Received: 15 November 2022 | Revised: 15 February 2023 | Accepted: 28 February 2023

DOI: 10.1002/cia2.12303

Journal of Cutaneous Immunology and Allergy

WILEY

RESEARCH ARTICLE

Safety and effectiveness of dupilumab in the real-world treatment of atopic dermatitis in Japan: 1-year interim analysis from a post-marketing surveillance

Hidehisa Saeki MD, PhD[1] | Hiroyuki Fujita MD, PhD[2] | Katsuhisa Suzuki BSc[2] | Kazuhiko Arima MD, PhD[2]

[1]Department of Dermatology, Nippon Medical School, Tokyo, Japan

[2]Sanofi K.K., Tokyo, Japan

Correspondence
Kazuhiko Arima, Sanofi K.K., 3-20-2 Nishishinjuku, Shinjuku-ku, Tokyo 163-1488, Japan.
Email: kazuhiko.arima@sanofi.com

Funding information
Sanofi K.K.

Abstract

Objectives: Atopic dermatitis (AD) is a common chronic inflammatory skin disorder in Japan. Dupilumab, a fully human monoclonal antibody, targets a shared subunit of the interleukin (IL)-4 and IL-13 receptors. Post-marketing surveillance of the safety and effectiveness of dupilumab in adult AD patients was conducted in Japan, where the drug is also allowed for use in older adolescents (i.e., ≥15 years), and interim results are reported here.

Methods: This observational, multicenter study enrolled Japanese patients with AD who initiated dupilumab between July 2018–June 2020 (UMIN-CTR Trials Registry: UMIN000032807). Baseline demographics, clinical history, medication data and dupilumab safety and effectiveness data were collected.

Results: By the data cut-off date of March 26, 2021, information from 600 patients has been collected. All the available safety and 1-year effectiveness data are presented. The mean (standard deviation) age was 42.0 (15.9) years, the majority (69.1%) were male, and asthma was present in 12.2%. Adverse drug reactions (ADRs) were observed in 98 patients (16.4%), including conjunctivitis ($n = 40$; 6.7%), conjunctivitis allergic ($n = 30$; 5.0%), blepharitis ($n = 5$; 0.8%), headache and eye pruritus ($n = 4$; 0.7% each) and eosinophilia ($n = 3$; 0.5%). Six patients experienced asthma, all of whom had a history of, or concurrent, asthma. Disease severity improved remarkably at 4 months in most patients, which was maintained up to 1 year.

Conclusion: Dupilumab appears to be a safe and effective treatment for patients aged ≥15 years with moderate-to-severe AD in routine clinical practice in Japan. Dupilumab was well tolerated, with no new safety signals and no new-onset asthma.

KEYWORDS
atopic dermatitis, biologics, dupilumab, Japan, post-marketing surveillance

1 | INTRODUCTION

Atopic dermatitis (AD) is one of the most common systemic, chronic inflammatory skin disorders, ranking 15th among the nonfatal diseases.[1] AD is the second most common dermatological disorder in Japan, with a prevalence of around 11% in children and 7% in adults.[2–4] In most patients, AD develops in early childhood and may persist into adulthood.[2,5] AD is often the precursor to other atopic diseases, such as asthma, allergic rhinitis and food allergy, also known as the atopic march, which represents the typical sequence of atopic manifestations in childhood to the development of other allergic disorders in advanced age.[6] It increases the risk of developing asthma to approximately 50% and the risk of developing allergic rhinitis to as much as 75%.[7]

Treatment for AD is focused on the alleviation of symptoms and maintaining remission so that patients do not experience disturbance in their daily activities.[8,9] Although mild AD can be controlled with emollients and low potency topical steroids, therapeutic options are limited for patients with moderate-to-severe AD who have had an inadequate response to topical treatments.[8–10] Oral antihistamines and anti-allergic drugs are widely used as adjunctive treatments for pruritus, whereas immunosuppressants like oral corticosteroids and oral cyclosporine are used to control inflammation, but these immunosuppressants have variable efficacy and are associated with multiple adverse effects during long-term use.[10,11] Therefore, therapies that target individual components of the inflammatory pathways – monoclonal antibodies that target interactions between cytokines and cytokine receptors and Janus kinase (JAK) inhibitors that target cytokine signal transduction molecules – have recently been introduced for topical therapy-refractory AD.[12]

Dupilumab is the first targeted biologic agent that received regulatory approval, first in the United States and then in the European Union, Japan and other countries, for the treatment of adults with inadequately controlled moderate-to-severe AD.[13] Dupilumab is a fully human monoclonal antibody that binds to the shared α chain subunit of the interleukin (IL)-4 and IL-13 receptors, thereby inhibiting signaling of IL-4 and IL-13. It has shown consistent and acceptable safety and robust efficacy in clinical trials in adults and adolescents with moderate-to-severe AD, and children (aged 6–11 years) with severe AD, as well as in other conditions with type 2 immunologic signatures.[14–16]

A post-marketing surveillance (PMS) was conducted in Japan to collect safety and effectiveness information on dupilumab in patients with AD not adequately controlled with existing therapies, to evaluate the incidence and severity of adverse drugs reactions (ADRs), including any previously unidentified ADRs, during real-world clinical use. Here, we report an interim analysis of the safety information obtained until the data cut-off date and the effectiveness data up to 1 year of dupilumab treatment to better inform the real-world use of dupilumab in Japan.

2 | METHODS

2.1 | Study design, patients, and data collection

This observational, multicenter study was conducted in patients who received dupilumab for the treatment of AD in Japan (UMIN-CTR Trials Registry: UMIN000032807). Patients were eligible for inclusion if they did not have previous treatment experience with dupilumab. Patients who were simultaneously participating in other interventional clinical trials were excluded.

The study duration was 4 years from 1 July 2018 to 30 June 2022; the patient registration period was from 1 July 2018 to 30 June 2020, and patients were followed for 2 years. Patients were registered within 2 weeks of dupilumab initiation. In Japan, dupilumab can only be administered to those who show inappropriate response after at least 6 months of treatment with standard of care (mainly topical anti-inflammatory medications), and the baseline disease severity had to meet all three following criteria: (a) Eczema Area and Severity Index (EASI) score of ≥16 or head and neck EASI subscore ≥2.4, (b) Investigator's Global Assessment (IGA) score of ≥3 (moderate), and (c) affected body surface area (BSA) ≥10%.[8,9] The licensed dosing regimen for dupilumab in Japan is a 600 mg (2 × 300 mg; subcutaneous injection) loading dose, followed by 300 mg every alternate week.

