Report on the Deliberation Results

February 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	(a) Dupixent 300 mg Syringe for S.C. Injection (b) Dupixent 300 mg Pen for S.C. Injection (c) Dupixent 200 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	(a), (b) March 31, 2023 (c) November 2, 2023

Results of Deliberation

In its meeting held on February 5, 2024, the Second Committee on New Drugs concluded that the partial change application for 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 re-examination period is 4 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

January 16, 2024
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	(a) Dupixent 300 mg Syringe for S.C. Injection (b) Dupixent 300 mg Pen for S.C. Injection (c) Dupixent 200 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	(a), (b) March 31, 2023, (c) November 2, 2023[1)]
Dosage Form/Strength	(a), (b) Injection: Each 2 mL syringe contains 300 mg of Dupilumab (Genetical Recombination). (c) Injection: Each 1.14 mL syringe contains 200 mg of Dupilumab (Genetical Recombination).
Application Classification	Prescription drugs, (4) Drugs with a new indication, (6) Drugs with a new dosage
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 chronic spontaneous urticaria that have not responded adequately to histamine H_1 receptor antagonists, and that the product has acceptable safety in view of its benefits (see Attachment).

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

1) On March 31, 2023, the applicant submitted an application for an additional dosage form and a new indication and a new dosage of chronic spontaneous urticaria. Thereafter, in September 2023, a new dosage of 200 mg syringe was approved for atopic dermatitis. In response to this, in November 2023, the applicant re-submitted an application for a new indication and new dosages of chronic spontaneous urticaria.

Indications

(a), (b) The following skin diseases that have not responded adequately to conventional treatments:

Atopic dermatitis
Prurigo nodularis
Chronic spontaneous urticaria

Bronchial asthma (only in patients with severe or intractable bronchial asthma whose asthmatic responses cannot be controlled by conventional treatments)

Chronic rhinosinusitis with nasal polyposis (only in patients who have not responded adequately to conventional treatments)

(c) The following skin diseases that have not responded adequately to conventional treatments:

Atopic dermatitis
Chronic spontaneous urticaria

(Underline denotes additions, dotted line denotes changes as of June 26, 2023.)

Dosage and Administration

(a), (b)

Atopic dermatitis

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

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥6 months is determined according to body weight and administered by subcutaneous injection.

≥5 kg and <15 kg: 200 mg every 4 weeks
≥15 kg and <30 kg: 300 mg every 4 weeks
≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks
≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Prurigo nodularis

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

Chronic spontaneous urticaria

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

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Bronchial asthma

The usual initial dose for adults and pediatric patients aged ≥12 years is 600 mg of dupilumab (genetical recombination) followed by 300 mg every 2 weeks, administered by subcutaneous injection.

Chronic rhinosinusitis with nasal polyposis

The usual dose for adults is 300 mg of dupilumab (genetical recombination) administered by subcutaneous injection every 2 weeks. After symptoms are stabilized, the dose of 300 mg may be subcutaneously administered every 4 weeks.

(c)

Atopic dermatitis

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥6 months is determined according to body weight and administered by subcutaneous injection.

≥5 kg and <15 kg: 200 mg every 4 weeks

≥15 kg and <30 kg: 300 mg every 4 weeks

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Chronic spontaneous urticaria

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

(Underline denotes additions, dotted line denotes changes as of June 26 or September 25, 2023.)

Approval Condition

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

Attachment

Review Report (1)

November 20, 2023

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

Product Submitted for Approval

Brand Name	(a) Dupixent 300 mg Syringe for S.C. Injection (b) Dupixent 300 mg Pen for S.C. Injection (c) Dupixent 200 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	(a), (b) March 31, 2023, (c) November 2, 2023[1)]
Dosage Form/Strength	(a), (b) Injection: Each 2 mL syringe contains 300 mg of Dupilumab (Genetical Recombination). (c) Injection: Each 1.14 mL syringe contains 200 mg of Dupilumab (Genetical Recombination).
Proposed Indications	(a), (b) <u>The following skin diseases</u> that have not responded adequately to conventional treatments: Atopic dermatitis <u>Chronic spontaneous urticaria</u> Bronchial asthma (only in patients with severe or intractable bronchial asthma whose asthmatic responses cannot be controlled by conventional treatments) Chronic rhinosinusitis with nasal polyposis (only in patients who have not responded adequately to conventional treatments) (c) The following skin diseases that have not responded adequately to conventional treatments: Atopic dermatitis <u>Chronic spontaneous urticaria</u> (Underline denotes additions.)

[1)] Applications for the drugs in an additional dosage form as well as with a new indication and a new dosage of chronic spontaneous urticaria (CSU) had been submitted on March 31, 2023, but the drug with a new dosage of 200 mg in a syringe dosage form was approved in September 2023 in response to addition of a new dosage for the treatment of atopic dermatitis. In November 2023, applications for the drugs with the new indication and new dosages of CSU were re-submitted.

Proposed Dosage and Administration

(a), (b)

Atopic dermatitis

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

Chronic spontaneous urticaria

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

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 and <18 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Bronchial asthma

The usual initial dose for adults and pediatric patients aged ≥12 years is 600 mg of dupilumab (genetical recombination) followed by 300 mg every 2 weeks, administered by subcutaneous injection.

Chronic rhinosinusitis with nasal polyposis

The usual dose for adults is 300 mg of dupilumab (genetical recombination) administered by subcutaneous injection every 2 weeks. After symptoms are stabilized, the dose of 300 mg may be subcutaneously administered every 4 weeks.

(c)

Atopic dermatitis

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥6 months is determined according to body weight and administered by subcutaneous injection.

≥5 kg and <15 kg: 200 mg every 4 weeks

≥15 kg and <30 kg: 300 mg every 4 weeks

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Chronic spontaneous urticaria

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 and <18 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

(Underline denotes additions.)

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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," etc., is a human immunoglobulin (Ig)G4 monoclonal antibody discovered by Regeneron Pharmaceuticals, Inc. in the US. 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. In Japan, since the 300 mg syringe product was approved for the indication of atopic dermatitis (AD) in January 2018, it has been approved for the indications of bronchial asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and prurigo nodularis (PN). Further, the 300 mg pen product was approved in September 2020 and the 200 mg syringe product in September 2023.

Urticaria is a disease characterized by vasodilatation (erythema), leakage of plasma component (hives), and pruritus caused by chemical substances such as histamine released into skin tissue through degranulation of skin mast cells. Urticaria is mainly classified into the following 4 disease types: The "inducible type" is characterized by symptoms induced by specific stimulation or burden; the "spontaneous type" is represented by hives that spontaneously appear without definite causes; the "angioedema type" appears as localized deep edema on the skin or mucosa; and the fourth type is the "urticaria associated diseases.[2)]" Spontaneous urticaria is largely classified according to its duration, namely, disease lasting ≤6 weeks is acute spontaneous urticaria, while that lasting >6 weeks is chronic spontaneous urticaria (CSU) (Guidelines for Diagnosis and Treatment of Urticaria 2018 edited by the Committee for Revision of Guidelines for Diagnosis and Treatment of Urticaria, the Japanese Dermatological Association [*Jpn J dermatol.* 2018;128:2503-624][hereafter, Clinical Practice Guideline]). For treatment of both diseases, the second generation histamine H_1 receptor antagonists (antihistamines) are used as the first-line drugs. Patients who have not adequately responded to multiple antihistamines even at increased doses are treated with a combination of adjunctive drugs (histamine H_2 receptor antagonists,[3)] leukotriene receptor antagonists,[3)] etc.) or with oral corticosteroids, omalizumab,[4)] etc. Spontaneous urticaria generally has a good prognosis, but the disease may become serious, affecting activities of daily living. Particularly, in patients whose symptoms are uncontrollable only with antihistamines, the symptoms often persist for years (Clinical Practice Guideline).

Causes of CSU that can explain the whole picture of its pathology cannot be identified, but a report (*J Immunol.* 2005;174:7716-24) showed that mast cells from mice deficient in IL-4 and IL-13 had decreased capacity of degranulation, and a case report (*J Allergy Clin Immunol Pract.* 2019;7:1659-61) presented that dupilumab improved the symptoms in patients with CSU. In view of these reports, the applicant developed dupilumab for CSU, expecting that dupilumab would have a therapeutic effect on CSU.

The applicant initiated the clinical development of dupilumab for CSU in [redacted] 20[redacted] and submitted applications for partial change approval of the 300 mg syringe product, 300 mg pen product, and

2) Urticarial vasculitis, urticaria pigmentosa, Schnitzler's syndrome, and cryopyrin-associated periodic syndrome
3) In Japan, these drugs have not been approved for the indication of urticaria.
4) Limited to chronic spontaneous urticaria in adults and pediatric patients aged ≥12 years

200 mg syringe product of dupilumab in March and November 2023 based on results from a global (including Japan) phase III study.

As of November 2023, dupilumab is approved in ≥60 countries and regions including the US and EU but is not approved for the indication of CSU in any countries or regions.

2. Quality and Outline of the Review Conducted by PMDA

The present application relates to new indications and new dosage, and no data relating to quality were submitted.

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

Although the present application relates to new indication and new dosage, no new data relating to non-clinical pharmacology were submitted because such data had been evaluated during the review process for the initial approval.

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

Although the present application related to new indication and new dosage, no new data relating to non-clinical pharmacokinetics were submitted because such data had been evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application relates to new indication and new dosage, and no data relating to toxicity were submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum dupilumab concentration was measured by enzyme-linked immunosorbent assay (ELISA) (lower limit of quantitation, 78 ng/mL). Concentrations of anti-drug antibody (ADA) and neutralizing antibody were measured by the electrochemical luminescence method (detection sensitivity; 13.9 ng/mL for ADA, 125 ng/mL for neutralizing antibody).

6.2 Clinical pharmacology

The applicant submitted evaluation data in the form of results from a global phase III study in patients with CSU and also submitted reference data in the form of results from a population pharmacokinetic analysis. Unless specified otherwise, the doses shown in this report are those of dupilumab.

6.2.1 Global phase III study (CTD 5.3.5.1-1, Study EFC16461 Study A [February 2020 to [redacted] 20[redacted]] and CTD 5.3.5.1-2, Study EFC16461 Study B [[redacted] 20[redacted] to [redacted] 20[redacted]])

In Study EFC16461 Study A (≥6 years of age) and Study B (≥12 years of age), patients with CSU subcutaneously received dupilumab for 24 weeks according to the age and weight category in Table 1. Table 1 also shows serum trough concentrations of dupilumab at steady state. Study A did not enroll pediatric patients aged ≥6 and <12 years who weighed <30 kg. Study A enrolled 2 pediatric patients

aged ≥6 and <12 years who weighed ≥30 kg, but their serum trough dupilumab concentrations could not be measured because both discontinued the study treatment prematurely.

In Study A, ADA was positive[5)] in 13.0% (9 of 69) of patients in the dupilumab group and 1.5% (1 of 66) of patients in the placebo group, and neutralizing antibody was positive in 11.6% (8 of 69) of patients in the dupilumab group.

In Study B, ADA was positive[5)] in 19.2% (10 of 52) of patients in the dupilumab group and 3.8% (2 of 53) of patients in the placebo group, and neutralizing antibody was positive in 15.4% (8 of 52) of patients in the dupilumab group and 3.8% (2 of 53) of patients in the placebo group.

