immunosorbent assay (ELISA) (lower limit of quantitation, 0.39 μg/mL for both). Serum anti-drug antibody (ADA) following the administration of the monkey homologous antibody was detected by immunological electrochemiluminescence (ECL).

Pharmacokinetic parameter values are expressed in mean or mean ± standard deviation (SD) unless specified otherwise.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 to 4.2.2.2-3)

Table 7 shows pharmacokinetic parameters following a single-dose administration of dupilumab to rats or cynomolgus monkeys. No clear sex difference was observed. Bioavailability following subcutaneous administration was 84.2% in rats and 92.5% in cynomolgus monkeys.

Table 7. Pharmacokinetic parameters following a single-dose administration of dupilumab to rats and cynomolgus monkeys

Animal species	Route of administration	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL or CL/F (mL/h/kg)	V_{ss} (mL/kg)
Rats	i.v.	1	F	7	29.7 ± 3.5	2480 ± 590	1.05 ± 2.19	116 ± 39	0.430 ± 0.120	63.3 ± 14.8
		5	M	7	142 ± 15	16,000 ± 1700	0.780 ± 1.070	175 ± 32	0.320 ± 0.030	74.3 ± 9.1
			F	6[a)]	158 ± 20	13,000 ± 3300	0.260 ± 0.370	111 ± 42	0.410 ± 0.110	58.5 ± 9.1
		15	F	7	549 ± 48	54,500 ± 8600	0.220 ± 0.350	168 ± 25	0.280 ± 0.050	64.2 ± 9.9
	s.c.	5	M	7	42.6 ± 7.1	12,000 ± 2000	69.6 ± 16.5	173 ± 31	0.430 ± 0.080	
			F	7	45.5 ± 9.1	12,600 ± 2500	73.0 ± 19.6	149 ± 6	0.410 ± 0.110	
Cynomolgus monkeys	i.v.	1	M	2	33.1, 28.1	7860, 5820	0.033, 0.033	336, 241	0.127, 0.172	59.0, 52.6
			F	2	24.1, 26.6	5640, 5200	0.500, 0.033	309, 242	0.177, 0.192	68.4, 60.1
		15	M	2	483, 479	144,000, 180,000	0.033, 2.00	489, 575	0.104, 0.083	74.1, 68.8
			F	2	479, 447	133,000, 73,000	0.250, 0.033	425, 152	0.112, 0.205	66.6, 46.2
	s.c.	1	M	2	9.81, 10.1	5310, 7810	192, 144	386, 449	0.188, 0.128	
			F	2	11.5, 10.6	6140, 7530	144, 72	299, 338	0.163, 0.133	
		15	M	2	160, 142	127,000, 119,000	120, 192	578, 472	0.118, 0.126	
			F	2	170, 162	156,000, 89,000	96.0, 72.0	548, 368	0.096, 0.169	

Mean ± SD. Pharmacokinetic parameters in cynomolgus monkeys are expressed in observed values (n = 2).
a) One animal with possible administration error was excluded from calculation.

Table 8 shows pharmacokinetic parameters following a single-dose administration of monkey homologous antibody to cynomolgus monkeys. No clear sex difference was observed. Bioavailability following subcutaneous administration was 70.0%.

Table 8. Pharmacokinetic parameters following a single-dose administration of monkey homologous antibody to cynomolgus monkeys

Route of administration	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)[a)]	CL or CL/F (mL/h/kg)	V_{ss} (mL/kg)
i.v.	1	M	3	29.0 ± 5.6	1510 ± 140	0.833 ± 1.01	43.8 ± 2.0	0.665 ± 0.061	41.0 ± 3.5
		F	3	32.3 ± 3.9	1850 ± 440	0.583 ± 0.382	53.2 ± 8.9	0.564 ± 0.143	38.1 ± 5.9
	5	M	3	150 ± 26	16,700 ± 5000	0.250 ± 0	37.8 ± 23.7	0.316 ± 0.081	45.2 ± 3.2
		F	3	149 ± 39	16,100 ± 2300	0.189 ± 0.269	33.6 ± 23.0	0.316 ± 0.046	46.4 ± 16.7
	15	M	3	460 ± 47	57,900 ± 10,800	0.178 ± 0.125	44.6 ± 32.1	0.264 ± 0.045	43.4 ± 2.8
		F	3	528 ± 153	82,600 ± 28,400	0.917 ± 0.946	54.4 ± 49.5	0.195 ± 0.057	40.9 ± 11.2
s.c.	15	M	3	181 ± 17	48,200 ± 1000	120 ± 0	32.5 ± 10.4	0.311 ± 0.007	
		F	3	180 ± 22	50,200 ± 9600	120 ± 0	43.9 ± 19.4	0.307 ± 0.062	

Mean ± SD
a) $t_{1/2}$ in terminal phase

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2-3 to 4.2.3.2-5)

Toxicokinetics in once weekly administration of the monkey homologous antibody was investigated in 5-week and 6-month intravenous dose toxicity studies and in 13-week and 6-month subcutaneous dose toxicity studies in cynomolgus monkeys [see Section 5.2]. Table 9 shows pharmacokinetic parameters of the monkey homologous antibody. The ADA-positive rate decreased with increase in dose, showing no ADA in high dose groups (Table 9). ADA formation was associated with a decrease in the exposure to the monkey homologous antibody.

Table 9. Pharmacokinetic parameters and immunogenicity in repeated administration of monkey homologous antibody to cynomolgus monkeys

Route of administration	Treatment period	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)		Estimated $AUC_{0\text{-}168h}$ (μg·h/mL)		Number of ADA-positive animals	
					Week 1	Last week	Week 1	Last week	Week 1	Last week
i.v.	5 weeks	1	M	5	23.0 ± 1.5	10.0 ± 7.5	1380 ± 110	347 ± 427	0/5	5/5
			F	5	24.7 ± 3.7	12.8 ± 6.7	1490 ± 240	220 ± 177	0/5	5/5
		5	M	5	111 ± 8	130 ± 66	9560 ± 1350	9990 ± 9370	0/5	2/5
			F	5	109 ± 10	127 ± 72	8820 ± 710	10,200 ± 8600	0/5	2/5
		25	M	5	609 ± 41	975 ± 277	55,200 ± 3800	85,300 ± 45,600	0/5	2/5
			F	5	583 ± 52	868 ± 234	50,900 ± 3300	84,800 ± 40,600	0/5	1/5
		100	M	5	2700 ± 290	4700 ± 430	233,000 ± 11,000	546,000 ± 55,000	0/5	0/5
			F	5	2780 ± 790	4400 ± 250	232,000 ± 48,000	482,000 ± 28,000	0/5	0/5
	6 months	25	M	6	715 ± 68	1630 ± 610	60,100 ± 6700	177,000 ± 87,000	0/6	1/6
			F	6	716 ± 93	1330 ± 670	59,400 ± 8100	122,000 ± 98,000	0/6	3/6
s.c.	13 weeks	1	M	6	9.15 ± 2.29	1.47 ± 3.60	1120 ± 310	192 ± 470	0/6	6/6
			F	6	7.16 ± 1.75	BLQ	810 ± 185	BLQ	0/6	6/6
		5	M	6	47.6 ± 10.7	175 ± 199	6270 ± 930	15,000 ± 15,800	1/6	3/6
			F	6	48.5 ± 8.2	41.6 ± 94.5	6490 ± 1130	5080 ± 11,630	0/6	5/6
		25	M	6	290 ± 108	1330 ± 620	39,500 ± 12,000	181,000 ± 58,000	0/6	0/6
			F	6	241 ± 52	761 ± 401	34,800 ± 7700	115,000 ± 62,000	0/6	1/6
		100	M	6	1260 ± 270	4790 ± 1620	174,000 ± 36,000	708,000 ± 226,000	0/6	0/6
			F	6	1170 ± 900	4170 ± 640	142,000 ± 30,000	661,000 ± 85,000	0/6	0/6
	6 months	25	M	4	298 ± 23	1110 ± 210	41,300 ± 4200	164,000 ± 33,000	0/4	0/4
			F	4	312 ± 40	768 ± 561	43,500 ± 6000	116,000 ± 87,000	0/4	1/4
		100	M	6	1200 ± 170	5280 ± 470	166,000 ± 22,000	789,000 ± 59,000	0/6	0/6
			F	6	1380 ± 170	5360 ± 210	179,000 ± 16,000	793,000 ± 53,000	0/6	0/6

Mean ± SD
BLQ, below the lower limit of quantification (0.39 μg/mL)

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.3-1)

In an extended pre- and postnatal development study in pregnant cynomolgus monkeys [see Section 5.5.2], the monkey homologous antibody (25 or 100 mg/kg) was administered subcutaneously once every week starting from Gestation Days 20 to 22 up to natural delivery (around Gestation Day 160),

and toxicokinetics was investigated. Table 10 shows serum concentrations of monkey homologous antibody in maternal animals and pups. Monkey homologous antibody was observed in serum of pups dependent on the exposure in maternal animals. ADA was observed in 9 of 20 maternal animals in the 25 mg/kg group and in 3 of 20 maternal animals in the 100 mg/kg group, and in 2 and 1 pup, respectively, in the 25 and 100 mg/kg groups.

Table 10. Placental transfer in cynomolgus monkeys
(serum concentrations of monkey homologous antibody in maternal animals and pups)

	25 mg/kg (μg/mL)		100 mg/kg (μg/mL)	
	Maternal animals	Pups	Maternal animals	Pups
Gestation Day 27-29	223 ± 31 (20)		774 ± 226 (20)	
Gestation Day 48-50	183 ± 197 (17)		1910 ± 600 (17)	
Gestation Day 97-99	176 ± 203 (17)		2430 ± 880 (16)	
Gestation Day 146-148	436 ± 291 (13)		2210 ± 910 (15)	
Lactation/birth Day 14	199 ± 173 (8)	167 ± 127 (8)	1370 ± 520 (13)	1060 ± 410 (14)
Lactation/birth Day 28	138 ± 94 (8)	107 ± 92 (8)	914 ± 258 (12)	658 ± 330 (12)
Lactation/birth Day 91	3.85 ± 3.82 (8)	BLQ (7)	57.0 ± 46.5 (12)	34.5 ± 41.1 (12)
Lactation/birth Day 180	BLQ (8)	BLQ (8)	BLQ (12)	BLQ (12)

Mean ± SD (number of animals)
BLQ, below the lower limit of quantification (0.39 μg/mL)

4.R Outline of the review conducted by PMDA

Based on the nonclinical pharmacokinetic data submitted, PMDA concluded that the behavior of dupilumab within the body has been elucidated to a sufficient extent, and that clinical use of dupilumab does not pose any concern from the pharmacokinetic point of view.

5. Toxicity and Outline of the Review Conducted by PMDA

Binding of dupilumab to mouse IL-4Rα was not observed up to 800 nmol/L. Dupilumab showed a low affinity to IL-4Rα of cynomolgus monkeys, rhesus monkeys, and common marmosets, but did not bind to IL-4Rα on the surface of lymphocytes in peripheral blood up to 1 μmol/L [see Section 3.1.1]. For these reasons, only a tissue cross reactivity study was conducted using dupilumab, and repeated-dose toxicity studies and reproductive and developmental toxicity studies were conducted using mouse and monkey homologous antibodies. The applicant explained that although no toxicity study was conducted using dupilumab, since the known process-related impurities present in the commercial product are contained in the mouse or monkey homologous antibody as well, the off-target toxicity evaluation for dupilumab meets the requirements.

In high dose groups of the repeated-dose toxicity studies and the reproductive and developmental studies, ADA formation was observed in only a small number of animals [see Sections 4.1.2 and 4.2], from which it was concluded that, in all of these studies, the exposure to the monkey homologous antibody during the administration period was sufficiently high for evaluating the toxicity.

[redacted] containing [redacted] mmol/L sodium acetate, [redacted] mmol/L L-histidine, [redacted]% (w/v) sucrose, and [redacted] was used as vehicle for dupilumab and the homologous antibody, unless specified otherwise.

5.1 Single-dose toxicity study

No single-dose toxicity study was conducted either on dupilumab or on the homologous antibody. In a repeated-dose toxicity study using the monkey homologous antibody [see Section 5.2], no death or acute toxicity findings associated with the monkey homologous antibody were observed following the initial intravenous or subcutaneous dose of the monkey homologous antibody up to 100 mg/kg.

5.2 Repeated-dose toxicity studies

Five-week and 6-month intravenous dose toxicity studies and 13-week and 6-month subcutaneous dose toxicity studies were conducted using the monkey homologous antibody.

5.2.1 Five-week intravenous dose toxicity study (CTD 4.2.3.2-3)

The monkey homologous antibody (0 [vehicle], 1, 5, 25, or 100 mg/kg) was administered intravenously once every week for a total of 5 doses to male and female cynomolgus monkeys. Some of the animals in each dose group were to undergo an 8-week recovery period after the last dose. There were no changes of toxicological significance associated with the administration of monkey homologous antibody.

5.2.2 Thirteen-week subcutaneous dose toxicity study (CTD 4.2.3.2-4)

The monkey homologous antibody (0 [vehicle], 1, 5, 25, or 100 mg/kg) was administered subcutaneously to male and female cynomolgus monkeys once every week for a total of 14 doses. Some of the animals in each dose group were to undergo a 13-week recovery period after the last dose.

No death occurred. Blood IgE concentration decreased in some animals in the ≥25 mg/kg groups, but the decrease was considered to be of little toxicological significance, judging from the large variation observed and from the lack of any abnormal findings related to the decreased blood IgE concentration.

5.2.3 Six-month intravenous and subcutaneous dose toxicity study (CTD 4.2.3.2-5)

The monkey homologous antibody was administered to male and female cynomolgus monkeys intravenously at a dose of 0 [vehicle] or 25 mg/kg, or subcutaneously at a dose of 0 [vehicle], 25, or 100 mg/kg, once every week for a total of 27 doses. Some animals in each dose group were to undergo a 3-month recovery period after the last dose.

No death occurred. Blood IgE concentration decreased in some animals in the ≥25 mg/kg groups, but the decrease was considered to be of little toxicological significance, judging from the large variation observed in the responses and from the lack of any abnormal findings related to the decreased blood IgE concentration. Animals in the ≥25 mg/kg subcutaneous dose groups showed perivascular lymphocyte infiltration suggestive of local irritation, but these findings were considered to be of little toxicological significance because they were mild to moderate and reversible. Animals in the intravenous dose groups did not show any change related to the administration of the monkey homologous antibody.

5.3 Genotoxicity

Since dupilumab is an antibody drug and is considered not to directly interact with DNA or other chromosomal components, no genotoxicity study was conducted.

5.4 Carcinogenicity

No carcinogenicity study using rodents was conducted.

The applicant explained that dupilumab is unlikely to be carcinogenic, based on the following findings:

- It is reported that IL-4Rα-mediated activation of IL-4 and IL-13 signal transduction enhances tumor formation *in vitro* and *in vivo* (*Cancer Immunol Immunother.* 1997;46:375-81, *J Immunol*. 1998;160:5869-73, etc.).
- It is reported that inhibition of IL-4Rα-mediated IL-4 and IL-13 signal transduction may reduce the risk of tumor formation and growth, including the report that administration of azoxymethane, a carcinogenic agent, to wild-type mice or IL-4Rα knockout mice caused tumor formation less frequently in IL-4Rα knockout mice compared with wild-type mice (*Carcinogenesis*. 2010;31:1010-7, etc.).
- In 6-month intravenous and subcutaneous dose toxicity studies using the monkey homologous antibody, no change suggestive of tumor formation was observed [see Section 5.2.3].
- In clinical studies, the incidence of adverse events classified under the system organ class (SOC) "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" was similar between the dupilumab group and the placebo group, showing no increase in the incidence of malignant tumor following dupilumab administration [see Section 7.R.3.7]. Also, there are no post-marketing spontaneous reports regarding adverse events classified under the SOC "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" (as of June 2017).

5.5 Reproductive and developmental toxicity

The following studies were conducted: A study of fertility and early embryonic development to implantation using the mouse homologous antibody, and an extended study for effects on pre- and postnatal development, including maternal function using the monkey homologous antibody. In cynomolgus monkeys, placental transfer of the monkey homologous antibody was observed [see Section 4.2.1].

5.5.1 Study of fertility and early embryonic development to implantation in mice (CTD 4.2.3.5.1-1)

The mouse homologous antibody (0 [vehicle],[1)] 25, 75, or 200 mg/kg) was administered subcutaneously once every week to male mice 9 doses from 4 weeks before mating and throughout the mating period, and to female mice ≥4 doses from 2 weeks before mating up to the early gestation period (Gestation Days 0-7). No death occurred. No changes associated with the administration of mouse homologous antibody were observed in the clinical signs, copulation, or fertility parameters (conception rate, pregnancy rate, pre-/post-implantation loss, and estrous cycle in females).

5.5.2 Extended study for effects on pre- and postnatal development, including maternal function, in cynomolgus monkeys (ePPND study) (CTD 4.2.3.5.3-1)

The monkey homologous antibody (0 [vehicle], 25, or 100 mg/kg) was administered subcutaneously once every week to pregnant cynomolgus monkeys starting from Gestation Days 20 to 22 until natural

1) [redacted] containing [redacted] mmol/L sodium acetate, [redacted] mmol/L L-histidine, [redacted] mmol/L L-arginine hydrochloride, [redacted]%(w/v) sucrose, and

delivery (around Gestation Day 160). Tests for lymphocyte subsets, etc., were performed in this study. Pups were necropsied on 178 to 182 days after birth and subjected to histopathological examination.

Maternal animals did not show any change related to the administration of monkey homologous antibody. Embryofetal death was observed in 5 of 20 animals in the 0 mg/kg group, in 10 of 20 animals in the 25 mg/kg group, and in 3 of 18 animals in the 100 mg/kg group. The applicant explained that the increase in the embryofetal lethality in the 25 mg/kg group is unlikely to be related to the administration of monkey homologous antibody, for the following reasons:

- There is a report that inhibition of IL-4 signal transduction increases the risk of embryofetal death in cynomolgus monkeys (*Regul Tox Pharm.* 2009;53:226-34). However, because of the high incidence of abortion, stillbirth, perinatal death, and post-natal death in macaque monkeys (*Am J Primatol*. 1996;40:41-53, *Birth Defects Res*. 2009;86:446-62, etc.), there is no agreement on the effect of the inhibition of IL-14 signal transduction on embryos and fetuses.
- In monkeys in the 25 and 100 mg/kg groups, trough serum concentration of the monkey homologous antibody on Gestation Day 139 to Gestation Day 141 (436 and 2211 μg/mL, respectively) was 5.4 and 27.5 times, respectively, higher than IC_{90} (80.3 μg/mL), suggesting that IL-4Rα is almost completely saturated with the monkey homologous antibody in both groups. The combined embryofetal lethality of both groups (34%) is within the mean historical data of the study sites (6.7%-38.9%).

The monkey homologous antibody was detected in the serum of newborns and decreased gradually over 180 days after birth [see Section 4.2.1]. Neonatal death was observed in 2 of 10 animals in the 25 mg/kg group and in 2 of 15 animals in the 100 mg/kg group. However, the monkey homologous antibody did not show any effect on any of the newborns, and the total mortality of the neonates was within the historical data in macaque monkeys including cynomolgus monkeys (*Lab Animal Sci*. 1989;39:205-12, etc.). Therefore, the applicant considered that the neonatal mortality is unlikely to be related to the administration of monkey homologous antibody.

5.6 Other toxicity studies

5.6.1 Tissue cross-reactivity (CTD 4.2.3.7.7-1)

Tissue cross-reactivity of dupilumab to the normal tissues of humans and tissue cross-reactivity of the monkey homologous antibody to normal tissues of cynomolgus monkeys were investigated. Staining was observed in the bone marrow and thymus tissues of cynomolgus monkeys, but no findings were observed in these tissues in the 6-month intravenous and subcutaneous dose toxicity studies in cynomolgus monkeys [see Section 5.2.3], based on which the staining was concluded to be of no toxicological significance. It is reported that human IL-4Rα is expressed on T and B lymphocytes, airway smooth muscles, hepatocytes, etc. (*Immunol*. 1993;150:149-58, *FASEB J*. 2007;21:1433-44, etc.), but no dupilumab-specific staining was observed in human tissues.

5.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that clinical use of dupilumab does not pose any concern from the toxicological point of view.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted results of pharmacokinetic studies in healthy adult subjects (Study PKM12350 [CTD 5.3.1.2-1] and Study PKM14161 [CTD 5.3.1.2-2]), and other studies.

Serum dupilumab concentration was measured by ELISA (lower limit of quantitation, 78 ng/mL). ADA and neutralizing antibody were detected by ECL.

Unless specified otherwise, the dose of Dupixent is expressed in the dose of dupilumab (genetical recombination), and pharmacokinetic parameters are expressed in mean or mean ± SD.

6.1.1 Comparison of pharmacokinetics between formulations (CTD 5.3.1.2-1, Study PKM12350 [February to July 2012]; CTD 5.3.1.2-2, Study PKM14161 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In a foreign randomized, double-blind, parallel-group study in healthy adult subjects, pharmacokinetics of dupilumab following a single subcutaneous administration was compared between 300 mg formulations manufactured by Process B [see Section 2.2.3] and by the Proposed Process using the drug substance prepared by Process S2 or S3 [see Section 2.1.4]. The applicant explained that the pharmacokinetic parameters of the compared formulations were similar (Table 11).

Table 11. Pharmacokinetic parameters following a single subcutaneous administration of 300 mg of dupilumab to non-Japanese healthy adult subjects

Study	Formulation		C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	Geometric mean ratio [90% CI]	
	Manufacturing process for drug substance	Manufacturing process for drug product			C_{max}	AUC_{last}
PKM12350	S2	Process B	27.2 ± 10.0 (13)	500 ± 179 (11)	1.10 [0.89, 1.35]	0.89 [0.69, 1.14]
	S3	Process B	28.9 ± 9.1 (15)	483 ± 204 (15)		
PKM14161	S3	Process B	34.3 ± 11.6 (19)	575 ± 235 (19)	0.96 [0.74, 1.25]	0.98 [0.71, 1.37]
	S3	Proposed Process	34.8 ± 17.5 (19)	587 ± 302 (19)		

Mean ± SD (number of patients)

6.2 Clinical pharmacology

The applicant submitted results of a Japanese clinical study (Study TDU12265 [CTD 5.3.3.1-3]) and global clinical studies (Study R668-AD-1021 [CTD 5.3.5.1-3], Study R668-AD-1334 [CTD 5.3.5.1-4], Study R668-AD-1224 [CTD 5.3.5.1-6 and 5.3.5.1-6a], and Study R668-AD-1225 [CTD 5.3.5.2-1]) as the evaluation data. In addition, the applicant submitted results of a foreign clinical study (Study R668-AS-0907 [CTD 5.3.3.1-1]), a population pharmacokinetic analysis, exposure-response analysis, etc., as the reference data.