The study was conducted in compliance with the Good Post-Marketing Study Practice (GPSP). The study protocol was approved by the Japanese Pharmaceuticals and Medical Device Agency. Ethics approval for the study was obtained from the participating medical institutions. Patients were enrolled after they provided voluntary informed consent.

Patient data including baseline demographic and clinical history information, data on previous and concomitant medications, and safety and effectiveness data were collected using electronic case report forms (CRFs). Data for this interim analysis were collected for up to 2 years after the initiation of dupilumab treatment in all patients, including those who discontinued dupilumab.

2.2 | Assessments

2.2.1 | Safety

All adverse events (AEs), including ADRs (i.e., AEs in which a causal relationship to dupilumab cannot be ruled out), infections, aggravation of a concurrent illness, subjective/objective symptoms, and abnormal laboratory test results were reported. AEs were classified according to the preferred terms in the Medical Dictionary of Regulatory Activities (MedDRA)/J version 23.1. AEs of interest were based on the regulatory-specified Risk Management Plan[17] and included the followings: information that may indicate an exacerbation of asthma symptoms; severe hypersensitivity; serious infections; aggravation of symptoms of allergic diseases

associated with asthma; events related to depression and suicidal behavior; and malignant tumor. In particular, monitoring asthma attacks among patients with AD treated with dupilumab was identified as an important clinical question for marketing authorization. Occurrence of serious AEs or previously unidentified ADRs (i.e., those not currently listed in the dupilumab package insert) was noted. The data cutoff date for the safety analysis was 26 March 2021 for all the CRFs.

2.2.2 | Effectiveness

Dupilumab effectiveness data were collected at baseline, 1 month, 2 months, and then every 2 months using the IGA, peak weekly pruritus numerical rating scale (NRS), BSA of AD involvement and EASI scores. The IGA describes skin lesions and measures of disease severity on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, and 4 = severe disease). Patients were asked to recall their most severe pruritus experienced in the preceding week and rate it on a NRS from 0 to 10, with zero meaning no itch and 10 being worst itch imaginable. The proportion of BSA of AD involvement was assessed by physicians. The EASI is a composite index of severity and body area scores: EASI scores range from 0 to 72, where the severity of the signs and symptoms of AD (erythema, papulation/edema, excoriation, and lichenification) were assessed on a 4-point scale ranging from 0 (absent) to 3 (severe) and the size of the affected AD area for each body region was expressed as a score between 0 and 6 (0, 1 [1–9% of region affected by AD], 2 [10–29%], 3 [30–49%], 4 [50–69%], 5 [70–89%], and 6 [90–100%]). EASI-50/75/90 is the percentage of patients with ≥50%/75%/90% improvement from baseline after drug treatment.

The change in AD biomarker levels was assessed if available. These included the serum levels of thymus and activation-regulated chemokine (TARC), total immunoglobulin E (IgE), and lactate dehydrogenase (LDH), and peripheral blood eosinophil count.

In the present interim analysis, only data from the first year of dupilumab treatment were included in the effectiveness analysis as the number of patients evaluated for more than 1 year at this data cut-off was still small compared with the number of patients enrolled.

2.3 | Statistical analysis

We estimated that 900 patients would need to be included in the safety analysis set to have an accuracy of ±1% at 95% confidence level, assuming that the true incidence of asthma is 2.2% in post-marketing use. Data were summarized using descriptive statistics, including the number of patients and frequency for dichotomous variables, and mean (standard deviation [SD]) for continuous variables. No imputation was made for missing data. Statistical analysis was undertaken using SAS version 9.1 or later (SAS Institute, Inc., Cary, NC).

3 | RESULTS

3.1 | Patient disposition

Overall, 987 patients registered at 184 sites consented for their data to be included in a publication, and CRFs were collected for 600 of these patients at 122 sites (Figure S1). The safety analysis set included 599 patients. One patient was excluded because their details were entered after the registration deadline. The effectiveness analysis set included 569 patients. Exclusion from the effectiveness analysis set was mainly because effectiveness data were unavailable for evaluation (n = 29) and one patient had disease other than AD (Figure S1).

A summary of the baseline characteristics of the safety analysis set is shown in Table 1. The mean (SD) age of the patients included in the analysis was 42.0 (15.9) years, and 69.1% of the patients were male. Asthma was present in 12.2% of patients in the safety analysis set; 21.9% had allergic rhinitis, and 15.7% had allergic conjunctivitis. A total of 338 patients (56.4%) self-administered

TABLE 1 Demographics and baseline characteristics of the safety analysis set.

Characteristic	N = 599
Age, mean (SD), years	42.0 (15.9)
Age, *n* (%)	
≥15–<18 years	32 (5.3)
≥18–<65 years	507 (84.6)
≥65 years	60 (10.0)
Age of AD onset, (%)	
<6 years	194 (32.4)
≥6–<18 years	113 (18.9)
≥18 years	130 (21.7)
Unknown	162 (27.0)
Gender, *n* (%)	
Male	414 (69.1)
Duration of AD, *n* (%)	
<10 years	54 (9.0)
≥10 years	383 (63.9)
Unknown	162 (27.0)
Patient care, *n* (%)	
Hospitalization	9 (1.5)
Outpatient	590 (98.5)
Body weight, mean (SD), kg	64.6 (13.8)
Current allergic comorbidities, *n* (%)	
Asthma	73 (12.2)
Allergic rhinitis	131 (21.9)
Allergic conjunctivitis	94 (15.7)
Food allergy	57 (9.5)

Abbreviations: AD, atopic dermatitis; SD, standard deviation.

dupilumab. The initial dupilumab dose was 600 mg in almost all patients (99.7%), while the subsequent dose was 300 mg in 98.3% of patients. The mean duration of dupilumab administration was 39.5 (27.8) weeks.

3.2 | Treatments

Treatment before dupilumab mostly involved topical corticosteroids (90.0%) and moisturizers (71.1%) (Table 2). Other than these, topical calcineurin inhibitors (44.9%), oral non-steroidal immunosuppressants (mostly cyclosporine A, 13.4%), and oral corticosteroids (9.3%) had also been used, as well as ultraviolet phototherapy (6.2%) and psychotherapy (0.5%). Concomitant medications were used with dupilumab by 95.5% of the patients, the most common being topical corticosteroids (89.8%) and moisturizers (72.5%). The frequency of concomitant topical medications for AD (topical corticosteroids/topical calcineurin inhibitors) tended to decrease over time (Figure S2). The frequency of concomitant systemic medications decreased after the start of dupilumab, but 25/34 and 40/53 patients reported concomitant use of oral corticosteroids and oral non-steroidal immunosuppressants, respectively, for a short period to seemingly avoid abrupt discontinuation of those drugs (Table 2). Ultraviolet phototherapy and hospital care were less commonly used concomitantly with dupilumab (Table 2).

