Dermatol Ther (Heidelb) (2022) 12:2731–2746
https://doi.org/10.1007/s13555-022-00822-x

ORIGINAL RESEARCH

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis is Efficacious Regardless of Age of Disease Onset: a Post Hoc Analysis of Two Phase 3 Clinical Trials

Jonathan I. Silverberg · Mark Boguniewicz · Jon Hanifin · Kim A. Papp · Haixin Zhang · Ana B. Rossi · Noah A. Levit

Received: July 8, 2022 / Accepted: September 21, 2022 / Published online: October 21, 2022

ABSTRACT

Introduction: Adults with atopic dermatitis (AD) commonly report adult-onset disease. AD is associated with different genetics, lesion morphology and distribution, and symptoms by age of onset. Yet little is known about possible differences in treatment efficacy between adults with adult-onset or childhood-onset AD.

Methods: We evaluated the efficacy of dupilumab by age of AD onset in adults with moderate-to-severe AD, using pooled data from the LIBERTY AD SOLO 1 and 2 studies (NCT02277743, NCT02277769). Results were stratified based on self-reported age of AD onset, divided into four age subgroups: 0–4, 5–9, 10–19, and over 20 years.

Results: This analysis included 460 patients treated with placebo and 457 treated with dupilumab 300 mg every 2 weeks (q2w), with a mean patient age of 38 years. Most patients (53.2%) reported AD onset at 0–4 years, with 14% at 5–9 years, 13.4% at 10–19 years, and 18.5% at 20 years or older. Dupilumab significantly improved AD signs and symptoms over 16 weeks compared with placebo, regardless of age of onset. Dupilumab treatment resulted in a significantly greater proportion of patients achieving Eczema Area and Severity Index (EASI)-50, EASI-75, and EASI-90 (50%, 75%, and 90% improvement from baseline EASI, respectively), and clear or almost clear skin (Investigator's Global Assessment score 0 or 1) across all age-of-onset subgroups compared with placebo. In addition, EASI improvements were significant across all anatomical regions in all subgroups. Weekly average peak pruritus Numerical Rating Scale and Dermatology Life Quality Index also improved consistently and significantly with dupilumab versus placebo, regardless of age of onset.

Conclusion: Despite possible differences in presentation and progression of AD linked to age of onset, dupilumab showed similar significant and sustained improvements in AD signs,

J. I. Silverberg
The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

M. Boguniewicz
Division of Allergy-Immunology, Department of Pediatrics, National Jewish Health and University of Colorado School of Medicine, Denver, CO, USA

J. Hanifin
OHSU Hospital Dermatology Clinic, Portland, OR, USA

K. A. Papp
Probity Medical Research, Waterloo, ON, Canada

H. Zhang · N. A. Levit (✉)
Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Rd, Tarrytown, NY 10591, USA
e-mail: noah.levit@regeneron.com