6.2.1 Studies in healthy adult subjects

6.2.1.1 Japanese phase I study (CTD 5.3.3.1-3, Study TDU12265 [February to October 2012])

In a placebo-controlled, randomized, stepwise dose escalation study in healthy adult subjects (dupilumab administered to 24 of 32 subjects), a single dose of dupilumab (75, 150, 300, or 600 mg) was administered subcutaneously. Table 12 shows the pharmacokinetic parameter values observed. The

exposure increased more than in proportion to dose. ADA was positive in 1 of 6 subjects in the 75 mg group, 2 of 6 subjects in the 150 mg group, 1 of 6 subjects in the 300 mg group, and 1 of 6 subjects in the 600 mg group.

Table 12. Pharmacokinetic parameters following a single subcutaneous administration of dupilumab to Japanese healthy subjects

Dose	N	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	t_{max} (day)	$t_{1/2}$[a] (day)
75 mg	6	5.33 ± 1.50	59.2 ± 20.8	7.01 [3.00, 7.03]	2.77 ± 0.57[b]
150 mg	6	10.4 ± 3.0	150 ± 41	7.01 [3.00, 7.03]	3.18 ± 0.81
300 mg	6	38.3 ± 15.3	700 ± 234	7.01 [6.99, 10.0]	5.13 ± 1.42
600 mg	6	70.1 ± 24.1	1780 ± 700	7.00 [3.00, 7.02]	8.77 ± 5.18

Mean ± SD. t_{max} is expressed in median [range].
a) $t_{1/2}$ in the terminal phase; b) n = 4

6.2.1.2 Foreign phase I study (CTD 5.3.3.1-1, Study R668-AS-0907 [November 2009 to July 2010])

In a placebo-controlled, randomized, stepwise dose escalation study in healthy adult subjects (dupilumab administered to 36 of 48 subjects), a single dose of dupilumab was administered intravenously at 1, 3, 8, or 12 mg/kg or subcutaneously at 150 or 300 mg. Table 13 shows the pharmacokinetic parameter values observed. ADA was positive in 3 or 6 subjects in the 1 mg/kg i.v. group, 2 of 6 subjects in the 3 mg/kg i.v. group, 3 of 6 subjects in the 150 mg s.c. group, and 1 of 6 subjects in the 300 mg s.c. group.

Table 13. Pharmacokinetic parameters following a single-dose administration of dupilumab to non-Japanese healthy subjects

Route of administration	Dose	n	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	t_{max} (day)
i.v.	1 mg/kg	6	34.8 ± 6.6	140 ± 15	0.105 [0.084, 0.167]
	3 mg/kg	6	92.0 ± 12.7	718 ± 82	0.105 [0.083, 0.250]
	8 mg/kg	6	266 ± 47	2810 ± 350	0.167 [0.083, 1.08]
	12 mg/kg	6	421 ± 66	5330 ± 1160	0.105 [0.083, 0.417]
s.c.	150 mg	6	13.5 ± 6.9	168 ± 95	7.04 [3.03, 7.20]
	300 mg	6	32.4 ± 10.1	594 ± 190	3.01 [2.99, 14.0]

Mean ± SD. t_{max} is expressed in median [range]

6.2.2 Studies in patients with atopic dermatitis

6.2.2.1 Global phase II study (CTD 5.3.5.1-3, Study R668-AD-1021 [May 2013 to September 2014])

In a placebo-controlled, randomized, double-blind, parallel-group study in patients with atopic dermatitis [see Section 7.1], dupilumab was administered subcutaneously at 100 mg (400 mg in the initial dose) once every 4 weeks, at 200 mg (400 mg in the initial dose) once every 2 weeks, and at 300 mg (600 mg in the initial dose) once every 4, 2, or 1 week. Table 14 shows changes over time in trough serum dupilumab concentration. ADA was positive in 23 of 65 patients in the 100 mg once every 4 weeks (Q4W) group, 17 of 61 patients in the 200 mg once every 2 weeks (Q2W) group, 12 of 65 patients in the 300 mg Q4W group, 12 of 64 patients in the 300 mg Q2W group, 9 of 63 patients in the 300 mg once every week (QW) group, and 1 of 61 patients in the placebo group.

Table 14. Changes over time in trough serum dupilumab concentration in repeated subcutaneous administration of dupilumab to patients with atopic dermatitis (μg/mL)

Dosage regimen	Population	Week 1	Week 2	Week 4	Week 16
100 mg Q4W	Entire population	41.7 ± 17.3 (63)	30.8 ± 13.9 (64)	11.3 ± 9.6 (59)	0.398 ± 1.20 (60)
	Japanese subpopulation	45.1 ± 13.2 (10)	35.8 ± 13.1 (10)	17.3 ± 9.6 (9)	0.833 ± 1.36 (9)
200 mg Q2W	Entire population	41.6 ± 15.1 (59)	31.1 ± 12.9 (59)	33.0 ± 18.7 (55)	35.9 ± 24.6 (52)
	Japanese subpopulation	49.0 ± 14.2 (9)	36.9 ± 13.1 (9)	39.2 ± 14.8 (8)	39.1 ± 19.2 (8)
300 mg Q4W	Entire population	74.9 ± 26.1 (64)	55.6 ± 21.5 (62)	24.8 ± 16.1 (64)	13.8 ± 12.1 (63)
	Japanese subpopulation	84.6 ± 28.2 (11)	64.1 ± 28.2 (9)	24.4 ± 18.1 (11)	15.7 ± 11.5 (10)
300 mg Q2W	Entire population	72.5 ± 26.3 (62)	54.3 ± 20.7 (62)	52.4 ± 19.8 (62)	61.5 ± 36.7 (61)
	Japanese subpopulation	68.3 ± 25.2 (9)	54.9 ± 21.0 (9)	59.4 ± 23.0 (9)	55.2 ± 44.6 (9)
300 mg QW	Entire population	67.0 ± 23.1 (61)	90.5 ± 32.1 (61)	113 ± 43 (59)	168 ± 81 (62)
	Japanese subpopulation	74.9 ± 18.5 (8)	86.6 ± 29.6 (8)	125 ± 45 (8)	165 ± 119 (9)

Mean ± SD (number of patients)

6.2.2.2 Global phase III studies (CTD 5.3.5.1-4, Study R668-AD-1334 [October 2014 to February 2016]; CTD 5.3.5.1-6 and 5.3.5.1-6a, Study R668-AD-1224 [September 2014 to October 2016]; CTD 5.3.5.2-1, Study R668-AD-1225 [ongoing since October 2013 (data cut-off [redacted] 20[redacted])])

In a placebo-controlled, randomized, double-blind, parallel-group study in patients with atopic dermatitis [see Sections 7.2.1 and 7.2.2], dupilumab was administered subcutaneously at 300 mg (600 mg in the initial dose) once every 2 or 1 week. Table 15 shows the changes over time in trough serum dupilumab concentration. ADA was positive in 32 of 222 patients in the Q2W group, 15 of 206 patients in the QW group, and 8 in 209 patients in the placebo group (neutralizing antibody-positive patients; 5 in the Q2W group, 2 in the QW group) in Study R668-AD-1334, and in 13 of 105 patients in the Q2W group, 37 of 308 patients in the QW group, and 42 of 306 patients in the placebo group (neutralizing antibody-positive patients; 1 in the Q2W group, 1 in the QW group, 3 in the placebo group) in Study R668-AD-1224. In the extension/re-administration study (Study R668-AD-1225), ADA was positive in 115 of 830 patients receiving dupilumab (neutralizing antibody-positive patients, 29).

Table 15. Changes over time in trough serum dupilumab concentration in repeated subcutaneous administration of dupilumab to patients with atopic dermatitis (μg/mL)

Study	Dosage regimen	Population	Week 2	Week 4	Week 16	Week 52
R668-AD-1334 (monotherapy study)	300 mg Q2W	Entire population	55.6 ± 20.2 (220)	60.5 ± 27.9 (220)	73.3 ± 40.0 (219)	
		Japanese subpopulation	59.4 ± 21.0 (36)	59.7 ± 27.6 (36)	71.8 ± 40.0 (36)	
	300 mg QW	Entire population	89.0 ± 30.7 (210)	117 ± 52 (209)	173 ± 76 (200)	
		Japanese subpopulation	92.8 ± 30.1 (35)	122 ± 54 (35)	167 ± 71 (35)	
R668-AD-1224 (TCS combination therapy study)	300 mg Q2W	Entire population	54.8 ± 18.0 (106)	58.7 ± 25.3 (103)	79.9 ± 39.2 (101)	81.5 ± 43.9 (100)
		Japanese subpopulation	63.7 ± 11.8 (16)	69.6 ± 17.8 (16)	103 ± 29 (16)	94.6 ± 44.1 (16)
	300 mg QW	Entire population	88.9 ± 26.6 (307)	114 ± 41 (305)	185 ± 72 (295)	187 ± 89 (286)
		Japanese subpopulation	97.0 ± 26.1 (47)	121 ± 36 (47)	192 ± 68 (47)	185 ± 80 (47)

Mean ± SD (number of patients)

6.2.3 Exposure-response analysis (CTD 5.3.3.5-1)

The exposure-response relationship was investigated using the data of the efficacy endpoints (rate of change in Eczema area and severity index [EASI] score from baseline and rate of achieving Investigator's global assessment [IGA] ≤1 [see Section "10. Other" for definitions], etc.), the data of

safety endpoints (incidences of conjunctivitis, herpes simplex, and oral herpes which are commonly reported adverse events), and data on trough serum dupilumab concentrations obtained from Japanese and foreign clinical studies in patients with atopic dermatitis (Studies R668-AD-1334, R668-AD-1416,[2)] and R668-AD-1224). The rate of change in EASI score from baseline and rate of achieving IGA ≤1, classified by exposure quartile, showed a tendency of a higher efficacy in the fourth quartile group compared with the first quartile group, as shown in Table 16. Table 17 shows the incidence of conjunctivitis, herpes simplex, and oral herpes classified by exposure quartile. There was no correlation between the exposure to dupilumab and the incidence of any of these events.

Table 16. The rate of change in EASI score at Week 16 and rate of achieving IGA ≤1, classified by exposure quartile (drug concentration-response analysis population, observed cases [OC])

	Studies R668-AD-1334 and R668-AD-1416			Study R668-AD-1224		
	Range of trough serum dupilumab concentration (μg/mL)	Rate of EASI change	Rate of achieving IGA ≤1	Range of trough serum dupilumab concentration (μg/mL)	Rate of EASI change	Rate of achieving IGA ≤1
Q1	≤66.3	−69.5 ± 2.1 (177)	37.1 (66/178)	≤95.9	−78.7 ± 2.4 (89)	40.4 (36/89)
Q2	>66.3 and ≤110	−73.1 ± 2.2 (179)	45.5 (81/178)	>95.9 and ≤150	−85.5 ± 1.5 (89)	41.6 (37/89)
Q3	>110 and ≤180	−78.2 ± 1.8 (175)	51.1 (91/178)	>150 and ≤216	−82.5 ± 2.1 (89)	47.2 (42/89)
Q4	>180	−80.6 ± 1.7 (177)	56.6 (99/175)	>216	−87.6 ± 1.7 (89)	57.3 (51/89)
	Range of AUC (μg·day/mL)	Rate of EASI change	Rate of achieving IGA ≤1	Range of AUC (μg·day/mL)	Rate of EASI change	Rate of achieving IGA ≤1
Q1	≤4445	−69.6 ± 2.1 (183)	38.3 (70/183)	≤5865	−81.3 ± 2.1 (89)	39.3 (35/89)
Q2	>4445 and ≤6740	−72.2 ± 2.2 (178)	41.9 (75/179)	>5865 and ≤8565	−80.4 ± 2.1 (90)	40.0 (36/90)
Q3	>6740 and ≤10,238	−77.8 ± 1.9 (179)	51.7 (93/180)	>8565 and ≤11,944	−85.2 ± 1.8 (90)	50.0 (45/90)
Q4	>10,238	−80.5 ± 1.7 (181)	56.9 (103/181)	>11,944	−87.4 ± 1.7 (88)	56.8 (50/88)

Rate of EASI change (%), mean ± SD (number of patients); rate of achieving IGA ≤1, % (number of patients)

Table 17. Incidences of adverse events during dupilumab treatment, classified by exposure quartile (drug concentration-response analysis population)

	Studies R668-AD-1334 and R668-AD-1416[a)]					Study R668-AD-1224[b)]				
	Q1 (n = 219)	Q2 (n = 219)	Q3 (n = 218)	Q4 (n = 218)	Placebo (n = 456)	Q1 (n = 102)	Q2 (n = 101)	Q3 (n = 101)	Q4 (n = 101)	Placebo (n = 315)
Oral herpes	8 (3.7)	7 (3.2)	7 (3.2)	8 (3.7)	8 (1.8)	3 (2.9)	4 (4.0)	3 (3.0)	9 (8.9)	9 (2.9)
Herpes simplex	2 (0.9)	4 (1.8)	1 (0.5)	3 (1.4)	4 (0.9)	2 (2.0)	2 (2.0)	2 (2.0)	2 (2.0)	2 (0.6)
Conjunctivitis-related events	24 (11.0)	20 (9.1)	17 (7.8)	15 (6.9)	10 (2.2)	24 (23.5)	11 (10.9)	23 (22.8)	18 (17.8)	25 (7.9)

Number of patients (%)

a) Q1, ≤4399; Q2, >4399 and ≤6764; Q3, >6764 and ≤10285; Q4, >10,285 (μg·day/mL)

b) Q1, ≤5954; Q2, >5954 and ≤8785; Q3, >8785 and ≤11,910; Q4, >11,910 (μg·day/mL)

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences of pharmacokinetics of dupilumab

The applicant explained that there is no clear difference in the pharmacokinetics of dupilumab between Japanese and non-Japanese subjects, based on the following findings:

- In the Japanese phase I study (Study TDU12265) and the foreign phase I study (Study R668-AS-0907), both in healthy adult subjects, pharmacokinetic parameters of dupilumab following a single subcutaneous administration did not show any clear difference between Japanese and non-Japanese subjects, as shown in Tables 12 and 13.
- In the global phase II study (Study R668-AD-1021) in patients with atopic dermatitis, changes over time in trough serum dupilumab concentration in repeated subcutaneous administration of dupilumab did not show any clear difference between the Japanese subpopulation and the entire population, as

2) A foreign placebo-controlled, randomized, double-blind, parallel-group study investigating the efficacy and safety of subcutaneous administration of dupilumab alone in patients with atopic dermatitis

shown in Table 14. Also, in the global phase III studies (Studies R668-AD-1334 and R668-AD-1224), no major difference was observed in the trough serum dupilumab concentration between the Japanese subpopulation and the entire population, as shown in Table 15 [see Section 6.2.2].

PMDA accepted the above explanation of the applicant.

6.R.2 Anti-dupilumab antibody

The applicant explained the incidence of ADA and the effect of ADA on the pharmacokinetics, efficacy, and safety of dupilumab as shown below. In the following description, antibody titer of <1000 was defined as low antibody titer, ≥1000 and ≤10,000 as intermediate titer, and >10,000 as high titer.

In the foreign phase I study (Study R668-AS-0907), ADA tended to be detected more frequently in patients receiving a low dose compared with patients receiving a high dose [see Section 6.2.1.2]. Antibody titer was low in 8 of 9 ADA-positive patients. ADA of intermediate titer was observed after 8 weeks of treatment in one subject in the 150 mg s.c. group, but the titer decreased to a low level after 12 weeks of treatment. In the Japanese phase I study (Study TDU12265), all ADA-positive patients showed low antibody titer.

In the global phase III studies (Studies R668-AD-1334, R668-AD-1224, and R668-AD-1225), the percentage of ADA-positive patients was as shown in Table 18.[3)]

Table 18. Percentage and number of ADA-positive patients in global phase III studies (safety analysis population)

		Study R668-AD-1334			Study R668-AD-1224			Study R668-AD-1225
Entire population		Q2W (n = 222)	QW (n = 206)	Placebo (n = 209)	Q2W (n = 105)	QW (n = 308)	Placebo (n = 306)	Dupilumab (n = 830)
ADA-negative		85.6 (190)	92.7 (191)	96.2 (201)	87.6 (92)	88.0 (271)	86.3 (264)	86.1 (715)
ADA-positive	Low antibody titer	14.0 (31)	5.3 (11)	3.8 (8)	11.4 (12)	11.4 (35)	13.7 (42)	12.4 (103)
	Intermediate antibody titer	0.5 (1)	1.0 (2)	0	1.0 (1)	0.6 (2)	0	1.3 (11)
	High antibody titer	0	1.0 (2)	0	0	0	0	0.1 (1)
Japanese subpopulation		Q2W (n = 36)	QW (n = 35)	Placebo (n = 35)	Q2W (n = 16)	QW (n = 47)	Placebo (n = 54)	Dupilumab (n = 59)
ADA-negative		80.6 (29)	88.6 (31)	97.1 (34)	87.5 (14)	93.6 (44)	88.9 (48)	78.0 (46)
ADA-positive	Low antibody titer	19.4 (7)	8.6 (3)	2.9 (1)	12.5 (2)	6.4 (3)	11.1 (6)	20.3 (12)
	Intermediate antibody titer	0	0	0	0	0	0	1.7 (1)
	High antibody titer	0	2.9 (1)	0	0	0	0	0

% (number of patients)

As for the pharmacokinetics and efficacy, the changes in trough serum dupilumab concentration and EASI score from baseline in global phase III studies (Studies R668-AD-1334 and R668-AD-1224) both tended to be lower in ADA-positive patients with intermediate or high antibody titer and neutralizing antibody-positive patients compared with ADA-negative patients (Tables 19 and 20). In 2 ADA-positive patients with a high antibody titer in Study R668-AD-1334, ADA of high antibody titer was observed

3) In ADA analysis, the cut point was specified to control the false positive rate at 5% in the screening test and at 1% in the confirmatory test. As a result, ADA was detected in a certain percentage of patients in the placebo group. In samples obtained from phase III studies, the cut point was calculated after excluding analytical or biological outliers from the baseline data set of samples. As a result, the percentage of false positive was 4.9% in the screening test and 3.2% in the confirmatory test.

after 16 weeks of treatment, associated with a marked decrease in the efficacy and exposure to dupilumab after 4 weeks of treatment (see Tables 19 and 20).

Table 19. Changes over time in trough serum dupilumab, classified by ADA (μg/mL)

			Study R668-AD-1334		Study R668-AD-1224		
			Week 4	Week 16	Week 4	Week 16	Week 52
Q2W	ADA-negative		64.3 ± 26.0 (187) [12.6, 187]	79.0 ± 37.7 (187) [0, 204]	62.4 ± 23.5 (89) [13.5, 179]	84.5 ± 38.9 (89) [0, 244]	86.0 ± 43.4 (89) [0, 195]
	ADA-positive	Low antibody titer	37.8 ± 27.3 (30) [0, 110]	41.7 ± 37.8 (31) [0, 154]	39.8 ± 25.3 (11) [4.56, 88.7]	47.4 ± 21.0 (11) [7.03, 72.6]	47.3 ± 30.6 (10) [0.347, 89.7]
		Intermediate antibody titer	14.1 (1)	0.128 (1)	5.46 (1)	32.0 (1)	24.9 (1)
		High antibody titer	NA	NA	NA	NA	NA
	Neutralizing antibody-positive		9.07 ± 7.87 (3) [0, 14.1]	28.0 ± 52.7 (4) [0, 107]	5.46 (1)	32.0 (1)	24.9 (1)
QW	ADA-negative		121 ± 49.7 (187) [22.6, 412]	179 ± 72.7 (185) [0, 425]	118 ± 37.4 (267) [16.4, 245]	189 ± 69.2 (261) [0, 405]	193 ± 86.3 (250) [0, 438]
	ADA-positive	ADA-positive	112 ± 57.9 (11) [15.6, 204]	136 ± 67.0 (11) [35.5, 236]	92.7 ± 54.3 (34) [5.36, 210]	154 ± 83.8 (32) [36.5, 386]	142 ± 98.8 (34) [0, 361]
		Intermediate antibody titer	2.41 (2) [0, 4.81]	17.8 (2) [9.25, 26.4]	14.5 (2) [8.41, 20.6]	80.1 (2) [68.9, 91.3]	165 (2) [144, 186]
		High antibody titer	0.04 (2) [0, 0.08]	0 (2) [0, 0]	NA	NA	NA
	Neutralizing antibody-positive		0.04 (2) [0, 0.08]	0 (1)	8.41 (1)	91.3 (1)	144 (1)

Upper row, mean ± SD (number of patients); lower row, [minimum, maximum]

Table 20. Rate of change in EASI score from baseline over time, classified by ADA (%) (OC)

			Study R668-AD-1334		Study R668-AD-1224		
			Week 4	Week 16	Week 4	Week 16	Week 52
Q2W	ADA-negative		−55.2 ± 30.5 (178) [−100, 34.5]	−81.1 ± 21.2 (153) [−100, 8.33]	−63.4 ± 25.9 (90) [−99.7, 0]	−83.3 ± 18.5 (81) [−100, −19.4]	−88.7 ± 12.2 (73) [−100, −57.2]
	ADA-positive	Low antibody titer	−47.3 ± 29.7 (25) [−95.7, 24.4]	−66.9 ± 31.6 (22) [−98.5, 14.0]	−68.4 ± 15.7 (11) [−85.9, −32.4]	−80.7 ± 18.2 (11) [−94.5, −38.3]	−84.7 ± 14.3 (10) [−99.1, −56.0]
		Intermediate antibody titer	−14.3 (1)	0 (1)	−39.7 (1)	−77.0 (1)	−87.1 (1)
		High antibody titer	NA	NA	NA	NA	NA
	Neutralizing antibody-positive		−37.0 ± 20.1 (3) [−53.0, −14.0]	−45.1 ± 54.1 (4) [−97.0, 3.14]	−40.0 (1)	−77.0 (1)	−87.0 (1)
QW	ADA-negative		−57.1 ± 31.2 (167) [−100, 65.9]	−78.6 ± 27.0 (148) [−100, 52.5]	−63.7 ± 24.7 (254) [−100, 10.9]	−84.6 ± 17.0 (234) [−100, 9.62]	−89.8 ± 13.7 (201) [−100, 0]
	ADA-positive	Low antibody titer	−46.7 ± 26.3 (9) [−9.57, 26.3]	−63.2 ± 28.6 (8) [−90.5, −22.8]	−65.5 ± 23.8 (32) [−95.1, 0.46]	−80.0 ± 25.0 (28) [−100, −4.69]	−86.0 ± 24.6 (28) [−100, 0]
		Intermediate antibody titer	−41.6 (2) [−46.7, −36.6]	NA	14.5 (2) [0, 29.1]	−21.3 (2) [−33.3, −9.36]	−25.8 (2) [−33.3, −18.2]
		High antibody titer	6.01 (2) [−13.0, 25.0]	17.2 (1)	NA	NA	NA
	Neutralizing antibody-positive		6.01 (2) [−13.0, 25.0]	17.2 (1)	29.1 (1)	−9.36 (1)	−18.0 (1)

Upper row, mean ± SD (number of patients); lower row, [minimum, maximum]
Data after a rescue treatment were handled as missing data.