Table 1. Serum trough concentrations of dupilumab at steady state in patients with CSU who received multiple subcutaneous administration of dupilumab (μg/mL, Study EFC16461 Study A and Study B)

		Dosage regimen[a)]	Study A	Study B
Adults	Overall population	300 mg Q2W (initial, 600 mg)	63.5 ± 34.2 (62)	57.7 ± 35.5 (46)
	Japanese subpopulation		78.2 ± 22.8 (6)	52.5 ± 24.8 (6)
Pediatric patients	Aged ≥12 and <18 years weighing ≥60 kg		78.8 (1)[b)]	64.6 (1)[c)]
	Aged ≥12 and <18 years weighing ≥30 kg and <60 kg	200 mg Q2W (initial, 400 mg)	22.4 (1)[d)]	-

Mean ± standard deviation (SD) or individual values (number of patients); -, No patients enrolled
a) The initial dose was composed of 2 units of 300 or 200 mg syringe
b) Aged 12 years weighing 60.2 kg at baseline
c) Aged 14 years weighing 72.0 kg at baseline
d) Aged 17 years weighing 57.0 kg at baseline

6.2.2 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis (NONMEM version 7.5.1) was performed using serum concentration data of dupilumab (239 sampling points in 118 patients) in Study EFC16461 Study A and Study B in patients with CSU, based on a population pharmacokinetic model developed from data in healthy adults, adult patients with AD, and adult and pediatric patients aged ≥12 years with asthma (2-compartment model with first-order absorption, first-order elimination, and parallel linear and non-linear Michaelis-Menten elimination, integrating body weight as a covariate for volume of distribution in the central compartment [V_2], elimination rate constant [k_e], and maximum non-linear elimination rate [V_{max}]).

The pharmacokinetics of dupilumab in patients with CSU was described appropriately by the model used, and all of the covariates[6)] included in post-hoc evaluation, except for body weight, had no clear impact on exposure to dupilumab in patients with CSU.

Table 2 shows estimated pharmacokinetics parameters of dupilumab at steady state.

5) A patient was classified as "ADA-positive" if ADA was negative at baseline but turned positive during the study treatment or if ADA was positive at baseline and the antibody titer increased ≥4 times from baseline during the study treatment.

6) The following parameters were investigated as covariates: Age, sex, body weight, race, creatinine clearance, albumin, ADA (positive or negative), severity of the disease at baseline (itch severity score over 7 days [ISS7], urticaria activity score over 7 days [UAS7], or hives severity score over 7 days [HSS7]), concomitant medication (without antihistamines, with an antihistamine at an approved dose, with an antihistamine at 2 to 3 times the approved dose, or with an antihistamine at 4 times the approved dose), and prior use of omalizumab (patients who were naive to, intolerant of, or inadequate responders to omalizumab).

Table 2. Estimated pharmacokinetics parameters of dupilumab at steady state based on the population pharmacokinetic model (Study EFC16461 Study A and Study B)

Dosage regimen	Population	Study A				Study B			
		No. of patients	$AUC_{\tau,SS}$ (μg•day/mL)	$C_{max,SS}$ (μg/mL)	$C_{trough,SS}$ (μg/mL)	No. of patients	$AUC_{\tau,SS}$ (μg•day/mL)	$C_{max,SS}$ (μg/mL)	$C_{trough,SS}$ (μg/mL)
300 mg Q2W (initial, 600 mg)	Japanese adults	6	1,360 ± 358	107 ± 26.8	80.6 ± 23.5	6	981 ± 427	79.4 ± 31.6	56.1 ± 27.9
	Non-Japanese adults	54	1,100 ± 489	87.4 ± 36.5	65.2 ± 32.7	41	1,030 ± 487	82.0 ± 35.9	60.8 ± 32.3
	Non-Japanese pediatric patients	1[a)]	1,430	113	86.2	1[b)]	1,140	90.3	66.7
200 mg Q2W (initial, 400 mg)	Non-Japanese pediatric patient	1[c)]	637	52.5	35.3				

Mean ± SD or individual value for n = 1
No pediatric patients weighing ≥15 kg and <30 kg (dosage regimen, 300 mg Q4W [initial, 600 mg]) were enrolled.
a) Aged 12 years weighing 60.2 kg at baseline
b) Aged 14 years weighing 72.0 kg at baseline;
c) Aged 17 years weighing 57.0 kg at baseline

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics and ADA development in patients with CSU

The applicant's explanation about pharmacokinetics and ADA development in patients with CSU:

In Study EFC16461 Study A and Study B, patients with CSU received dupilumab at the same dosage regimen as that in a clinical study in patients with AD, which had demonstrated the efficacy of dupilumab in treatment of itch. The mean ± standard deviation (SD) of serum trough concentrations of dupilumab in adult patients with CSU was 63.5 ± 34.2 mg/L in Study A and 57.7 ± 35.5 mg/L in Study B. These values were similar to the mean serum trough concentrations of dupilumab (58.8-79.9 mg/L) in populations of adult patients with AD, asthma, CRSwNP, and PN, which are the already approved indications of dupilumab. Serum trough concentrations of dupilumab in pediatric patients with CSU (78.8, 64.6, and 22.4 mg/L) fell within the range of individual serum trough concentrations of dupilumab in populations including adult patients with CSU and pediatric patients with AD. These findings support the appropriateness of evaluating the efficacy and safety in patients with CSU using the same dosage regimen as that for AD.

The exposure tended to be higher in the Japanese subpopulation than in the non-Japanese subpopulation, but the difference in exposure is not considered clinically meaningful for the following reason:

The higher trend of exposure in the Japanese subpopulation is considered attributable to the difference in mean body weight (81.1 kg in non-Japanese subjects, 62.8 kg in Japanese subjects) because only body weight was included in the population pharmacokinetic model as a covariate, and no additional covariates were identified in the post-hoc evaluation. However, no clinically meaningful differences are observed in change in itch severity score over 7 days (ISS7) from baseline to Week 24 (Table 12) or incidence[7)] of adverse events between body weight categories.

[7)] In the pooled population of global phase III studies (Study EFC16461 Study A and Study B), the incidence of all adverse events according to body weight category was 59.4% (38 of 64 patients) in the placebo group and 59.6% (34 of 57 patients) in the dupilumab group in the <75 kg category subgroup and 52.6% (30 of 57 patients) and 55.2% (37 of 67 patients) in the ≥75 kg category subgroup; and the incidence of serious adverse events was 3.1% (2 of 64 patients) and 3.5% (2 of 57 patients) in the <75 kg category subgroup and 8.8% (5 of 57 patients) and 4.5% (3 of 67 patients) in the ≥75 kg category subgroup.

As observed in clinical studies in patients with the approved indications, the exposure to dupilumab tended to be lower in ADA-positive patients than in ADA-negative patients, but no clinically meaningful differences were observed in the efficacy or safety of dupilumab between ADA-positive and ADA-negative patients, although evaluation on ADA development in patients with CSU had limitations because of the small sample size of ADA-positive patients.[8)]

PMDA accepted the applicant's explanation.

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 from 2 studies (see Table 3).

Table 3. Main clinical studies related to efficacy and safety

Phase	Study	Region	Subjects	No. of enrolled subjects (Japanese subjects)	Dosage regimen	Main endpoint (primary endpoint)
III	Study EFC16461 Study A	Global	Patients with CSU with inadequate response to antihistamines	(a) 70 (6) (b) 68 (6)	(a) Subcutaneous dupilumab (Table 4, Dosage regimen according to age and body weight) (b) Placebo	Efficacy and safety (change in ISS7 from baseline to Week 24)
III	Study EFC16461 Study B	Global	Patients with CSU with inadequate response to omalizumab	(a) 54 (6) (b) 54 (7)	(a) Subcutaneous dupilumab (Table 4, Dosage regimen according to age and body weight) (b) Placebo	Efficacy and safety (change in ISS7 from baseline to Week 24)

Table 4. Dosage regimen according to age and body weight

Age	Body weight	Dosage regimen [a)]
Adult	-	300 mg Q2W (initial, 600 mg)
≥12 and <18 years	≥60 kg	
	<60 kg	200 mg Q2W (initial, 400 mg)
≥6 and <12 years	≥30 kg	
	<30 kg	300 mg Q4W (initial 600 mg)

a) The initial dose was composed of 2 units of 300 mg or 200 mg syringe.

7.1 Phase III studies

7.1.1 Global phase III study (CTD 5.3.5.1-1, Study EFC16461 Study A [February 2020 to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of dupilumab in adult and pediatric patients aged ≥6 years with CSU who were

8) $C_{trough,SS}$ (pooled data from Study EFC16461 Study A and Study B) was 35.8 ± 20.8 mg/L in ADA-positive patients (n = 17) and 65.9 ± 34.8 mg/L in ADA-negative patients (n = 92); the change in ISS7 from baseline to Week 24 (data from Study EFC16461 Study A) was −10.3 ± 6.9 mg/L in ADA-positive patients (n = 9) and −10.2 ± 7.1 mg/L in ADA-negative patients (n = 57); and the incidence of adverse events (pooled data from Study EFC16461 Study A and Study B) was 68.4% (13 of 19) of ADA-positive patients and 56.0% (56 of 100) of ADA-negative patients.

inadequate responders to antihistamines (Table 5) (target sample size, 130 patients [65 per group][9]) in 9 countries or regions including Japan, Canada, and the US.

Table 5. Major inclusion and exclusion criteria

Major inclusion criteria: 1. ≥6 and ≤80 years of age 2. A diagnosis of CSU was given >6 months before screening. 3. Presence of itch and hives for >6 consecutive weeks despite use of second-generation non-sedating antihistamines 4. Use of second-generation non-sedating antihistamines at a constant dose for at least 3 days before screening 5. Presence of record on UAS and ISS for 7 days before baseline, showing UAS7 ≥16 and ISS7 ≥8 6. Naïve to omalizumab Major exclusion criteria: 1. Clearly defined underlying etiology for urticaria (e.g., inducible urticaria, diseases potentially accompanied by symptoms of urticaria or angioedema) 2. Active AD 3. Body weight <30 kg in patients aged ≥12 years or body weight <15 kg in patients aged ≥6 and <12 years

The study consisted of the treatment period (24 weeks) and post-treatment period (12 weeks). Patients subcutaneously received dupilumab or placebo for 24 weeks at the dosage regimen according to age and body weight at screening (Table 4), while receiving long-acting non-sedating antihistamines[10] at a constant dose throughout a period covering the screening (2-4 weeks before baseline) and study periods. Concomitant use of systemic immunosuppressants/immunomodulators, phototherapy, etc.[11] were prohibited, but the dose of an antihistamine could be increased to 4 times the recommended dose (2 times in Japan) for rescue treatment at the discretion of the investigator. Patients who had not responded adequately to such treatment were allowed to receive short-term oral corticosteroid (OCS) therapy.[12] Before the first dose, the investigator instructed the patients (or parents/caregivers for pediatric patients aged ≥6 and <12 years) how to prepare the study drug and perform self-administration. Of 2 units for the first dose, the first unit was administered by the investigator, etc. and the second unit by the patients (or parents/caregivers for pediatric patients aged ≥6 and <12 years) under the supervision of the investigator, etc. The subsequent doses were administered by the patients (or parents/caregivers for pediatric patients aged ≥6 and <12 years) when the investigator, etc. considered their self-administration acceptable.