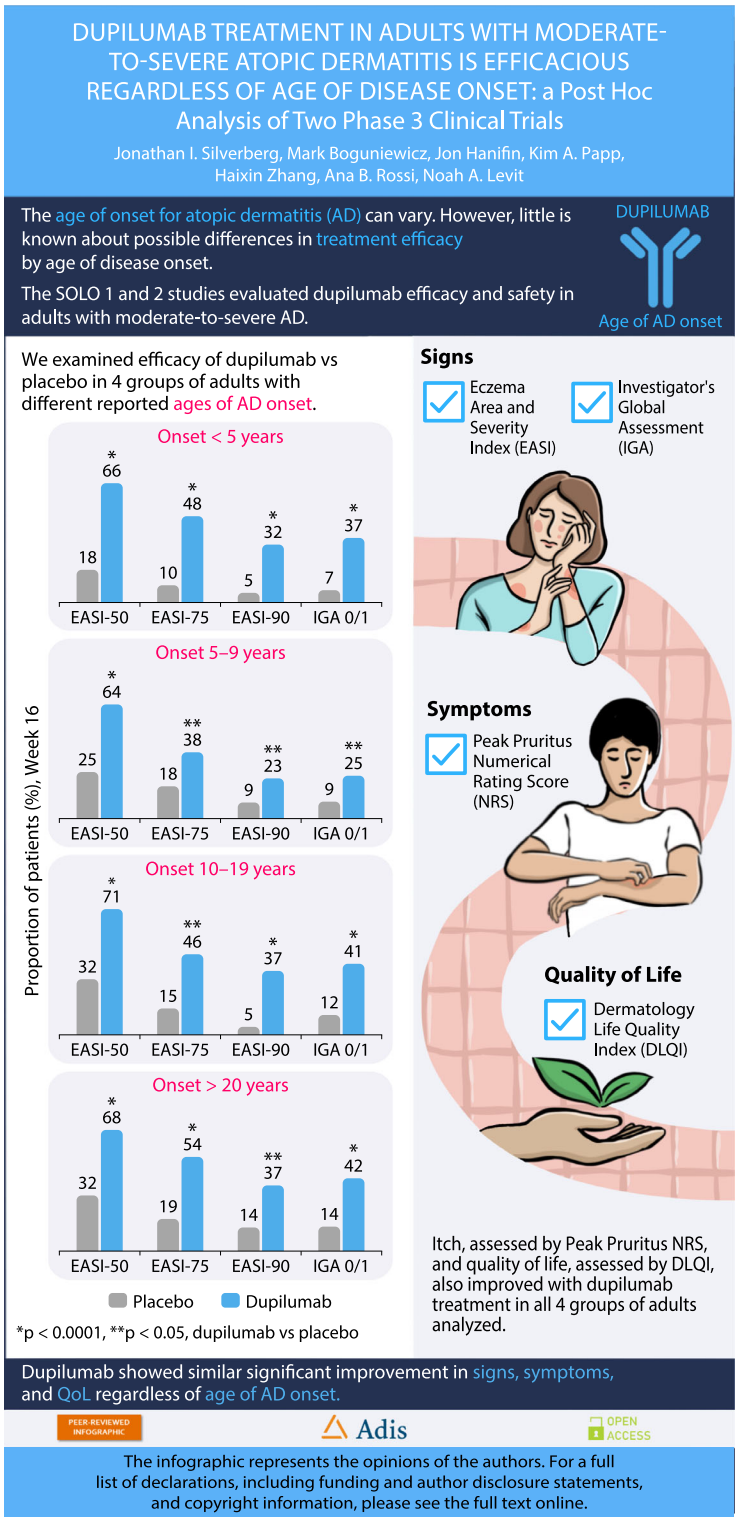
A. B. Rossi
Sanofi, Cambridge, MA, USA

symptoms, and quality of life in adults compared with placebo, over 16 weeks of treatment. ***Trial Registration***: LIBERTY AD SOLO 1: NCT02277743; LIBERTY AD SOLO 2: NCT02277769.
Infographic available for this article.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD, also known as eczema) is a skin disease with itchy, red rashes. AD often develops during childhood, but can also start in adulthood. Depending on the age it starts, AD may have different triggers and appearance, and might require different treatment. A medicine called dupilumab, which targets two proteins that cause inflammation, has provided benefit in children and adults with AD. We wanted to know if the age at which AD starts (during infancy, childhood, adolescence, or adulthood) impacts the improvement of dupilumab in adult patients. We looked at 917 adults, who participated in two studies taking dupilumab or a dummy treatment (placebo) every 2 weeks for 4 months. We compared four groups of patients with different ages of AD onset. The results showed that dupilumab compared with the placebo reduced skin lesions, relieved itch, and improved quality of life in a similar way in all adults, regardless of whether their disease started earlier or later in life. In the four groups, dupilumab reduced skin lesions across all areas of the body. Together with the previously reported safety data, our results support the use of dupilumab in adults with moderate-to-severe AD, irrespective of age of disease onset.

Infographic:



Keywords: Age; Atopic dermatitis; Dupilumab; Treatment efficacy

Key Summary Points

Why carry out this study?

Little is known about possible differences in treatment efficacy between adults with adult-onset or childhood-onset atopic dermatitis (AD).

Dupilumab, a fully human monoclonal antibody, inhibits the signaling of both interleukin (IL)-4 and IL-13, which are key drivers of type 2-mediated inflammation, a molecular signature common to AD across age groups and clinical phenotypes.

We hypothesize that dupilumab treatment responses in adults with moderate-to-severe AD would be similar, regardless of age of AD-onset.

What has been learned from this study?

Our findings show that dupilumab is efficacious in adults with moderate-to-severe AD regardless of age of AD-onset; despite possible endophenotypic differences linked to age of onset and differences in AD duration at baseline, dupilumab showed similar improvements in AD signs, symptoms, and quality of life (QoL) in adults during 16 weeks of treatment.

These findings support targeting of both IL-4 and IL-13 as an effective treatment strategy for AD across all ages of onset.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.20750128.

INTRODUCTION

Atopic dermatitis (AD) frequently develops during childhood and, in a proportion of patients, may remit by adolescence. There is mounting evidence that adult-onset AD occurs more commonly than previously thought [1–5]. Adult-onset AD is estimated to account for approximately one-quarter of AD cases among adult patients, and studies have shown that it has distinct clinical characteristics, including localized hand, head, and neck lesions [4, 6–10]. Laboratory characteristics also differ in adult-onset AD, with lower immunoglobulin E (IgE) responses. Furthermore, genetic analysis revealed a reduced prevalence of filaggrin loss-of-function mutations in this group [6, 11]. Adult-onset patients are less likely to report a family history of atopic conditions, show less predilection for flexural sites, and possibly have a greater frequency of associated morphologic variants [12, 13].

Dupilumab, a fully human monoclonal antibody, inhibits the signaling of both interleukin (IL)-4 and IL-13, which are key drivers of type 2-mediated inflammation [14, 15]. Although evidence is mounting of different endotypes of AD based on age, ethnicity, and race, type 2 predominant inflammatory skewing is a molecular signature common to AD across multiple age groups and clinical phenotypes [9, 16, 17]. We therefore hypothesize that dupilumab treatment responses in adults with moderate-to-severe AD would be similar regardless of age of AD onset. We evaluated dupilumab treatment efficacy by age of AD onset in adults with moderate-to-severe AD, using pooled data from the LIBERTY AD SOLO 1 and 2 studies [18].

METHODS

This study was a post hoc analysis of patient characteristics and treatment efficacy from two phase 3 randomized, placebo-controlled trials of dupilumab in adults with AD (LIBERTY AD SOLO 1 [18], NCT02277743; and LIBERTY AD SOLO 2 [18], NCT02277769). Detailed methods

of the studies, including full inclusion and exclusion criteria, were previously reported [18]. Briefly, patients from both studies were aged 18 years and older, with moderate-to-severe AD (Investigator's Global Assessment [IGA] score 3 or 4) inadequately controlled by topical corticosteroids (TCS). In addition, the diagnosis had to meet American Academy of Dermatology Consensus Criteria for chronic AD, and patients were required to have had the diagnosis for at least 3 years before the screening visit and had other differential diagnoses ruled out [18]. Patients received dupilumab 300 mg or placebo once weekly (qw) or once every 2 weeks (q2w) for 16 weeks. Only patients from the approved 300 mg q2w treatment and control (placebo) groups were included in this analysis to be consistent with the approved posology in this age group [19, 20].