As for safety, incidences of adverse events, classified by presence or absence of ADA, in the global phase III studies (Studies R668-AD-1334, R668-AD-1224, and R668-AD-1225) are shown in Table 21. In Study R668-AD-1334, the incidence of adverse events in the dupilumab group tended to be higher in ADA-positive patients than in ADA-negative patients. The main event observed more commonly in ADA-positive patients than in ADA-negative patients was injection site reaction (26.7% [4 of 15] of ADA-positive patients in the Q2W group, 6.8% [14 of 207] of ADA-negative patients in the Q2W group, 50.0% [3 of 6] of ADA-positive patients in the QW group, 18.5% [37 of 200] of ADA-negative patients in the QW group). On the other hand, no consistent results were obtained in Studies R668-AD-1224 and

R668-AD-1225, precluding any clear conclusion regarding the effect of ADA on safety. However, of the 3 ADA-positive patients with high antibody titer observed in global phase III studies (Table 18), 1 patient in Study R668-AD-1225 experienced serious serum sickness, and an ADA-positive patient with high antibody titer in a foreign phase III study (Study R668-AD-1314[4)]) also showed serious serum sickness-like reaction, suggesting a possible effect of high titer ADA on the safety of dupilumab.

Table 21. Incidences of adverse events, classified by ADA, in global phase III studies

	Q2W		QW		Placebo	
	ADA-positive	ADA-negative	ADA-positive	ADA-negative	ADA-positive	ADA-negative
Study R668-AD-1334	86.7 (13/15)	74.9 (155/207)	100 (6/6)	69.5 (139/200)	100 (2/2)	67.1 (139/207)
Study R668-AD-1224	90.0 (9/10)	92.6 (88/95)	94.7 (18/19)	89.3 (258/289)	95.8 (23/24)	87.9 (248/282)
Study R668-AD-1225			83.3 (20/24)	79.9 (579/725)		

% (number of patients)

The above results suggest that a high titer ADA affects the pharmacokinetics, efficacy, and safety of dupilumab. The relevant information will be provided in the package insert.

PMDA's view:

Regardless of antibody titer class, ADA-positive patients tend to show decreased efficacy, decreased exposure to dupilumab, and increased incidence of adverse events. In addition, the possibility cannot be excluded that the antibody titer changes from low or intermediate titer to high titer with continued treatment. Therefore, the effect of ADA should be continuously monitored. Also, since serious serum sickness and serious serum sickness-like reaction were observed in high titer ADA-positive patients, physicians should be advised to take appropriate safety measures against serious systemic reactions such as shock and anaphylaxis.

[4)] A foreign placebo-controlled, randomized, double-blind, parallel-group study investigating serological response to vaccine following subcutaneous administration of dupilumab in patients with atopic dermatitis

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 4 clinical studies listed in Table 22.

Table 22. Main clinical studies related to efficacy and safety

Data category	Region	Study	Phase	Subjects	Number of enrollments	Dosage regimen	Main endpoints
Evaluation	Global	R668-AD-1021	II	Patients with atopic dermatitis for whom TCS was not recommended for a reason of insufficient response to TCS of medium potency (corresponding to TCS of strong class in Japanese classification) or higher potency, or for a safety reason	(a) 65 (b) 62 (c) 65 (d) 64 (e) 63 (f) 61	(a) Dupilumab 100 mg (400 mg in the initial dose), Q4W (b) Dupilumab 200 mg (400 mg in the initial dose), Q2W (c) Dupilumab 300 mg (600 mg in the initial dose), Q4W (d) Dupilumab 300 mg (600 mg in the initial dose), Q2W (e) Dupilumab 300 mg (600 mg in the initial dose), QW (f) Placebo, QW	Efficacy Safety
		R668-AD-1334	III	Patients with atopic dermatitis for whom TCS was not recommended for a reason of insufficient response to medium or higher potency TCS or for a safety reason	(a) 224 (b) 223 (c) 224	(a) Dupilumab 300 mg (600 mg in the initial dose), Q2W (b) Dupilumab 300 mg (600 mg in the initial dose), QW (c) Placebo, QW	Efficacy Safety
		R668-AD-1224	III	Patients with atopic dermatitis with an inadequate response to medium or higher potency TCS	(a) 106 (b) 319 (c) 315	(a) Dupilumab 300 mg (600 mg in the initial dose), Q2W (b) Dupilumab 300 mg (600 mg in the initial dose), QW (c) Placebo, QW	Efficacy Safety
		R668-AD-1225	III	Patients with atopic dermatitis who completed the preceding study or were screened for the phase III dupilumab monotherapy study but not randomized due to the termination of the registration period	1492	• If the period from the last dose in the preceding study to the start of administration in this study was ≥4 weeks: Dupilumab 300 mg (600 mg in the initial dose), QW • If the period from the last dose in the preceding study to the start of administration in this study was <4 weeks: Dupilumab 300 mg, QW	Safety

7.1 Global phase II study (CTD 5.3.5.1-3, Study R668-AD-1021 [May 2013 to September 2014])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in patients[5)] aged ≥18 years with atopic dermatitis for whom TCS was not recommended for a reason of insufficient response to TCS of medium potency (corresponding to TCS of strong class in Japanese classification) or higher potency, or for a safety reason (target sample size, 240 subjects [40 per group]) in order to investigate the efficacy and safety of dupilumab in 7 countries including Japan and US.

5) Patients who met all of the following: (a) EASI score ≥12 and IGA score ≥3, (b) a record within 6 months indicating that TCS is not recommended for a reason of insufficient response or for a reason of safety, and diagnosis of atopic dermatitis ≥3 years before. "Insufficient response" was defined as failure to maintain remission or low disease activity (IGA score 0-2) by daily administration of TCS of medium or higher potency (with addition of TCI as necessary) for at least 28 days or for the maximum period recommended by the package insert, whichever is shorter. A "safety reason" was defined as a risk (e.g., hypersensitivity reaction, marked skin atrophy, systemic effect) outweighing the benefit of the treatment.

The study consisted of a treatment period (16 weeks) and a follow-up period (16 weeks). The patients were to receive, for a total of 16 weeks, dupilumab subcutaneously at 100 mg (400 mg in the initial dose) once every 4 weeks, at 200 mg (400 mg in the initial dose) once every 2 weeks, at 300 mg (600 mg in the initial dose) once every 4, 2, or 1 week, or to receive placebo subcutaneously according to the above dosing schedule. For at least 7 days before and after baseline, a topical skin moisturizer was to be applied at a constant dose and, in the event of an intolerable symptom, a rescue treatment[6)] was allowed.

Of 380 patients randomized[7)] using the severity at baseline (IGA score 3 or 4) and region (Japan or elsewhere) as stratification factors, 379 patients (65 in the 100 mg Q4W group, 61 in the 200 mg Q2W group, 65 in the 300 mg Q4W group, 64 in the 300 mg Q2W group, 63 in the 300 mg QW group, 61 in the placebo group) excluding 1 patient not receiving the study drug were included in the full analysis set (FAS) and the safety analysis population, and the FAS was subjected to efficacy analysis. Study discontinuation occurred in 35.4% (23 of 65) of patients in the 100 mg Q4W group, 45.9% (28 of 61) of patients in the 200 mg Q2W group, 15.4% (10 of 65) of patients in the 300 mg Q4W group, 18.8% (12 of 64) of patients in the 300 mg Q2W group, 17.5% (11 of 63) of patients in the 300 mg QW group, and 31.1% (19 of 61) of patients in the placebo group. The main reasons for the discontinuation included insufficient response (7 patients in the 100 mg Q4W group, 5 patients in the 200 mg Q2W group, 1 patient in the 300 mg Q2W group, 1 patient in the 300 mg QW group, 9 patients in the placebo group) and consent withdrawal (2 patients in the 100 mg Q4W group, 4 patients in the 200 mg Q2W group, 3 patients in the 300 mg Q4W group, 3 patients in the 300 mg Q2W group, 6 patients in the 300 mg QW group, 2 patients in the placebo group).

The Japanese subpopulation in FAS consisted of 58 patients (11 in the 100 mg Q4W group, 9 in the 200 mg Q2W group, 11 in the 300 mg Q4W group, 10 in the 300 mg Q2W group, 9 in the 300 mg QW group, 8 in the placebo group). Study discontinuation occurred in 18.2% (2 of 11) of patients in the 100 mg Q4W group, 77.8% (7 of 9) of patients in the 200 mg Q2W group, 18.2% (2 of 11) of patients in the 300 mg Q4W group, 10% (1 of 10) of patients in the 300 mg Q2W group, 22.2% (2 of 9) of patients in the 300 mg QW group, and 37.5% (3 of 8) of patients in the placebo group. Main reasons for the discontinuation included adverse events (1 patient in the 100 mg Q4W group, 1 patient in the 300 mg Q4W group, 2 patients in the 300 mg QW group, 1 patient in the placebo group) and lost to follow-up (1 patient in the 100 mg Q4W group, 2 patients in the 200 mg Q2W group, 1 patient in the 300 mg Q2W group)

Table 23 shows the rate of change in EASI score at 16 weeks of administration from baseline, the primary efficacy endpoint [see Section “10. Other” for the definition]. A statistically significant difference was observed in the paired comparison between the placebo group and each dupilumab group. Table 24 shows the results in the Japanese subpopulation.

6) If a prohibited drug or therapy was administered as a rescue treatment, administration of the study drug was to be discontinued.
7) Patients with baseline EASI score of ≥16 were randomized.

Table 23. Rate of change in EASI score after 16 weeks of treatment from baseline (FAS, last observation carried forward [LOCF])

	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 64)	300 mg QW (n = 63)	Placebo (n = 61)
Baseline	32.2 ± 13.5	32.9 ± 15.5	29.4 ± 11.5	33.8 ± 14.5	30.1 ± 11.2	32.9 ± 13.8
Week 16 [a)]	17.4 ± 15.3	10.9 ± 12.4	9.8 ± 11.2	10.7 ± 12.9	7.2 ± 8.8	25.6 ± 18.3
Change from baseline (%)	−46.7 ± 42.0	−67.4 ± 32.0	−64.9 ± 37.2	−70.5 ± 35.1	−75.5 ± 26.9	−20.2 ± 46.2
Difference from placebo [95% CI][b)] *P* value[b) c)]	−26.8 [−39.8, −13.7] <0.0001	−47.4 [−60.6, -34.1] <0.0001	−45.4 [−58.5, −32.3] <0.0001	−50.1 [−63.3, -37.0] <0.0001	−55.7 [−68.9, −42.4] <0.0001	

Mean ±SD. Difference from the placebo group is expressed in the least squares mean.

a) Data after a rescue treatment were handled as missing values.

b) Analysis of covariance (ANCOVA) model with treatment group, baseline severity, region, and baseline value as explanatory variables

c) Adjusted for multiplicity of testing by closed testing procedure in the order of between the 300 mg QW group and the placebo group, the 300 mg Q2W group and the placebo group, the 200 mg Q2W group and the placebo group, the 300 mg Q4W group and the placebo group, and the 100 mg Q4W group and the placebo group

Table 24. Rate of change in EASI score after 16 weeks of treatment from baseline (Japanese subpopulation, LOCF)

	100 mg Q4W (n = 11)	200 mg Q2W (n = 9)	300 mg Q4W (n = 11)	300 mg Q2W (n = 10)	300 mg QW (n = 9)	Placebo (n = 8)
Baseline	36.4 ± 14.2	49.4 ± 15.4	33.5 ± 12.7	37.6 ± 12.6	32.9 ± 12.1	38.6 ± 18.2
Week 16 [a)]	12.6 ± 15.0	14.8 ± 14.6	16.6 ± 16.5	11.6 ± 12.2	13.6 ± 17.3	38.6 ± 25.4
Change from baseline (%)	−65.8 ± 35.3	−72.8 ± 23.1	−51.1 ± 46.0	−69.4 ± 29.3	−54.3 ± 49.4	−4.9 ± 47.1
Difference from placebo [95% CI][b)]	−60.3 [−97.7, −22.9]	−70.1 [−111, −29.2]	−45.1 [−82.8, −7.3]	−64.3 [−104, −25.0]	−47.7 [−88.3, −7.0]	

Mean ±SD. Difference from the placebo group is expressed in the least squares mean.

a) Data after a rescue treatment were handled as missing values.

b) ANCOVA model with treatment group, baseline severity, region, and baseline value as explanatory variables

Adverse events throughout the entire period was observed in 81.5% (53 of 65) of patients in the 100 mg Q4W group, 75.4% (46 of 61) of patients in the 200 mg Q2W group, 86.2% (56 of 65) of patients in the 300 mg Q4W group, 78.1% (50 of 64) of patients in the 300 mg Q2W group, 84.1% (53 of 63) of patients in the 300 mg QW group, and 80.3% (49 of 61) of patients in the placebo group. Table 25 shows main events. No death occurred. Serious adverse events were observed in 7.7% (5 of 65) of patients in the 100 mg Q4W group, 1.6% (1 of 61) of patients in the 200 mg Q2W group, 4.6% (3 of 65) of patients in the 300 mg Q4W group, 3.1% (2 of 64) of patients in the 300 mg Q2W group, 1.6% (1 of 63) of patients in the 300 mg QW group, and 6.6% (4 of 61) of patients in the placebo group. The main event was atopic dermatitis (4 patients in the 100 mg Q4W group, 1 patient in the 300 mg Q2W group, 1 patient in the placebo group). Adverse events leading to discontinuation were observed in 15.4% (10 of 65) of patients in the 100 mg Q4W group, 4.9% (3 of 61) of patients in the 200 mg Q2W group, 4.6% (3 of 65) of patients in the 300 mg Q4W group, 6.3% (4 of 64) of patients in the 300 mg Q2W group, 1.6% (1 of 63) of patients in the 300 mg QW group, and 4.9% (3 of 61) of patients in the placebo group.

Adverse drug reactions were observed in 33.8% (22 of 65) of patients in the 100 mg Q4W group, 26.2% (16 of 61) of patients in the 200 mg Q2W group, 24.6% (16 of 65) of patients in the 300 mg Q4W group, 29.7% (19 of 64) of patients in the 300 mg Q2W group, 38.1% (24 of 63) of patients in the 300 mg QW group, and 24.6% (15 of 61) of patients in the placebo group.

Table 25. Adverse events reported by ≥3 patients in any group throughout the entire period (safety analysis population)

	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 64)	300 mg QW (n = 63)	Placebo (n = 61)
Nasopharyngitis	20 (30.8)	16 (26.2)	21 (32.3)	16 (25.0)	16 (25.4)	16 (26.2)
Dermatitis atopic	14 (21.5)	8 (13.1)	10 (15.4)	14 (21.9)	8 (12.7)	11 (18.0)
Headache	7 (10.8)	9 (14.8)	5 (7.7)	5 (7.8)	8 (12.7)	2 (3.3)
Herpes simplex	5 (7.7)	3 (4.9)	1 (1.5)	2 (3.1)	1 (1.6)	0
Upper respiratory tract infection	5 (7.7)	2 (3.3)	5 (7.7)	6 (9.4)	5 (7.9)	11 (18.0)
Oral herpes	5 (7.7)	2 (3.3)	3 (4.6)	3 (4.7)	0	0
Urticaria	4 (6.2)	1 (1.6)	0	0	1 (1.6)	0
Abdominal pain upper	4 (6.2)	0	0	2 (3.1)	1 (1.6)	1 (1.6)
Pruritus	3 (4.6)	2 (3.3)	2 (3.1)	1 (1.6)	3 (4.8)	3 (4.9)
Skin infection	3 (4.6)	2 (3.3)	1 (1.5)	2 (3.1)	0	0
Back pain	3 (4.6)	0	2 (3.1)	2 (3.1)	2 (3.2)	5 (8.2)
Gastroenteritis	3 (4.6)	0	2 (3.1)	1 (1.6)	1 (1.6)	2 (3.3)
Bronchitis	3 (4.6)	0	1 (1.5)	2 (3.1)	1 (1.6)	2 (3.3)
Cystitis	3 (4.6)	0	1 (1.5)	0	1 (1.6)	2 (3.3)
Urinary tract infection	2 (3.1)	6 (9.8)	3 (4.6)	3 (4.7)	0	2 (3.3)
Diarrhoea	2 (3.1)	3 (4.9)	2 (3.1)	3 (4.7)	1 (1.6)	2 (3.3)
Oropharyngeal pain	2 (3.1)	2 (3.3)	0	2 (3.1)	3 (4.8)	1 (1.6)
Folliculitis	2 (3.1)	0	1 (1.5)	1 (1.6)	3 (4.8)	3 (4.9)
Conjunctivitis allergic	1 (1.5)	6 (9.8)	3 (4.6)	2 (3.1)	3 (4.8)	2 (3.3)
Arthralgia	1 (1.5)	4 (6.6)	1 (1.5)	4 (6.3)	1 (1.6)	0
Blood lactate dehydrogenase increased	1 (1.5)	3 (4.9)	1 (1.5)	0	0	0
Blood creatine phosphokinase increased	1 (1.5)	2 (3.3)	3 (4.6)	1 (1.6)	2 (3.2)	2 (3.3)
Dizziness	1 (1.5)	0	0	0	2 (3.2)	3 (4.9)
Vomiting	0	4 (6.6)	0	0	1 (1.6)	3 (4.9)
Cough	0	2 (3.3)	1 (1.5)	4 (6.3)	4 (6.3)	1 (1.6)
Fatigue	0	1 (1.6)	4 (6.2)	1 (1.6)	2 (3.2)	3 (4.9)
Eosinophilia	0	1 (1.6)	2 (3.1)	3 (4.7)	0	1 (1.6)
Acne	0	1 (1.6)	1 (1.5)	3 (4.7)	0	1 (1.6)
Blood triglycerides increased	0	0	4 (6.2)	1 (1.6)	0	0
Injection site erythema	0	0	3 (4.6)	3 (4.7)	2 (3.2)	0
Dysmenorrhoea	0	0	3 (4.6)	0	1 (1.6)	0
Conjunctivitis	0	0	1 (1.5)	1 (1.6)	4 (6.3)	0
Furuncle	0	0	1 (1.5)	1 (1.6)	0	3 (4.9)
Dermatitis	0	0	0	0	3 (4.8)	0

Number of patients (%)

In the Japanese subpopulation, adverse events were observed in 10 patients in the 100 mg Q4W group, 7 patients in the 200 mg Q2W group, 11 patients in the 300 mg Q4W group, 8 patients in the 300 mg Q2W group, 7 patients in the 300 mg QW group, and 7 patients in the placebo group. The main events were dermatitis atopic (3 patients in the 100 mg Q4W group, 2 patients in the 200 mg Q2W group, 5 patients in the 300 mg Q4W group, 4 patients in the 300 mg Q2W group, 3 patients in the 300 mg QW group, 5 patients in the placebo group) and nasopharyngitis (4 patients in the 100 mg Q4W group, 3 patients in the 200 mg Q2W group, 3 patients in the 300 mg Q4W group, 3 patients in the 300 mg Q2W group, 1 patient in the 300 mg QW group, 2 patients in the placebo group). Neither death nor serious adverse event was observed. Adverse events leading to discontinuation were observed in 2 patients in the 100 mg Q4W group, 2 patients in the 300 mg Q4W group, 1 patient in the 300 mg Q2W group, 1 patient in the 300 mg QW group, and 1 patient in the placebo group.

Adverse drug reactions were observed in 3 patients in the 100 mg Q4W group, 1 patient in the 200 mg Q2W group, 2 patients in the 300 mg Q4W group, 3 patients in the 300 mg Q2W group, 2 patients in the 300 mg QW group, and 2 patients in the placebo group.

7.2 Global phase III studies

7.2.1 Monotherapy study (CTD 5.3.5.1-4, Study R668-AD-1334 [October 2014 to February 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients[8)] aged ≥18 years with atopic dermatitis for whom TCS was not recommended for a reason of insufficient response to TCS of medium potency (corresponding to TCS of strong class in Japanese classification) or higher potency or for a safety reason (target sample size, 600 subjects [200 per group]) in order to investigate the efficacy and safety of dupilumab in 10 countries including Japan and US.

The study consisted of a treatment period (16 weeks) and a follow-up period (12 weeks).[9)] Dupilumab at 300 mg (600 mg in the initial dose) or placebo was to be administered subcutaneously once every 2 or 1 week for 16 weeks. From at least 7 days before baseline, a topical skin moisturizer was to be applied at a constant dose, and, in the event of an intolerable symptom, a rescue treatment[10)] was allowed.

All of 671 patients (224 in the Q2W group, 223 in the QW group, 224 in the placebo group), randomized with baseline severity (IGA score 3 or 4) and region (Asia, Eastern Europe, Western Europe, or North and South America) as the stratification factors, were included in FAS. Of the patients in the FAS, 669 patients[11)] (229 in the Q2W group, 218 in the QW group, 222 in the placebo group), excluding 2 not receiving the study drug, were included in the safety analysis population, and the FAS was subjected to efficacy analysis. Study discontinuation occurred in 7.1% (16 of 224) of patients in the Q2W group, 11.7% (26 of 223) of patients in the QW group, and 17.9% (40 of 224) of patients in the placebo group. Main reasons for the discontinuation were adverse events (6 patients in the Q2W group, 6 patients in the QW group, 10 patients in the placebo group) and insufficient response (4 patients in the Q2W group, 3 patients in the QW group, 11 patients in the placebo group).