All of the randomized 138 patients[13,14] (70 in the dupilumab group, 68 in the placebo group) were included in the intent-to-treat (ITT) population, which was the efficacy analysis population. All of 138

9) The target sample size of 130 patients (65 per group) was determined to ensure 96% power in the test on each primary endpoint at the two-sided significance level of 5% with the drop-out rate of 15% based on the following assumptions: The change in ISS7 from baseline to Week 24, the primary endpoint in Japan and countries or regions other than the EU and EU reference countries, had the effect size of 0.7 (5 for the difference between the dupilumab and placebo groups and 7 for common SD in both groups); and the change in UAS7 from baseline to Week 24, the primary endpoint in the EU and EU reference countries, had the effect size of 0.7 (10 for the difference between the dupilumab and placebo groups and 14 for common SD in both groups).

10) The dose could be increased to 4 times the approved dose (2 times in Japan).

11) Concomitant use of systemic immunosuppressants/immunomodulators (systemic steroids, cyclosporine, mycophenolate mofetil, etc.), tranexamic acid, epsilon-aminocaproic acid, biologics, phototherapy, immunoglobulin therapy, and plasmapheresis were prohibited. Subjects were withdrawn from the study treatment if they received any of these medications and therapies. Concomitant use of the following treatments were also prohibited: topical corticosteroids, topical calcineurin inhibitors, topical and oral antihistamines (other than drugs allowed for basic treatment), periodic use of doxepin (unapproved in Japan), leukotriene receptor antagonists, and H_2 receptor antagonists (except for stable use for diseases other than CSU). However, subjects were not withdrawn from the study treatment even if they received any of these treatments.

12) The starting dose (for the first 5 to 7 days) of OCS was 40 mg prednisone equivalent and subsequent tapering was allowed at the discretion of the investigator, etc.

13) Stratification factors were age (≥6 and <12 years/≥12 and <18 years/≥18 years) and country in the ≥18-year age subgroup. The study was planned to include pediatric patients aged ≥12 years accounting for approximately 5% of the target sample size.

patients who were randomized and received at least 1 dose of the study drug (70 in the dupilumab group, 68 in the placebo group) were included in the safety analysis population.

In total, 10.0% (7 of 70) of patients in the dupilumab group and 19.1% (13 of 68) of patients in the placebo group discontinued the study mainly because of consent withdrawal (4 patients in the dupilumab group, 8 patients in the placebo group) and adverse events (2 patients in the dupilumab group, 3 patients in the placebo group).

Table 6 shows data on a change in ISS7 from baseline to Week 24, the primary efficacy endpoint in Japan [for definition, see Section 10]. Pairwise comparison of the data between the dupilumab and placebo groups showed a statistically significant difference, demonstrating superiority of dupilumab over placebo. Table 6 also shows results in the Japanese subpopulation.

Table 6. Results of primary efficacy endpoint (ITT population)

	Dupilumab	Placebo
Overall population		
ISS7 at baseline (OC)	16.1 ± 4.0 (70)	15.7 ± 4.1 (68)
ISS7 at Week 24 (OC)	5.3 ± 5.9 (64)	8.1 ± 6.6 (53)
Change in ISS7 from baseline to Week 24[a),b)]	−10.2 [−12.0, −8.5]	−6.0 [−7.9, −4.2]
Difference from placebo[a), b)] *P* value[c)]	−4.2 [−6.6, −1.8] 0.0005	
Japanese subpopulation		
ISS7 at baseline (OC)	15.5 ± 3.7 (6)	18.2 ± 4.5 (6)
ISS7 at Week 24 (OC)	4.5 ± 4.0 (6)	6.0 ± 2.4 (6)
Change in ISS7 from baseline to Week 24[a),b)]	−11.8 [−18.7, −4.8]	−3.0 [−10.4, 4.4]
Difference from placebo[a),b)]	−8.8 [−18.5, 0.9]	

Mean ± SD (number of patients) or least mean square [95% confidence interval (CI)]

a) Analysis of covariance model using the baseline value, treatment group, angioedema at baseline, and region (Asia/Latin America/Western Europe and North America/Eastern Europe) as covariates

b) If a patient started prohibited concomitant medication/therapy or rescue treatment, their subsequent measurements were deemed to be missing, and the missing data (including missing values due to treatment discontinuation owing to inadequate response) were imputed by worst observation carried forward (WOCF). The other missing values were imputed using multiple imputation.

c) Two-sided significance level of 5%

Adverse events occurred in 54.3% (38 of 70) of patients in the dupilumab group and 58.8% (40 of 68) of patients in the placebo group. Table 7 shows main events.

Death occurred in 1 patient in the placebo group (completed suicide), but its causal relationship to the study drug was ruled out.

Serious adverse events occurred in 2.9% (2 of 70) of patients in the dupilumab group (depression and haemorrhoids in 1 patient each) and 7.4% (5 of 68) of patients in the placebo group (COVID-19 pneumonia, completed suicide, angioedema, dermatitis atopic, and dyspnoea/abdominal pain upper/nausea in 1 patient each). The causal relationship between these events and the study drug was ruled out.

Adverse events leading to treatment discontinuation occurred in 2.9% (2 of 70) of patients in the dupilumab group and 5.9% (4 of 70) of patients in the placebo group.

[14)] Breakdown of pediatric patients is as follows: 2 patients aged ≥6 and <12 years (both weighing ≥30 kg in the dupilumab group); 4 patients aged ≥12 years consisting of 1 weighing <60 kg (dupilumab group) and 3 weighing ≥60 kg (1 in the dupilumab group, 2 in the placebo group)

Adverse drug reactions occurred in 14.3% (10 of 70) of patients in the dupilumab group and 23.5% (16 of 68) of patients in the placebo group.

Table 7. Adverse events reported by ≥2% of patients in either group (safety analysis population)

Event	Dupilumab (N = 70)	Placebo (N = 68)	Event	Dupilumab (N = 70)	Placebo (N = 68)
Injection site reaction	4 (5.7)	2 (2.9)	Alanine aminotransferase increased	2 (2.9)	0
Chronic spontaneous urticaria	3 (4.3)	6 (8.8)	Angioedema	1 (1.4)	5 (7.4)
Injection site erythema	3 (4.3)	4 (5.9)	Nasopharyngitis	1 (1.4)	3 (4.4)
Urticaria	3 (4.3)	1 (1.5)	Injection site pain	1 (1.4)	3 (4.4)
Headache	2 (2.9)	3 (4.4)	Dermatitis contact	1 (1.4)	3 (4.4)
Depression	2 (2.9)	1 (1.5)	Oral herpes	1 (1.4)	2 (2.9)
Pharyngitis	2 (2.9)	0	Back pain	0	3 (4.4)
Viral upper respiratory tract infection	2 (2.9)	0	Abdominal pain upper	0	2 (2.9)
Injection site induration	2 (2.9)	0	Atopic dermatitis	0	2 (2.9)

n (%)

In the Japanese subpopulation, adverse events occurred in 50.0% (3 of 6) of patients in the dupilumab group and 66.7% (4 of 6) of patients in the placebo group, and events reported by ≥2 patients in either group were chronic spontaneous urticaria (1 patient in the dupilumab group, 2 patients in the placebo group) and dermatitis contact (2 patients in the placebo group).

No deaths, serious adverse events, or adverse drug reactions occurred.

An adverse event leading to treatment discontinuation occurred in 16.7% (1 of 6) of patients in the placebo group.

7.1.2 Global phase III study (CTD 5.3.5.1-2, Study EFC16461 Study B, [redacted] 20[redacted] to [redacted] 20[redacted])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of dupilumab in adult and pediatric patients aged ≥12 years with CSU who were inadequate responders to or intolerant of omalizumab (Table 8) (target sample size, 104 patients [52 per group][15]) in 11 countries or regions including Japan, the US, and Russia.

[15] The target sample size of 104 patients (52 per group) was determined to ensure 90% power in the test on each primary endpoint at the two-sided significance level of 5% based on the following assumptions: The change in ISS7 from baseline to Week 24, the primary endpoint in Japan and countries or regions other than the EU and EU reference countries, had the effect size of 0.7 (5 for the difference between the dupilumab and placebo groups and 7 for common SD in both groups); and the change in UAS7 from baseline to Week 24, the primary endpoint in the EU and EU reference countries, had the effect size of 0.7 (10 for the difference between the dupilumab and placebo groups and 14 for common SD in both groups).

Table 8. Major inclusion and exclusion criteria

Major inclusion criteria: 1. ≥12 years and ≤80 years of age 2. A diagnosis of CSU was given >6 months before screening. 3. Presence of itch and hives for >6 consecutive weeks despite use of second-generation non-sedating antihistamines 4. Use of second-generation non-sedating antihistamines at a constant dose for at least 3 days before screening 5. Presence of record on UAS and ISS for 7 days before baseline, showing UAS7 ≥16 and ISS7 ≥8 6. Intolerability to omalizumab, or termination of omalizumab for futility after receiving 300 mg Q4W or more intense dosage regimen for ≥3 months, is documented in the medical record. Major exclusion criteria: 1. Clearly defined underlying etiology for urticaria (e.g., inducible urticaria or diseases potentially accompanied by symptoms of urticaria or angioedema) 2. Active AD 3. Body weight <30 kg

The study consisted of the treatment period (24 weeks) and post-treatment period (12 weeks). Patients subcutaneously received dupilumab or placebo for 24 weeks at the dosage regimen according to age and body weight at screening (Table 4), while receiving long-acting non-sedating antihistamines[10] at a constant dose throughout a period covering the screening (2-4 weeks before baseline) and study periods. Concomitant use of systemic immunosuppressants/immunomodulators including omalizumab, phototherapy, etc.[11] were prohibited, but the dose of an antihistamine could be increased to 4 times the recommended dose (2 times in Japan) for rescue treatment at the discretion of the investigator. Patients who had not responded adequately to such treatment were allowed to receive short-term OCS therapy.[12] Before the first dose, the investigator instructed the patients how to prepare the study drug and perform self-administration. Of 2 units for the first dose, the first unit was administered by the investigator, etc., and the second unit by the patients under the supervision of the investigator, etc. The subsequent doses were administered by the patients when the investigator, etc. considered their self-administration acceptable.

The study had difficulty enrolling patients owing to COVID-19 pandemic. The protocol was therefore amended to perform an interim analysis to determine whether the study should be continued or early terminated for futility by evaluating the efficacy at an early stage during the study (amended protocol version [redacted] dated [redacted], 20[redacted]). The interim analysis was scheduled when the first randomized 83 patients[16] completed or were likely to complete the assessment at Week 24 by the cut-off date for this interim analysis.

For the interim analysis, the randomized 83 patients (43 in the dupilumab group, 40 in the placebo group) were included in the ITT24 population, which was the efficacy analysis population.

In total, 11.6% (5 of 43) of patients in the dupilumab group and 10.0% (4 of 40) of patients in the placebo group discontinued the study mainly because of consent withdrawal (2 patients in the dupilumab group, 3 patients in the placebo group).