The studies were approved by their respective institutional review boards and conducted per the ethical principles outlined in the Declaration of Helsinki, the International Council on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. All patients provided written informed consent before participating in the trials.

Assessments

This analysis includes results using the following disease severity metrics: IGA (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe), Eczema Area and Severity Index (EASI; range 0–72), weekly peak pruritus Numerical Rating Scale (NRS; range 0–10), and Dermatology Life Quality Index (DLQI; range 0–30). For each of these metrics, higher scores represent a greater AD burden. EASI scores were also analyzed by body region: head/neck, upper extremities, lower extremities, and trunk. Treatment efficacy endpoints included EASI-50, -75, and -90, which represent the proportion of patients achieving a decrease in EASI from baseline of 50%, 75%, or 90%, respectively. The proportion of patients who achieved IGA scores of 0 or 1 were also analyzed.

Statistical Analysis

The study population was the full analysis set (FAS), including all randomized patients from the two studies. Patients were analyzed by subgroups based on patient-reported age of AD-onset as follows: 0–4 years, 5–9 years, 10–-19 years, and 20 years or older. Confidence intervals (CI) and *p* values were based on treatment difference (dupilumab group versus placebo) of the LS (least squares) mean or LS mean percent change using an Analysis of Variance (ANOVA) model with baseline measurements as covariate and the treatment group, randomization strata, region, disease severity (IGA 3 versus IGA 4), and study identifier as fixed factors. Multiple imputation methods were used including censoring after rescue treatment for analysis of EASI scores by body region; EASI-50, -75, and -90; and achievement of IGA 0 or 1. No adjustments were made for multiple comparisons.

RESULTS

Patient Demographics and Medical History

In total, 460 patients in the placebo group and 457 in the dupilumab 300 mg q2w group were included in this analysis. The mean age of patients at baseline was 38 years, with a mean duration of AD of approximately 28 years (Table 1). Age of AD onset (self-reported) showed a peak in early childhood, with 53.2% of patients developing AD at 0–4 years (Fig. 1, Table 1), while 18.5% of patients reported developing AD as an adult (20 years or above). For the patients included in this analysis, age of AD onset was relatively well balanced between treatment groups. Baseline demographics and disease characteristics were also relatively balanced between treatment arms and age groups, except for Patient-Oriented Eczema Measure (POEM) and DLQI, which were reported to be more severe with an earlier age of onset (Table 2).

In general, a family history of atopic and allergic conditions was reported by fewer

Table 1 Overview of AD age of onset and duration

	Placebo (*N* = 460)	Dupilumab 300 mg q2w (*N* = 457)
Age, mean (SD), years	38.4 (14.0)	38.3 (14.4)
Duration of AD, mean (SD), years	28.8 (14.4)	27.9 (15.2)
Self-reported AD age of onset, *n* (%)		
< 5 years	249 (54.1)	239 (52.3)
5 to < 10 years	67 (14.6)	61 (13.3)
10 to < 20 years	60 (13.0)	63 (13.8)
20 to < 30 years	28 (6.1)	38 (8.3)
30 to < 40 years	21 (4.6)	21 (4.6)
≥ 40 years	30 (6.5)	32 (7.0)
Unsure	4 (0.9)	3 (0.7)
Missing	1 (0.2)	0

AD atopic dermatitis, *q2w* every 2 weeks, *SD* standard deviation

patients in the onset age of 20 years or older group, with allergic rhinitis being reported in 24–30% of the 0–4 years group compared with 10–17% of the 20 years or older group (Table 3).

Patient history of atopic and allergic conditions was more frequent in patients with an earlier age of AD onset, with asthma reported in 47–54% of those with onset at 0–4 years versus 23–31% in the 20 years or older age-of-onset group (Table 3). Similar trends were seen for allergic rhinitis, food allergies, atopic kerato-conjunctivitis, and allergic conjunctivitis (Table 3).

Physician Assessed Efficacy Outcomes at 16 Weeks

EASI-75 was achieved in significantly more patients treated with dupilumab (LS mean range 38–54%) versus placebo (LS mean range 10–19%, $p < 0.0001$), irrespective of age of AD onset (Fig. 2). Dupilumab treatment also resulted in a significantly greater proportion of patients achieving EASI-50 and EASI-90 in all age-of-onset subgroups versus placebo. IGA 0 or 1 was achieved in 25–42% of patients across the dupilumab age-of-onset subgroups versus 7–14% in the placebo groups; $p < 0.05$ for all comparisons (Fig. 2).

Lastly, EASI improvements were significantly higher in dupilumab-treated patients across all four anatomic regions, regardless of age of AD onset (Fig. 3).