TABLE 2 AD treatments prior to, and concomitant with, dupilumab.

Medication or treatment for AD, *n* (%)	Previous (*N* = 599) *n* (%)	Concomitant (*N* = 599) *n* (%)
Any medications for AD	570 (95.2)	572 (95.5)
Topical corticosteroids	539 (90.0)	538 (89.8)
Topical calcineurin inhibitor	269 (44.9)	290 (48.4)
Moisturizer	426 (71.1)	434 (72.5)
Oral corticosteroids	56 (9.3)	34 (5.7)
Overlapping transition to dupilumab	–	25 (4.2)
Oral non-steroidal immunosuppressant	80 (13.4)	53 (8.8)
Overlapping transition to dupilumab	–	40 (6.7)
Others	372 (62.1)	359 (59.9)
Any treatments for AD	52 (8.7)	13 (2.2)
Ultraviolet phototherapy	37 (6.2)	7 (1.2)
Hospital care	22 (3.7)	5 (0.8)
Psychotherapy	3 (0.5)	1 (0.2)

Abbreviation: AD, atopic dermatitis.

3.3 | Safety

Adverse drug reactions were observed in 98 patients (16.4%), including conjunctivitis in 40 patients (6.7%), conjunctivitis allergic in 30 patients (5.0%), blepharitis in 5 patients (0.8%), headache and eye pruritus in 4 patients (0.7%) each, and eosinophilia in 3 patients (0.5%) (Table 3). Serious ADRs occurred in 3 patients, which included conjunctivitis, conjunctivitis allergic, pyoderma, and eczema herpeticum (Kaposi's varicelliform eruption); 1 patient presented with both conjunctivitis and eczema herpeticum at 2 different times. Regarding AEs of interest, the occurrence of asthma as an AE (regardless of relatedness with dupilumab) was observed in 6 patients and all of them had a history of, or concurrent, asthma; it was considered non-serious in 5 of the 6 patients. Serious comorbid asthma occurred in 1 patient approximately 2 months after the final dose of dupilumab. Serious hypersensitivity was identified in 2 patients, while 2 patients developed serious infections. No patients developed aggravation of symptoms of allergic diseases associated with asthma, events related to depression or suicidal behavior, and malignant tumors.

A total of 64 patients (10.7%) discontinued treatment with dupilumab, with a mean time to discontinuation of 9.4 (7.8) weeks. Dupilumab treatment was discontinued due to economic reasons (14 patients; 2.3%), occurrence of an AE (9 patients; 1.5%), inadequate clinical effectiveness (6 patients; 1.0%) or improvement in the primary disease (2 patients; 0.3%). The reason for treatment discontinuation was not known in 33 patients (5.5%).

3.4 | Effectiveness

Disease severity and biomarker levels before initiation of dupilumab treatment for AD are presented in Table 4. There was a remarkable improvement in disease severity at 4 months in the majority of patients and it was maintained during treatment of up to 1 year. At baseline, most (98.4%) patients had IGA 3 or 4. Data from patients receiving dupilumab showed that a high proportion achieved IGA ≤2 at 4 months and that IGA improvements were maintained for up to 1 year (Figure 1A,B).

The mean (SD) EASI score decreased from 30.7 (13.1) at baseline to 7.2 (7.7) (n = 394) at 4 months and 3.7 (4.8) (n = 116) at 1 year (Figure 2A). A similar pattern was observed in all regions of the body (Figure 2B). After 4 months of treatment, the EASI-75 (the percentage of patients whose EASI score decreased by 75% or more from baseline) was achieved by 63.9% of patients. This improvement in disease severity was also maintained at 12 months (Figure 2C). The mean (SD) BSA decreased from 57.0 (25.8) % at the baseline to 22.7 (22.5) % (n = 341) at 4 months, and had decreased further by 1 year (12.5 (17.4) %, n = 104) (Figure 2D).

The mean (SD) weekly peak pruritus NRS score (0–10) was 6.9 (2.2) at baseline and decreased to 2.4 (1.7) at 4 months and

TABLE 3 ADRs occurring in the safety analysis set ($N = 599$).

Type of ADR, *n* (%)	All ADRs	Serious ADRs
Any ADR	98 (16.4)	3 (0.5)
Infections and infestations	43 (7.2)	2 (0.3)
Conjunctivitis	40 (6.7)	1 (0.2)
Herpes simplex	1 (0.2)	0
Nasopharyngitis	1 (0.2)	0
Pyoderma	1 (0.2)	1 (0.2)
Kaposi's varicelliform eruption	1 (0.2)	1 (0.2)
Oral herpes	1 (0.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.2)	0
Skin papilloma	1 (0.2)	0
Blood and lymphatic system disorders	1 (0.2)	0
Eosinophilia	1 (0.2)	0
Nervous system disorder	6 (1.0)	0
Dizziness	2 (0.3)	0
Headache	4 (0.7)	0
Hypoesthesia	1 (0.2)	0
Eye disorders	39 (6.5)	1 (0.2)
Blepharitis	5 (0.8)	0
Conjunctivitis allergic	30 (5.0)	1 (0.2)
Dry eye	1 (0.2)	0
Eye discharge	1 (0.2)	0
Ocular hyperemia	1 (0.2)	0
Eye pruritus	4 (0.7)	0
Ear and labyrinth disorders	1 (0.2)	0
Vertigo	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	2 (0.3)	0
Asthma	2 (0.3)	0
Gastrointestinal disorder	1 (0.2)	0
Vomiting	1 (0.2)	0
Skin and subcutaneous tissue disorders	8 (1.3)	0
Acne	1 (0.2)	0
Alopecia	2 (0.3)	0
Dry skin	1 (0.2)	0
Erythema	2 (0.3)	0
Leukoderma	1 (0.2)	0
Skin exfoliation	1 (0.2)	0
Urticaria	1 (0.2)	0
Nail ridging	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.2)	0
Myalgia	1 (0.2)	0
General disorders and administration site conditions	4 (0.7)	0
Injection site erythema	2 (0.3)	0
Injection site pruritus	1 (0.2)	0
Injection site reaction	1 (0.2)	0
Pyrexia	1 (0.2)	0
Investigations	4 (0.7)	0
Alanine aminotransferase increased	1 (0.2)	0
Eosinophil count increased	3 (0.5)	0

Abbreviation: ADR, adverse drug reaction.