The Japanese subpopulation in FAS consisted of 106 patients (36 in the Q2W group, 35 in the QW group, 35 in the placebo group). No study discontinuation occurred.

For efficacy assessment, the rates of achieving both IGA ≤1 and EASI-75 [see Section "10. Other" for the definitions] were used as the co-primary endpoints. A statistically significant difference was

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8) Patient who met all of the following: (a) EASI score ≥16, IGA score ≥3, the area of atopic dermatitis ≥10% of body surface area (BSA), and mean maximum pruritus numerical rating scale (NRS) ≥3, (b) a record within 6 months indicating that TCS is not recommended for a reason of insufficient response or for a reason of safety, and diagnosis of atopic dermatitis ≥3 years before. "Insufficient response" was defined as failure to maintain remission or low disease activity (IGA score 0-2) by daily administration of TCS of medium or higher potency (with addition of TCI as necessary) for at least 28 days or for the maximum period recommended by the package insert, whichever is shorter. Patients with a record of systemic treatment for atopic dermatitis within the past 6 months were also regarded as patients with insufficient response to TCS. A "safety reason" was defined as a risk (e.g., intolerance to treatment, hypersensitivity reaction, marked skin atrophy, systemic effect) outweighing the benefit of the treatment.

9) Patients who had baseline IGA score of 0 or 1 and showed a decrease from baseline in IGA score by ≥2 points or in EASI score by ≥75% were to be transitioned to the foreign phase III study (Study R668-AD-1415) without entering the follow-up period.

10) For the rescue treatment, a step-wise treatment method was recommended whereby the treatment was started with a topical medication and, only if no sufficient response was observed after treatment for 7 days, systemic drugs were administered. If the stepwise treatment was not acceptable for a reason of severity or other medical reason, treatment with high potency (corresponding to "very strong class" in the Japanese classification) or stronger TCS or systemic drugs was allowed. When an oral steroid or a systemic nonsteroidal immunosuppressant was administered as a rescue treatment, administration of the study drug was to be discontinued. After approximately 5 times the elimination half-life after the last dose of the rescue drug, administration of the study drug could be resumed.

11) Dupilumab 300 mg was administered to 1 patient who had been randomized to the placebo group, and a smaller-than-scheduled dose of dupilumab was administered to 5 patients who had been randomized to the QW group. These 6 patients were handled as patients in the Q2W group in safety analysis.

observed in both endpoints in the paired comparison between the placebo group and the dupilumab Q2W group and between the placebo group and the dupilumab QW group, as shown in Table 26, demonstrating the superiority to placebo of dupilumab 300 mg once every 1 or 2 weeks. Results in the Japanese subpopulation were as shown in Table 27.

Table 26. Rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment (FAS, non-responder imputation [NRI])

	Q2W	QW	Placebo
Rate of achieving IGA ≤1	37.9 (85/224)	37.2 (83/223)	10.3 (23/224)
Difference from placebo [95% CI] *P* value[a) b)]	27.7 [20.2, 35.2] <0.0001	27.0 [19.5, 34.4] <0.0001	
Rate of achieving EASI-75	51.3 (115/224)	52.5 (117/223)	14.7 (33/224)
Difference from placebo [95% CI] *P* value[a) b)]	36.6 [28.6, 44.6] <0.0001	37.7 [29.7, 45.8] <0.0001	

% (number of patients)
Patients who discontinued the study or received a rescue treatment were handled as non-responders.
a) Cochran-Mantel-Haenszel test stratified by region and baseline severity (IGA score 3 or 4)
b) Adjusted for the multiplicity of test by setting the significance level in the comparison between the placebo group and each dupilumab group at 2.5% (two-sided)

Table 27. Rate of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment (Japanese subpopulation, NRI)

	Q2W	QW	Placebo
Rate of achieving IGA ≤1	19.4 (7/36)	28.6 (10/35)	2.9 (1/35)
Difference from placebo [95% CI]	16.6 [−6.4, 38.8]	25.7 [1.0, 48.2]	
Rate of achieving EASI-75	25.0 (9/36)	51.4 (18/35)	0 (0/35)
Difference from placebo [95% CI]	25.0 [2.2, 46.5]	51.4 [28.0, 70.3]	

% (number of patients)
Patients who discontinued the study or received a rescue treatment were handled as non-responders

During the entire study period, adverse events were observed in 74.7% (171 of 229) of patients in the Q2W group, 69.3% (151 of 218) of patients in the QW group, and 66.7% (148 of 222) of patients in the placebo group. Table 28 shows the main events observed. No death occurred. Serious adverse events were observed in 3.1% (7 of 229) of patients in the Q2W group, 0.9% (2 of 218) of patients in the QW group, and 5.4% (12 of 222) of patients in the placebo group. The main event was dermatitis atopic (2 patients in the Q2W group, 3 patients in the placebo group). Adverse events leading to discontinuation were observed in 1.7% (4 of 229) of patients in the Q2W group, 1.8% (4 of 218) of patients in the QW group, and 0.9% (2 of 222) of patients in the placebo group.

Adverse drug reactions were observed in 29.3% (67 of 229) of patients in the Q2W group, 31.2% (68 of 218) of patients in the QW group, and 18.9% (42 of 222) of patients in the placebo group.

Table 28. Adverse events reported by ≥2% of patients in any group during the entire study period (safety analysis population)

	Q2W (n = 229)	QW (n = 218)	Placebo (n = 222)
Dermatitis atopic	36 (15.7)	21 (9.6)	68 (30.6)
Nasopharyngitis	27 (11.8)	26 (11.9)	22 (9.9)
Headache	21 (9.2)	11 (5.0)	13 (5.9)
Injection site reaction	19 (8.3)	41 (18.8)	13 (5.9)
Conjunctivitis allergic	12 (5.2)	8 (3.7)	3 (1.4)
Conjunctivitis	11 (4.8)	7 (3.2)	3 (1.4)
Oral herpes	9 (3.9)	4 (1.8)	4 (1.8)
Diarrhoea	8 (3.5)	7 (3.2)	4 (1.8)
Herpes simplex	8 (3.5)	2 (0.9)	3 (1.4)
Upper respiratory tract infection	7 (3.1)	12 (5.5)	7 (3.2)
Arthralgia	6 (2.6)	1 (0.5)	3 (1.4)
Blood creatine phosphokinase increased	5 (2.2)	2 (0.9)	4 (1.8)
Fatigue	5 (2.2)	2 (0.9)	2 (0.9)
Nausea	5 (2.2)	2 (0.9)	1 (0.5)
Back pain	2 (0.9)	5 (2.3)	4 (1.8)
Folliculitis	2 (0.9)	3 (1.4)	5 (2.3)
Urinary tract infection	2 (0.9)	0	5 (2.3)
Impetigo	1 (0.4)	3 (1.4)	5 (2.3)
Pruritus	0	1 (0.5)	5 (2.3)

Number of patients (%)

In the Japanese subpopulation, adverse events were observed in 80.6% (29 of 36) of patients in the Q2W group, 77.1% (27 of 35) of patients in the QW group, and, 80.0% (28 of 35) of patients in the placebo group. The main events included dermatitis atopic (36.1% [13 of 36] of patients in the Q2W group, 8.6% [3 of 35] of patients in the QW group, 57.1% [20 of 35] of patients in the placebo group) and nasopharyngitis (11.1% [4 of 36] of patients in the Q2W group, 28.6% [10 of 35] of patients in the QW group, 11.4% [4 of 35] of patients in the placebo group). No death occurred. Serious adverse events were observed in 1 patient in the Q2W group and in 2 patients in the placebo group. There were no adverse events leading to discontinuation.

Adverse drug reactions were observed in 41.7% (15 of 36) of patients in the Q2W group, 31.4% (11 of 35) of patients in the QW group, and 22.9% (8 of 35) of patients in the placebo group.

7.2.2 TCS combination therapy study (CTD 5.3.5.1-6 and 5.3.5.1-6a, Study R668-AD-1224 [October 2014 to October 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients[12)] aged ≥18 years with atopic dermatitis with an inadequate response to TCS of medium potency (corresponding to TCS of strong class in Japanese classification) or higher potency (target sample size, 700 subjects) in order to investigate the efficacy and safety of dupilumab in combination with TCS in 14 countries including Japan and US.

The study consisted of a treatment period (52 weeks) and a follow-up period (12 weeks). Dupilumab at 300 mg (600 mg in the initial dose) or placebo was to be administered subcutaneously once every 2 or

[12)] Patient who met all of the following: (a) IGA score ≥3, the area of atopic dermatitis ≥10% of BSA, EASI score ≥16, and mean maximum pruritus NRS ≥3, (b) a record within 6 months indicating that TCS is not sufficiently effective, and diagnosis of atopic dermatitis ≥3 years before. "Insufficient response" was defined as failure to maintain remission or low disease activity (IGA score 0-2) by daily administration of TCS of medium or higher potency (with addition of TCI as necessary) for at least 28 days or for the maximum period recommended by the package insert, whichever is shorter. Patients with a record of systemic treatment for atopic dermatitis within the past 6 months were also regarded as patients with insufficient response to TCS.

1 week for 16 weeks. From at least 7 days before baseline, a topical skin moisturizer was to be applied at a constant dose. TCS treatment was to be started from baseline and, when the disease activity subsided, to be discontinued.[13)] If an intolerable symptom developed after week 2 of treatment, administration of a rescue treatment[14)] was allowed.

All of 740 patients (106 in the Q2W group, 319 in the QW group, 315 in the placebo group), randomized in a 1:3:3 ratio to the Q2W group, the QW group, or the placebo group using the baseline severity (IGA score 3 or 4) and region (Asia, Eastern Europe, Western Europe, North and South America) as the stratification factors, were included in FAS. All patients in FAS received at least 1 dose of the study drug. A total of 740 patients[15)] (110 in the Q2W group, 315 in the QW group, 315 in the placebo group) were included in the safety analysis population. The FAS was subjected to efficacy evaluation. Study discontinuation occurred in 8.5% (9 of 106) of patients in the Q2W group, 12.2% (39 of 319) of patients in the QW group, and 18.7% (59 of 315) of patients in the placebo group. Main reasons for the discontinuation were consent withdrawal (4 patients in the Q2W group, 14 patients in the QW group, 24 patients in the placebo group) and adverse events (1 patient in the Q2W group, 8 patients in the QW group, 10 patients in the placebo group).

The Japanese subpopulation in FAS consisted of 117 patients (16 in the Q2W group, 47 in the QW group, 54 in the placebo group). Study discontinuation occurred in 6.3% (1 of 16) of patients in the Q2W group, 10.6% (5 of 47) of patients in the QW group, and 16.7% (9 of 54) of patients in the placebo group. The main reason for the discontinuation was consent withdrawal (1 patient in the Q2W group, 2 patients in the QW group, 5 patients in the placebo group).

As for efficacy, the rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment [see Section "10. Other" for the definitions] were used as the co-primary endpoints. A statistically significant difference in both endpoints was observed in the paired comparison between the placebo group and the dupilumab Q2W group and between the placebo group and the dupilumab QW group, as shown in Table 29, demonstrating the superiority to placebo of dupilumab 300 mg once every 1 or 2 weeks. Results in the Japanese subpopulation were as shown in Table 30.

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13) The active site of dermatitis was to be treated with once daily application of a medium potency TCS and, after the disease activity subsided, the treatment was to be switched to once daily application of a low potency (low to medium class in the Japanese classification) TCS for 7 days and then to be discontinued. In case of flare-up, the treatment was to be resumed with a medium potency TCS. If the medium potency TCS did not improve the symptom, a high potency (very strong class in Japanese classification) or higher potency TCS was to be used while consideration is given to safety.

14) For a rescue treatment, a high or higher potency TCS, oral corticosteroid, and nonsteroidal immunosuppressant could be used at the discretion of the physician. When oral steroid, nonsteroidal immunosuppressant, or phototherapy was administered as a rescue treatment, administration of the study drug was to be interrupted, but could be resumed after approximately 5 times the elimination half-life of the rescue drug passed after the last dose of the rescue drug or after 1 month after the phototherapy.

15) Four patients randomized to the QW group received a lower-than-targeted dose of the study drug. They were handled as patients in the Q2W group in safety analysis.

Table 29. Rate of achieving IGA ≤1 or EASI-75 after 16 weeks of treatment (FAS, NRI)

	Q2W	QW	Placebo
Rate of achieving IGA ≤1	38.7 (41/106)	39.2 (125/319)	12.4 (39/315)
Difference from placebo [95% CI] *P* value[a) b)]	26.3 [16.3, 36.3] <0.0001	26.8 [20.3, 33.3] <0.0001	
Rate of achieving EASI-75	68.9 (73/106)	63.9 (204/319)	23.2 (73/315)
Difference from placebo [95% CI] *P* value[a) b)]	45.7 [35.7, 55.7] <0.0001	40.8 [33.7, 47.8] <0.0001	

% (number of patients)
Patients who discontinued the study or received a rescue treatment were handled as non-responders.
a) Cochran-Mantel-Haenszel test stratified by region and baseline severity (IGA score 3 or 4)
b) Adjusted for the multiplicity of test by setting the significance level in the comparison between the placebo group and each dupilumab group at 2.5% (two-sided)

Table 30. Rate of achieving IGA ≤1 or EASI-75 after 16 weeks of treatment (Japanese subpopulation, NRI)

	Q2W	QW	Placebo
Rate of achieving IGA ≤1	18.8 (3/16)	31.9 (15/47)	3.7 (2/54)
Difference from placebo [95% CI]	15.0 [−13.2, 41.7]	28.2 [8.8, 46.0]	
Rate of achieving EASI-75	62.5 (10/16)	63.8 (30/47)	22.2 (12/54)
Difference from placebo [95% CI]	40.3 [12.5, 65.0]	41.6 [22.6, 58.2]	

% (number of patients)
Patients who discontinued the study or received a rescue treatment were handled as non-responders.

During the entire study period, adverse events were observed in 91.8% (101 of 110) of patients in the Q2W group, 88.3% (278 of 315) of patients in the QW group, and 88.3% (278 of 315) of patients in the placebo group. Table 31 shows the main events observed. Death occurred in 1 patient in the QW group (road traffic accident), but its causal relationship to the study drug was ruled out. Serious adverse events were observed in 3.6% (4 of 110) of patients in the Q2W group, 3.8% (12 of 315) of patients in the QW group, and 6.3% (20 of 315) of patients in the placebo group. The main event was dermatitis atopic (1 patient in the Q2W group, 1 patient in the QW group, 1 patient in the placebo group). Adverse events leading to discontinuation were observed in 2.7% (3 of 110) of patients in the Q2W group, 2.9% (9 of 315) of patients in the QW group, and 8.3% (26 of 315) of patients in the placebo group.

Adverse drug reactions were observed in 33.6% (37 of 110) of patients in the Q2W group, 35.2% (111 of 315) of patients in the QW group, and 30.2% (95 of 315) of patients in the placebo group.

Table 31. Adverse events reported by ≥2% of patients in any group during the entire study period (safety analysis population)

	Q2W (n = 110)	QW (n = 315)	Placebo (n = 315)
Dermatitis atopic	51 (46.4)	111 (35.2)	179 (56.8)
Nasopharyngitis	26 (23.6)	66 (21.0)	64 (20.3)
Injection site reaction	16 (14.5)	61 (19.4)	25 (7.9)
Conjunctivitis allergic	12 (10.9)	48 (15.2)	17 (5.4)
Upper respiratory tract infection	11 (10.0)	49 (15.6)	35 (11.1)
Blepharitis	7 (6.4)	12 (3.8)	3 (1.0)
Asthma	6 (5.5)	7 (2.2)	19 (6.0)
Headache	5 (4.5)	26 (8.3)	19 (6.0)
Arthralgia	5 (4.5)	10 (3.2)	15 (4.8)
Gastroenteritis	5 (4.5)	5 (1.6)	12 (3.8)
Oral herpes	4 (3.6)	17 (5.4)	10 (3.2)
Eye pruritus	4 (3.6)	14 (4.4)	5 (1.6)
Cough	4 (3.6)	10 (3.2)	9 (2.9)
Seasonal allergy	4 (3.6)	10 (3.2)	7 (2.2)
Influenza	4 (3.6)	9 (2.9)	16 (5.1)
Pyrexia	4 (3.6)	7 (2.2)	7 (2.2)
Blood lactate dehydrogenase increased	4 (3.6)	1 (0.3)	6 (1.9)
Urinary tract infection	3 (2.7)	15 (4.8)	15 (4.8)
Oropharyngeal pain	3 (2.7)	11 (3.5)	12 (3.8)
Blood creatine phosphokinase increased	3 (2.7)	11 (3.5)	10 (3.2)
Viral upper respiratory tract infection	3 (2.7)	9 (2.9)	9 (2.9)
Herpes simplex	3 (2.7)	8 (2.5)	2 (0.6)
Pharyngitis	3 (2.7)	7 (2.2)	10 (3.2)
Ligament sprain	3 (2.7)	7 (2.2)	5 (1.6)
Depression	3 (2.7)	6 (1.9)	6 (1.9)
Dry eye	3 (2.7)	6 (1.9)	4 (1.3)
Vomiting	3 (2.7)	4 (1.3)	8 (2.5)
Anxiety	3 (2.7)	4 (1.3)	2 (0.6)
Osteoarthritis	3 (2.7)	2 (0.6)	3 (1.0)
Sinusitis	2 (1.8)	19 (6.0)	9 (2.9)
Back pain	2 (1.8)	11 (3.5)	12 (3.8)
Nausea	2 (1.8)	9 (2.9)	12 (3.8)
Conjunctivitis bacterial	2 (1.8)	9 (2.9)	5 (1.6)
Folliculitis	2 (1.8)	7 (2.2)	8 (2.5)
Dermatitis contact	2 (1.8)	7 (2.2)	5 (1.6)
Urticaria	2 (1.8)	3 (1.0)	10 (3.2)
Diarrhoea	1 (0.9)	12 (3.8)	13 (4.1)
Fatigue	1 (0.9)	11 (3.5)	10 (3.2)
Erythema	1 (0.9)	10 (3.2)	2 (0.6)
Conjunctivitis	1 (0.9)	9 (2.9)	5 (1.6)
Rhinitis	1 (0.9)	8 (2.5)	4 (1.3)
Pain in extremity	1 (0.9)	8 (2.5)	2 (0.6)
Acne	1 (0.9)	7 (2.2)	8 (2.5)
Toothache	1 (0.9)	5 (1.6)	9 (2.9)
Impetigo	1 (0.9)	4 (1.3)	10 (3.2)
Pruritus	1 (0.9)	4 (1.3)	9 (2.9)
Hypertension	1 (0.9)	4 (1.3)	7 (2.2)
Abdominal pain	0	7 (2.2)	4 (1.3)
Skin infection	0	2 (0.6)	7 (2.2)
Sunburn	0	2 (0.6)	7 (2.2)
Muscle spasms	0	1 (0.3)	7 (2.2)

Number of patients (%)

In the Japanese subpopulation, adverse events were observed in 81.3% (13 of 16) of patients in the Q2W group, 85.1% (40 of 47) of patients in the QW group, and 85.2% (46 of 54) of patients in the placebo group. The main events included nasopharyngitis (50.0% [8 of 16] of patients in the Q2W group, 40.4% [19 of 47] of patients in the QW group, 42.6% [23 of 54] of patients in the placebo group) and dermatitis atopic (37.5% [6 of 16] of patients in the Q2W group, 19.1% [9 of 47] of patients in the QW group,

51.9% [28 of 54] of patients in the placebo group). No death occurred. Serious adverse events were observed in 1 patient in the QW group and in 2 patients in the placebo group. Adverse events leading to discontinuation were observed in 2 patients in the QW group and in 3 patients in the placebo group.

Adverse drug reactions were observed in 18.8% (3 of 16) of patients in the Q2W group, 25.5% (12 of 47) of patients in the QW group, and 22.2% (12 of 54) of patients in the placebo group.

7.2.3 Extension/re-administration study (CTD 5.3.5.2-1, Study R668-AD-1225 [ongoing since October 2013 (data cut-off [redacted])])

An open-label, uncontrolled study was conducted to investigate the safety in long-term administration of dupilumab in subjects who had completed phase I studies (Studies R668-AD-0914, R668-AD-1026, and R668-AD-1433), phase II studies (Studies R668-AD-1021, R668-AD-1117, R668-AD-1121, R668-AD-1307, R668-AD-1314, and R668-AD-1412), or phase III studies (Studies R668-AD-1224, R668-AD-1334, R668-AD-1415, R668-AD-1416, R668-AD-1424, and R668-AD-1526), or patients with atopic dermatitis[16)] who were not randomized after screening due to the termination of the registration period in phase III studies (Studies R668-AD-1334 and R668-AD-1416) (target sample size, approximately 2000 subjects) in 22 countries including Japan and US.

The study consisted of a treatment period (3 years at the maximum) and a follow-up period (16 weeks). At the time point of the study initiation, subcutaneous administration of dupilumab 200 mg (400 mg in the initial dose) once every week may be to be the maximum dose in the phase III studies, as expected from the data so far obtained from clinical studies. Therefore, dupilumab 200 mg was to be administered subcutaneously once every week as shown in Table 32, according to the length of the period from the last dose of dupilumab in the preceding study until the start of treatment in this study. Subsequently, results of Study R668-AD-1021 suggested that subcutaneous administration of dupilumab 300 mg (600 mg in the initial dose) once every week was the maximum dose investigated in phase III studies, whereupon the study plan was changed as follows: Dupilumab 300 mg was to be administered subcutaneously once every week as shown in Table 32, according to the length of the period from the last dose of dupilumab in the preceding study until the start of treatment in this study. It was allowable to use a topical skin moisturizer, TCS, and TCI and, in case of intolerable symptoms or in order to control serious concurrent disease, to administer a rescue treatment.[17)]

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16) Patient who met all of the following: (a) EASI score ≥16, IGA score ≥3, and the area of atopic dermatitis ≥10% of BSA, (b) a record within 6 months indicating that TCS is not recommended for a reason of insufficient response or for a reason of safety, and diagnosis of atopic dermatitis ≥3 years before. The definitions for "insufficient response" and "safety reason" were the same as those in Study R668-AD-1334.