Patient-Reported Efficacy Measures

Weekly average peak pruritus NRS (baseline LS mean range across subgroups 7.1–7.6) decreased significantly by weeks 1–3, with further improvement through 16 weeks of dupilumab 300 mg q2w (LS mean range 3.9–4.0) versus placebo (LS mean range 5.3–6.0), regardless of age of AD onset (Fig. 4). Quality of Life (QoL), as

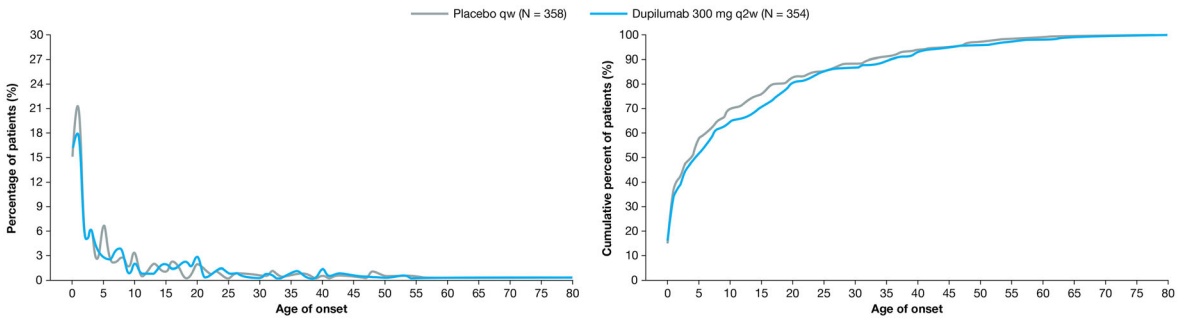


Fig. 1 Age of AD onset in study patients. Left: incidence; Right: cumulative incidence. *AD* atopic dermatitis, *q2w* every 2 weeks

Table 2 Baseline characteristics by age of AD onset

Age of AD onset (self-reported)	0–4 years		5–9 years		10–19 years		≥ 20 years	
	Placebo (*N* = 249)	Dupilumab 300 mg q2w (*N* = 239)	Placebo (*N* = 67)	Dupilumab 300 mg q2w (*N* = 61)	Placebo (*N* = 60)	Dupilumab 300 mg q2w (*N* = 63)	Placebo (*N* = 79)	Dupilumab 300 mg q2w (*N* = 91)
Age, mean (SD), years	35.1 (12.59)	36.1 (13.10)	36.8 (11.84)	34.1 (12.05)	35.9 (13.71)	35.3 (13.26)	51.8 (12.6)	49.4 (14.54)
Sex, male, *n* (%)	133 (53.4)	132 (55.2)	31 (46.3)	38 (62.3)	37 (61.7)	36 (57.1)	48 (60.8)	59 (64.8)
Race, *n* (%)								
White	172 (69.1)	178 (74.5)	35 (52.2)	37 (60.7)	31 (51.7)	34 (54.0)	61 (77.2)	69 (75.8)
Black	14 (5.6)	10 (4.2)	9 (13.4)	2 (3.3)	7 (11.7)	4 (6.3)	5 (6.3)	7 (7.7)
Asian	51 (20.5)	42 (17.6)	19 (28.4)	21 (34.4)	22 (36.7)	20 (31.7)	13 (16.5)	14 (15.4)
Duration of AD, mean (SD), years	34 (12.66)	34.9 (13.10)	30.6 (11.99)	27.7 (12.21)	22.8 (14.06)	21.1 (14.59)	15.7 (11.95)	14.2 (10.47)
EASI score (0–72), mean (SD)	34.7 (14.22)	34.2 (14.12)	32.7 (12.95)	33.3 (11.29)	33.0 (15.76)	29.6 (12.06)	33.4 (14.46)	29.1 (12.53)
IGA score (0–4), mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.6 (0.50)	3.4 (0.50)	3.4 (0.49)	3.5 (0.50)	3.4 (0.49)
BSA (0–100), mean (SD)	57.5 (23.20)	56.3 (22.84)	54.9 (22.05)	55.8 (20.48)	52.2 (25.02)	50.9 (21.58)	53.5 (22.69)	47.6 (21.23)
Weekly peak pruritus NRS (0–10), mean (SD)	7.5 (1.67)	7.6 (1.69)	7.4 (2.02)	7.3 (1.73)	7.2 (1.78)	7.1 (1.68)	7.6 (1.98)	7.2 (1.98)
SCORAD score (0–103), mean (SD)	69.5 (14.12)	69.2 (13.64)	67.2 (13.72)	67.8 (11.31)	66.4 (16.04)	63.7 (13.45)	69.0 (14.50)	63.5 (14.51)
o-SCORAD (0–83), mean (SD)	56.5 (12.11)	56.2 (11.83)	54.4 (11.96)	55.0 (10.19)	54.8 (13.56)	52.2 (10.89)	55.8 (12.04)	51.6 (11.93)

Table 2 continued

Age of AD onset (self-reported)	0–4 years		5–9 years		10–19 years		≥ 20 years	
	Placebo (*N* = 249)	Dupilumab 300 mg q2w (*N* = 239)	Placebo (*N* = 67)	Dupilumab 300 mg q2w (*N* = 61)	Placebo (*N* = 60)	Dupilumab 300 mg q2w (*N* = 63)	Placebo (*N* = 79)	Dupilumab 300 mg q2w (*N* = 91)
SCORAD VAS Itch (0–10), mean (SD)	7.5 (1.83)	7.6 (1.91)	7.8 (1.78)	7.7 (1.91)	7.0 (2.22)	6.9 (2.20)	7.6 (2.11)	7.0 (2.43)
SCORAD VAS Sleep (0–10), mean (SD)	5.6 (3.11)	5.5 (3.11)	5.1 (3.30)	5.5 (3.11)	4.7 (3.45)	4.6 (3.27)	5.6 (3.49)	4.9 (3.35)
POEM score (0–28), mean (SD)	21.1 (5.69)	21.4 (5.32)	21.1 (5.27)	20.6 (5.53)	19.6 (5.66)	18.0 (6.38)	19.7 (7.17)	19.0 (6.91)
DLQI score (0–30), mean (SD)	15.6 (7.24)	15.3 (6.79)	15.6 (7.07)	15.5 (7.11)	14.1 (7.46)	13.7 (7.82)	13.9 (8.27)	13.5 (7.79)