TABLE 4 Disease severity at baseline in the effectiveness analysis set.

Parameters	*N*	Measured value Mean (SD)
Disease severity assessments		
IGA	550	3.5 (0.5)
IGA2, *n* (%)	9 (1.6)	
IGA3, *n* (%)	277 (50.4)	
IGA4, *n* (%)	264 (48.0)	
BSA	537	57.0 (25.8)
EASI	539	30.7 (13.1)
Weekly peak pruritus score (NRS)	295	6.9 (2.2)
Biomarkers		
Serum TARC level, pg/mL	402	5152.8 (7750.9)
Peripheral blood eosinophil count, /mm^3	393	778.8 (839.7)
Serum total IgE level, IU/mL	385	10568.5 (12172.9)
Serum LDH level, IU/L	397	303.9 (129.2)

Abbreviations: BSA, body surface area of involvement of atopic dermatitis; EASI, eczema area and severity index; IGA, Investigator's global assessment, IgE, immunoglobulin E; LDH, lactate dehydrogenase; *N*, number of patients at baseline; NRS, numerical rating scale; SD, standard deviation; TARC, thymus and activation-regulated chemokine.

this decrease in pruritus intensity was maintained for up to 1 year (Figure 3A). Responder analysis showed that a high proportion of patients achieved a ≥3-point reduction (76.3%) or ≥4-point reduction (68.5%) in weekly peak pruritus NRS score at 4 months, and this trend was maintained for up to 1 year (Figure 3B).

Biomarkers of AD severity were monitored if available over 1 year. At 4 months, an apparent decrease was observed in the serum levels of TARC, total IgE and LDH (Figure 4A–C). This decrease was maintained for up to 1 year. Peripheral eosinophil counts gradually decreased over 1 year (Figure 4D).