Table 9 shows a change in ISS7 from baseline to Week 24, the primary efficacy endpoint in Japan [for the definition, see Section 10], and a change in urticaria activity score over 7 days (UAS7) from baseline to Week 24, the primary endpoint in the EU and EU reference countries [for the definition,

[16] Stratification factors were age (≥12 and <18 years/≥18 years) and country in the ≥18-year age subgroup. The study was designed to ensure that pediatric patients aged ≥12 years account for approximately 5% of the study population.

see Section 10]. Results met the protocol-specified criteria for futility ($P > 0.1$ for both ISS7 and UAS7), leading to issuance of a recommendation for early termination. The sponsor accepted the recommendation, sent a notification to the investigators and study sites, and instructed them to complete early termination visits.

Table 9. Results of the primary efficacy endpoint in the interim analysis (ITT24 population)

		Dupilumab	Placebo
ISS7			
	Baseline (OC)	15.7 ± 3.9 (43)	16.7 ± 3.5 (40)
	Week 24 (OC)	5.8 ± 4.8 (37)	8.8 ± 6.6 (35)
	Change from baseline to Week 24[a),b)]	−7.4 [−10.3, −4.5]	−5.5 [−8.4, −2.5]
	Difference from placebo[a),b)] *P* value[c)]	−2.0 [−5.3, 1.4] 0.2555	
UAS7			
	Baseline (OC)	30.7 ± 8.0 (43)	32.8 ± 7.5 (40)
	Week 24 (OC)	13.0 ± 10.9 (37)	18.1 ± 13.8 (35)
	Change from baseline to Week 24[a),b)]	−13.3 [−18.9, −7.6]	−10.1 [−15.9, −4.3]
	Difference from placebo[a,)b)] *P* value[c)]	−3.2 [−9.8, 3.5] 0.3529	

Mean ± SD (number of patients) or least mean square [97.9% CI]

a) Analysis of covariance model using the baseline value, treatment group, angioedema at baseline, and region (Asia/Latin America/Western Europe and North America/Eastern Europe) as covariates

b) If a patient started prohibited concomitant medication/therapy or rescue treatment, their subsequent measurements were deemed to be missing, and the missing data (including missing values due to treatment discontinuation owing to inadequate response) were imputed by WOCF. The other missing values were imputed using multiple imputation.

c) Two-sided significance level of 2.1%; multiplicity in the interim and final analyses was adjusted using O' Brien-Fleming α spending function.

By the time of the interim analysis, the number of enrolled patients reached the target sample size. All of 108 patients who were randomized and received ≥1 dose of the study drug (54 in the dupilumab group [including 1 pediatric patient weighing ≥60 kg], 54 in the placebo group [including 1 pediatric patient weighing <60 kg]) were included in the safety analysis population for the final analysis.

By the time of the final analysis, adverse events occurred in 61.1% (33 of 54) of patients in the dupilumab group and 53.7% (29 of 54) of patients in the placebo group. Table 10 shows the main events.

Neither deaths nor adverse events leading to treatment discontinuation occurred.

Serious adverse events occurred in 5.6% (3 of 54) of patients in the dupilumab group (intestinal obstruction, chronic spontaneous urticaria, and idiopathic angioedema in 1 patient each) and 3.7% (2 of 54) of patients in the placebo group (osteoarthritis and pain in extremity in 1 patient each). The causal relationship between these events and the study drug was ruled out.

Adverse drug reactions occurred in 9.3% (5 of 54) of patients in the dupilumab group and 9.3% (5 of 54) of patients in the placebo group.

Table 10. Adverse events reported by ≥2% of patients in either group (safety analysis population for the final analysis)

Event	Dupilumab (N = 54)	Placebo (N = 54)	Event	Dupilumab (N = 54)	Placebo (N = 54)
Chronic spontaneous urticaria	7 (13.0)	3 (5.6)	Injection site pain	2 (3.7)	0
COVID-19	5 (9.3)	4 (7.4)	Nasopharyngitis	1 (1.9)	4 (7.4)
Accidental overdose	3 (5.6)	2 (3.7)	Urinary tract infection	1 (1.9)	2 (3.7)
Hypertension	3 (5.6)	1 (1.9)	Injection site erythema	0	3 (5.6)
Cystitis	2 (3.7)	0	Blood creatine phosphokinase increased	0	2 (3.7)
Angioedema	2 (3.7)	0			

n (%)

In the Japanese subpopulation, adverse events occurred in 50.0% (3 of 6) of patients in the dupilumab group and 42.9% (3 of 7) of patients in the placebo group. None of the events were reported by ≥2 patients.

Neither deaths nor adverse events leading to treatment discontinuation occurred.

A serious adverse event occurred in 1 patient in the dupilumab group (intestinal obstruction), but its causal relationship to the study drug was ruled out.

Adverse drug reactions occurred in 16.7% (1 of 6) of patients in the dupilumab group and 14.3% (1 of 7) of patients in the placebo group.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about development plan of dupilumab:

The same definition and diagnosis criteria for CSU are used in and outside Japan. CSU is defined as urticaria that persists for ≥6 weeks without any specific etiology (the international EAACI/GA²LEN/EuroGuiDerm/APAAA CI guideline for the definition, classification, diagnosis, and management of urticaria [hereafter, International Guideline] and Clinical Practice Guideline).

Both in and outside Japan, the first-line drugs for CSU are second-generation non-sedating antihistamines, and for inadequate responders to such treatment, a dose increase of an antihistamine or addition of omalizumab is recommended. In addition, the diagnosis criteria and treatment of pediatric patients with CSU are similar to those for adults (Clinical Practice Guideline).

In patients with the approved indications of dupilumab, including pediatric patients, no clear ethnic differences are observed in pharmacokinetics of dupilumab (see Review Report on "Dupixent 300 mg Syringe for S.C. Injection" dated October 26, 2017, Review Report on "Dupixent 300 mg Syringe for S.C. Injection" dated February 6, 2019, Review Report on "Dupixent 300 mg Syringe for S.C. Injection" dated February 17, 2020, and Review Report on "Dupixent 300 mg Syringe for S.C. Injection and others" dated August 8, 2023).

Based on the above, the applicant considered it possible to compose the clinical data package mainly including results from global phase III studies involving Japan and thereby evaluate the efficacy and safety of dupilumab in Japanese adult and pediatric patients with CSU.

The applicant's explanation about the target patients, primary efficacy endpoint, and dosage regimen:

● **Target patients**

In view of the therapeutic system for CSU [see Section 1], dupilumab was intended to be added on to antihistamines in patients who have persistent symptoms despite appropriate treatment with second-generation non-sedating antihistamines. Therefore Study EFC16461 Study A enrolled patients with CSU who were inadequate responders to non-sedating antihistamines. Supplementary Study EFC16461 Study B enrolled inadequate responders to omalizumab, which is the only treatment option currently available for inadequate responders to antihistamines.

To minimize a confounding effect on endpoints related to itch, patients with active AD were excluded. Further, in view of the age distribution of patients with CSU, the study was planned to ensure that pediatric patients aged ≥12 years accounts for approximately 5% of all subjects.

● **Primary efficacy endpoints**

In this study, itch was assessed using ISS7, a validated patient-reported outcome scale, because it is the most common symptom that greatly affects quality of life (QOL) in patients with CSU. ISS7 is one component of UAS7 (International Guideline recommends UAS7 for assessment of the disease activity of CSU), and is used in clinical settings and clinical studies of other drugs. The period of evaluating the efficacy of dupilumab in patients with CSU was planned to be 24 weeks for the following reason:

When the development of dupilumab for CSU was planned, a completed phase III study of dupilumab for another indication had demonstrated its clinical effect before Week 24. Further, in clinical studies in patients with AD, the reduction in total serum IgE concentration reached plateau between Weeks 16 and 24.

● **Dosage regimen**

At the time of planning the development for CSU, the planned dosage regimen in the clinical studies for CSU were similar to those approved or under development for adult and pediatric patients with AD aged ≥12 years, for the following reasons:

(1) Most patients with CSU were expected to achieve blood dupilumab concentration that saturates IL-4 receptor α if they use the dosage regimen for the approved indication AD, which manifests as itch as with CSU.
(2) Case reports showed improvements in UAS7 in patients with CSU who had received dupilumab at the dosage regimen approved for AD *(J Allergy Clin Immunol Pract.* 2019;7:1659-61, etc.).

To assess relapse of symptoms after treatment termination, the post-treatment period of 12 weeks was included based on the estimated time required for the blood dupilumab concentration to reach below the lower limit of quantification.

PMDA accepted the above applicant's explanation about the development plan and thereafter evaluated the efficacy and safety of dupilumab in patients with CSU mainly based on results from Study EFC16461 Study A.

7.R.2 Efficacy

The applicant's explanation about the efficacy of dupilumab:

Table 6 shows data on a change in ISS7 from baseline to Week 24, the primary efficacy endpoint in Study EFC16461 Study A in patients with CSU who were inadequate responders to antihistamines. A pairwise comparison of the data between the dupilumab and placebo groups showed a statistically significant difference, demonstrating superiority of dupilumab over placebo [see Section 7.1.1]. Table 11 shows results of the major efficacy endpoints in Study EFC16461 Study A. The results of all the endpoints related to itch, hives, QOL, etc. in patients with CSU were generally better in the dupilumab group than in the placebo group at the assessment points during the treatment period. Treatment termination of dupilumab led to reduction of its effect. The results in the Japanese subpopulation tended to be generally similar to those in the overall population.

Table 11. Results of the major efficacy endpoints (Study EFC16461 Study A, ITT)