AD atopic dermatitis, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *LS* least squares, *NRS* Numerical Rating cale, o-*SCORAD* objective SCORing Atopic Dermatitis, *POEM* Patient-Oriented Eczema Measure, *q2w* every 2 weeks, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation, *VAS* visual analog scale

Table 3 Medical history by age of AD onset

Age of AD onset (self-reported)	0–4 years		5–9 years		10–19 years		≥ 20 years	
	Placebo (*N* = 249)	Dupilumab 300 mg q2w (*N* = 243)	Placebo (*N* = 66)	Dupilumab 300 mg q2w (*N* = 63)	Placebo (*N* = 60)	Dupilumab 300 mg q2w (*N* = 63)	Placebo (*N* = 78)	Dupilumab 300 mg q2w (*N* = 93)
Family history of atopic/allergic conditions, *n* (%)								
AD	99 (39.8)	125 (51.4)	30 (45.5)	29 (46.0)	24 (40.0)	22 (34.9)	25 (32.1)	29 (31.2)
Asthma	72 (28.9)	78 (32.1)	24 (36.4)	15 (23.8)	12 (20.0)	12 (19.0)	22 (28.2)	18 (19.4)
Allergic rhinitis	75 (30.1)	58 (23.9)	17 (25.8)	15 (23.8)	18 (30.0)	13 (20.6)	8 (10.3)	16 (17.2)
Other allergies	55 (22.1)	63 (25.9)	18 (27.3)	16 (25.4)	11 (18.3)	9 (14.3)	8 (10.3)	12 (12.9)
Food allergy	54 (21.7)	52 (21.4)	14 (21.2)	7 (11.1)	5 (8.3)	4 (6.3)	4 (5.1)	13 (14.0)
Allergic conjunctivitis	34 (13.7)	30 (12.3)	10 (15.2)	6 (9.5)	5 (8.3)	3 (4.8)	4 (5.1)	6 (6.5)
Hives	24 (9.6)	25 (10.3)	11 (16.7)	7 (11.1)	4 (6.7)	6 (9.5)	2 (2.6)	5 (5.4)
Chronic rhinosinusitis	11 (4.4)	14 (5.8)	3 (4.5)	2 (3.2)	2 (3.3)	2 (3.2)	2 (2.6)	2 (2.2)
Nasal polyps	9 (3.6)	5 (2.1)	2 (3.0)	0	0	1 (1.6)	1 (1.3)	2 (2.2)
Eosinophilic esophagitis	1 (0.4)	2 (0.8)	1 (1.5)	0	0	0	0	1 (1.1)
Patient history of atopic/allergic conditions other than AD, *n* (%)								
Asthma	117 (47.0)	132 (54.3)	18 (27.3)	22 (34.9)	13 (21.7)	15 (23.8)	18 (23.1)	29 (31.2)
Allergic rhinitis	131 (52.6)	143 (58.8)	30 (45.5)	32 (50.8)	22 (36.7)	26 (41.3)	29 (37.2)	25 (26.9)
Other allergies	172 (69.1)	174 (71.6)	39 (59.1)	36 (57.1)	31 (51.7)	33 (52.4)	37 (47.4)	44 (47.3)
Food allergy	121 (48.6)	117 (48.1)	19 (28.8)	20 (31.7)	14 (23.3)	15 (23.8)	16 (20.5)	20 (21.5)
Allergic conjunctivitis	76 (30.5)	87 (35.8)	18 (27.3)	13 (20.6)	10 (16.7)	11 (17.5)	14 (17.9)	11 (11.8)
Hives	38 (15.3)	52 (21.4)	8 (12.1)	8 (12.7)	5 (8.3)	8 (12.7)	9 (11.5)	4 (4.3)
Chronic rhinosinusitis	14 (5.6)	13 (5.3)	1 (1.5)	2 (3.2)	2 (3.3)	4 (6.3)	4 (5.1)	6 (6.5)

Table 3 continued

Age of AD onset (self-reported)	0–4 years		5–9 years		10–19 years		≥ 20 years	
	Placebo (N = 249)	Dupilumab 300 mg q2w (N = 243)	Placebo (N = 66)	Dupilumab 300 mg q2w (N = 63)	Placebo (N = 60)	Dupilumab 300 mg q2w (N = 63)	Placebo (N = 78)	Dupilumab 300 mg q2w (N = 93)
Atopic keratoconjunctivitis	13 (5.2)	16 (6.6)	0	1 (1.6)	0	3 (4.8)	2 (2.6)	1 (1.1)

AD atopic dermatitis, *q2w* every 2 weeks

measured by DLQI (baseline LS mean range across subgroups 13.5–15.6), showed a similar, consistent pattern of significant improvement irrespective of age of AD onset, with dupilumab subgroups achieving a DLQI score of 5.6–5.9 (corresponding to a small effect on QoL) versus 9.6–11.4 (a moderate or large effect on QoL) by week 16 with the placebo subgroups (Fig. 5).