17) For a rescue treatment, oral corticosteroid, nonsteroidal immunosuppressant, or phototherapy could be used at the discretion of the physician. When a rescue treatment was administered, administration of the study drug was to be interrupted during the period approximately 5 times the elimination half-life of the rescue drug after the last dose of the rescue drug, and the study was to be discontinued prematurely.

Table 32. Dosage regimen in Study R668-AD-1225 classified by period from preceding study

Period from the last dose of dupilumab in the preceding study until the start of treatment in this study	Dosage regimen of dupilumab in Study R668-AD-1225	
	Before the change of plan (at the start of the study)	After the change of plan
≥4 weeks	Dupilumab 200 mg (400 mg in the initial dose) administered subcutaneously once every week	Dupilumab 300 mg (600 mg in the initial dose) administered subcutaneously once every week
<4 weeks	Dupilumab 200 mg administered subcutaneously once every week from ≥1 week after the last dose of dupilumab in the preceding study	Dupilumab 300 mg administered subcutaneously once every week from ≥1 week after the last dose of dupilumab in the preceding study

Of 1492 patients enrolled, 1491 patients (7 in Study R668-AD-0914, 11 in Study R668-AD-1026, 2 in Study R668-AD-1433, 295 in Study R668-AD-1021, 51 in Study R668-AD-1117, 17 in Study R668-AD-1121, 43 in Study R668-AD-1307, 168 in Study R668-AD-1314, 121 in Study R668-AD-1224, 344 in Study R668-AD-1334, 35 in Study R668-AD-1415, 397 in Study R668-AD-1416), excluding 1 patient who did not receive the study drug, were included in the safety analysis population. Study discontinuation occurred in 7.1% (106 of 1491) of patients. The main reasons for the discontinuation included adverse events in 1.7% (26 of 1491) of patients and insufficient response in 1.5% (22 of 1491) of patients.

The Japanese subpopulation in the safety analysis population consisted of 121 patients. Study discontinuation occurred in 5.8% (7 of 121) of patients, with the main reason for the discontinuation being consent withdrawal (4 patients).

Table 33 shows changes over time in the rate of achieving IGA ≤1 and the rate of achieving EASI-75, the efficacy endpoints [see Section “10. Other” for definitions].

Table 33. Changes over time in the rate of achieving IGA ≤1 and the rate of achieving EASI-75 (safety analysis population, OC)

		Entire population			Japanese subpopulation		
		Baseline	After 16 weeks	After 52 weeks	Baseline	After 16 weeks	After 52 weeks
All patients	Rate of achieving IGA ≤1	4.6 (68/1491)	37.8 (448/1185)	56.0 (225/402)	5.0 (6/121)	25.3 (22/87)	43.5 (20/46)
	Rate of achieving EASI-75	18.2 (266/1460)	75.0 (875/1166)	87.1 (350/402)	22.3 (27/121)	77.0 (67/87)	82.6 (38/46)
Results of subpopulation analysis classified by the mode of administration in the preceding study							
No dupilumab administered in the preceding study	Rate of achieving IGA ≤1	2.0 (12/606)	42.5 (204/480)	58.8 (57/97)	0 (0/40)	34.6 (9/26)	40.0 (2/5)
	Rate of achieving EASI-75	10.1 (58/577)	77.2 (356/461)	87.6 (85/97)	10.0 (4/40)	80.8 (21/26)	100 (5/5)
Period from the last dose of dupilumab in the preceding study until the start of treatment in this study: >13 weeks	Rate of achieving IGA ≤1	5.5 (21/381)	46.0 (144/313)	54.8 (149/272)	10.7 (6/56)	29.5 (13/44)	43.9 (18/41)
	Rate of achieving EASI-75	23.4 (89/381)	78.9 (247/313)	87.5 (238/272)	32.1 (18/56)	75.0 (33/44)	80.5 (33/41)
Period from the last dose of dupilumab in the preceding study until the start of treatment in this study: ≥6 and ≤13 weeks	Rate of achieving IGA ≤1	4.4 (18/409)	25.8 (87/337)	56.7 (17/30)	0 (0/23)	0 (0/15)	NA
	Rate of achieving EASI-75	21.1 (86/408)	68.0 (229/337)	80.0 (24/30)	17.4 (4/23)	73.3 (11/15)	NA
Period from the last dose of dupilumab in the preceding study until the start of treatment in this study: <6 weeks	Rate of achieving IGA ≤1	1.7 (1/60)	23.6 (13/55)	66.7 (2/3)	0 (0/2)	0 (0/2)	NA
	Rate of achieving EASI-75	11.9 (7/59)	78.2 (43/55)	100 (3/3)	50.0 (1/2)	100 (2/2)	NA

% (number of patients)

During the entire study period, adverse events were observed in 70.7% (1054 of 1491) of patients. Table 34 shows main events observed. No death occurred. Serious adverse events were observed in 5.0% (74 of 1491) of patients, with main events being squamous cell carcinoma of skin, osteoarthritis, and dermatitis atopic (3 patients each). Adverse events leading to discontinuation were observed in 1.8% (27 of 1491) of patients receiving dupilumab.

Adverse drug reactions were observed in 27.4% (408 of 1491) of patients receiving dupilumab.

Table 34. Adverse events reported by ≥2% of patients during the entire study period (safety analysis population)

	Patients receiving dupilumab (n = 1491)		Patients receiving dupilumab (n = 1491)
Nasopharyngitis	306 (20.5)	Blood creatine phosphokinase increased	53 (3.6)
Upper respiratory tract infection	142 (9.5)	Bronchitis	47 (3.2)
Dermatitis atopic	123 (8.2)	Diarrhoea	41 (2.7)
Headache	106 (7.1)	Back pain	41 (2.7)
Injection site reaction	82 (5.5)	Viral upper respiratory tract infection	38 (2.5)
Conjunctivitis	78 (5.2)	Injection site erythema	35 (2.3)
Oral herpes	64 (4.3)	Cough	34 (2.3)
Conjunctivitis allergic	63 (4.2)	Influenza	31 (2.1)

Number of patients (%)

In the Japanese subpopulation, adverse events were observed in 74.4% (90 of 121) of patients receiving dupilumab. Main events included nasopharyngitis (39 patients) and injection site reaction (13 patients). No death occurred. A serious adverse event was observed in 1 patient. Adverse events leading to discontinuation were observed in 2 patients.

Adverse drug reactions were observed in 24.8% (30 of 121) of patients receiving dupilumab.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of dupilumab in the treatment of atopic dermatitis:

Symptoms of atopic dermatitis are diverse depending on the stage and severity of the disease. In some cases, they may be mild with only temporary dryness and scales, whereas in other cases, the disease is accompanied by severe skin lesions such as wide-spread distinct dryness, erythema, infiltration/papule, scab/oozing, and lichenification (*J Dtsch Dermatol Ges*. 2011;9:12-20, *J Allergy Clin Immunol*. 2014;134:769-79).

In the drug therapy of atopic dermatitis, topical skin moisturizers are used to maintain and improve the dermal barrier function, and combinations of topical anti-inflammatory drugs such as TCS and TCI are recommended for the treatment of inflammatory skin symptoms. When topical anti-inflammatory drugs such as TCS and TCI are not sufficiently effective, oral cyclosporine is administered intermittently, and oral corticosteroid is sometimes used to achieve remission from acute exacerbation or from severe to most severe atopic dermatitis. The oral immunosuppressant cyclosporine requires caution against the occurrence of systemic adverse drug reactions such as renal disorder, hypertension, and infection during the treatment. In addition, it is essential that the drug be switched to topical therapy promptly after the symptoms have been alleviated, because the long-term safety of cyclosporine has not been established. Because of various serious systemic adverse drug reactions that occur in long-term use of oral corticosteroid, the drug should be used for only a short period, if at all (Japanese clinical practice guidelines).

There are a certain percentage of patients who have flare-ups frequently and for a long period despite appropriate treatment with topical anti-inflammatory drugs such as TCS and TCI, and long-term treatments that can be used in these patients are limited. Dupilumab has been developed as a drug for patients with moderate or severe atopic dermatitis that is active despite appropriate use of topical anti-inflammatory drugs such as TCS and TCI or for which these drugs are not recommended.

PMDA accepted the above explanation of the applicant. Patients eligible for treatment with dupilumab will be carefully evaluated, based on the results of clinical studies, etc. [see Section 7.R.4].

7.R.2 Efficacy

7.R.2.1 Development plan

The applicant's explanation about the plan for dupilumab development:

In Japan, atopic dermatitis is diagnosed and treated according to the Japanese clinical practice guidelines, and there seems to be no major difference in the diagnostic and therapeutic system for atopic dermatitis including the diagnostic criteria and treatment algorithm between the US and European guidelines (*J Am Acad Dermatol*. 2014;70:338-51, *J Am Acad Dermatol*. 2014;71:116-32 and 327-49) and the Japanese guideline. Also, taking account of the facts that there is no clear difference in the pharmacokinetics of dupilumab between Japanese and non-Japanese patients [see Section 6.R.1] and that there is currently no report of any clinically significant difference in mutations of the gene encoding the target molecule (IL-4Rα) between Japanese and non-Japanese patients, it was considered appropriate to evaluate the efficacy and safety in Japanese patients with atopic dermatitis based on the clinical data package constructed from global clinical studies including Japan.

- **Target patients**

Based on the clinical positioning of dupilumab proposed by the applicant [see Section 7.R.1], phase II and III studies were conducted in patients who met the following criteria: Patients with atopic dermatitis for which treatment with TCS (TCI added as necessary) is unable to achieve remission or maintain the activity at a low level or TCS is not recommended for a safety reason. Pivotal clinical studies (Studies R668-AD-1334 and R668-AD-1224) were conducted in patients with atopic dermatitis with disease activity (meeting all of the following criteria; IGA score ≥3, EASI score ≥16, and atopic dermatitis covering ≥10% of body surface area [BSA]) even after treatment with TCS of medium potency (strong class in the Japanese classification) or higher potency (TCI added as necessary) for ≥28 days. In Study R668-AD-1334, "patients with atopic dermatitis for whom TCS is not recommended for a safety reason, etc.," as set in the above inclusion criteria were further required to be those in whom TCS was confirmed by the investigator to cause intolerable effects, hypersensitivity reaction, marked skin atrophy, or systemic effects.

- **Efficacy endpoints**

The purpose of the treatment for atopic dermatitis is suppression of clinical signs such as skin lesions and improvement of subjective symptoms such as pruritus. Therefore, EASI, which evaluates the disease by scoring the physician's assessment of the severity, area, etc., of skin lesion for each affected site, and IGA, which is an overall assessment of skin lesion by the physician, were used as the primary endpoints. Also, numerical rating scale (NRS), a patient-reported outcome designed to evaluate the severity of pruritus, a subjective symptom, was used as one of the main efficacy endpoints. In Japan, there is no guideline for the clinical development of therapeutic agents for atopic dermatitis. However, IGA and EASI used as the primary endpoints in phase III studies are used in Japan in the development of drugs for atopic dermatitis.

- **Justification for dosage and administration used in phase III studies**

In the global phase II study investigating the dose response of dupilumab (100 mg Q4W, 200 mg Q2W, 300 mg Q4W, 300 mg Q2W, or 300 mg QW) in patients with atopic dermatitis for whom TCS is not recommended for a reason of insufficient efficacy or safety problem [see Section 7.1], the rate of change in EASI score after 16 weeks of treatment from baseline, the primary endpoint, was the greatest in the 300 mg QW group (Table 23). Also, a clinically significant change was observed with all dosage regimens tested [see Section "10. Other"] although caution is required in the interpretation of the results

because of the limited number of patients studied in the Japanese subpopulation (Table 24). Furthermore, no difference was observed in the safety among treatment groups. Based on the above results, the applicant considered appropriate to use dupilumab 300 mg once every week in phase III studies. Taking into account that there was no major difference in the efficacy between the 300 mg QW group and the 300 mg Q2W group (Table 23) and that convenience for patients was considered, 300 mg Q2W, a regimen of less frequent dosing, was added to the dosage regimen. Thus, in phase III studies, dupilumab 300 mg once every 1 or 2 weeks was selected as the dosage regimen. In order to allow serum dupilumab concentration to promptly reach the steady state, a loading dose was specified as the initial dose. The treatment period was selected 16 weeks, the period required for the serum dupilumab concentration to reach the steady, or nearly steady, state in a majority of patients in clinical studies during the early stage of development.

- **Concomitant drugs**

For the treatment of atopic dermatitis, it is the standard method to continuously use topical skin moisturizers aimed at improvement and maintenance of skin barrier function. Therefore, in each clinical study in patients with atopic dermatitis, a topical skin moisturizer was to be concomitantly administered at a constant dose.

In Study R668-AD-1334, concomitant use with TCS or TCI was prohibited from ≥7 days before baseline in order to allow investigation of efficacy and safety of dupilumab monotherapy. However, in case of an intolerable symptom, they could be concomitantly administered as a rescue treatment.

In Study R668-AD-1224, given the therapeutic system for atopic dermatitis, it is expected that dupilumab and TCS are concomitantly administered in routine clinical practice. Therefore, efficacy and safety in concomitant use with TCS were investigated. For this purpose, concomitant use with TCS and TCI was prohibited from ≥7 days before baseline. Treatment with TCS was to be started from baseline and, if the disease activity subsided, TCS treatment was to be discontinued.[18)]

PMDA accepted the above explanation of the applicant and concluded that it is appropriate to evaluate the efficacy and safety of dupilumab in patients with atopic dermatitis based on the submitted clinical data package, with the emphasis on the data of phase III studies in which Japanese patients participated. Also, it is understandable that the confirmatory study on dupilumab was conducted in patients with atopic dermatitis for whom TCS is not recommended for a reason of insufficient efficacy or safety problem, and that IGA and EASI, parameters that objectively evaluate the extent and severity of the signs and symptoms of atopic dermatitis, were used as the primary endpoints for global phase III studies.

18) The active site of dermatitis was to be treated with once daily application of a medium potency TCS and, after the disease activity subsided, the treatment was to be switched to once daily application of a low potency (low to medium class in the Japanese classification) TCS for 7 days and then to be discontinued. In case of flare-up, the treatment was to be resumed with a medium potency TCS. If the medium potency TCS did not improve the symptom, a high potency (very strong class in Japanese classification) or higher potency TCS was to be used while consideration is given to safety.

7.R.2.2 Efficacy

The applicant's explanation about the efficacy of dupilumab:

Both in a global phase III study in patients with atopic dermatitis for whom TCS is not recommended for a reason of insufficient efficacy or safety problem (Study R668-AD-1334), and a global phase III study in patients with atopic dermatitis with an inadequate response to TCS (Study R668-AD-1224), superiority of dupilumab 300 mg once every 1 or 2 weeks to placebo in the rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment, the primary efficacy endpoints, was demonstrated, as shown in Table 26 [see Section 7.2.1] and Table 29 [see Section 7.2.2]. Changes over time in main efficacy endpoints are shown in Table 35. All of the endpoint values tended to be higher in the dupilumab group compared to the placebo group. The percentage of patients showing ≥4 points decrease in the weekly average of NRS score from baseline was higher in the dupilumab 300 mg once every 1 and 2 weeks groups compared to the placebo group, suggesting the efficacy against pruritus, one of the major symptoms of atopic dermatitis.

The applicant considers that the above study results demonstrated the efficacy of dupilumab against atopic dermatitis in dupilumab monotherapy and in concomitant use with TCS.

Table 35. Changes over time in main efficacy endpoints (FAS, NRI)

	Timing of evaluation	Study R668-AD-1334			Study R668-AD-1224		
		Q2W	QW	Placebo	Q2W	QW	Placebo
Primary endpoints							
Rate of achieving IGA ≤1	Week 4	12.9 (29/224)	12.1 (27/223)	2.7 (6/224)	15.1 (16/106)	15.0 (48/319)	7.0 (22/315)
	Week 8	24.1 (54/224)	23.3 (52/223)	3.1 (7/224)	26.4 (28/106)	29.8 (95/319)	11.7 (37/315)
	Week 16	37.9 (85/224)	37.2 (83/223)	10.3 (23/224)	38.7 (41/106)	39.2 (125/319)	12.4 (39/315)
	Week 52				34.9 (37/106)	37.3 (119/319)	12.4 (39/315)
Rate of achieving EASI-75	Week 4	27.2 (61/224)	28.7 (64/223)	6.3 (14/224)	37.7 (40/106)	37.0 (118/319)	17.1 (54/315)
	Week 8	45.1 (101/224)	48.0 (107/223)	10.7 (24/224)	53.8 (57/106)	57.7 (184/319)	24.1 (76/315)
	Week 16	51.3 (115/224)	52.5 (117/223)	14.7 (33/224)	68.9 (73/106)	63.6 (203/319)	23.5 (74/315)
	Week 52				62.3 (66/106)	63.9 (204/319)	21.9 (69/315)
Secondary endpoints							
Rate of achieving EASI-50	Week 4	53.6 (120/224)	55.2 (123/223)	16.5 (37/224)	67.9 (72/106)	66.1 (211/319)	39.0 (123/315)
	Week 8	66.1 (148/224)	64.1 (143/223)	21.4 (48/224)	77.4 (82/106)	79.3 (253/319)	43.5 (137/315)
	Week 16	68.8 (154/224)	61.0 (136/223)	24.6 (55/224)	80.2 (85/106)	77.7 (248/319)	38.1 (120/315)
	Week 52				78.3 (83/106)	69.9 (223/319)	31.1 (98/315)
Rate of achieving EASI-90	Week 4	10.7 (24/224)	9.0 (20/223)	2.7 (6/224)	11.3 (12/106)	13.2 (42/319)	5.1 (16/315)
	Week 8	20.5 (46/224)	27.8 (62/223)	4.0 (9/224)	25.5 (27/106)	32.0 (102/319)	10.2 (32/315)
	Week 16	35.7 (80/224)	33.2 (74/223)	7.6 (17/224)	39.6 (42/106)	43.3 (138/319)	11.4 (36/315)
	Week 52				48.1 (51/106)	47.6 (152/319)	14.3 (45/315)
Rate of subjects showing improvement in pruritus NRS score[a)]	Week 4	16.0 (34/213)	23.4 (47/201)	6.1 (13/212)	37.3 (38/102)	27.1 (80/295)	16.4 (49/299)
	Week 8	33.3 (71/213)	33.8 (68/201)	8.5 (18/212)	46.1 (47/102)	45.8 (135/295)	18.7 (56/299)
	Week 16	40.8 (87/213)	40.3 (81/201)	12.3 (26/212)	58.8 (60/102)	50.5 (149/295)	19.7 (59/299)
	Week 52				48.0 (49/102)	38.6 (114/295)	13.4 (40/299)

% (number of patients)

Patients who discontinued the study or received a rescue treatment were handled as non-responders.

a) Percentage of subjects showing ≥4 points decrease in the week average of the daily maximum pruritus NRS score from baseline

The demographic factor that tended to differ between the entire population and the Japanese subpopulation in Studies R668-AD-1334 and R668-AD-1224 was body weight (mean body weight in Study R668-AD-1334, 76.6 kg in the entire population, 67.3 kg in the Japanese subpopulation; mean body weight in R668-AD-1224, 74.5 kg in the entire population, 63.9 kg in the Japanese subpopulation). Analysis of subpopulations classified by the body weight group did not show any clear difference between subpopulation groups, as shown in Table 36, suggesting that the difference in the distribution in body weight between Japanese and non-Japanese patients is unlikely to affect the efficacy evaluation. Also, in Studies R668-AD-1334 and R668-AD-1224, data of the Japanese subpopulation tended to be

similar to those of the entire population (Table 27 [see Section 7.2.1] and Table 30 [see Section 7.2.2]). The applicant therefore considers that it is appropriate to evaluate the efficacy of dupilumab in Japanese patients with atopic dermatitis based on the results of global phase III studies.

Table 36. Difference in rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment from placebo group, classified by body weight group (FAS, NRI)

Body weight group	Number of patients (Q2W/QW/placebo)	Difference from placebo [95% CI][a)]			
		Rate of achieving IGA ≤1		Rate of achieving EASI-75	
		Q2W	QW	Q2W	QW
Study R668-AD-1334					
<70 kg	85/71/100	27.5 [13.2, 40.9]	33.3 [18.5, 47.0]	37.2 [23.2, 50.8]	39.7 [25.1, 53.0]
≥70 kg and <100 kg	121/123/101	27.1 [14.1, 39.4]	25.7 [12.7, 38.0]	33.4 [20.5, 45.3]	35.8 [23.2, 47.6]
≥100 kg	18/29/22	30.8 [−0.3, 57.9]	13.9 [−14.0, 39.9]	48.5 [17.5, 72.5]	33.5 [5.6, 57.1]
Study R668-AD-1224					
<70 kg	49/147/141	22.0 [5.71, 37.6]	30.2 [18.8, 40.9]	42.0 [26.3, 56.5]	46.1 [35.4, 56.0]
≥70 kg and <100 kg	51/140/147	30.1 [14.4, 45.1]	23.6 [12.1, 34.7]	48.0 [32.8, 61.7]	36.3 [25.1, 46.8]
≥100 kg	6/32/27	25.9 [−19.4, 67.7]	27.0 [1.5, 50.0]	51.9 [7.2, 88.1]	38.3 [12.9, 59.9]

%
a) Calculated by normal approximation

PMDA's view:
The global phase III studies (Studies R668-AD-1334 and R668-AD-1224) in patients with atopic dermatitis with an inadequate response to TCS demonstrated the superiority of dupilumab 300 mg once every 1 and 2 weeks to placebo in the rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment, the primary endpoints. The data of the secondary endpoints also suggest the efficacy of dupilumab. These results demonstrate the efficacy of dupilumab against atopic dermatitis.

In addition to the above, results of efficacy evaluation in the Japanese subpopulation were similar to those observed in the entire population in all clinical studies. Dupilumab is thus expected to be effective in Japanese patients with atopic dermatitis.

7.R.2.3 Efficacy in long-term administration

The applicant explained the efficacy of dupilumab in long-term administration as follows, based on the results of clinical studies:
In Study R668-AD-1224, efficacy evaluated by parameters such as the rates of achieving IGA ≤1 and EASI-75 did not show any major change from Week 16 to Week 52 of administration (Table 35), suggesting that the efficacy of dupilumab is generally maintained during continued administration. In the global phase III study (Study R668-AD-1415) which was conducted by changing the dosing interval of dupilumab in patients who had achieved IGA ≤1 or EASI-75 after 16 weeks of treatment in phase III monotherapy studies (Studies R668-AD-1334 and R668-AD-1416), the changes over time in the rate of achieving EASI-75 from baseline in the preceding study were as shown in Table 37. The rate of achieving EASI-75 tended to be higher in groups continuously receiving dupilumab compared with the placebo group, and the prolongation of the dosing interval tended to result in a decrease in the rate of achieving EASI-75. The placebo group did not show any disease aggravation exceeding the baseline level after discontinuation of dupilumab.