Endpoint	Assessment point	Overall population		Japanese subpopulation	
		Dupilumab	Placebo	Dupilumab	Placebo
UAS7 (OC)	Baseline	31.9 ± 7.2 (70)	30.8 ± 8.2 (68)	31.5 ± 6.1 (6)	36.0 ± 8.8 (6)
	Week 4	22.2 ± 10.8 (70)	24.0 ± 11.8 (65)	21.7 ± 10.0 (6)	23.3 ± 7.5 (6)
	Week 8	17.7 ± 13.0 (67)	19.7 ± 12.8 (62)	22.8 ± 11.7 (6)	21.5 ± 9.9 (6)
	Week 12	14.5 ± 12.5 (67)	16.2 ± 11.9 (62)	16.3 ± 9.6 (6)	18.7 ± 5.4 (6)
	Week 24	10.4 ± 11.8 (64)	15.9 ± 13.4 (53)	9.2 ± 8.3 (6)	13.3 ± 6.0 (6)
	End of post-treatment period	9.9 ± 11.3 (50)	12.9 ± 12.1 (44)	15.3 ± 11.5 (5)	15.8 ± 12.1 (5)
ISS7 (OC)	Baseline	16.1 ± 4.0 (70)	15.7 ± 4.1 (68)	15.5 ± 3.7 (6)	18.2 ± 4.5 (6)
	Week 4	11.3 ± 5.5 (70)	12.0 ± 6.2 (65)	11.2 ± 6.8 (6)	11.8 ± 3.5 (6)
	Week 8	8.9 ± 6.6 (67)	10.1 ± 6.6 (62)	11.7 ± 6.7 (6)	10.8 ± 4.4 (6)
	Week 12	7.3 ± 6.3 (67)	8.2 ± 6.2 (62)	8.6 ± 5.4 (6)	10.3 ± 3.6 (6)
	Week 24	5.3 ± 5.9 (64)	8.1 ± 6.6 (53)	4.5 ± 4.0 (6)	6.0 ± 2.4 (6)
	End of post-treatment period	5.4 ± 6.1 (50)	6.7 ± 6.2 (44)	7.7 ± 5.8 (5)	8.1 ± 5.7 (5)
HSS7 (OC)	Baseline	15.8 ± 3.8 (70)	15.0 ± 4.8 (68)	16.0 ± 3.0 (6)	17.8 ± 4.3 (6)
	Week 4	10.9 ± 5.9 (70)	12.0 ± 6.2 (65)	10.4 ± 3.6 (6)	11.5 ± 4.0 (6)
	Week 8	8.8 ± 6.8 (67)	9.6 ± 6.6 (62)	11.1 ± 5.4 (6)	10.8 ± 5.6 (6)
	Week 12	7.1 ± 6.7 (67)	8.0 ± 6.1 (62)	7.6 ± 4.5 (6)	8.3 ± 3.3 (6)
	Week 24	5.1 ± 6.3 (64)	7.8 ± 7.1 (53)	4.7 ± 4.3 (6)	7.3 ± 4.3 (6)
	End of post-treatment period	4.5 ± 5.5 (50)	6.3 ± 6.2 (44)	7.7 ± 5.8 (5)	7.7 ± 6.5 (5)
Proportion of patients who achieved UAS of 0[a)]	Week 4	1.4 (1/70)	2.9 (2/68)	0 (0/6)	0 (0/6)
	Week 8	8.6 (6/70)	13.2 (9/68)	0 (0/6)	0 (0/6)
	Week 12	15.7 (11/70)	10.3 (7/68)	0 (0/6)	0 (0/6)
	Week 24	32.9 (23/70)	14.7 (10/68)	33.3 (2/6)	0 (0/6)
	End of post-treatment period[b)]	36.0 (18/50)	18.2 (8/44)	20.0 (1/5)	0 (0/5)
Proportion of patients who achieved ISS of 0[a)]	Week 4	1.4 (1/70)	5.9 (4/68)	0 (0/6)	0 (0/6)
	Week 8	12.9 (9/70)	13.2 (9/68)	0 (0/6)	0 (0/6)
	Week 12	18.6 (13/70)	14.7 (10/68)	0 (0/6)	0 (0/6)
	Week 24	34.3 (24/70)	14.7 (10/68)	33.3 (2/6)	0 (0/6)
	End of post-treatment period[b)]	36.0 (18/50)	18.2 (8/44)	20.0 (1/5)	0 (0/5)
Proportion of patients who achieved HSS of 0[a)]	Week 4	1.4 (1/70)	2.9 (2/68)	0 (0/6)	0 (0/6)
	Week 8	11.4 (8/70)	14.7 (10/68)	0 (0/6)	0 (0/6)
	Week 12	21.4 (15/70)	10.3 (7/68)	0 (0/6)	0 (0/6)
	Week 24	38.6 (27/70)	17.6 (12/68)	33.3 (2/6)	0 (0/6)
	End of post-treatment period[b)]	46.0 (23/50)	25.0 (11/44)	20.0 (1/5)	0 (0/5)
Proportion of patients with UAS7 of ≤6[a)]	Week 4	10.0 (7/70)	10.3 (7/68)	0 (0/6)	0 (0/6)
	Week 8	24.3 (17/70)	17.6 (12/68)	0 (0/6)	0 (0/6)
	Week 12	34.3 (24/70)	20.6 (14/68)	33.3 (2/6)	0 (0/6)
	Week 24	48.6 (34/70)	26.5 (18/68)	50.0 (3/6)	16.7 (1/6)
	End of post-treatment period[b)]	50.0 (25/50)	36.4 (16/44)	20.0 (1/5)	20.0 (1/5)
UCT (OC)	Baseline	3.8 ± 2.3 (69)	3.6 ± 2.3 (68)	5.0 ± 2.0 (6)	3.3 ± 2.9 (6)
	Week 12	10.2 ± 4.0 (69)	8.5 ± 4.6 (66)	10.7 ± 2.3 (6)	6.8 ± 3.4 (6)
	Week 24	11.4 ± 3.8 (66)	9.5 ± 4.8 (57)	11.2 ± 4.4 (6)	8.0 ± 5.8 (6)
	End of post-treatment period	11.1 ± 4.4 (62)	10.2 ± 4.8 (55)	11.7 ± 5.0 (6)	9.7 ± 5.3 (6)
AAS7 (OC)	Baseline	32.1 ± 23.2 (28)	35.3 ± 27.4 (34)	43.0, 60.0 (2)	13.0 (1)
	Week 4	17.9 ± 23.6 (28)	15.0 ± 24.7 (33)	0.0, 6.0 (2)	0.0 (1)
	Week 8	14.8 ± 24.8 (27)	11.3 ± 25.2 (31)	0.0, 16.3 (2)	0.0 (1)
	Week 12	7.6 ± 15.8 (26)	7.4 ± 18.1 (31)	0.0, 7.0 (2)	0.0 (1)
	Week 24	5.0 ± 10.3 (25)	8.4 ± 20.8 (27)	0.0, 0.0 (2)	0.0 (1)
	End of post-treatment period	3.6 ± 9.0 (18)	6.2 ± 11.6 (22)	0.0 (1)	0.0 (1)
DLQI (OC)	Baseline	13.5 ± 5.9 (66)	15.3 ± 6.7 (67)	11.0 ± 4.9 (6)	17.0 ± 6.4 (6)
	Week 12	4.6 ± 4.9 (65)	7.2 ± 6.9 (65)	3.0 ± 2.6 (6)	9.0 ± 5.5 (6)
	Week 24	3.5 ± 4.8 (64)	5.6 ± 6.6 (57)	2.0 ± 2.2 (6)	5.2 ± 5.3 (6)
	End of post-treatment period	3.9 ± 5.1 (60)	5.5 ± 6.6 (55)	4.2 ± 5.3 (6)	5.5 ± 8.1 (6)
CU-Q2oL (OC)	Baseline	41.0 ± 17.3 (69)	46.7 ± 20.3 (68)	31.9 ± 11.2 (6)	45.1 ± 22.4 (6)
	Week 12	17.4 ± 16.0 (69)	24.9 ± 20.6 (66)	11.8 ± 7.3 (6)	26.8 ± 23.6 (6)
	Week 24	13.1 ± 13.6 (66)	20.1 ± 19.3 (57)	10.1 ± 6.5 (6)	17.6 ± 14.6 (6)
	End of post-treatment period	14.5 ± 16.1 (62)	20.0 ± 20.2 (55)	15.9 ± 16.5 (6)	18.8 ± 25.2 (6)

Mean ± SD (number of patients); Individual values for n = ≤2; Proportion of patients who achieved, % (number of patients)

a) Patients were handled as non-responders if they received prohibited concomitant drugs or therapies or rescue treatment before any of the assessment points up to Week 36 or if they had missing data at any of the assessment points up to Week 24.

b) Proportion of patients achieving the target score among patients assessed for the endpoint at the end of post-treatment period

In most of the subgroups formed according to patient characteristics, the change in ISS7 from baseline to Week 24 tended to be larger (i.e., better) in the dupilumab group than in the placebo group (Table 12). In the subgroups of "≥12 and <18 years," "≥65 years," and "Latin America," the change from baseline in ISS7 was similar in both the dupilumab and placebo groups. However, the change from

baseline in ISS7 in subjects receiving dupilumab in these subgroups were similar to that in the overall population.

Table 12. Change in ISS7 from baseline to Week 24 in subgroups defined by patient characteristics (Study EFC16461 Study A, ITT)

Patient characteristics		Dupilumab	Placebo
Overall population		−10.2 [−12.0, −8.5] (70)	−6.0 [−7.9, −4.2] (68)
Sex	Male	−11.0 [−14.0, −8.0] (29)	−6.3 [−10.0, −2.5] (18)
	Female	−9.9 [−12.2, −7.5] (41)	−5.9 [−8.0, −3.8] (50)
Age	≥12 and <18 years	−14.0, −13.0 (2)	−13.0 (1)
	≥18 and <65 years	−10.1 [−12.1, −8.1] (60)	−5.5 [−7.5, −3.5] (62)
	≥65 years	−8.3 [−16.8, 0.1] (8)	−12.8 [−20.7, −4.9] (4)
Body weight	<73 kg	−10.3 [−12.8, −7.8] (34)	−5.0 [−7.6, −2.4] (34)
	≥73 kg	−10.5 [−13.1, −7.8] (36)	−6.6 [−9.6, −3.6] (33)
Region	Asia	−11.1 [−14.3, −8.0] (17)	−5.3 [−8.7, −1.9] (16)
	Latin America	−7.6 [−13.0, −2.3] (9)	−8.1 [−13.6, −2.5] (10)
	Western Europe and North America	−8.9 [−11.4, −6.4] (33)	−4.9 [−7.7, −2.1] (30)
	Eastern Europe	−11.4 [−16.3, −6.4] (11)	−7.0 [−11.6, −2.4] (12)
Duration of the disease	<2 years	−9.8 [−12.6, −7.1] (33)	−6.6 [−9.5, −3.6] (34)
	≥2 and ≤10 years	−9.6 [−12.7, −6.4] (25)	−5.6 [−8.8, −2.3] (22)
	>10 years	−12.9 [−18.1, −7.7] (12)	−4.7 [−9.8, 0.3] (12)
ISS7 at baseline	<13	−7.0 [−11.5, −2.4] (12)	−2.0 [−5.8, 1.9] (16)
	≥13	−11.2 [−13.2, −9.2] (58)	−7.4 [−9.5, −5.2] (52)
Dose of antihistamine	Approved dose	−9.3 [−12.0, −6.5] (31)	−6.7 [−9.0, −4.4] (41)
	More than approved dose	−11.1 [−14.1, −8.0] (39)	−4.9 [−8.2, −1.5] (27)
Angioedema at baseline	Yes	−7.5 [−10.5, −4.6] (28)	−4.9 [−7.8, −2.1] (34)
	No	−12.2 [−14.5, −9.9] (42)	−6.8 [−9.5, −4.1] (34)

Least mean square [95% CI] (number of patients), Individual values for n = ≤2
If a patient started prohibited concomitant medication/therapy or rescue treatment, their subsequent measurements were deemed to be missing, and the missing data (including missing values due to treatment discontinuation owing to inadequate response) were imputed by WOCF. The other missing values were imputed using multiple imputation.

Supplementarily conducted Study EFC16461 Study B in patients with CSU who were inadequate responders to or intolerant of omalizumab was early terminated for futility as a result of the interim analysis [see Section 7.1.2]. However, the final analysis[17] (which included 25 patients[18] who were not included in the interim analysis) showed that the dupilumab group tended to achieve better improvement than the placebo group for both the primary endpoints: (1) the change in ISS7 from baseline to Week 24, the primary efficacy endpoint [for the definition, see Section 10] and (2) the change in UAS7 from baseline to Week 24, the primary endpoint in the EU and EU reference countries (see Table 13).

17) By the time of the interim analysis, the number of enrolled patients reached the target sample size. All of the randomized 108 patients (54 each in the dupilumab and placebo groups, including 1 pediatric patient weighing <60 kg who received placebo and 1 pediatric patient weighing ≥60 kg who received dupilumab) were included in the ITT population, which was the efficacy analysis population. All of 108 patients (54 each in the dupilumab and placebo groups) who were randomized and received at least 1 dose of the study drug were included in the safety analysis population. In total, 9.3% (5 of 54) of patients in the dupilumab group and 13.0% (7 of 54) of patients in the placebo group discontinued the study mainly because of consent withdrawal (2 patients in the dupilumab group, 5 patients in the placebo group).