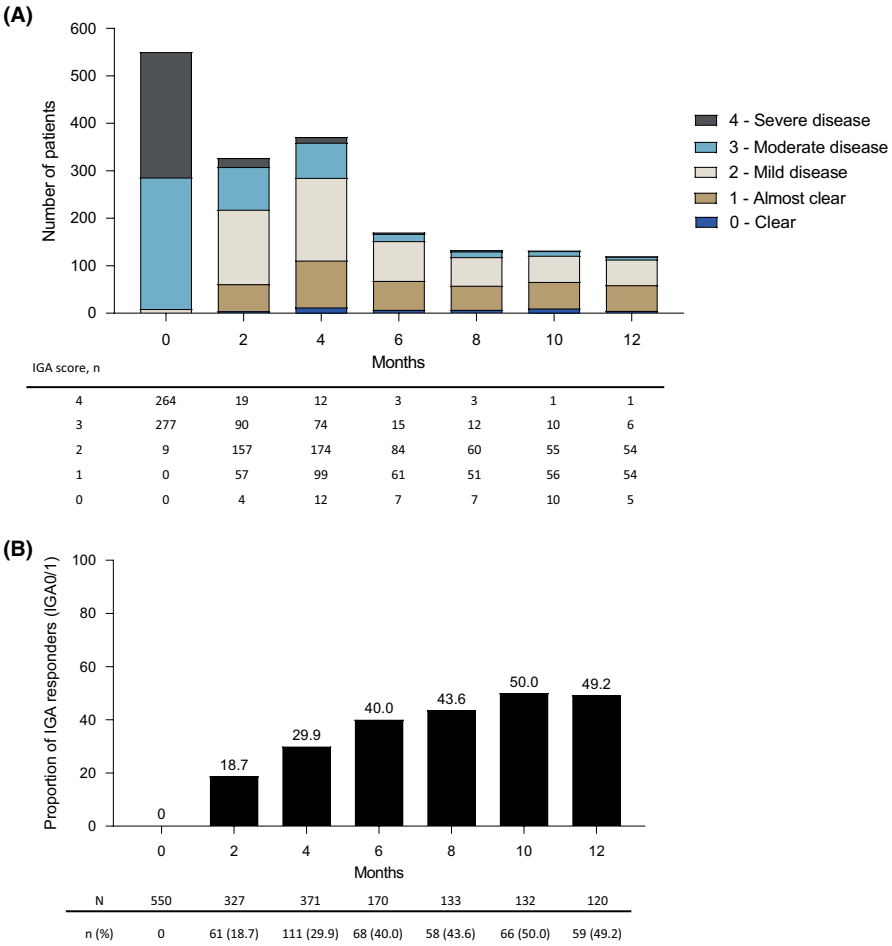


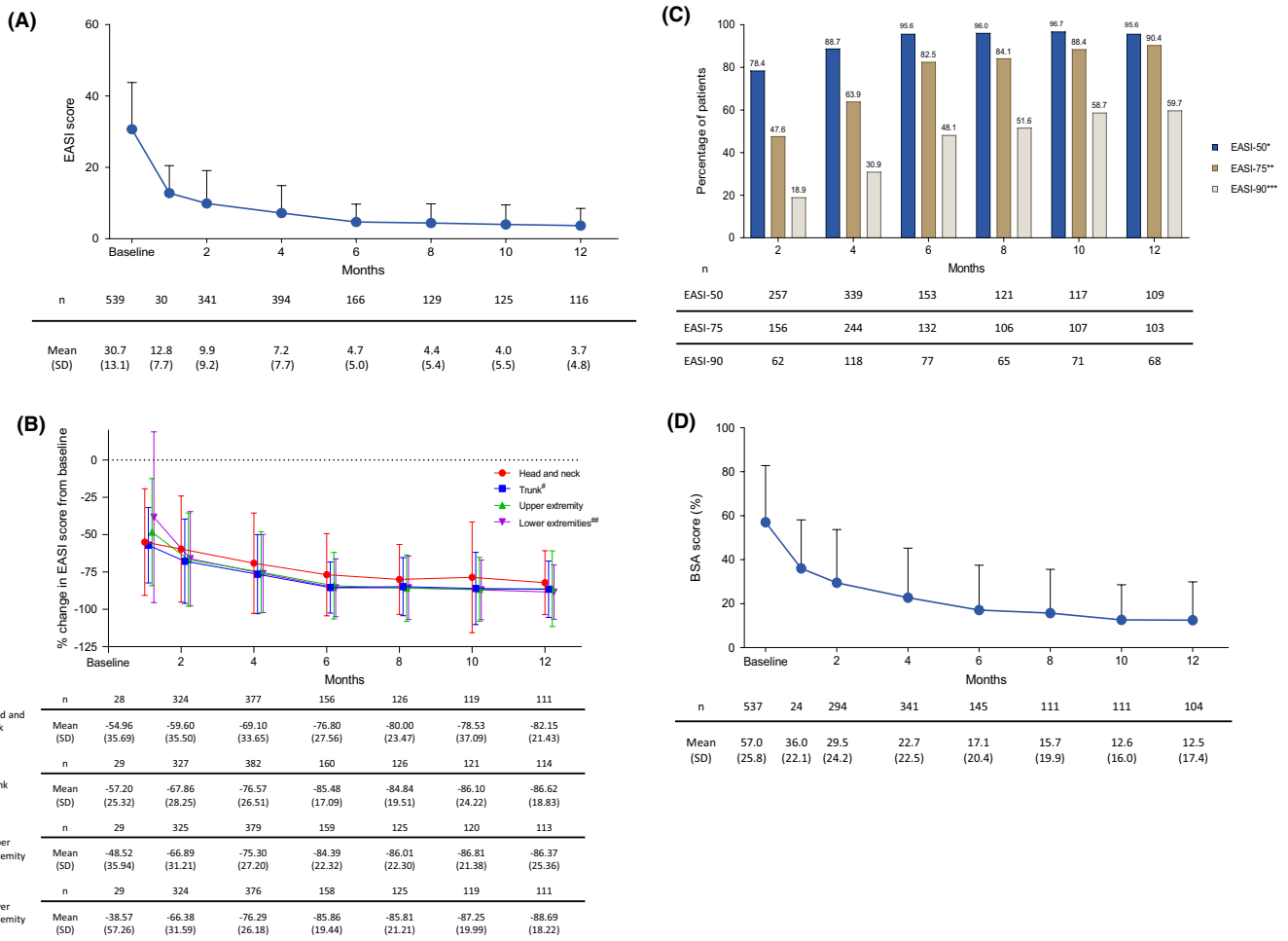
FIGURE 1 Effectiveness outcomes up to 1 year in the study population: (A) distribution of IGA scores at different time points and (B) proportion of IGA responders, where responders denote patients who achieved an IGA score of 0 or 1 at the said time point. IGA, Investigator's Global Assessment.

4 | DISCUSSION

An interim analysis of this PMS provides real-world evidence of the safety and effectiveness of dupilumab over 1 year in the largest cohort of patients with moderate-to-severe AD ever reported in Japan. Dupilumab was found to have an acceptable safety profile and was well tolerated. The incidence of ADRs was lower than that observed in the clinical trials, with four serious ADRs (conjunctivitis, allergic conjunctivitis, pyoderma and eczema herpeticum) in three patients among 599 patients (0.5%); there were no new safety signals, and no cases of new-onset asthma.

In Japan, dupilumab is administered to patients aged ≥15 years with moderate-to-severe AD and inadequate response to topical anti-inflammatory medications for 6 months or longer, along with a pre-defined baseline disease severity.[8,9] Dupilumab is supposed to be prescribed in combination with topical treatments. In the current PMS, the proportion of patients who used topical anti-inflammatory treatment every day decreased over time. Whether this suggests a topical corticosteroid-sparing effect of dupilumab, or merely decreasing adherence needs to be assessed in the future. There is still uncertainty regarding how patients can effectively transition from systemic immunosuppressants to dupilumab. In an earlier report, while 65% (62/95) of patients were using systemic immunosuppressants at the start of dupilumab treatment, and 45% (43/95) continued to use systemic immunosuppressants after the initiation of dupilumab, 67% (29/43) stopped concomitant systemic immunosuppressant treatment after 4 months.[18] Similarly, in the present cohort, >60% of patients continued to use systemic agents during dupilumab treatment. Concomitant systemic agents were gradually tapered off and most patients discontinued their use after 4 months of treatment with dupilumab (data not shown). Recently, de Wijs et al. proposed that systemic immunosuppressant dosage can be gradually tapered after 8 weeks of dupilumab treatment and completely discontinued after 12 or 14 weeks depending upon treatment response.[19] Nevertheless, further studies are warranted to determine the optimal approach for transition from systemic immunosuppressants to dupilumab.

Clinical trials with dupilumab, either as monotherapy or with concomitant use of topical corticosteroids, demonstrated a low incidence of AEs and serious AEs compared with the placebo.[20,21] In all these trials, conjunctivitis (either allergic or of unspecified cause) was reported at a higher rate in patients receiving dupilumab compared with placebo, in addition to injection-site reactions.[20–22] The most common ADRs in the present interim analysis were eye disorders, including conjunctivitis (6.7%), conjunctivitis allergic (5.0%), blepharitis (0.8%), and eye pruritus (0.7%). The incidence of drug-related conjunctivitis was lower than in the placebo-controlled phase 3 LIBERTY AD CHRONOS trial, which reported an incidence



(A)								
n	539	30	341	394	166	129	125	116
Mean (SD)	30.7 (13.1)	12.8 (7.7)	9.9 (9.2)	7.2 (7.7)	4.7 (5.0)	4.4 (5.4)	4.0 (5.5)	3.7 (4.8)

(B)								
Head and neck	n	28	324	377	156	126	119	111
	Mean (SD)	-54.96 (35.69)	-59.60 (35.50)	-69.10 (33.65)	-76.80 (27.56)	-80.00 (23.47)	-78.53 (37.09)	-82.15 (21.43)
Trunk	n	29	327	382	160	126	121	114
	Mean (SD)	-57.20 (25.32)	-67.86 (28.25)	-76.57 (26.51)	-85.48 (17.09)	-84.84 (19.51)	-86.10 (24.22)	-86.62 (18.83)
Upper extremity	n	29	325	379	159	125	120	113
	Mean (SD)	-48.52 (35.94)	-66.89 (31.21)	-75.30 (27.20)	-84.39 (22.32)	-86.01 (22.30)	-86.81 (21.38)	-86.37 (25.36)
Lower extremity	n	29	324	376	158	125	119	111
	Mean (SD)	-38.57 (57.26)	-66.38 (31.59)	-76.29 (26.18)	-85.86 (19.44)	-85.81 (21.21)	-87.25 (19.99)	-88.69 (18.22)