Table 37. Changes over time in rate of achieving EASI-75 in Study R668-AD-1415 from baseline in the preceding study (FAS, NRI)

	n	End of preceding study	[redacted] weeks after the end of preceding study	[redacted] weeks after the end of preceding study	[redacted] weeks after the end of preceding study	[redacted] weeks after the end of preceding study	[redacted] weeks after the end of preceding study	36 weeks after the end of preceding study
Dupilumab 300 mg QW/Q2W	[redacted]							
Dupilumab 300 mg Q4W								
Dupilumab 300 mg Q8W								
Placebo								

% (number of patients)
Patients who received a rescue treatment were handled as non-responders.

In the global phase III extension/re-administration study (Study R668-AD-1225), efficacy data were compared between patients receiving dupilumab for ≥13 weeks[19] from the last dose of dupilumab in the preceding study (re-administration group) and patients not receiving dupilumab in the preceding study (untreated group). Changes over time in the rate of achieving IGA ≤1 in the untreated group and the re-administration group were as shown in Table 33, indicating a similar tendency in these two populations although there are limitations to the comparison. These results suggest that efficacy of dupilumab is unlikely to decrease by re-administration.

In Study R668-AD-1224 with the dupilumab administration period of 52 weeks, the changes over time in the rates of achieving IGA ≤1 and EASI-75 were as shown in Table 35. Since therapeutic response to dupilumab was obtained by 16 weeks of treatment, it was considered possible to evaluate the therapeutic response to dupilumab at or before 16 weeks of treatment. Therefore, if therapeutic response was not available within 16 weeks after the start of the treatment, it is essential to reconsider and select a plan appropriate for each patient from among all possible options taking account of the clinical symptoms, under the guidance of a physician experienced in the treatment of atopic dermatitis.

PMDA's view:
PMDA accepts the applicant's explanation that the response to the treatment with dupilumab is possible to be evaluable by Week 16. In patients with atopic dermatitis unresponsive to dupilumab, physicians should be cautioned not to continue treatment with dupilumab excursively and to consider switching to other treatment methods. In patients who responded to dupilumab, whether or not to continue treatment with dupilumab should be carefully determined by the physician including the option of switching to the treatment with a topical skin moisturizer and a topical anti-inflammatory drug only, depending on the condition of individual patients, by taking account of the observations that a certain percentage of patients maintained EASI-75 even 36 weeks after the end of dupilumab administration (Study R668-AD-1415, Table 37) and that the Japanese and foreign clinical practice guidelines recommend that, once improvement in symptoms has been achieved by immunosuppressant, etc., the patient be switched to treatment with TCS and a topical skin moisturizer.

[19] This criterion was established by taking account of the time required for the serum dupilumab to become undetectable from the last dose (the time point when serum dupilumab concentration is in the steady state) in dupilumab 300 mg once every 2 or 1 week in other studies.

7.R.2.4 Efficacy in patients with an inadequate response to oral cyclosporine

The applicant's explanation about the efficacy of dupilumab in patients with atopic dermatitis with an inadequate response to oral cyclosporine:

In a foreign phase III study (Study R668-AD-1424) in patients with atopic dermatitis for whom oral cyclosporine is not recommended for a reason of insufficient efficacy or safety problem, the rate of achieving EASI-75 after 16 weeks of treatment, the primary efficacy endpoint, was 62.6% (67 of 107) of patients in the dupilumab 300 mg Q2W group, 59.1% (65 of 110) of patients in the 300 mg QW group, and 29.6% (32 of 108) of patients in the placebo group, demonstrating the superiority of dupilumab to placebo (difference from the placebo group [%] [95% confidence interval (CI)], 29.5 [16.9, 42.1] in the 300 mg Q2W group, 33.0 [20.4, 45.6] in the 300 mg QW group). The rate of achieving IGA ≤1 also tended to be higher in the dupilumab groups than in the placebo group. The safety profile was not significantly different between the treatment groups, showing no new safety concern related to dupilumab.

PMDA's view:

Dupilumab is expected to be effective even in patients with atopic dermatitis with an inadequate response to oral cyclosporine. However, since dupilumab has not been investigated in Japanese patients with atopic dermatitis with an inadequate response to oral cyclosporine, the efficacy, etc., should be investigated in this patient group after the market launch. In addition, the toxicity and adverse drug reactions due to oral cyclosporine should be considered. However, because of the limited information currently available regarding the benefit-risk balance between dupilumab and oral cyclosporine, the appropriate choice between these drugs should be continuously investigated based on the safety information, etc., for dupilumab to be collected in the post-marketing surveillance, etc.

7.R.3 Safety

7.R.3.1 Outline of safety

The applicant explained the safety of dupilumab as follows based on (1) the pooled safety data of 3 dupilumab monotherapy studies (Studies R668-AD-1021, R668-AD-1334, and R668-AD-1416) in patients with atopic dermatitis (pooled data of 3 monotherapy studies), (2) safety data of Study R668-AD-1224, a TCS combination therapy study, (3) pooled safety data obtained during dupilumab administration period in 8 Japanese and foreign clinical studies (Studies R668-AD-1021, R668-AD-1117, R668-AD-1314, R668-AD-1307, R668-AD-1334, R668-AD-1416, R668-AD-1224, and R668-AD-1225) (pooled data of 8 Japanese and foreign studies), and (4) pooled safety data obtained during dupilumab administration period in 3 global studies (Studies R668-AD-1021, R668-AD-1334, and R668-AD-1224) (pooled data of 3 global studies), and other studies:

Table 38 shows the outline of the safety of dupilumab in the pooled data of 3 monotherapy studies and in Study R668-AD-1224. The safety up to 16 weeks of administration was generally similar between the pooled data of 3 monotherapy studies and Study R668-AD-1224, suggesting that TCS combination therapy does not significantly affect the safety profile of dupilumab. As for the safety up to 52 weeks of treatment in Study R668-AD-1224, there were no events occurring at a higher incidence in the dupilumab group than in the placebo group.

Table 39 shows the safety outline of dupilumab in the pooled data of 8 Japanese and foreign studies and in the pooled data of 3 global studies. The safety profile was similar between the entire population and the Japanese subpopulation.

Table 38. Outline of safety up to 16 and 52 weeks of dupilumab administration (pooled data of 3 monotherapy studies and Study R668-AD-1224, safety analysis population)

		Pooled data of 3 monotherapy studies			Study R668-AD-1224 (TCS combination therapy)		
		Q2W (n = 529)	QW (n = 518)	Placebo (n = 517)	Q2W (n = 110)	QW (n = 315)	Placebo (n = 315)
Up to 16 weeks of dupilumab administration	All adverse events	366 (69.2)	357 (68.9)	359 (69.4)	81 (73.6)	228 (72.4)	215 (68.3)
	Serious adverse events	13 (2.5)	11 (2.1)	26 (5.0)	3 (2.7)	4 (1.3)	6 (1.9)
	Death	0	1 (0.2)	0	0	0	0
	Adverse events leading to discontinuation	10 (1.9)	8 (1.5)	10 (1.9)	1 (0.9)	8 (2.5)	15 (4.8)
	Adverse drug reactions	146 (27.6)	158 (30.5)	104 (20.1)	28 (25.5)	87 (27.6)	67 (21.3)
Up to 52 weeks of dupilumab administration	All adverse events				97 (88.2)	263 (83.5)	268 (85.1)
	Serious adverse events				4 (3.6)	10 (3.2)	16 (5.1)
	Death				0	1 (0.3)	0
	Adverse events leading to discontinuation				2 (1.8)	9 (2.9)	25 (7.9)
	Adverse drug reactions				37 (33.6)	110 (34.9)	92 (29.2)

Number of patients (%)

Table 39. Outline of the safety of dupilumab
(pooled data of 8 Japanese and foreign studies and pooled data of 3 global studies, safety analysis populations)

	Pooled data of 8 Japanese and foreign studies	Pooled data of 3 global studies					
Entire population	Patients receiving dupilumab[a)] (n = 2484)	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 403)	300 mg QW (n = 596)	Placebo (n = 598)
Total exposure period (patient-years)	1864.9	19.5	17.3	20.0	191.1	381.5	368.7
All adverse events	1920 (77.3) 343.6	51 (78.5) 609.5	43 (70.5) 512.8	48 (73.8) 516.6	309 (76.7) 453.6	463 (77.7) 377.5	459 (76.8) 373.4
Serious adverse events	119 (4.8) 6.6	3 (4.6) 15.7	1 (1.6) 5.9	0	13 (3.2) 6.9	13 (2.2) 3.4	29 (4.8) 8.1
Death	2 (0.1) 0.1	0	0	0	0	1 (0.2) 0.3	0
Adverse events leading to discontinuation	80 (3.2) 4.4	10 (15.4) 55.2	3 (4.9) 17.5	3 (4.6) 15.3	10 (2.5) 5.3	14 (2.3) 3.7	30 (5.0) 8.4
Adverse drug reactions	842 (33.9) 63.3	21 (32.3) 141.9	16 (26.2) 109.9	16 (24.6) 95.1	119 (29.5) 81.0	202 (33.9) 72.1	147 (24.6) 50.3
Japanese subpopulation	Patients receiving dupilumab[a)] (n = 228)	100 mg Q4W (n = 11)	200 mg Q2W (n = 9)	300 mg Q4W (n = 11)	300 mg Q2W (n = 62)	300 mg QW (n = 91)	Placebo (n = 97)
Total exposure period (patient-years)	194.7	3.2	2.6	3.4	29.1	58.1	62.4
All adverse events	189 (82.9) 349.7	8 (72.7) 601.2	6 (66.7) 320.9	10 (90.9) 901.9	48 (77.4) 421.0	72 (79.1) 353.4	80 (82.5) 406.4
Serious adverse events	3 (1.3) 1.5	0	0	0	1 (1.6) 3.5	1 (1.1) 1.7	4 (4.1) 6.6
Death	0	0	0	0	0	0	0
Adverse events leading to discontinuation	10(4.4) 5.3	2 (18.2) 73.6	0	2 (18.2) 65.8	1 (1.6) 3.4	3 (3.3) 5.2	4 (4.1) 6.6
Adverse drug reactions	72 (31.6) 48.5	3 (27.3) 123.0	1 (11.1) 39.3	2 (18.2) 66.2	20 (32.3) 87.7	25 (27.5) 53.6	22 (22.7) 41.7

Upper row, number of patients (%); lower row, incidence per 100 patient-years adjusted for the exposure period[b)]
a) All patients receiving dupilumab regardless of the dosage regimen
b) Sum of the period until the occurrence of the first event (observation period in patients without event)

Table 40 shows main adverse events observed in the pooled data of 8 Japanese and foreign studies and in the pooled data of 3 global studies. Adverse events with a higher incidence in the dupilumab group compared with the placebo group included injection site reaction, headache, conjunctivitis allergic, conjunctivitis, and oral herpes. Main adverse events observed in the Japanese subpopulation in the pooled data of 3 global studies included dermatitis atopic (25.8% [16 of 62] of patients in the 300 mg Q2W group, 6.6% [6 of 91] of patients in the 300 mg QW group, 48.5% [47 of 97] of patients in the placebo group), nasopharyngitis (21.0% [13 of 62] of patients in the 300 mg Q2W group, 31.9% [29 of 91] of patients in the 300 mg QW group, 26.8% [26 of 97] of patients in the placebo group), and injection site reaction (6.5% [4 of 62] of patients in the 300 mg Q2W group, 16.5% [15 of 91] of patients in the 300 mg QW group, 1.0% [1 of 97] of patients in the placebo group), showing no clear difference either in the type or incidence of adverse events compared with the entire population.

Table 40. Adverse events reported by ≥2% of patients in the dupilumab group in the pooled data of 8 Japanese and foreign studies
(pooled data of 8 Japanese and foreign studies and pooled data of 3 global studies, safety analysis populations)

	Pooled data of 8 Japanese and foreign studies	Pooled data of 3 global studies					
	Patients receiving dupilumab[a)] (n = 2484)	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 403)	300 mg QW (n = 596)	Placebo (n = 598)
Total exposure period (patient-years)	1864.9	19.5	17.3	20.0	191.1	381.5	368.7
Nasopharyngitis	499 (20.1) 32.6	16 (24.6) 96.2	12 (19.7) 76.6	12 (18.5) 68.9	60 (14.9) 35.3	100 (16.8) 29.8	92 (15.4) 28.2
Dermatitis atopic	331 (13.3) 19.6	13 (20.0) 75.3	5 (8.2) 29.4	6 (9.2) 31.8	60 (14.9) 34.8	79 (13.3) 22.9	224 (37.5) 84.8
Injection site reaction	227 (11.2) 16.2	0	0	0	35 (8.7) 19.9	102 (17.1) 31.4	38 (6.4) 11.0
Headache	236 (9.5) 13.9	7 (10.8) 39.1	9 (14.8) 58.6	3 (4.6) 15.4	31 (7.7) 17.2	44 (7.4) 12.3	34 (5.7) 9.7
Upper respiratory tract infection	238 (9.6) 13.8	2 (3.1) 10.4	2 (3.3) 11.8	2 (3.1) 10.1	22 (5.5) 12.2	58 (9.7) 16.4	42 (7.0) 12.1
Conjunctivitis allergic	159 (6.4) 9.0	1 (1.5) 5.2	5 (8.2) 30.5	2 (3.1) 10.1	26 (6.5) 14.3	56 (9.4) 15.8	18 (3.0) 5.0
Conjunctivitis	139 (5.6) 7.8	1 (1.5) 5.2	0	1 (1.5) 5.1	13 (3.2) 6.9	19 (3.2) 5.1	7 (1.2) 1.9
Oral herpes	119 (4.8) 6.7	4 (6.2) 21.3	2 (3.3) 11.9	3 (4.6) 15.4	16 (4.0) 8.6	19 (3.2) 5.1	13 (2.2) 3.6
Diarrhoea	86 (3.5) 4.8	2 (3.1) 10.5	1 (1.6) 5.9	2 (3.1) 10.2	10 (2.5) 5.3	19 (3.2) 5.1	19 (3.2) 5.3
Blood creatine phosphokinase increased	85 (3.4) 4.7	1 (1.5) 5.2	2 (3.3) 12.0	1 (1.5) 5.1	9 (2.2) 4.8	15 (2.5) 4.0	15 (2.5) 4.1
Back pain	75 (3.0) 4.1	1 (1.5) 5.2	0	1 (1.5) 5.0	4 (1.0) 2.1	15 (2.5) 4.0	18 (3.0) 5.0
Fatigue	68 (2.7) 3.7	0	1 (1.6) 5.9	3 (4.6) 15.5	7 (1.7) 3.7	15 (2.5) 4.0	14 (2.3) 3.9
Cough	67 (2.7) 3.7	0	0	1 (1.5) 5.1	10 (2.5) 5.3	15 (2.5) 4.0	11 (1.8) 3.0
Bronchitis	64 (2.6) 3.5	2 (3.1) 10.4	0	1 (1.5) 5.0	6 (1.5) 3.2	6 (1.0) 1.6	9 (1.5) 2.5
Arthralgia	61 (2.5) 3.3	0	4 (6.6) 24.1	1 (1.5) 5.0	14 (3.5) 7.5	12 (2.0) 3.2	18 (3.0) 5.0
Oropharyngeal pain	59 (2.4) 3.2	2 (3.1) 10.5	2 (3.3) 11.9	0	6 (1.5) 3.2	15 (2.5) 4.0	13 (2.2) 3.6
Nausea	58 (2.3) 3.2	2 (3.1) 10.5	1 (1.6) 5.8	0	7 (1.7) 3.7	13 (2.2) 3.5	14 (2.3) 3.9
Urinary tract infection	58 (2.3) 3.2	0	5 (8.2) 30.5	3 (4.6) 15.3	7 (1.7) 3.7	13 (2.2) 3.5	18 (3.0) 5.0
Injection site erythema	59 (2.4) 3.2	0	0	3 (4.6) 15.5	6 (1.5) 3.2	7 (1.2) 1.8	1 (0.2) 0.3
Influenza	56 (2.3) 3.1	2 (3.1) 10.3	1 (1.6) 5.8	1 (1.5) 5.0	5 (1.2) 2.6	12 (2.0) 3.2	17 (2.8) 4.7
Viral upper respiratory tract infection	57 (2.3) 3.1	0	0	1 (1.5) 5.1	3 (0.7) 1.6	11 (1.8) 2.9	12 (2.0) 3.3
Sinusitis	54 (2.2) 2.9	1 (1.5) 5.2	0	0	4 (1.0) 2.1	20 (3.4) 5.4	10 (1.7) 2.7
Conjunctivitis bacterial	54 (2.2) 2.9	0	2 (3.3) 11.8	1 (1.5) 5.1	5 (1.2) 2.6	13 (2.2) 3.5	6 (1.0) 1.6
Herpes simplex	52 (2.1) 2.8	4 (6.2) 20.9	1 (1.6) 5.9	1 (1.5) 5.0	12 (3.0) 6.4	8 (1.3) 2.1	5 (0.8) 1.4

Upper row, number of patients (%); lower row, incidence per 100 patient-years adjusted for the exposure period[b)]
a) All patients receiving dupilumab regardless of the dosage regimen
b) Sum of the period until the occurrence of the first event (observation period in patients without event)

In the pooled data of 8 Japanese and foreign studies, death was observed in 2 patients in the 300 mg QW group (completed suicide, road traffic accident) and, during the follow-up period, death was observed in 1 patient in the 300 mg Q2W group (asthma/respiratory failure/hypoxic-ischaemic encephalopathy), but the causal relationship to the study drug was ruled out for all of these events.

Serious adverse events were observed in 4.8% (119 of 2484) of patients receiving dupilumab. Main events included dermatitis atopic (0.4% [11 patients]), squamous cell carcinoma of skin (0.2% [5 patients]), osteoarthritis (0.2% [4 patients]), squamous cell carcinoma, and syncope (0.1% [3 patients] each).

Adverse events leading to discontinuation were observed in 3.2% (80 of 2484) of patients receiving dupilumab.

Adverse events possibly related to dupilumab were investigated focusing on the following events, taking account of the pharmacological action of dupilumab.

7.R.3.2 Hypersensitivity, anaphylactic reaction, and injection site reaction

The applicant's explanation about the incidences of hypersensitivity, anaphylactic reaction, and injection site reaction following dupilumab administration:
Hypersensitivity including anaphylactic reaction is reported following the administration of various monoclonal antibodies. Also, injection site reaction is reported with other biological products for subcutaneous injection. These results suggest the possibility that similar events are induced by dupilumab as well.

Table 41 shows the incidences of hypersensitivity and anaphylactic reaction requiring treatment in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies. Evident causative agents other than dupilumab were identified for all anaphylactic reactions. For most of the treatment-requiring hypersensitivity events as well, distinct causative substances other than dupilumab were identified, whereas serum sickness and serum sickness-like reaction in 1 patient each were considered to be related to high-titer ADA [see Section 6.R.2].

Table 41. Incidences of hypersensitivity and anaphylactic reaction requiring treatment in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies

	Pooled data of 8 Japanese and foreign studies	Pooled data of 3 global studies					
	Patients receiving dupilumab[a)] (n = 2484)	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 403)	300 mg QW (n = 596)	Placebo (n = 598)
Total exposure period (patient-years)	1864.9	19.5	17.3	20.0	191.1	381.5	368.7
Treatment-requiring hypersensitivity (narrow SMQ)	23 (0.9) 1.2	2 (3.1) 10.3	2 (3.3) 11.8	0	4 (1.0) 2.1	1 (0.2) 0.3	4 (0.7) 1.1
Anaphylactic reaction (narrow SMQ)	4 (0.2) 0.2	0	1 (1.6) 5.9	0	0	0	0

Upper row, number of patients (%); lower row, incidence per 100 patient-years adjusted for the exposure period[b)]
a) All patients receiving dupilumab regardless of the dosage regimen
b) Sum of the period until the occurrence of the first event (observation period in patients without event)

In the pooled data of 3 global studies, injection site reaction was observed in 8.7% (35 of 403) of patients in the 300 mg Q2W group, 17.1% (102 of 596) of patients in the 300 mg QW group, and 6.4% (38 of 598) of patients in the placebo group, and injection site erythema was observed in 1.5% (6 of 403) of patients in the 300 mg Q2W group, 1.2% (7 of 596) of patients in the 300 mg QW group, and 0.2% (1 of 598) of patients in the placebo group, with both events being more frequent in the dupilumab groups, whereas there were no severe injection site reactions lasting for >24 hours. In the pooled data of 8 Japanese and foreign studies, severe injection site reaction lasting for >24 hours was observed in 1 patient. The reaction resolved after administration of dupilumab was discontinued, thus a causal relationship of the event to the study drug could not be ruled out. The severity of dupilumab-induced injection site reaction is generally similar to that caused by subcutaneous administration of biological products.

Since serum sickness and serum sickness-like reaction were observed as dupilumab-induced serious hypersensitivity events as described above, the package insert will include this information and the caution statement that patients should be closely monitored after administration of dupilumab and, if a pertinent event is observed, appropriate measures should be taken.

PMDA's view:
Although dupilumab-related anaphylactic reaction was not observed in clinical studies, the possibility cannot be excluded that dupilumab induces shock or anaphylactic reaction because dupilumab is a monoclonal antibody. In fact, dupilumab-related serious hypersensitivity has been observed. Also, results of clinical studies show that the incidence of injection site reaction is higher in the dupilumab group than in the placebo group, and serious injection site reaction was observed. The caution statement regarding these events should be included in the package insert. Also, occurrences of hypersensitivity, anaphylactic reaction, and injection site reaction should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

7.R.3.3 Infection

The applicant's explanation about the incidences of infection following dupilumab administration:
Infections were investigated with focus on parasitic infection which is considered to be related to compromised regulation of type 2 immune reaction and opportunistic infection, by referring to experience with other biological products.