18) Including 1 patient who had discontinued the study treatment and 3 patients who discontinued the study treatment in response to results of the interim analysis

Table 13. Results of the primary efficacy endpoints
(Study EFC16461 Study B, ITT population, final analysis)

		Overall population		Japanese subpopulation	
		Dupilumab	Placebo	Dupilumab	Placebo
ISS7					
	Baseline (OC)	15.9 ± 4.0 (54)	16.2 ± 3.8 (54)	11.8 ± 2.8 (6)	17.3 ± 4.9 (7)
	Week 24 (OC)	6.2 ± 5.1 (49)	9.3 ± 6.9 (45)	5.2 ± 4.1 (6)	12.2 ± 5.8 (6)
	Change from baseline to Week 24[a),b),c)]	−7.7 [−9.9, −5.5]	−4.8 [−7.0, −2.6]	−7.3 [−13.7, −0.9]	−0.4 [−5.5, 4.7]
	Difference from placebo[a),b),c)]	−2.9 [−5.8, 0.0]		−6.9 [−14.5, 0.7]	
UAS7					
	Baseline (OC)	31.0 ± 7.9 (54)	31.9 ± 8.1 (54)	26.2 ± 7.1 (6)	35.9 ± 9.1 (7)
	Week 24 (OC)	13.0 ± 10.7 (49)	19.0 ± 14.2 (45)	15.7 ± 11.1 (6)	22.5 ± 11.2 (6)
	Change from baseline to Week 24[a),b),c)]	−14.4 [−18.7, −10.0]	−8.5 [−12.9, −4.2]	−10.2 [−23.2, 2.8]	−3.0 [−13.0, 7.0]
	Difference from placebo[a),b),c)]	−5.8 [−11.6, −0.1]		−7.2 [−21.8, 7.5]	

Mean ± SD (number of patients) or least mean square [95.7% CI]

a) Analysis of covariance model using the baseline value, treatment group, angioedema at baseline, and region (Asia/Latin America/Western Europe and North America/Eastern Europe) as covariates

b) If a patient started to receive prohibited concomitant medication/therapy or rescue treatment, their subsequent measurements were deemed to be missing, and the missing data (including missing values due to treatment discontinuation owing to inadequate response) were imputed by WOCF. The other missing values were imputed using multiple imputation.

c) If the study was continued without early termination for futility, the final analysis would use the two-sided significance level of 4.3% according to the O' Brien-Fleming α spending function. Figures in square brackets represent the confidence interval corresponding to this significance level.

PMDA's view:

In Study EFC16461 Study A in patients with CSU who were inadequate responders to antihistamines, (a) the change in ISS7 from baseline to Week 24, the primary efficacy endpoint, demonstrated superiority of dupilumab over placebo, (b) the results of the other efficacy endpoints such as one related to hives were better in the dupilumab group than in the placebo group, and (c) itch and hives tended to be alleviated at the same time. As demonstrated by these findings, dupilumab has efficacy in the treatment of CSU. In addition, since results in the Japanese subpopulation had a similar trend to those in the overall population, dupilumab is expected to have efficacy in Japanese patients with CSU as well.

Study EFC16461 Study B in patients with CSU who were inadequate responders to or intolerant of omalizumab was early terminated for futility. The announcement of early termination for futility may have affected the subsequent final results, but the final results of both ISS7 and UAS7 tended to be better in the dupilumab group than in the placebo group. Thus the early termination does not deny the efficacy of dupilumab in omalizumab-experienced patients with CSU.

The efficacy of dupilumab therapy for longer than 24 weeks in patients with CSU is reviewed in Section 7.R.5.2.

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

7.R.3 Safety

The applicant explained the safety of dupilumab in patients with CSU based on (a) safety results from Study EFC16461 Study A, a pivotal study, (b) safety results in the pooled population from 2 global phase III studies in patients with CSU (Study EFC16461 Study A and Study B), and (c) pooled data from foreign and Japanese clinical studies in patients with the approved indications.

The applicant's explanation:

Table 14 shows the safety summary of dupilumab and incidences of adverse events of special interest in each population. Use of dupilumab in patients with CSU posed no additional safety concerns although comparisons had limitations owing to differences in patient characteristics and concomitant medication among the studies.

Table 14 also shows the safety summary of dupilumab and incidences of adverse events of special interest in the Japanese subpopulation of Study EFC16461 Study A. No clear differences were found in the incidence of adverse events between the overall population and Japanese subpopulation, and no safety concerns specific to Japanese patients with CSU have been suggested. No adverse events occurred in 5 pediatric patients with CSU in the dupilumab group in the pooled population of 2 global phase III studies (Study EFC16461 Study A and Study B).

Table 14. Safety summary (safety analysis population)

Target disease	CSU					AD	Pediatric AD	PN	CRSwNP	Asthma
Study	Study EFC16461 Study A				Pooled data of 2 global studies[a]	Pooled data of 8 foreign and Japanese studies[b]	Pooled data of 6 foreign and Japanese studies[c]	Pooled data of 2 foreign and Japanese studies[d]	Pooled data of 2 foreign and Japanese studies[e]	Pooled data of 4 foreign and Japanese studies[f]
Treatment	Overall population		Japanese subpopulation		Dupilumab[g]	Dupilumab[g]	Dupilumab[g]	Dupilumab[g]	Dupilumab[g]	Dupilumab[g]
	Dupilumab	Placebo	Dupilumab	Placebo						
No. of patients	70	68	6	6	124	2,484	1,346	152	440	2,597
Overall observation period (patient-years)	45.8	39.8	4.1	3.5	80.8	1,864.9	755.7	99.0	428.0	3,167.3
All adverse events	38 (54.3) 134.1	40 (58.8) 197.1	3 (50.0) 89.7	4 (66.7) 303.7	71 (57.3) 142.2	1,920 (77.3) 343.6	834 (62.0) 297.7	97 (63.8) 183.9	349 (79.3) 228.7	1,983 (76.4) 202.4
Serious adverse events	2 (2.9) 4.4	5 (7.4) 12.9	0	0	5 (4.0) 6.3	119 (4.8) 6.6	25 (1.9) 3.4	7 (4.6) 7.2	24 (5.5) 5.8	220 (8.5) 7.3
Deaths	0	1 (1.5) 2.5	0	0	0	2 (<0.1) 0.1	0	0	1 (0.2) 0.2	9 (0.3) 0.3
Adverse events leading to treatment discontinuation	2 (2.9) 4.4	4 (5.9) 10.2	0	1 (16.7) 30.7	2 (1.6) 2.5	80 (3.2) 4.4	5 (0.4) 0.7	0	13 (3.0) 3.1	131 (5.0) 4.2
Adverse drug reactions	10 (14.3) 25.1	16 (23.5) 50.6	0	0	15 (12.1) 20.7	842 (33.9) 63.3	185 (13.7) 28.4	26 (17.1) 30.1	97 (22.0) 28.0	598 (23.0) 24.4
Hypersensitivity	1 (1.4) 2.2	0	0	0	1 (0.8) 1.2	23 (0.9) 1.2	317 (23.6) 56.0	1 (0.7) 1.0	9 (2.0) 2.1	94 (3.6) 3.1
Anaphylactic reaction	0	0	0	0	0	4 (0.2) 0.2	8 (0.6) 1.1	0	0	5 (0.2) 0.2
Injection site reaction	8 (11.4) 19.4	9 (13.2) 25.6	0	0	11 (8.9) 14.6	383 (15.4) 23.6	67 (5.0) 9.3	6 (3.9) 6.3	63 (14.3) 17.0	434 (16.7) 16.6
Infections	14 (20.0) 33.9	13 (19.1) 39.5	1 (16.7) 24.4	1 (16.7) 34.8	27 (21.8) 37.4	1,236 (49.8) 119.1	555 (41.2) 130.8	37 (24.3) 45.0	205 (46.6) 69.8	1,447 (55.7) 85.7
Serious infections	0	1 (1.5) 2.5	0	0	0	15 (0.6) 0.8	8 (0.6) 1.1	2 (1.3) 2.0	4 (0.9) 0.9	50 (1.9) 1.6
Herpes virus infection	1 (1.4) 2.2	3 (4.4) 7.9	0	1 (16.7) 34.8	1 (0.8) 1.2	195 (7.9) 11.2	51 (3.8) 7.2	5 (3.3) 5.1	9 (2.0) 2.1	45 (1.7) 1.4
Skin infection	2 (2.9) 4.4	1 (1.5) 2.5	1 (16.7) 24.4	0	3 (2.4) 3.7	219 (8.8) 12.8	143 (10.6) 21.7	7 (4.6) 7.3	5 (1.1) 1.2	91 (3.5) 2.9
Eye disorders	0	0	0	0	1 (0.8) 1.2	386 (15.5) 23.9	115 (8.5) 16.6	8 (5.3) 8.4	19 (4.3) 4.6	99 (3.8) 3.2
Serious eye disorders	0	0	0	0	0	4 (0.2) 0.2	0	0	1 (0.2) 0.2	3 (0.1) 0.1
Keratitis	0	0	0	0	0	44 (1.8) 2.4	4 (0.3) 0.5	0	0	4 (0.2) 0.1
Conjunctivitis	0	1 (1.5) 2.6	0	0	2 (1.6) 2.5	441 (17.8) 27.8	132 (9.8) 19.3	8 (5.3) 8.3	15 (3.4) 3.6	71 (2.7) 2.3
Sleep disorder	1 (1.4) 2.2	0	0	0	1 (0.8) 1.2	29 (1.2) 1.6	6 (0.4) 0.8	0	8 (1.8) 1.9	22 (0.8) 0.7
Psychiatric disorders	2 (2.9) 4.4	1 (1.5) 2.5	0	0	2 (1.6) 2.5	52 (2.1) 2.8	8 (0.6) 1.1	2 (1.3) 2.0	6 (1.4) 1.4	59 (2.3) 1.9
Suicidal behaviour-related events	0	1 (1.5) 2.5	0	0	0	1 (<0.1) 0.1	1 (<0.1) 0.1	0	0	0
Neoplasms benign, malignant and unspecified	1 (1.4) 2.2	1 (1.5) 2.5	0	0	3 (2.4) 3.8	66 (2.7) 3.6	20 (1.5) 2.7	4 (2.6) 4.1	4 (0.9) 0.9	54 (2.1) 1.7
Eosinophilia	0	0	0	0	0	36 (1.4)[h] 2.0	8 (0.6)[h] 1.1	0	8 (1.8)[i] 1.9	91 (3.5)[i] 3.0
Epistaxis	0	0	0	0	0	22 (0.9) 1.2	19 (1.4) 2.6	0	31 (7.0) 7.6	22 (0.8) 0.7

Top, number of patients (%); Bottom, incidence per 100 patient-years adjusted for the exposure period[j]

a) Study EFC16461 Study A and Study EFC16461 Study B
b) 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
c) Study R668-AD-1539 Parts A and B, Studies R668-AD1652, R668-AD1526, R668-AD1434, R668-AD1412, and EFC16823
d) Studies EFC16459 and EFC16460
e) Studies EFC14280 and EFC14146
f) Studies DRI12544, EFC13579, EFC13691, and LTS12551
g) All of the patients who received dupilumab regardless of the dosage regimen
h) When the concerned study was conducted, "Eosinophilia with clinical symptoms" was not designated as an adverse event of special interest.
i) Eosinophil count >3,000 /μL was reported as an adverse event regardless of clinical symptoms.
j) Time to occurrence of the first event (observation period in patients without events)

PMDA's view on the safety of dupilumab in patients with CSU:
Although comparisons had limitations owing to differences in patient characteristics and concomitant medication among the studies, a comparison of the safety profile of dupilumab between patients with CSU and those with the approved indications did not suggest a clearly different trend. For patients with CSU, the safety measures should be continuously taken as done for patients with the approved indications (e.g., precautionary statements to the effect that attention should be paid to known adverse drug reactions, and that dupilumab should be used by physicians versed in treatment of CSU). In addition, the safety information of dupilumab should be collected through post-marketing surveillance, and the obtained information should be appropriately provided to healthcare professionals. Since only 3 pediatric patients aged ≥12 years with CSU received dupilumab, the safety information of dupilumab in pediatric patients aged ≥12 years should be continuously collected through post-marketing surveillance. The safety of >24-week treatment with dupilumab in patients with CSU is reviewed in Section 7.R.5.2.