(C)						
n	2	4	6	8	10	12
EASI-50	257	339	153	121	117	109
EASI-75	156	244	132	106	107	103
EASI-90	62	118	77	65	71	68

(D)								
n	537	24	294	341	145	111	111	104
Mean (SD)	57.0 (25.8)	36.0 (22.1)	29.5 (24.2)	22.7 (22.5)	17.1 (20.4)	15.7 (19.9)	12.6 (16.0)	12.5 (17.4)

FIGURE 2 Effectiveness outcomes up to 1 year in the study population: (A) EASI score at different time points, (B) change in EASI scores in the different regions of the body, (C) proportion of patients with ≥50%/75%/90% decrease in EASI scores from baseline and (D) change in affected BSA from baseline. BSA, Body surface area of involvement of atopic dermatitis; EASI, Eczema Area and Severity Index. #Includes genital area; ##Includes buttocks; *Proportion of patients whose EASI score improved by ≥50% from baseline among patients for whom the change rate can be calculated; **Proportion of patients for whom the EASI score improved by ≥75% from baseline among patients for whom the change rate can be calculated; ***Proportion of patients whose EASI score improved by 90% or more from baseline among patients for whom the change rate can be calculated.

of 14%, irrespective of its relationship to dupilumab.[20] Interestingly, this complication is not observed when dupilumab is used for asthma and chronic rhinosinusitis with nasal polyps.[22,23] A probable reason could be that conjunctivitis occurs due to underlying AD pathogenesis and a history of atopic conditions.[22–24] A pooled analysis of the real-world evidence of dupilumab reported blepharitis in 9.6% of AD patients and keratitis in 6.2% of patients.[25] Overall, ocular surface disease was reported in 45.2% of AD patients receiving dupilumab ($n = 387$) in this pooled analysis of real-world studies.[25]

The current interim analysis of this PMS so far confirms the results of clinical trials showing that targeting the type 2 inflammation pathway with dupilumab brings about large improvements in disease severity, as indicated by improvements in IGA, BSA, EASI, and peak pruritus NRS scores. The results of this interim analysis were not only consistent with those observed in phase 3 clinical trials,[20,21,26] but also with real-world data, such as that reported from the Dutch BioDay registry.[27] The primary clinician-reported outcome EASI-75 used in the clinical trials was achieved after 4 months of treatment by 63.9% of the patients in the current analysis, 44%–69% of the patients in the phase 3 trials,[20,21,26] and 62% of patients in the multicenter BioDay registry.[27] In agreement with these studies, dupilumab achieved an IGA score of 0 (clear) or 1 (almost clear), and 3-point or 4-point reduction in peak pruritus NRS at 4 months in a substantial proportion of patients in the present report. Moreover, the decrease in EASI score and affected BSA were similarly observed up to 1 year, indicating a continuous treatment response to dupilumab over 1 year. Given that EASI score and affected BSA are well correlated in patients with moderate-to-severe AD[28] and BSA is simpler to measure, it may be a clinically useful alternative to EASI score during routine practice.

Measurement of biomarkers, such as serum levels of TARC, LDH, and total IgE and circulating eosinophils provides an objective evaluation of AD severity, since elevated levels of these biomarkers are associated with increased severity.[9] In the current analysis,

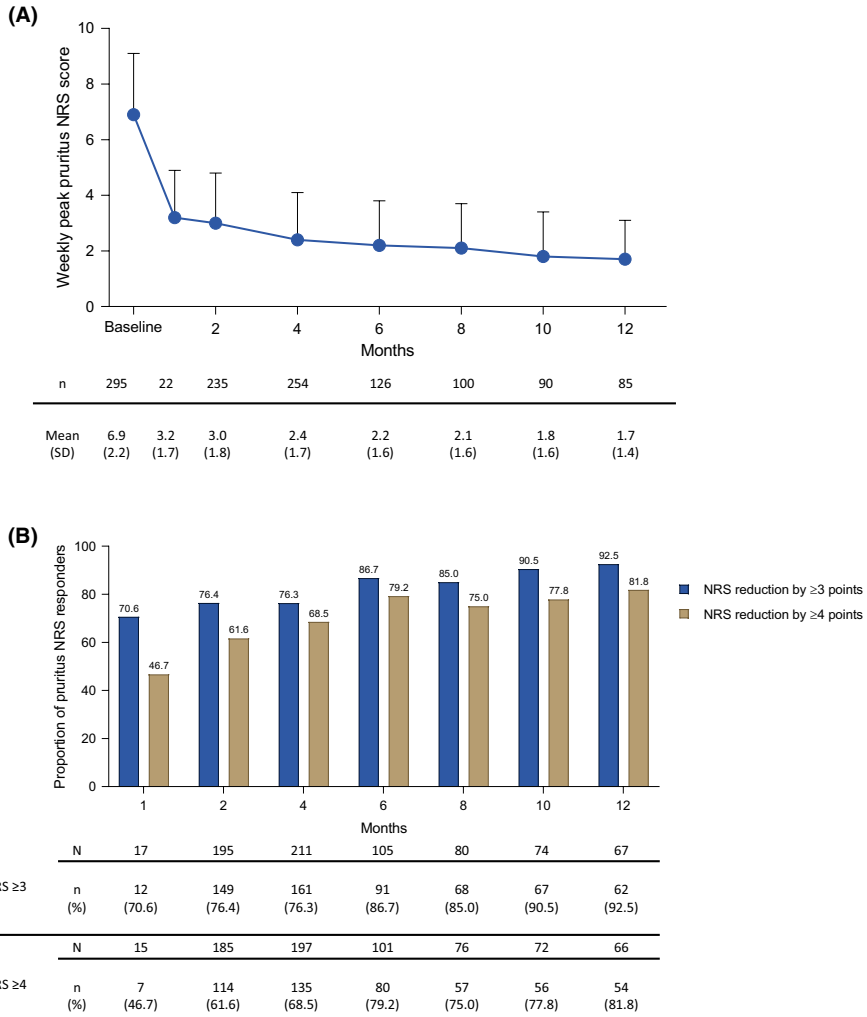


FIGURE 3 Pruritus severity up to 1 year in the study population: (A) pruritus NRS score over time and (B) proportion of patients with a ≥3- or ≥4-point reduction in pruritus NRS from baseline. NRS, numerical rating scale.