Safety

The number of patients with treatment-emergent adverse events were generally balanced across treatment arms for each age-of-onset subgroup. Treatment emergent severe adverse events were either balanced or more commonly reported in the placebo group across all age-of-onset subgroups. The most commonly reported treatment-emergent adverse events (≥ 5% in any group) were consistent across age-of-onset subgroups. Adverse events leading to treatment discontinuation were rare and similar for all age-of-onset subgroups (< 2%).

DISCUSSION

In this post hoc analysis of 917 adults with AD, dupilumab treatment resulted in significant improvements in the extent and severity of lesions, patient assessed symptoms, and QoL, irrespective of the (self-reported) age of AD onset. Proportions achieving physician assessed EASI-50, -75, and -90 increased similarly and significantly in all age-of-onset groups with dupilumab versus placebo, as did the proportion of patients attaining an IGA score of 0 or 1. Peak pruritus NRS decreased significantly with dupilumab as early as weeks 1–3 in all age-of-onset groups, with DLQI improving significantly within the first month of treatment.

Of note, in the earliest age-of-onset group (under 5 years), with correspondingly the longest mean disease duration, dupilumab-treated patients had differentiating improvements versus placebo in both pruritus NRS and DLQI at week 1. Interestingly, a recent real-world study of adolescents with moderate-to-severe AD treated with dupilumab found that early age of onset (≤ 1 year of age) may

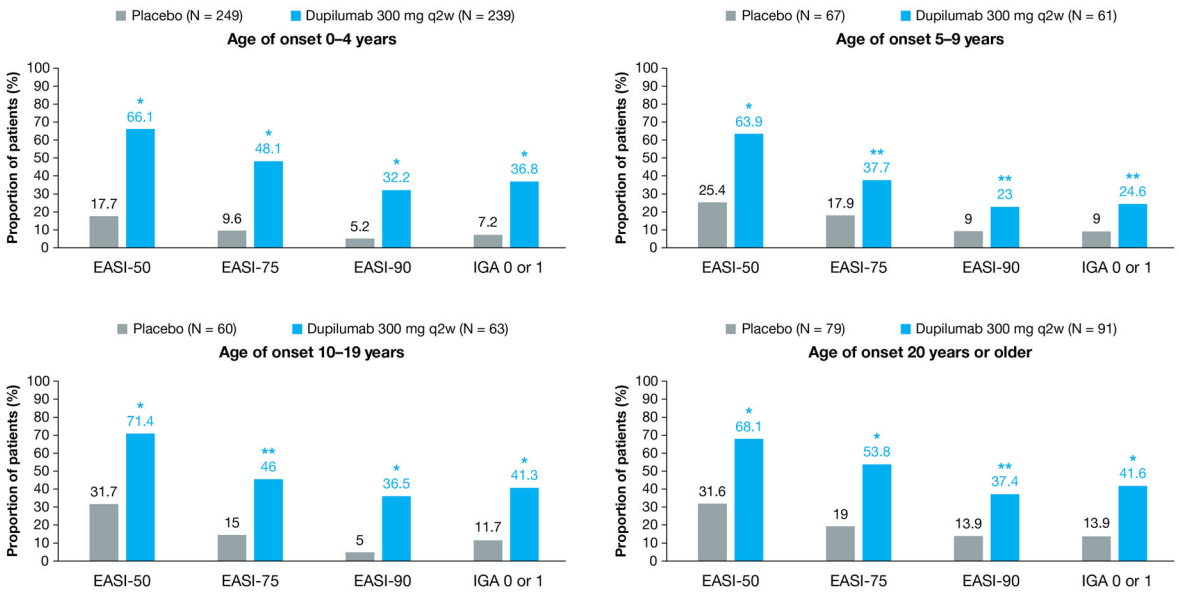


Fig. 2 Proportion of patients achieving EASI-50, -75, or -90 or IGA 0 or 1 at 16 weeks, age of AD onset. $^{*}p < 0.0001$, $^{**}p < 0.05$ for dupilumab versus placebo. *AD* atopic dermatitis, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment Score, *q2w* every 2 weeks