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

7.R.4 Clinical positioning and indication

PMDA's view:
Based on results of the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] of dupilumab shown by Study EFC16461 Study A (whose eligible patients were defined in view of the current therapeutic system for CSU), dupilumab can offer a treatment option for patients with CSU who have not responded adequately even to appropriate treatment with antihistamines. In addition, as reviewed in Section 7.R.2, the results from Study EFC16461 Study B in patients with CSU who were inadequate responders to or intolerant of omalizumab do not deny the efficacy of dupilumab in omalizumab-experienced patients with CSU. Further, no safety concerns for dupilumab therapy were identified in the safety data of dupilumab-treated patients in the pooled population of global phase III studies (Study EFC16461 Study A and Study B), which included patients with CSU who were inadequate responders to or intolerant of omalizumab enrolled in Study EFC16461 Study B [see Section 7.R.3]. Therefore it is unnecessary to exclude omalizumab-experienced patients from the population eligible for dupilumab, provided that these study results are appropriately disseminated through information materials, and that eligible patients are appropriately selected by physicians versed in treatment of CSU.

In view of the above, PMDA has concluded that the indication of dupilumab should be "Chronic spontaneous urticaria that has not responded adequately to conventional treatments," as proposed by the applicant. To ensure that patients eligible for dupilumab are accurately identified and selected, healthcare professionals should be appropriately informed of the following precautions through the package insert: (1) Dupilumab should be used by physicians versed in diagnosis and treatment of urticaria; (2) patients with clearly defined etiology for urticaria such as stimulant or food are not eligible for dupilumab; and (3) dupilumab should be used in patients who have persistent hives accompanied by severe itch affecting activities of daily living even when receiving appropriate treatment with antihistamines.

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

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration

The proposed dosage and administration (see below) were defined based on the age and body weight of subjects enrolled in Study EFC16461 Study A who were evaluable for the efficacy and safety.

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.

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 and <18 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

PMDA's conclusion:

According to the submitted data and review in Sections 7.R.2, 7.R.3, and 7.R.4, dupilumab at the dosage regimen used in Study EFC16461 Study A was shown to have efficacy in patients with CSU and is considered to have acceptable safety. Therefore the proposed dosage and administration is acceptable.

The 200 mg syringe product is intended to be used only in pediatric patients with CSU, as with atopic dermatitis. Therefore the dosage and administration of the 200 mg syringe product should be defined only for pediatric patients.

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

7.R.5.2 Use after Week 24

The applicant's explanation:

Both Study EFC16461 Study A and Study B in patients with CSU had the treatment period of 24 weeks, but patients with CSU are expected to use dupilumab for a longer time because it is a chronic disease requiring long-term treatment. The efficacy and safety of >24-week treatment with dupilumab in patients with CSU can be explained by the following results from studies in patients with AD, which is accompanied by itch as with CSU. The dosage regimen for CSU was specified based on these results.

Study R668-AD-1224, which evaluated dupilumab administered to patients with AD for 52 weeks, demonstrated the maintained efficacy in relief from itch throughout the treatment period (see Review Report on "Dupixent 300 mg Syringe for S.C. Injection" dated October 26, 2017). Dupilumab is expected to have long-term efficacy also in patients with CSU as in those with AD.

Based on the investigation below, there is no particular concerns about the long-term safety of dupilumab in patients with CSU.

- Study EFC16461 Study A and Study B in patients with CSU present no increasing trend of the incidence of adverse events with increasing treatment period.[19)]
- The clinical studies that evaluated ≥52-week treatment of dupilumab in patients with AD[20)] included 156 patients with concurrent urticaria. Of the 156 patients, 78.2% (122 patients) had adverse events, 1.9% (3 patients) had serious adverse events, and 37.8% (59 patients) had adverse drug reactions. A comparison of these data with the corresponding data in Table 14 showed no differences in safety profile between patients with and without concurrent urticaria.
- In the post-marketing surveillance in patients with AD,[21)] 971 patients[22)] provided the survey form and were included in safety analysis. Of the 971 patients, 25 had concurrent urticaria, including 15 who received dupilumab for ≥24 weeks. In the 15 patients, no adverse drug reactions occurred after Week 24.

PMDA's view:

No clinical study results are available from patients with CSU who received dupilumab for more than 24 weeks. In Study EFC16461 Study A, the efficacy of dupilumab was maintained to a certain extent at the end of post-treatment period (i.e., 12 weeks after the end of dupilumab treatment) (Table 11). In view of this, appropriateness of >24-week treatment with dupilumab in Japanese patients with CSU remains inconclusive.

However, data available at present have suggested no concerns about the long-term safety of dupilumab for the approved indications, and thus >24-week treatment with dupilumab need not be prohibited on the condition that the following information and caution are disseminated:

- Dupilumab has not been used in Japanese patients with CSU for >24 weeks.
- Whether to administer dupilumab for >24 weeks, including its necessity, should be carefully determined according to the patient's individual condition by physicians versed in treatment of CSU.

Through the post-marketing surveillance, the applicant should investigate the safety and efficacy of >24-week treatment with dupilumab and of re-challenge of dupilumab in patients with CSU who have interrupted dupilumab therapy because of alleviated symptoms, etc.

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

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19) The incidence of adverse events by term in Study EFC16461 Study A is as follows: Days 1-28, 20.0% (14 of 70 patients); Days 29-56, 15.7% (11 of 70 patients); Days 57-84, 19.1% (13 of 68 patients); Days 85-112, 7.4% (5 of 68 patients); Days 113-140, 9.0% (6 of 67 patients); and Days 141-168, 11.9% (8 of 67 patients).
The incidence of adverse events by term in Study EFC16461 Study B is as follows: Days 1-28, 16.7% (9 of 54 patients); Days 29-56, 13.0% (7 of 54 patients); Days 57-84, 9.3% (5 of 54 patients); Days 85-112, 13.2% (7 of 53 patients); Days 113-140, 14.0% (7 of 50 patients); and Days 141-168, 14.3% (7 of 49 patients).

20) Studies R668-AD-1224 and R668-AD-1225

21) The planned sample size for the surveillance is 900 patients, who were to be included in safety analysis. The surveillance period is from [redacted], 20[redacted] to [redacted], 20[redacted].

22) [redacted] patients were enrolled by [redacted], 20[redacted], the end of enrollment period. [redacted] patients submitted the survey forms, and [redacted] patients did not. Of the patients who submitted the survey forms, 971 were included in safety analysis. The remaining patients were excluded for the following reasons: [redacted] patients submitted the survey form without a physician's signature; the presence or absence of adverse events was unknown in [redacted] patients; and [redacted] patients fell outside the enrollment period.

7.R.6 Self-administration

The applicant's explanation about self-administration of dupilumab:

In Study EFC16461 Study A, all of the 6 Japanese patients with CSU self-injected ≥1 dose of dupilumab, and the efficacy and safety in the Japanese subpopulation were similar to those in the overall population. This shows that self-administration of dupilumab in patients with CSU will pose no particular concerns about the efficacy or safety, as in patients treated for the approved indications.

PMDA's view:

Although experience of self-administration of dupilumab is limited in Japanese patients with CSU, no particular concerns about the efficacy or safety associated with self-administration have been suggested in clinical studies. As done for approved self-administration in patients with AD, the applicant should provide the following precautionary statement in the Important Precautions section of the package insert and continue taking safety measures such as preparation of an information material for patients and their families: Self-administration should be introduced only in patients considered eligible for it by the physician after the start of dupilumab therapy.

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

PMDA's view:

As reviewed in Sections 7.R.3 and 7.R.5, clinical study results in patients with CSU up to Week 24 have suggested no additional concerns beyond the safety risk of dupilumab used for the approved indications, and dupilumab has the acceptable safety in patients with CSU. However, no information is available about the safety or efficacy of >24-week treatment with dupilumab in patients with CSU; and the studies included only a very small number of pediatric patients aged ≥12 years with CSU. Therefore, the applicant should conduct post-marketing surveillance to collect information about the safety and efficacy in Japanese patients with CSU in clinical settings, and should provide the obtained information to healthcare professionals promptly.

As done for the approved indications, the applicant should take safety measures to ensure that (1) dupilumab is used by physicians with adequate knowledge and experience in treatment of CSU; (2) other allergic diseases, if they develop, are treated in cooperation with the other departments or facilities; and (3) healthcare professionals such as physicians are provided with information via materials in order to promote proper use of dupilumab.

The above conclusion of PMDA and 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 new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of

Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

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

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

On the basis of the data submitted, PMDA has concluded that dupilumab has efficacy in the treatment of CSU with inadequate response to conventional treatments, and that dupilumab has acceptable safety in view of its benefits. Dupilumab is clinically meaningful because it offers a new option for the treatment of patients with CSU who have not responded adequately to conventional treatments. The safety and efficacy of dupilumab in Japanese patients with CSU in clinical settings should be further investigated in post-marketing surveillance, etc.

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

10. Other

The efficacy evaluation methods and definitions of endpoints in clinical studies of dupilumab are as shown below.

Endpoint	Definition
ISS	Itch severity score (ISS) is a score of itch severity during the past 24 hours on a 4-point scale of 0 (None) to 3 (Severe [affecting activities of daily living or sleep]) scored by the subject once daily.
ISS7	ISS over the last 7 days (range, 0-21)
HSS	Hives severity score (HSS) is a score of hives count during the past 24 hours on a 4-point scale of 0 (None) to 3 (>50) scored by the subject once daily.
HSS7	HSS over the last 7 days (range, 0-21)
UAS	Sum of ISS and HSS scored on the same day
UAS7	UAS over the last 7 days (range, 0-42; ≤6 indicates a well-controlled condition[23])
UCT	Urticaria control test (UCT) is the total score of the following 4 items scored on a 4-point scale by the subject over the past 4 weeks (range, 0-16; a higher score indicates better-controlled urticaria): (a) severity of urticaria, (b) impact on QOL, (c) frequency of treatment that could not control symptoms of urticaria, and (d) overall control status of urticaria
AAS7	Angioedema activity score (ASS) is calculated in the following manner: Whether angioedema occurred during the past 24 hours is assessed by the subject once daily. If angioedema occurred, the subject scores the following 5 items on a 4-point scale of 0 to 3: (a) duration of angioedema, (b) severity of discomfort caused by swelling, (c) impact of swelling on activities of daily living, (d) impact of swelling on appearance, and (d) severity of swelling. The total score of the 5 items is ASS. ASS7 is ASS over the last 7 days (range, 0-105; a higher score indicates more active angioedema).
DLQI	Dermatology life quality index (DLQI), used to evaluate the impact of skin disease on health-related QOL over the past 1 week, is the total score of 10 questions scored on a 4- or 3-point scale by the subject (range, 0-30; a higher total score indicates lower QOL).
CU-Q2oL	Chronic urticaria quality of life questionnaire (CU-Q2oL), used to evaluate the impact of symptoms of chronic urticaria on QOL over the past 2 weeks, is a score (range, 0 - 100) calculated from 23 questions scored on a 4-point scale by the subject (a higher score indicates lower QOL).