treatment with dupilumab apparently suppressed these severity-related biomarkers. Analysis of the efficacy and safety of dupilumab in the Japanese cohorts of phase 2 and 3 clinical trials showed a numerically higher disease severity in the Japanese cohort than in the overall study population.[29] Nevertheless, consistent with the overall study population, dupilumab significantly improved signs and symptoms of AD compared with placebo in the Japanese subgroup. Dupilumab was also associated with rapid reduction in TARC and gradual total IgE reductions among Japanese patients.[29] The present report confirmed this trend with a greater number of patients. Likewise, other real-world studies in Japanese patients with AD have also shown marked and rapid improvement in skin eruptions and erythema, as well as in TARC and LDH serum levels at 1 month, while there was a gradual improvement in prurigo nodules and serum total IgE level.[30–33]

This PMS included the largest prospective cohort of Japanese patients with AD who were treated with dupilumab. The strength of this analysis is the long duration of follow-up and the large study population. There are several limitations. As it was conducted in routine clinical practice, the safety and effectiveness data may be underreported and affected by factors unrelated to dupilumab. Furthermore, this was an interim analysis and the number of patients evaluated at the data cut-off was lower than the estimated number in the sample size calculation.

In conclusion, the results to date of this interim PMS support the use of dupilumab as a safe and effective option for the treatment of adults and older adolescents with moderate-to-severe AD in routine clinical practice in Japan. The tolerability of dupilumab has thus far been comparable with the reported safety profile, with a low incidence of serious ADRs and without any new safety signals.

AUTHOR CONTRIBUTIONS

Hidehisa Saeki enrolled patients. All authors contributed to study design and interpretation of the data, critically revised the manuscript for intellectual content and approved the final version of the manuscript for publication.

ACKNOWLEDGMENTS

We would like to express our gratitude to all of the institutions, patients, and people concerned for their cooperation. We would also like to thank Mitali Choudhury, PhD, of inScience Communications, Springer Healthcare, who provided medical writing support under the author's guidance. This support was funded by Sanofi K.K. This

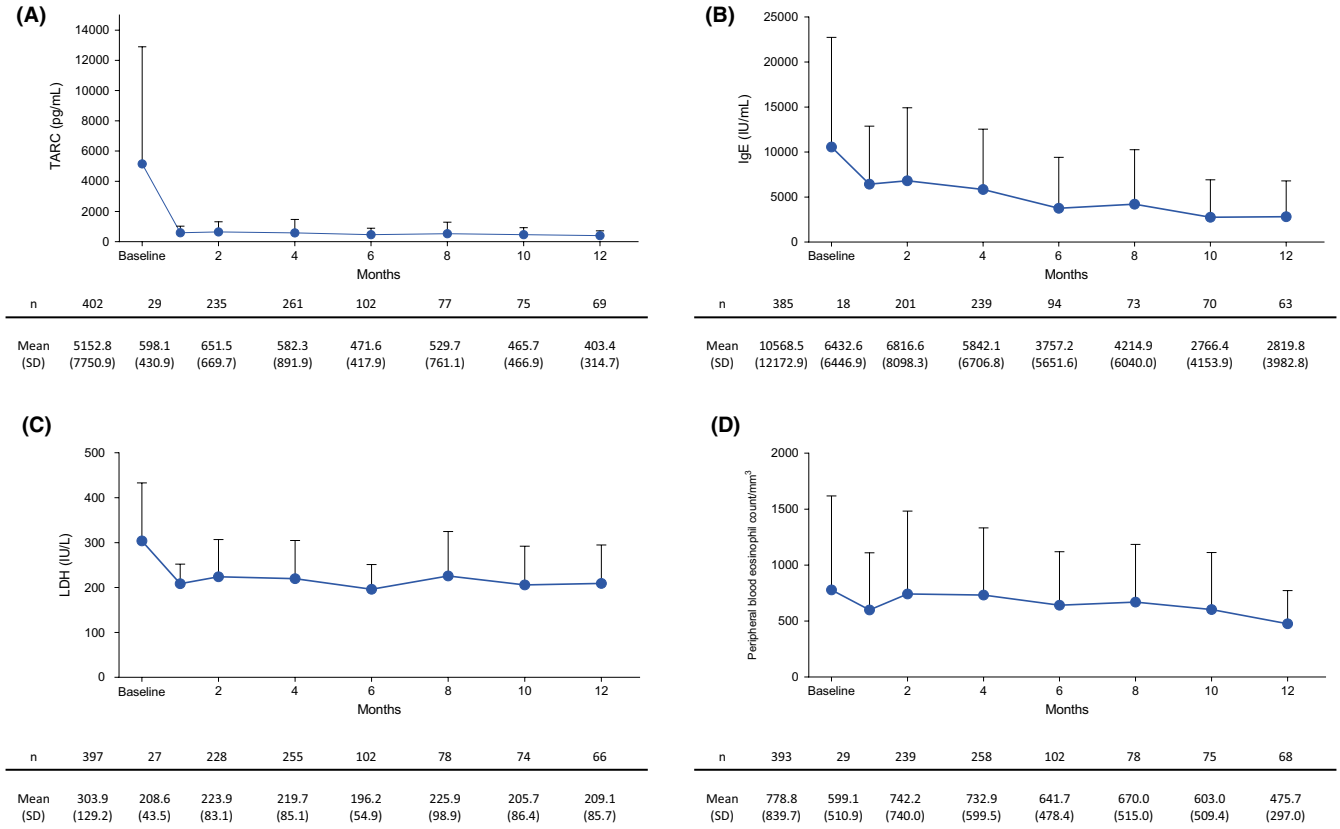


FIGURE 4 Evaluation of AD severity up to 1 year using biomarkers (A) serum TARC levels, (B) serum total IgE levels, (C) serum LDH levels, and (D) peripheral blood eosinophil counts. AD, atopic dermatitis; IgE, immunoglobulin E; LDH, lactate dehydrogenase; SD, standard deviation; TARC, thymus and activation-regulated chemokine.

study and the associated article publication charges were funded by Sanofi K.K.

CONFLICT OF INTEREST STATEMENT

Hidehisa Saeki was an external advisor and received honoraria for lectures from AbbVie, Kyorin Pharmaceutical, Kyowa Kirin, Maruho, Mitsubishi Tanabe Pharma, Sanofi, and Taiho Pharma; research grants from Eisai, Tokiwa Pharmaceutical, and Torii Pharmaceutical. Hiroyuki Fujita, Katsuhisa Suzuki, and Kazuhiko Arima are employees and may be shareholders of Sanofi K.K.

DATA AVAILABILITY STATEMENT

Data sharing is not currently available for this article as it is an interim analysis of a yet unfinalized surveillance.