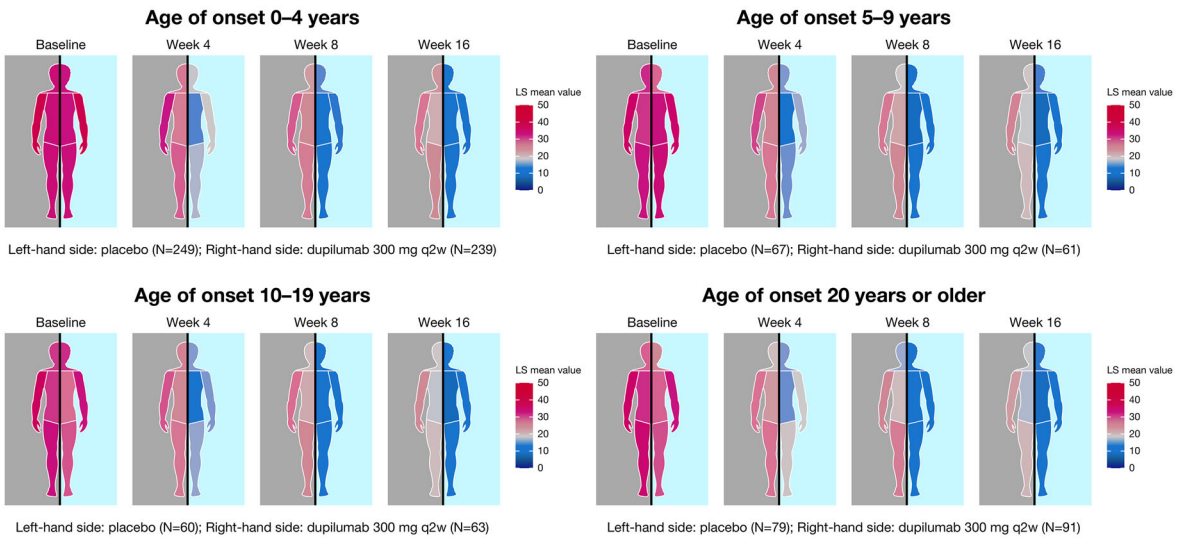


Fig. 3 LS mean EASI scores per body regions at baseline and 16 weeks by age of AD onset. *AD* atopic dermatitis, *EASI* Eczema Area and Severity Index, *LS* least squares, *q2w* every 2 weeks

positively influence the effectiveness of dupilumab in terms of EASI-75, EASI-90, and EASI-100 [21].

The lower rate of personal and family history of allergic and atopic comorbidities observed in the older age of AD-onset group (20 years or older) is consistent with other reports in patients with adult-onset AD [4, 6–9, 11, 16, 22].

The clinical presentation of AD is complex and variable in morphology, distribution,

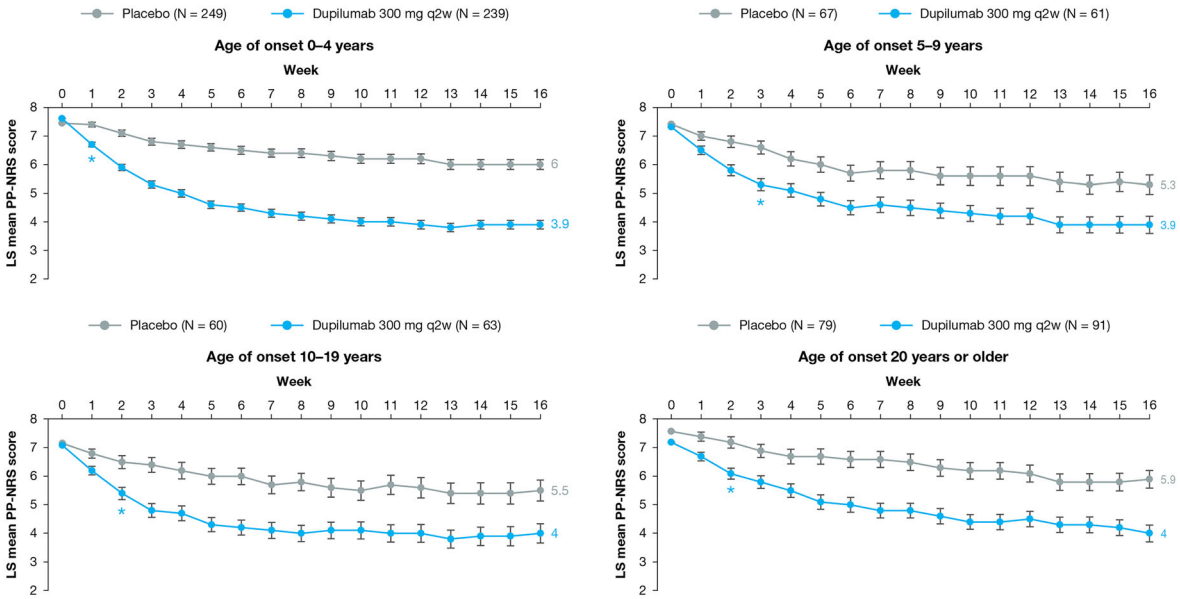


Fig. 4 Weekly average peak pruritus NRS over time, by age of AD onset. *$p < 0.0001$ for dupilumab versus placebo. *AD* atopic dermatitis, *LS* least squares, *NRS* Numerical Rating Scale, *PP* peak pruritus, *q2w* every 2 weeks