[23] *Am J Clin Dermatol.* 2018;19:267-74

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

Endpoint	Definition
Hypersensitivity	Hypersensitivity (narrow SMQ) is an event for which treatment or symptomatic therapy is available or for which an action on the therapy is "discontinuation of the study treatment" or "suspension of the study treatment" and which is identified by blinded medical review to specify relevant systemic hypersensitivity events.
Anaphylactic reaction	Anaphylactic reaction (narrow SMQ) term or events meeting algorithm criteria that are ones identified based on ≥2 PT events occurring within 24 hours by clinical development program (algorithmic approach of anaphylactic reaction [Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1])
Injection site reaction	Injection site reaction (HLT)
Infections	Infections and infestations (SOC)
Serious infections	Serious events under Infections and infestations (SOC)
Herpes virus infection	Herpes virus infections (HLT)
Skin infection	Skin and subcutaneous tissue infections and infestations (HLGT), skin structures and soft tissue infections (HLT), postoperative wound infection, wound infection, wound infection staphylococcal, wound infection pseudomonas, wound infection bacterial, wound infection viral, wound infection fungal, wound infection helminthic, chalazion, hordeolum, and skin papilloma (PTs)
Eye disorders	Eye disorders (SOC)
Serious eye disorders	Serious events under Eye disorders (SOC)
Keratitis	Keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, ophthalmic herpes simplex, herpes ophthalmic, and corneal infection (PTs)
Conjunctivitis	Conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperaemia, and conjunctival hyperaemia (PTs)
Sleep disorder	Sleep disorders and disturbances (HLGT)
Psychiatric disorders	Completed suicide, suicidal ideation, depression suicidal, suicidal behaviour, suicide attempt, mental status changes, delirium, anxiety, stress, depression, psychotic disorder, major depression, adjustment disorder with depressed mood, bipolar disorder (PTs)
Suicidal behaviour-related events	Completed suicide, suicidal ideation, depression suicidal, suicidal behaviour, suicide attempt (PTs)
Neoplasms benign, malignant and unspecified	Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)
Eosinophilia	Eosinophilic disorders (HLT), eosinophil count increased (PT)
Epistaxis	Epistaxis (PT)

Review Report (2)

January 16, 2024

Product Submitted for Approval

Brand Name	(a) Dupixent 300 mg Syringe for S.C. Injection (b) Dupixent 300 mg Pen for S.C. Injection (c) Dupixent 200 mg Syringe for S.C. Injection
Non-proprietary Name	Dupilumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	(a), (b) March 31, 2023, (c) November 2, 2023[1)]

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, clinical positioning, indications, and dosage and administration

The expert advisors at the Expert Discussion supported the conclusions of PMDA on the efficacy, clinical positioning, and indications of dupilumab described in the Review Report (1). The conclusion of PMDA on the dosage regimen was supported at the Expert Discussion, but the statement should be as shown below in view of the dosage regimen of dupilumab in pediatric patients with AD.

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.

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

1.2 Safety, post-marketing investigations and safety measures, and risk management plan (draft)

The expert advisors at the Expert Discussion supported the conclusions of PMDA on the safety and post-marketing investigations and safety measures in the Review Report (1). Further, the expert advisors commented that the efficacy and safety of dupilumab in omalizumab-experienced patients with CSU should be continuously investigated using information gathered from post-marketing surveillance, etc.

In view of the review presented in Section "7.R.7 Post-marketing investigations and 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 15, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 16.

PMDA instructed the applicant to conduct post-marketing surveillance, etc. that can investigate these matters and, based on the collected information, continuously investigate the safety and efficacy of (a) >24-week treatment with dupilumab, (b) dupilumab in pediatric patients aged ≥12 years with CSU, (c) dupilumab in omalizumab-experienced patients with CSU, and (d) re-challenge of dupilumab in patients with CSU who have interrupted dupilumab therapy because of alleviated symptoms.

Table 15. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity	• Serious infections • Aggravation of symptoms of concurrent allergic diseases such as asthma • Eosinophilia with clinical symptoms • Immunogenicity • Events related to depression and suicidal behaviour • Malignant tumor	• None
Efficacy specification		
• Efficacy of dupilumab used alone (chronic rhinosinusitis with nasal polyps) • Long-term efficacy of dupilumab (prurigo nodularis) (chronic spontaneous urticaria)		

(Underline denotes additions in present report.)

Table 16. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance [pediatric atopic dermatitis] • Specified use-results survey (long term use) [atopic dermatitis] • Specified use-results survey (long term use) [bronchial asthma] • Specified use-results survey (long term use) [prurigo nodularis] [chronic spontaneous urticaria] • Specified use-results survey (long term use) [pediatric atopic dermatitis]	• Post-marketing clinical study (monotherapy) [chronic rhinosinusitis with nasal polyps] • Specified use-results survey (long term use) [prurigo nodularis] [chronic spontaneous urticaria]	• Disseminate data gathered during the early post-marketing phase vigilance [pediatric atopic dermatitis] • Organize and disseminate information material for healthcare professionals • Organize and disseminate information material for patients (brochure for self-injection) • Ensure to provide information on proper use prior to delivery of dupilumab

(Underline denotes additions.)

The applicant explanation:

A specified use-results survey will be conducted in patients with CSU who have not responded adequately to conventional treatments including omalizumab-experienced patients to investigate the safety and efficacy of long-term use of dupilumab in clinical settings (see Table 17).

Table 17. Outline of specified use-results survey (draft)

Objective	Safety and efficacy of long-term use of dupilumab in clinical settings
Survey method	Central registration system
Population	Patients with CSU who have not responded adequately to conventional treatments
Observation period	1 year
Planned sample size	100 patients (who will be included in safety analysis, including ≥5 pediatric patients aged ≥12 years)
Main survey items	• Safety specification: Serious hypersensitivity, serious infections, aggravation of symptoms of concurrent allergic diseases such as asthma, eosinophilia with clinical symptoms, events related to depression and suicidal behaviour, and malignant tumor • Patient characteristics (age, duration of CSU, past or concurrent allergic diseases, prior treatments, etc.) • Use status of dupilumab • Adverse events • Efficacy (UAS7, ISS7, HSS7, UCT, DLQI, physician‐rated clinical global impression)

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

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indications and the dosage and administration as shown below, with the following approval condition. Since the present application is for drugs with a new indication and new dosage, the re-examination period for the indication and the dosage and administration relevant to present application is 4 years.

Indications

(a), (b) The following skin diseases that have not responded adequately to conventional treatments:

Atopic dermatitis

Prurigo nodularis

Chronic spontaneous urticaria

Bronchial asthma (only in patients with severe or intractable bronchial asthma whose asthmatic responses cannot be controlled by conventional treatments)

Chronic rhinosinusitis with nasal polyposis (only in patients who have not responded adequately to conventional treatments)

(c) The following skin diseases that have not responded adequately to conventional treatments:
Atopic dermatitis
Chronic spontaneous urticaria

(Dotted line denotes changes as of June 26, 2023.)

Dosage and Administration

(a), (b)

Atopic dermatitis

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

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥6 months is determined according to body weight and administered by subcutaneous injection.

≥5 kg and <15 kg: 200 mg every 4 weeks
≥15 kg and <30 kg: 300 mg every 4 weeks
≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks
≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Prurigo nodularis

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

Chronic spontaneous urticaria

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

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12 ~~and <18~~ years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks
≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Bronchial asthma

The usual initial dose for adults and pediatric patients aged ≥12 years is 600 mg of dupilumab (genetical recombination) followed by 300 mg every 2 weeks, administered by subcutaneous injection.

Chronic rhinosinusitis with nasal polyposis

The usual dose for adults is 300 mg of dupilumab (genetical recombination) administered by subcutaneous injection every 2 weeks. After symptoms are stabilized, the dose of 300 mg may be subcutaneously administered every 4 weeks.

(c)

Atopic dermatitis

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥6 months is determined according to body weight and administered by subcutaneous injection.

≥5 kg and <15 kg: 200 mg every 4 weeks

≥15 kg and <30 kg: 300 mg every 4 weeks

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

Chronic spontaneous urticaria

The usual dose of dupilumab (genetical recombination) for pediatric patients aged ≥12~~ and <18~~ years is determined according to body weight and administered by subcutaneous injection.

≥30 kg and <60 kg: Initial dose of 400 mg followed by 200 mg every 2 weeks

≥60 kg: Initial dose of 600 mg followed by 300 mg every 2 weeks

(Strikethrough denotes deletion from the proposed text.
Dotted line denotes changes as of June 26 or September 25, 2023.)

Approval Condition

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

Appendix

List of Abbreviations

AAS7	Angioedema activity score over 7 days
AD	Atopic dermatitis
ADA	Anti-drug antibody
Antihistamine	Histamine H_1 receptor antagonist
$AUC_{\tau,SS}$	Area under the concentration time curve over the dosing interval (τ) at steady state
CI	Confidence interval
Clinical Practice Guideline	Guidelines for Diagnosis and Treatment of Urticaria 2018 edited by the Committee for Revision of Guidelines for Diagnosis and Treatment of Urticaria, the Japanese Dermatological Association (*Jpn J dermatol.* 2018;128:2503-624)
$C_{max,SS}$	Maximum serum concentration at steady state
COVID-19	Coronavirus disease 2019
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CSU	Chronic spontaneous urticaria
$C_{trough,SS}$	Trough serum concentration at steady state
CU-Q2oL	Chronic urticaria quality of life questionnaire
DLQI	Dermatology life quality index
Dupilumab	Dupilumab (Genetical Recombination)
Dupixent	Dupixent 300 mg Syringe for S.C. Injection, etc.
HSS	Hives severity score
HSS7	Hives severity score over 7 days
Ig	Immunoglobulin
IL	Interleukin
International Guideline	The international EAACI/GA²LEN/EuroGuiDerm/APAACI guideline for the definition, classification, diagnosis, and management of urticaria (*Allergy.* 2022;77:734-66)
ISS	Itch severity score
ISS7	Itch severity score over 7 days
ITT	Intent-to-treat
MedDRA	Medical dictionary for regulatory activities
OC	Observed cases
OCS	Oral corticosteroid
Omalizumab	Omalizumab (Genetical Recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
PN	Prurigo nodularis
PT	Preferred term
QOL	Quality of life
QxW	Once every x weeks
SMQ	Standardized MedDRA query
UAS	Urticaria activity score
UAS7	Urticaria activity score over 7 days
UCT	Urticaria control test
WOCF	Worst observation carried forward