Table 42 shows the incidences of infection in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies. The incidences of upper respiratory tract infection, conjunctivitis, oral herpes, and herpes simplex tended to be higher in the dupilumab group than in the placebo group, but most of the events were mild to moderate in severity. There was no tendency of serious infection or opportunistic infection occurring more commonly in the dupilumab group than in the placebo group.

As an event related to parasitic infection, 1 patient in the 300 mg QW group was found to be serology positive (reported event name: *Strongyloides stercoralis* serologically positive), but the event was diagnosed as mild by the investigator and its causal relationship to the study drug was ruled out. The event did not lead to treatment discontinuation nor was it symptomatic. Since the effect of dupilumab on the immune reaction to parasitic infection is unknown, caution against parasitic infection will be provided.

Table 42. Incidences of infection in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies (safety analysis population)

	Pooled data of 8 Japanese and foreign studies	Pooled data of 3 global studies					
	Patients receiving dupilumab[a)] (n = 2484)	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 403)	300 mg QW (n = 596)	Placebo (n = 598)
Total exposure period (patient-years)	1864.9	19.5	17.3	20.0	191.1	381.5	368.7
Infections and infestations (SOC)	1236 (49.8) 119.1	35 (53.8) 257.4	26 (42.6) 202.9	30 (46.2) 212.1	174 (43.2) 132.7	276 (46.3) 113.4	273 (45.7) 115.1
Serious infections and infestations (SOC)	15 (0.6) 0.8	0	0	0	2 (0.5) 1.1	2 (0.3) 0.5	4 (0.7) 1.1
Severe infections and infestations (SOC)	23 (0.9) 1.2	1 (1.5) 5.1	0	0	4 (1.0) 2.1	2 (0.3) 0.5	10 (1.7) 2.7
Infections and infestations (SOC) requiring treatment with parenteral antibacterial agent	13 (0.5) 0.7	0	0	0	1 (0.2) 0.5	4 (0.7) 1.1	3 (0.5) 0.8
Infections and infestations (SOC) requiring treatment with oral antibacterial agent/antiviral agent/antifungal agent for >2 weeks	18 (0.7) 1.0	0	0	0	1 (0.2) 0.5	2 (0.3) 0.5	6 (1.0) 1.6
Parasitic infection[b)]	1 (<0.1) <0.1	0	0	0	0	1 (0.2) 0.3	0
Opportunistic infection[c)]	33 (1.3) 1.8	0	0	0	4 (1.0) 2.1	3 (0.5) 0.8	14 (2.3) 3.9

Upper row, number of patients (%); lower row, incidence per 100 patient-years adjusted for the exposure period[d)]

a) All patients receiving dupilumab regardless of the dosage regimen
b) Cestode infection, helminthic infection not elsewhere classified (NEC), nematode infection, trematode infection (high level term [HLT])
c) Pneumocystis infection, fungal infection NEC, *Pseudallescheria* infection, herpes virus infection, *Paracoccidioides* infection, *Sporothrix schenckii* infection, cryptosporidiosis infection, *Trypanosoma* infection, *Campylobacter* infection, *Shigella* infection, Vibrio infection (HLT), Polyomavirus-associated nephropathy, BK virus infection, Cytomegalovirus infection, post transplant lymphoproliferative disorder, progressive multifocal leukoencephalopathy, bartonellosis, blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, *Aspergillus* infection, systemic candida, oropharyngeal candidiasis, cryptococcosis, listeriosis, tuberculosis, nocardiosis, mycobacterial infection, salmonellosis, hepatitis B, herpes zoster, strongyloidiasis, microsporidia infection, visceral leishmaniasis, hepatitis C (preferred term [PT])
d) Sum of the period until the occurrence of the first event (observation period in patients without event)

In clinical studies, there were no adverse events associated with reactivation of hepatitis virus B or C. However, since patients who had chronic hepatitis B, had a risk of reactivation of hepatitis virus B infection, or had chronic hepatitis C were excluded from clinical studies, the effect of dupilumab on the reactivation of hepatitis virus B and C is unknown. Also, adverse events associated with the reactivation of tuberculosis were not observed in clinical studies. Patients with active tuberculosis were excluded from clinical studies, precluding the assessment of the effect of dupilumab on tuberculosis. However, in light of the observation that Th1 cells or cytokines have more important roles than Th2 cytokines in the host defense against many pathogens including *Mycobacterium tuberculosis* (*Eur J Immunol*. 2007;37:729-37), dupilumab-induced decrease in type 2 immune reaction is unlikely to inhibit the host defense against facultative intracellular pathogens including *Mycobacterium tuberculosis*.

PMDA's view:

The pharmacological action of dupilumab suggests its effect on the immune system, and the incidences of oral herpes and herpes simplex tend to be higher in the dupilumab group than in the placebo group (Table 40). Caution not only against parasitic infection but also against other infections should be included in the package insert, and the incidences of infections should be carefully monitored continuously in the post-marketing surveillance. As for the caution statement regarding the activation of tuberculosis and the reactivation of hepatitis virus B and C, appropriate measures should be taken

upon close examination of the data on their occurrences collected in the post-marketing surveillance, etc.

7.R.3.4 Conjunctivitis

The applicant's explanation about the incidences of conjunctivitis following dupilumab administration: Results of phase III studies showed higher incidences of conjunctivitis and conjunctivitis-associated events in the dupilumab group than in the placebo group, although the mechanism of the occurrences is unclear. Therefore, these events were investigated as adverse events of special interest.

Table 43 shows the incidences of conjunctivitis in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies. All events were observed more commonly in the dupilumab group than in the placebo group. As conjunctivitis-related events, blepharitis, eye pruritus, dry eye, etc., were also observed more commonly in the dupilumab group than in the placebo group in the pooled data of 3 global studies. (blepharitis 1.5% [6 of 403] of patients in the 300 mg Q2W group, 2.3% [14 of 596] of patients in the 300 mg QW group, 0.7% [4 of 598] of patients in the placebo group; eye pruritus 1.0% [4 of 403] of patients in the 300 mg Q2W group, 2.3% [14 of 596] of patients in the 300 mg QW group, 0.7% [4 of 598] of patients in the placebo group; dry eye 0.7% [3 of 403] of patients in the 300 mg Q2W group, 1.7% [10 of 596] of patients in the 300 mg QW group, 0.7% [4 of 598] of patients in the placebo group). Most of these events were mild or moderate, and resolved or improved during treatment with the study drug. A serious conjunctivitis (atopic keratoconjunctivitis) was observed in 1 patient in the pooled data of 8 Japanese and foreign studies. Its causal relationship to the study drug was ruled out, and the outcome was recovery.

Table 43. Incidences of conjunctivitis in the pooled data of 8 Japanese and foreign studies and the pooled data of 3 global studies (safety analysis population)

	Pooled data of 8 Japanese and foreign studies	Pooled data of 3 global studies					
	Patients receiving dupilumab[a)] (n = 2484)	100 mg Q4W (n = 65)	200 mg Q2W (n = 61)	300 mg Q4W (n = 65)	300 mg Q2W (n = 403)	300 mg QW (n = 596)	Placebo (n = 598)
Total exposure period (patient-years)	1864.9	19.5	17.3	20.0	191.1	381.5	368.7
Conjunctivitis allergic (PT)	159 (6.4) 9.0	1 (1.5) 5.2	5 (8.2) 30.5	2 (3.1) 10.1	26 (6.5) 14.3	56 (9.4) 15.8	18 (3.0) 5.0
Conjunctivitis (PT)	139 (5.6) 7.8	1 (1.5) 5.2	0	1 (1.5) 5.1	13 (3.2) 6.9	19 (3.2) 5.1	7 (1.2) 1.9
Conjunctivitis bacterial (PT)	54 (2.2) 2.9	0	2 (3.3) 11.8	1 (1.5) 5.1	5 (1.2) 2.6	13 (2.2) 3.5	6 (1.0) 1.6
Conjunctivitis viral (PT)	11 (0.4) 0.6	0	0	0	2 (0.5) 1.1	1 (0.2) 0.3	0
Atopic keratoconjunctivitis (PT)	8 (0.3) 0.4	0	0	0	0	3 (0.5) 0.8	1 (0.2) 0.3

Upper row, number of patients (%); lower row, incidence per 100 patient-years adjusted for the exposure period[b)]
a) All patients receiving dupilumab regardless of the dosage regimen
b) Sum of the period until the occurrence of the first event (observation period in patients without event)

Among patients receiving dupilumab in the pooled data of 3 monotherapy studies, patients who experienced conjunctivitis tended to have a longer mean duration of atopic dermatitis (33.0 years in patients with conjunctivitis, 27.4 years in patients without conjunctivitis), show a higher baseline disease activity (mean EASI score) (36.8 in patients with conjunctivitis, 31.9 in patients without conjunctivitis),

and show a higher percentage of patients with a past history of conjunctivitis compared with patients who did not experience conjunctivitis (37.8% [34 of 90] of patients with conjunctivitis, 14.5% [139 of 957]) of patients without conjunctivitis).

PMDA's view:
Since the results of clinical studies showed a tendency of higher incidence of conjunctivitis in the dupilumab group than in the placebo group, caution against the occurrences of conjunctivitis should be included in the package insert. Also, occurrences of conjunctivitis, together with the factors related to the risk of conjunctivitis, should be investigated in the post-marketing surveillance, and results thus obtained should be provided appropriately to healthcare professionals.

7.R.3.5 Asthma

The applicant's explanation about the incidences of asthma following dupilumab administration:
In the pooled data of 3 global studies, the incidence of asthma was 2.2% (9 of 403) of patients in the 300 mg Q2W group, 0.5% (3 of 596) of patients in the 300 mg QW group, and 3.8% (23 of 598) of patients in the placebo group. In patients who were transitioned to the follow-up period of phase III studies (Studies R668-AD-1334, R668-AD-1224, and R668-AD-1416), the incidence of asthma during the follow-up period was 0.6% (2 of 345) of patients in the 300 mg Q2W group, 1.2% (6 of 489) of patients in the 300 mg QW group, and 0.2% (1 of 626) of patients in the placebo group. In clinical studies in patients with atopic dermatitis, asthma-associated serious events were observed in 1 patient (asthma) in the 100 mg Q4W group and in 2 patients (asthma, status asthmaticus) in the 300 mg QW group during the dupilumab administration period, and in 1 patient (asthma) in the 300 mg Q2W group during the follow-up period. The outcome in the patient who had asthma during the follow-up period was death [see Section 7.R.3.1]. A causal relationship to the study drug could not be ruled out for serious asthma in 1 patient in the 100 mg Q4W group.

In a clinical study in patients with asthma, the efficacy of dupilumab against asthma was suggested.[20)] Also, in a global phase II study in patients with asthma (Study DRI12544), the asthma exacerbation rate increased at approximately 6 weeks after discontinuation of dupilumab up to the level observed in the placebo group, and forced expiratory volume in 1 second decreased to the baseline level after approximately 4 weeks.

Given the above results, in patients with atopic dermatitis complicated with other allergic disease such as asthma, sufficient control of other allergic diseases during dupilumab administration may lead to a reduction in the dose of the co-administered antiasthmatic drugs, which in turn may result in exacerbation of the symptoms of other allergic diseases when administration of dupilumab is discontinued. Therefore, the package insert will include the caution statements that patients should be instructed to consult the physician regarding the treatment of other allergic diseases and that effect on other allergic diseases should be considered when administration of dupilumab is discontinued. Also,

[20)] In a global phase II study involving patients with asthma (Study DRI12544), the mean change in forced expiratory volume in one second after 12 weeks of treatment from baseline, the primary efficacy endpoint, was 0.45 L in the 200 mg Q2W group, 0.35 L in the 300 mg Q4W group, 0.36 L in the 300 mg Q2W group, and 0.18 L in the placebo group, showing a statistically significant difference in paired comparison between the placebo group and each dupilumab group.

coordination with a physician experienced in the treatment of asthma will be advised to facilitate the proper use of dupilumab in patients with atopic dermatitis complicated with asthma.

PMDA's view:
Given the occurrences of serious asthma during or after administration of dupilumab, attention should be paid to the control of allergic diseases such as asthma during and after administration of dupilumab in patients with atopic dermatitis complicated with allergic diseases such as asthma. Therefore, it should be advised that the physician who prescribes dupilumab coordinate with the physician in charge of treatment of allergic diseases such as asthma, and that patients should be instructed to comply with the use of the drugs for concurrent allergic diseases and with periodical office visits. Also, because of the limited number of patients complicated with allergic disease in clinical studies, safety in patients with atopic dermatitis complicated with other allergic diseases such as asthma should be investigated continuously in the post-marketing surveillance, etc., and results thus obtained should be provided appropriately to healthcare professionals.

7.R.3.6 Depression and suicidal behaviour

The applicant's explanation about the effect of dupilumab on depression and suicidal behaviour:
It is reported that patients with atopic dermatitis show a high incidence of depression, anxiety, and suicidal ideation (*J Allergy Clin Immunol.* 2006;118:226-3, *Hautarzt.* 2009;60:641-62, etc.), and that the incidence of suicidal ideation is 19.6% among patients with severe atopic dermatitis (*Suicide Life Threat Behav.* 2006;36:120-4). A correlation between blood IL-4 concentration and the condition of depression is suggested, and it is reported that major depression is improved by selective serotonin reuptake inhibitors and the improvement is associated with increased blood IL-4 concentration (*Clin Dev Immunol.* 2007;2007:76396).

In the pooled data of 3 global studies, the incidence of suicidal behaviour-related events[21)] was 0.3% (2 of 598) of patients in the placebo group and 0% in the dupilumab group. In the pooled data of 8 Japanese and foreign studies, a suicidal behaviour-related event was observed in 0.1% (1 of 2484) of patients receiving dupilumab (completed suicide). In a clinical study in patients with atopic dermatitis, serious psychiatric disorder-related events were observed in 10 patients receiving dupilumab, which were depression in 2 patients, suicidal ideation, completed suicide, mental status changes, delirium, anxiety, stress, psychotic disorder, and major depression in 1 patient each. The causal relationship to dupilumab was ruled out for all of these events. Death occurred in 1 of them (completed suicide).

Table 44 shows changes over time in Hospital anxiety and depression scale (HADS) score from baseline in an exploratory analysis of the pooled data of 2 phase III studies using dupilumab monotherapy (Studies R668-AD-1334 and R668-AD-1416). HADS score did not worsen in the dupilumab group compared to the placebo group.

[21)] Completed suicide, suicidal ideation, suicide attempt, suicidal depression, and suicidal behavior (PT)

Table 44. Changes over time in HADS score from baseline (pooled data of Studies R668-AD-1334 and R668-AD-1416, FAS, missing values imputed by multiple imputation method)

	Number of patients	Week 2	Week 4	Week 8	Week 16
Q2W	457	−3.0 ± 4.3	−4.0 ± 5.0	−4.7 ± 5.4	−5.0 ± 5.5
QW	462	−3.2 ± 4.8	−4.2 ± 5.3	−5.3 ± 5.9	−5.6 ± 5.7
Placebo	460	−0.9 ± 4.2	−1.3 ± 4.3	−1.5 ± 4.6	−1.6 ± 4.5

Mean ± SD (number of patients)
Data after a rescue treatment were handled as missing data.

Thus, the results of clinical studies do not suggest any risk of worsening depressive symptoms in patients with atopic dermatitis. Completed suicide occurred in 1 patient receiving dupilumab, but the patient had a history of suicidal ideation and depression, and a causal relation of the completed suicide to the study drug was ruled out. Thus, there are no findings suggesting that dupilumab induces suicidal behaviour.

PMDA's view:
Given the results of clinical studies, there is no information currently that suggests the relationship between treatment with dupilumab and depression or events related to suicidal behaviour. However, taking account of the observations that completed suicide was observed in 1 patient although its causal relationship to dupilumab was ruled out and that patients with atopic dermatitis have a high incidence of depression, anxiety, and suicidal ideation, attention should be continuously paid to the possible effect of dupilumab on depression and events related to suicidal behaviour.

7.R.3.7 Malignant tumor

The applicant's explanation about the risk of malignant tumor caused by dupilumab administration:
Since patients with mycosis fungoides or other cutaneous T-cell lymphoma at the initial stage are sometimes misdiagnosed with atopic dermatitis, mycosis fungoides and cutaneous T-cell dyscrasia were investigated as adverse events of special interest.

In the safety results of the pooled data of 9 placebo-controlled, randomized, double-blind, parallel-group studies in patients with atopic dermatitis who were completed by September 30, 2016 (Studies R668-AD-0914, R668-AD-1021, R668-AD-1026, R668-AD-1121, R668-AD-1117, R668-AD-1307, R668-AD-1314, R668-AD-1334, and R668-AD-1416) (poled data of 9 Japanese and foreign studies), the incidence of neoplasms benign, malignant and unspecified (incl. cysts and polyps) (SOC) was 1.5% (22 of 1489) of patients in the dupilumab group and 1.5% (11 of 721) of patients in the placebo group, and the incidence of mycosis fungoides or cutaneous T-cell dyscrasia was <0.1% (1 of 1489) of patients in the dupilumab group and 0.1% (1 of 721) of patients in the placebo group, showing that the incidence in the dupilumab group did not exceed that in the placebo group for either of the diseases. Also, during the entire period of Study R668-AD-1224 using dupilumab for 1 year, the incidence of neoplasms benign, malignant and unspecified (incl. cysts and polyps) (SOC) was 3.3% (14 of 425) of patients in the dupilumab group and 3.2% (10 of 315) of patients in the placebo group, and the incidence of mycosis fungoides or cutaneous T-cell dyscrasia was 0% (0 of 425) of patients in the dupilumab group and 0.3% (1 of 315) of patients in the placebo group, showing that the incidence in the dupilumab group did not exceed that in the placebo group for either of the diseases.

Based on the above, the applicant considers that there is no risk of dupilumab increasing the incidences of malignant tumor, mycosis fungoides, or cutaneous T-cell dyscrasia.

PMDA's view:
It is difficult to draw a conclusion on the risk of dupilumab causing malignant tumor based on the currently available data. Given the pharmacological action of dupilumab, and taking account of the facts that the immunosuppressive effect may possibly affect the suppressive mechanism against malignant tumor and that malignant tumor were observed in clinical studies, the effect of dupilumab on the occurrence of malignant tumor should be investigated continuously.

Thus, based on the reviews in Sections 7.R.3.1 to 7.R.3.7, PMDA concluded the overall safety of dupilumab as follows:
The submitted clinical data do not suggest major safety concerns affecting the tolerability of dupilumab in patients with atopic dermatitis, and the observed adverse events can be managed. However, serious events including death (e.g., asthma aggravation, serious hypersensitivity) were observed in clinical studies. Also, dupilumab, which is expected to be administered for a long-term period, may pose a risk of infection, etc., by suppressing IL-4 and IL-13 signal transduction over an extended period. Therefore, patients should be closely monitored for their conditions during treatment with dupilumab. The safety information obtained from the Japanese subpopulation does not show any unique events. However, because of the limited use experience of dupilumab in Japanese patients, the safety information during the long-term administration should be continuously collected in the post-marketing surveillance.

The above conclusion by PMDA will be finalized, taking account of comments raised in the Expert Discussion.

7.R.4 Indication

The applicant's explanation about the justification for the indication:
As described in Section 7.R.2, the pivotal clinical studies (Studies R668-AD-1334 and R668-AD-1224) were conducted in "patients with atopic dermatitis with an inadequate response to TCS," who were defined as patients with atopic dermatitis with disease activity (meeting all of the following criteria; IGA score ≥3, EASI score ≥16, and atopic dermatitis covering ≥10% of BSA) even after treatment with TCS of medium potency (strong class in the Japanese classification) or higher potency (TCI added as necessary) for ≥28 days. In Study R668-AD-1334, "patients with atopic dermatitis for whom TCS is not recommended for a safety reason, etc.," in whom TCS was confirmed by the investigator to cause intolerable effects, hypersensitivity reaction, marked skin atrophy, or systemic effects, were included in addition to patients who met the above criteria. Dupilumab was shown to be effective and had a favorable safety profile in Study R668-AD-1224 using dupilumab in combination with TCS which is the standard treatment for atopic dermatitis and in Study R668-AD-1334 investigating the efficacy of dupilumab monotherapy. These results suggest that patients with atopic dermatitis with disease characteristics similar to those of patients treated in these clinical studies are eligible for treatment with dupilumab.

Therefore, the applicant considered appropriate to select the target patients for treatment with dupilumab as patients with atopic dermatitis with disease activity despite appropriate treatment with TCS and TCI, the treatment method recommended by the Japanese clinical practice guidelines, or patients with moderate or severe atopic dermatitis for whom TCS is not recommended because of the risk outweighing the benefit of the treatment.

PMDA's view:
Based on the results of clinical studies, etc., patients to be treated with dupilumab should be specified as patients with atopic dermatitis that frequently flares up over an extended period and is poorly controlled even by an appropriate treatment with TCS and TCI for a certain period of time, or patients with atopic dermatitis for whom TCS, etc., is not recommended due to a safety reason, etc.

Therefore, the indication for dupilumab should be "atopic dermatitis that have not responded adequately to conventional treatments," and the Precautions Concerning Indications section of the package insert should include the caution statement that the target patients should be patients with disease activity not adequately responsive to appropriate treatment with topical anti-inflammatory drugs such as TCS and TCI, including patients for whom use of topical anti-inflammatory drugs such as TCS is not recommended. The information on the inclusion criteria used in clinical studies should be provided as reference information for selecting patients eligible for the treatment with dupilumab. In order to facilitate appropriate diagnosis and selection of patients treatable with dupilumab and proper use of dupilumab, it should be advised that dupilumab be administered by physicians experienced in the diagnosis and treatment of atopic dermatitis. Appropriateness of treatment with dupilumab in individual patients should be carefully evaluated upon thorough consideration of the expected benefits.

The above conclusion by PMDA will be finalized, taking account of comments raised in the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration

Based on the results of the global phase III studies (Studies R668-AD-1334 and R668-AD-1224) in patients with atopic dermatitis, as described below, the applicant explained that it is appropriate to specify the dosage and administration of dupilumab as "600 mg in the initial dose, followed by 300 mg once every 2 weeks."

- In Studies R668-AD-1334 and R668-AD-1224, the initial dose was twice the usual dose in order to allow serum dupilumab concentration to promptly reach the steady state and, by the above dosage regimen (600 mg in the initial dose and 300 mg in subsequent doses), the superiority of dupilumab 300 mg once every 1 and 2 weeks to placebo was demonstrated in the rate of achieving IGA ≤1 and the rate of achieving EASI-75, the primary endpoints (see Sections 7.2.1 and 7.2.2).