ETHICS STATEMENT

Approval of the Research Protocol: The protocol for this research project was conducted in compliance with the Good Post-Marketing Study Practice (GPSP) and has been approved by a suitably constituted Ethics Committee of the institution (Committee of Japanese Pharmaceuticals and Medical Device Agency). Ethics approval was also obtained from the participating medical institutions.

Informed Consent: Voluntary informed consent was obtained from the study participants.

Registry and Registration No.: This study is registered in the UMIN-CTR Trials Registry (UMIN000032807).

Animal Studies: N/A.

ORCID

Hidehisa Saeki https://orcid.org/0000-0002-1095-0355
Kazuhiko Arima https://orcid.org/0000-0002-0607-8787

REFERENCES

1. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the global burden of disease study 1990-2017. Br J Dermatol. 2021;184(2):304–9.
2. Takeuchi S, Esaki H, Furue M. Epidemiology of atopic dermatitis in Japan. J Dermatol. 2014;41(3):200–4.
3. Furue M, Yamazaki S, Jimbow K, Tsuchida T, Amagai M, Tanaka T, et al. Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. J Dermatol. 2011;38(4):310–20.
4. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy. 2018;73(6):1284–93.
5. Nakano-Tahara M, Matsumoto M, Yamauchi-Takihara K, Iso H, Katayama I, Murota H. Retrospective survey for clinical course and aggravating factors of adolescent atopic dermatitis in two years' cohort study on first-year university students. J Cutan Immunol Allergy. 2022;5(2):47–55.

6. Davidson WF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "atopic dermatitis and the atopic march: mechanisms and interventions". J Allergy Clin Immunol. 2019;143(3):894–913.
7. Takizawa T, Morikawa A, Arakawa H. Epidemiology of atopic dermatitis in Japan. In: Katayama I, Murota H, Satoh T, editors. Evolution of atopic dermatitis in the 21st century. Singapore: Springer Singapore; 2018. p. 13–24.
8. Miyano K, Tsunemi Y. Current treatments for atopic dermatitis in Japan. J Dermatol. 2021;48(2):140–51.
9. Saeki H, Ohya Y, Furuta J, Arakawa H, Ichiyama S, Katsunuma T, et al. English version of clinical practice guidelines for the management of atopic dermatitis 2021. J Dermatol. 2022;49(10):e315–75.
10. Katoh N, Saeki H, Kataoka Y, Etoh T, Teramukai S, Takagi H, et al. Evaluation of standard treatments for managing adult Japanese patients with inadequately controlled moderate-to-severe atopic dermatitis: two-year data from the ADDRESS-J0 disease registry. J Dermatol. 2022;49(9):903–11.
11. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: a systematic review and meta-analysis. Allergy. 2021;76(4):1053–76.
12. Ahn J, Grinich EE, Choi Y, Guttman-Yassky E, Simpson EL. Emerging systemic therapeutic biologics and small molecules for atopic dermatitis: how to decide which treatment is right for your patients. J Allergy Clin Immunol Pract. 2021;9(4):1449–60.
13. Chang HY, Nadeau KC. IL-4Rα inhibitor for atopic disease. Cell. 2017;170(2):222.
14. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85–96.
15. Paller AS, Siegfried EC, Thaci D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282–93.
16. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156(1):44–56.
17. Sanofi KK. Risk management plan for DUPIXENT (dupilumab) [Online document]. 2021 [cited April 18 2022]. Available from: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/GeneralList/4490405
18. de Wijs LEM, Bosma AL, Erler NS, Hollestein LM, LAA G, Middelkamp-Hup MA, et al. Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. Br J Dermatol. 2020;182(2):418–26.
19. de Wijs LEM, Thyssen JP, Vestergaard C, Thio HB, Kunkeler ACM, Biedermann T, et al. An approach for the transition from systemic immunosuppressants to dupilumab. J Eur Acad Dermatol Venereol. 2021;35(3):e221–3.
20. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287–303.
21. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.
22. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019;181(3):459–73.
23. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. J Am Acad Dermatol. 2018;78(3 Suppl 1):S28–36.
24. Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. JAMA Dermatol. 2018;154(10):1208–11.
25. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. J Am Acad Dermatol. 2021;84(1):139–47.
26. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin a or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol. 2018;178(5):1083–101.
27. Ariëns LFM, van der Schaft J, Bakker DS, Balak D, MLE R, Kouwenhoven T, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. Allergy. 2020;75(1):116–26.
28. Katoh N, Saeki H, Kataoka Y, Etoh T, Teramukai S, Takagi H, et al. Atopic dermatitis disease registry in Japanese adult patients with moderate to severe atopic dermatitis (ADDRESS-J): baseline characteristics, treatment history and disease burden. J Dermatol. 2019;46(4):290–300.
29. Katoh N, Kataoka Y, Saeki H, Hide M, Kabashima K, Etoh T, et al. Efficacy and safety of dupilumab in Japanese adults with moderate-to-severe atopic dermatitis: a subanalysis of three clinical trials. Br J Dermatol. 2020;183(1):39–51.
30. Matsutani M, Imai Y, Inoue Y, Hosotani Y, Kusakabe M, Natsuaki M, et al. Real-world use of dupilumab for 53 patients with atopic dermatitis in Japan. J Cutan Immunol Allergy. 2020;3(2):35–6.
31. Kato A, Kamata M, Ito M, Uchida H, Nagata M, Fukaya S, et al. Higher baseline serum lactate dehydrogenase level is associated with poor effectiveness of dupilumab in the long term in patients with atopic dermatitis. J Dermatol. 2020;47(9):1013–9.
32. Uchida H, Kamata M, Kato A, Mizukawa I, Watanabe A, Agematsu A, et al. One-year real-world clinical effectiveness, safety, and laboratory safety of dupilumab in Japanese adult patients with atopic dermatitis: a single-center retrospective study. J Am Acad Dermatol. 2021;84(2):547–50.
33. Takeuchi S, Inoue K, Kuretake K, Kiyomatsu-Oda M, Furue M. Dupilumab shows slow, steady effectiveness for intractable prurigo in patients with atopic dermatitis. J Dermatol. 2021;48(5):638–44.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Saeki H, Fujita H, Suzuki K, Arima K. Safety and effectiveness of dupilumab in the real-world treatment of atopic dermatitis in Japan: 1-year interim analysis from a post-marketing surveillance. J Cutan Immunol Allergy. 2023;6:78–87. https://doi.org/10.1002/cia2.12303