- In the Japanese and foreign clinical studies, administration of dupilumab 300 mg once every 2 weeks did not pose any safety problems [see Section 7.R.3].

In some patients, a higher serum dupilumab concentration was obtained by once weekly administration of dupilumab 300 mg, suggesting a superior efficacy. Therefore, in the proposed dosage and administration, once weekly administration was allowed in patients not sufficiently responsive to once every 2 weeks administration of 300 mg. However, taking account of the findings that, in Studies R668-AD-1334 and R668-AD-1224, no significant difference was observed in multiple efficacy endpoints between the QW group and the Q2W group, and the efficacy in long-term administration in Study R668-AD-1224 was similar between the two groups, that clinical characteristics or biomarkers could not be identified that are commonly seen in patients in whom a higher benefits are obtained by once weekly administration of dupilumab 300 mg than by once every 2 weeks administration, and that no clinical studies were conducted to investigate the effect of the decrease in the intervals of administration of dupilumab, the applicant considered appropriate to select the dosing interval of dupilumab as "once every 2 weeks" only.

PMDA concluded, based on the submitted data and on the results of reviews in Sections 7.R.2 and 7.R.3, that it is appropriate to specify the dosage and administration of dupilumab for atopic dermatitis as "600 mg in the initial dose, followed by 300 mg once every 2 weeks."

7.R.5.2 Concomitant use with topical skin moisturizer and topical anti-inflammatory drugs such as TCS and TCI

The applicant's explanation about the concomitant use of dupilumab with topical skin moisturizer and topical anti-inflammatory drugs such as TCS and TCI:

Dupilumab was demonstrated to be superior to placebo both in Study R668-AD-1224 which investigated the efficacy in concomitant use with TCS and Studies R668-AD-1334 and R668-AD-1416 which investigated the efficacy of dupilumab monotherapy [see Section 7.R.2], and concomitant use with TCS did not significantly affect the safety profile of dupilumab [see Section 7.R.3], which suggests that it is appropriate to use dupilumab either with or without topical anti-inflammatory drugs. The treatment with dupilumab may lead to a decrease in the percentage of the atopic dermatitis area relative in BSA, allowing a dose decrease or discontinuation of concomitant use with TCS. However, taking account of the following, topical anti-inflammatory drugs such as TCS and TCI should be applied to the affected areas periodically during treatment with dupilumab, as a general rule:

- In Studies R668-AD-1334, R668-AD-1416, and R668-AD-1224, the percentage of patients who received a rescue treatment at least once within 16 weeks of administration of dupilumab was as shown in Table 45, which suggested that the flare-up rate was lower during TCS combination therapy than during dupilumab monotherapy.

- The Japanese clinical practice guidelines recommend the concomitant use of topical anti-inflammatory drugs such as TCS and TCI with systemic treatment such as cyclosporine.

In all clinical studies investigating the efficacy of dupilumab, use of a constant dose of a topical skin moisturizer was required. Since it is considered that flare-up is preventable by continued use of a topical skin moisturizer after remission is achieved by treatment (Japanese clinical practice guidelines), it is plausible that the concomitant use with a topical skin moisturizer contributed to the efficacy of

dupilumab observed in clinical studies, warranting continued skin care, particularly with topical skin moisturizer.

Table 45. Percentage of patients who received rescue treatment at least once within 16 weeks of administration of dupilumab

	Q2W	QW	Placebo
Study R668-AD-1334 (dupilumab monotherapy)	21.0 (48/229)	23.4 (51/218)	51.8 (115/222)
Study R668-AD-1416 (dupilumab monotherapy)	16.1 (38/236)	19.8 (47/237)	52.1 (122/234)
Study R668-AD-1224 (TCS combination therapy)	10.9 (12/110)	11.1 (35/315)	37.5 (118/315)

% (number of patients)

PMDA's view:

Clinical studies demonstrated the efficacy of dupilumab regardless of use or non-use of concomitant topical anti-inflammatory drugs, without any serious safety problems. However, taking account of the fact that, in Japan, the concomitant use of a topical skin moisturizer and a topical anti-inflammatory drug is the standard treatment for atopic dermatitis, dupilumab should be used in combination with a continued use of a topical skin moisturizer and, as a general rule, with a topical anti-inflammatory drug in patients with atopic dermatitis with an inadequate response to an appropriate treatment with topical anti-inflammatory drugs such as TCS over a certain period.

The above conclusion by PMDA will be finalized, taking account of comments raised in the Expert Discussion.

7.R.6 Self-administration

The applicant explained the efficacy and safety of dupilumab self-administration as follows, based on the results of the self-administration in Japanese patients in the pivotal global phase III studies (Studies R668-AD-1334 and R668-AD-1224):

In Studies R668-AD-1334 and R668-AD-1224, patients who wished, and were capable of, self-injection at home (including injection by the caregiver) were to self-inject the first dose of dupilumab upon receiving thorough explanation and training at the study site on the first day of treatment, then self-inject the second dose on the first day of treatment (loading dose) and subsequent doses up to 3 weeks after the start of treatment at the study site under the supervision of the physician, etc., after which patients were to self-inject dupilumab at home.

Among the Japanese subpopulation, dupilumab was self-injected at least once in 32 of 36 patients in the Q2W group, in 29 of 35 patients in the QW group, and in 28 of 35 patients in the placebo group in Study R668-AD-1334; and in 15 of 16 patients in the Q2W group, in 43 of 47 patients in the QW group, and in 49 of 54 patients in the placebo group in Study R668-AD-1224.

Table 46 shows the rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment in the Japanese self-administration population. Self-administration did not affect the efficacy of dupilumab.

Table 46. Rates of achieving IGA ≤1 and EASI-75 after 16 weeks of treatment (Japanese self-injection population, NRI)

	Study R668-AD-1334			Study R668-AD-1224		
	Q2W	QW	Placebo	Q2W	QW	Placebo
Rate of achieving IGA ≤1	18.8 (6/32)	34.5 (10/29)	0 (0/28)	20.0 (3/15)	36.6 (15/41)	4.1 (2/49)
Difference from placebo [95% CI]	18.8 [−7.0, 42.5]	34.5 [9.5, 57.3]		15.9 [−12.9, 43.6]	32.5 [12.1, 51.0]	
Rate of achieving EASI-75	25.0 (8/32)	48.3 (14/29)	0 (0/28)	66.7 (10/15)	68.3 (28/41)	22.4 (11/49)
Difference from placebo [95% CI]	25.0 [−0.6, 48.2]	48.3 [24.4, 69.0]		44.2 [15.2, 68.5]	45.8 [25.9, 62.9]	

% (number of patients)
Patients who discontinued the study or received a rescue treatment were handled as non-responders.

As for safety, adverse events during the entire study period were observed in 78.1% (25 of 32) of patients in the Q2W group, 75.9% (22 of 29) of patients in the QW group, and 78.6% (22 of 28) of patients in the placebo group in Study R668-AD-1334; and in 80.0% (12 of 15) of patients in the Q2W group, 83.7% (36 of 43) of patients in the QW group, and 81.6% (40 of 49) of patients in the QW group in Study R668-AD-1224. The incidence of injection site reaction was 12.5% (4 of 32) of patients in the Q2W group, 13.8% (4 of 29) of patients in the QW group, and 3.6% (1 of 28) of patients in the placebo group in Study R668-AD-1334; and 0% (0 of 15) of patients in the Q2W group, 20.9% (9 of 43) of patients in the QW group, and 0% (0 of 49) of patients in the placebo group in Study R668-AD-1224. No clinically significant events were observed in self-injecting patients.

These results suggest that self-injection of dupilumab does not pose any particular efficacy or safety problems in Japanese patients with atopic dermatitis.

PMDA's view:
Currently, results of clinical studies do not suggest any particular safety or efficacy problems in self-administration. However, the appropriateness of self-injection should be carefully checked by the physician, and only if the patient is confirmed to be capable of self-injecting dupilumab after having received thorough training and fully understanding the risk and the coping method, he/she should be allowed to self-inject dupilumab. Physicians should be cautioned that when, after self-injection has been started, dupilumab-induced adverse drug reactions such as hypersensitivity are suspected or continued self-injection becomes difficult, self-injection should be stopped immediately and appropriate measures, such as careful monitoring of the patient, should be taken under the supervision of the physician. Also, safety measures such as preparation of information material should be taken by referring to the situations with approved biological products.

7.R.7 Post-marketing safety measures

The applicant's explanation about the post-marketing safety measures:
A post-marketing surveillance will be conducted to confirm the safety, etc., of dupilumab in routine clinical practice after the market launch, including the safety during long-term administration, thereby to collect the data on the occurrences of adverse events such as hypersensitivity and to identify unknown adverse drug reactions and understand the factors affecting the safety or efficacy.

PMDA concluded that the currently available data do not suggest any serious safety problems. However, given that serious events (e.g., asthma aggravation, serious hypersensitivity) including fatal cases were observed in clinical studies and that dupilumab is expected to be used for a long-term period, and the risk of infection, etc., caused by the resulting suppression of IL-4 and IL-13 signal transduction over an extended period is unclear, a post-marketing surveillance, etc., should be conducted to investigate the safety profile during the long-term use of dupilumab, including the occurrences of unknown adverse events.

It is essential that dupilumab should be used by physicians with thorough knowledge of dupilumab and sufficient knowledge and experience in atopic dermatitis and that, in case of the occurrence of adverse events such as asthma and psychiatric disorder, they should be addressed in coordination with other medical departments or institutions. Also, information should be provided to healthcare professionals by using material to facilitate the proper use of dupilumab.

The above conclusion of PMDA and the necessity of further 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 assessment is currently ongoing. Results and PMDA's conclusion will be reported in Review Report (2).

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

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that dupilumab has efficacy in the treatment of atopic dermatitis, and that dupilumab has acceptable safety in view of its benefits. Dupilumab provides a new option for the treatment of patients with atopic dermatitis that have not responded adequately conventional treatments, and thus has a clinical significance. The safety of dupilumab in routine clinical practice should be further investigated in the post-marketing surveillance.

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

10. Other

The definitions of efficacy endpoints in clinical studies are as shown below.

Endpoint	Definition
Common to all studies	
EASI score	A score for eczema area and severity calculated by the following equation, by assigning the scores of severity of erythema, infiltration/papule, scratch scars, and lichenification (none = 0, mild = 1, moderate = 2, severe = 3) and eczema area (0% = 0, 1%-9% = 1, 10%-29% = 2, 30%-49% = 3, 50%-69% = 4, 70%-89% = 5, 90%-100% = 6) in each of head and neck, trunk, upper limbs, and lower limbs. The minimal clinically significant change is reported to be 6.6 (*Allergy.* 2012;67:99-106). EASI score = subtotal of severity scores of head and neck × eczema area score of head and neck × 0.1 + subtotal of severity scores of trunk × eczema area score of trunk × 0.3 + subtotal of severity scores of upper limbs × eczema area score of upper limbs × 0.2 + subtotal of severity scores of lower limbs × eczema area score of lower limbs × 0.4
HADS score	An index for measuring anxiety and depression-related mental conditions by self-entry questionnaire. Answers to each of the questions on 7 anxiety-related items and on 7 depression-related items, 14 items in total, are scored (0-3; the higher the score, the greater the psychological distress) and the total score is calculated.
IGA score	A score measured by 5-point rating scale of 0 to 4 by the global assessment of skin rash by the investigator according to the following criteria: 0 = Clear (no signs of inflammation due to atopic dermatitis) 1 = Almost clear (just perceptible erythema or very mild pathological protrusion [papulation/humectation]) 2 = Mild (visibly detectable, pale pink erythema, or very mild protrusion [papulation/humectation]) 3 = Moderate (dusky-red, clearly discernible erythema, clearly recognizable protrusion [papulation/humectation], but not wide-spread) 4 = Severe (crimson/dark red erythema, marked and wide-spread protrusion [papulation/humectation])
Pruritus NRS score	A pruritus score self-assessed by the patient according to 11-point rating scale of 0 to 10 on a horizontal line, where "0" indicates "no itching" and "10" denotes "the worst imaginable itching." The patient marks the point that most adequately expresses the worst pruritus he/she has experienced during the past 24 hours.
Studies R668-AD-1334, R668-AD-1224, R668-AD-1416	
Rate of achieving EASI-50 Rate of achieving EASI-75 Rate of achieving EASI-90	Percentage of patients who showed ≥50%, ≥75%, or ≥90% decrease in EASI score from baseline
Rate of achieving IGA ≤1	Percentage of patients in whom IGA score is 0 or 1, and decreased by ≥2 points from baseline
Studies R668-AD-1225 and R668-AD-1415	
Rate of achieving EASI-75	Percentage of patients who showed ≥75% decrease in EASI score from baseline in the preceding study in which he/she participated
Rate of achieving IGA ≤1	Percentage of patients with IGA score of 0 or 1

Review Report (2)

October 26, 2017

Product Submitted for Approval

Brand Name	Dupixent 300 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 21, 2017

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized 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 and dosage and administration

The expert advisors at the Expert Discussion supported the PMDA's conclusion on the efficacy and dosage and administration of dupilumab described in the Review Report (1), and made the following comments:

- The goal of treatment of atopic dermatitis varies from patient to patient. To avoid unnecessary dupilumab administration to patients who have achieved the goal of treatment, physicians should periodically examine the necessity of continuing dupilumab therapy, including the necessity of switching to treatment only with a topical skin moisturizer and a topical anti-inflammatory drug, depending on the condition of individual patients. Also, information on the duration of dupilumab therapy and the clinical course after the discontinuation should be collected in the post-marketing surveillance, etc., and the information thus obtained should be used to improve the usage of dupilumab.
- In the Japanese subpopulation, the QW group tended to show superior results compared with the Q2W group [see Tables 27 and 30 in the Review Report (1)], suggesting the possibility that some Japanese patients with atopic dermatitis may gain greater benefit from once weekly administration of dupilumab 300 mg.

Based on the discussion, etc., at the Expert Discussion, PMDA instructed the applicant to collect information on the exposure to dupilumab (treatment duration, presence/absence of re-administration

after discontinuation), clinical course after discontinuation, and clinical course after re-administration, if any, in the post-marketing surveillance, etc., and to appropriately provide the information thus obtained to healthcare professionals. Also, a report has shown that Th17-mediated pathway is more strongly involved in Asian patients with atopic dermatitis than in Caucasian patients (*J Allergy Clin Immunol*. 2015;136:1254-64). Taking account of the report, PMDA instructed the applicant to investigate the necessity of shortening the dosing intervals based on the information to be obtained in the future.

The applicant agreed to follow the above instructions.

1.2 Clinical positioning and indications

The expert advisors at the Expert Discussion supported the PMDA's conclusion on the clinical positioning and indication of dupilumab described in the Review Report (1), and made the following comments:

- It is essential that physicians well experienced in the diagnosis and treatment of atopic dermatitis carefully select patients who need dupilumab therapy even after a certain period of appropriate treatment administered in accordance with the clinical practice guidelines. To ensure the proper use of dupilumab, relevant information should be provided appropriately.
- Treatment with dupilumab is expected to be switched eventually to topical anti-inflammatory drugs according to the condition of the individual patients at the discretion of the physician.

Taking account of the results of the review in Section "7.R.4 Indication" in the Review Report (1) and of the comments raised by the expert advisors at the Expert Discussion, PMDA instructed the applicant to include the following caution statements in the Precautions Concerning Indications section to ensure that healthcare professionals are fully aware of the cautions. The applicant agreed.

Precautions Concerning Indications

- Dupilumab should be used in patients with wide-spread, severe inflammatory rash who show an inadequate response even after a certain period of appropriate treatment with topical anti-inflammatory drugs, such as topical corticosteroid and topical tacrolimus (see the "Clinical Studies" section).
- As a general rule, dupilumab should be administered in combination with topical anti-inflammatory drugs according to the condition of the sites affected by atopic dermatitis.
- A topical skin moisturizer should be used continuously during the treatment with dupilumab.

1.3 Safety and risk management plan (draft)

The expert advisors at the Expert Discussion supported the PMDA's conclusion on the safety of dupilumab and the post-marketing safety measures described in the Review Report (1), and made the following comments:

- Some patients showed aggravation of symptoms of concurrent asthma during, or after discontinuation of, dupilumab therapy, and death occurred among patients who had asthma aggravation after discontinuation of dupilumab. When administering dupilumab to patients who have concurrent allergic disease such as asthma, it is essential to cooperate with the physician in charge of

the concurrent allergic disease so that the allergic disease is appropriately treated during, and after discontinuation of, dupilumab therapy.

- Respiratory system-related clinical information (e.g., global improvement, frequency of asthmatic attack, exposure to anti-asthmatic drugs) should be collected from patients with past or concurrent asthma, in order to investigate the effect of dupilumab on asthmatic symptoms in patients with past or concurrent asthma.
- The long-term safety and efficacy of dupilumab should be further investigated.
- Possibility of the abrupt flare-up of atopic dermatitis after the discontinuation of dupilumab should be continuously investigated
- Dupilumab is the first biological product indicated for atopic dermatitis. Therefore information on drugs co-administered with dupilumab and on the efficacy and safety of the co-administration should be collected extensively.

In view of the results of the review in Section "7.R.7 Post-marketing safety measures" in the Review Report (1) and of the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for dupilumab should include the safety and efficacy specifications presented in Table 47, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 48, and instructed the applicant to conduct post-marketing surveillance that allows these investigations.

Table 47. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity	• Serious infection • Aggravation of symptoms of concurrent allergic diseases such as asthma • Immunogenicity • Events related to depression and suicidal behaviour • Malignant tumor	• None
Efficacy specification		
• Efficacy in routine clinical practice		

Table 48. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (long-term use)	• Disseminate data gathered during the early post-marketing phase vigilance • Organize and disseminate information material for healthcare professionals • Organize and disseminate information material for patients • Ensure to provide information on proper use prior to delivery of dupilumab

The applicant's explanation about the main survey items:

As shown in Table 49, a specified use-results survey will be conducted in patients with atopic dermatitis that have not responded adequately to conventional treatments, to investigate the safety and efficacy of dupilumab in routine clinical practice. The observation period is 2 years, and the target sample size is 900. The specified use-results survey will primarily investigate the incidence of asthmatic attacks in patients with past or concurrent asthma, because only a small number of such patients were included in the clinical studies. Then the incidence will be compared with that in patients without past asthma and with that in the clinical studies. In patients who discontinued or interrupted the treatment during the

observation period, information on the clinical course after discontinuation or re-administration will be collected to evaluate the safety and efficacy of dupilumab.

Table 49. Outline of specified use-results survey (draft)

Objective	To collect and evaluate information on the safety and efficacy of dupilumab in routine clinical practice
Survey method	Central registration system
Population	Patients with atopic dermatitis that have not responded adequately to conventional treatments
Observation period	2 years
Planned sample size	900 patients (safety analysis population)
Main survey items	• Key survey item: Asthmatic attack • Patient characteristics (body weight, age, severity, disease duration, prior treatments, past history/concurrent illness, etc.) • Post-marketing exposure to dupilumab • Concomitant drugs and therapies • Laboratory tests • Adverse events • Efficacy • Diagnostic information related to the respiratory system

PMDA accepted the above response of the applicant. Information thus obtained should be provided appropriately and promptly to healthcare professionals.

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

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

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

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

The new drug application data (CTD 5.3.5.1-3, CTD 5.3.5.1-4, CTD 5.3.5.1-6, 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that, because the clinical studies as a whole were conducted in compliance with GCP, there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding at a study site although it did not significantly affect the overall evaluation of the clinical studies. The head of study site was notified of the finding because it requires corrective action.

Finding requiring corrective action

A study site

- Improper description in the contract document regarding partial consignment of the tasks related to the implementation of clinical studies

3. Overall Evaluation

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

Indication

Atopic dermatitis that have not responded adequately to conventional treatments ~~(only in patients with moderate to severe symptoms)~~

(Underline denotes text added to the proposed text. Strikethrough denotes deletion.)

Dosage and Administration

The usual initial dose for adults is 600 mg of dupilumab (genetical recombination)~~ once on the first day~~, followed by 300 mg ~~once~~ every 2 weeks, administered by subcutaneous injection. ~~If 300 mg once every 2 weeks does not demonstrate adequate efficacy, the dosage may be changed to 300 mg once weekly.~~

(Underline denotes text added to the proposed text. Strikethrough denotes deletion.)

Approval Conditions

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

Appendix

List of Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AEX	Anion exchange chromatography
AUC	Area under the serum concentration-time curve
BLQ	Below the lower limit of quantification
BSA	Body surface area
CAL	Cells at the limit of *in vitro* cell age used for production
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CEX	Cation exchange chromatography
CHO cells	Chinese hamster ovary cells
cIEF	Capillary isoelectric focusing
CL	Total body clearance for intravenous administration
CL/F	Total body clearance for extravascular administration
C_{max}	Maximum serum concentration
EASI	Eczema area and severity index
ECL	Immunological electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
HADS	Hospital anxiety and depression scale
HEK293 cells	Human embryonic kidney 293 cells
HIC	Hydrophobic interaction chromatography
HLT	High level term
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
Ig	Immunoglobulin
IGA	Investigator's global assessment
IL	Interleukin
IL-4Rα	Interleukin-4 receptor α-subunit
Japanese clinical practice guidelines	Clinical Practice Guidelines for the Management of Atopic Dermatitis, 2016 (edited by the Committee for Clinical Practice Guidelines for the management of Atopic Dermatitis of Japanese Dermatological Association) and Guidelines for the Management of Atopic Dermatitis, 2015 (edited by the Atopic Dermatitis Guidelines Advisory Committee, Japanese Society of Allergology)
K_D	Equilibrium dissociation constant
LOCF	Last observation carried forward
[redacted]	[redacted]
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
N.D.	Not detected
NEC	Not elsewhere classified
NRI	Non-responder imputation
NRS	Numerical rating scale
OC	Observed cases
PBMC	Peripheral blood mononuclear cells
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
QW	Once every week
QxW	Once every x weeks

SEC	Size exclusion chromatography
SMQ	Standardized MedDRA Query
SOC	System organ class
STAT	Signal transducer and activator of transcription
$t_{1/2}$	Half-life
TARC	Thymus and activation regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th2	T-helper type 2
t_{max}	Time of occurrence of maximum serum concentration
V_{ss}	Volume of distribution at steady-state
WCB	Working cell bank