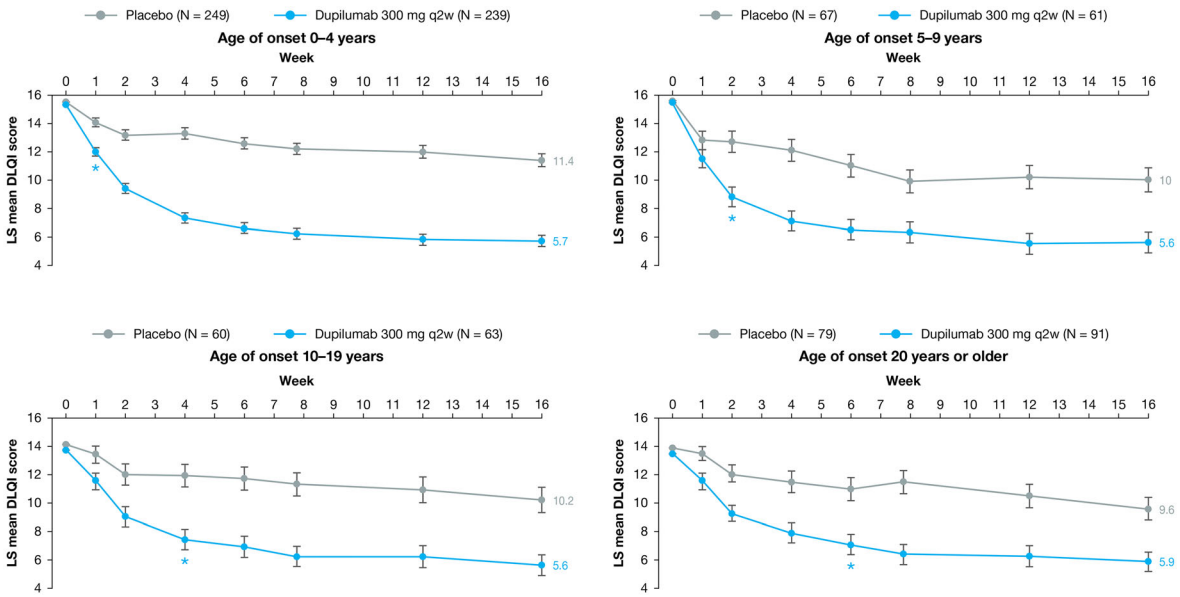


Fig. 5 DLQI LS mean over time, by age of AD onset. *$p < 0.0001$ for dupilumab versus placebo. *AD* atopic dermatitis, *DLQI* Dermatology Life Quality Index, *LS* least squares, *q2w* every 2 weeks

course, and prominence and/or pattern of symptoms, with mechanistic studies revealing a diverse underlying pattern of immune disturbance and skin-barrier defects [23, 24]. Recent studies reported distinct clinical presentation in early- versus late-onset AD, based on age groupings of infant (under 6 years), child (6–-11 years), adolescent (12–17 years), adult

(18 years and over), and late onset (over 60 years) [4, 6–9, 11, 16, 22]. These differences include an association found between family history and other coexisting allergies and atopic disorders in patients with early-onset AD, and higher nonflexural presentation and focal hotspots of disease on the hands, head, and neck in patients with late-onset AD [4, 7, 8, 11, 22]. In a retrospective case review study of 214 adults with AD, conducted by Ha et al. [8], an association was found between allergic asthma and rhinitis, family history of atopic disease, elevated total serum IgE, and food allergies and early-onset AD (prior to 12 years). In the same study, the late-onset group (12 years and over) was significantly associated with nonflexural involvement, with pre-/post-age 12 being another arbitrary designation of early- or late-onset AD. A further study of 356 adults revealed an association between adult-onset AD and lesions occurring predominately on the hand, neck, and face [4]. The present study did not show differences in improvement of AD by anatomic region in the different age-of-onset subgroups, as measured by EASI score per body region (head, lower extremities, trunk, upper extremities). However, the pattern of lesions in specific body areas such as hands, genitals, and flexures was not captured and could not be analyzed. The prevalence of family history of atopic conditions was found to be lower in the older age-of-onset group (20 years or older) in comparison with the younger groups. This is in agreement with findings reported in prior studies [12, 13].

Pathobiologic differences in age of AD-onset subgroups were reported, such as loss-of-function filaggrin mutations, which were strongly correlated with AD onset in infancy [13]. With regards to the immune responses detected in AD patients, several studies reported differences in IgE response or serum levels, T cell subsets, and IL-9 and IL-17 changes across age-of-onset groups [6, 24, 25]. This differing pathobiology may underscore the need for utilization of different treatments depending on characteristics of AD in each patient. However, a study analyzing AD skin biopsies from patients in different age groups (n = 54) compared with the skin of same-age controls revealed a common genomic fingerprint in all age groups of patients with AD, suggesting that type-2 mediated inflammation is present across all age-of-onset subgroups [16]. This signature included Th2 and Th22 skewing and Th2-related markers including IL-13, CCL17/TARC (thymus and activation-regulated chemokine), CCL18/PARC (pulmonary and activation-regulated chemokine), and IL-4R [16].

Previous analyses of clinical studies also showed that dupilumab significantly improved clinical signs, symptoms, and QoL across patients with AD in different life stages, for adults and adolescents with moderate-to-severe AD and for children with severe AD, with an acceptable safety profile [26–29]. These findings are supported by real-world experiences with dupilumab in children, adolescents, adults, and elderly with AD [21, 30–32]. The similar efficacy of dupilumab, which inhibits key drivers of type 2-mediated inflammation, in the different age-of-onset subgroups analyzed in this study confirms the high clinical relevance of dysregulated type 2 inflammation in AD among different age-of-onset groups [14, 15].

Limitations

A potential limitation of this analysis is that the sample sizes of the age-of-onset subgroups are small, and the age of AD onset is self reported, which could lead to incorrect categorization of age of onset.

CONCLUSION

Dupilumab is efficacious in adults with moderate-to-severe AD regardless of age of onset. Despite possible endophenotypic differences linked to age of onset and differences in AD duration at baseline, dupilumab showed similar improvements in AD signs, symptoms, and QoL in adults during 16 weeks of treatment. These findings support targeting of both IL-4 and IL-13 as an effective treatment strategy for AD across all ages of onset.

ACKNOWLEDGEMENTS

Funding. Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. The journal's Rapid Service Fees were funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Medical Writing and Editorial Assistance. Medical writing/editorial assistance was provided by Carolyn Ellenberger, PhD, of Excerpta Medica, funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline [33].

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Ana B. Rossi and Noah A. Levit contributed to study concept and design, analysis, and interpretation. Haixin Zhang conducted the statistical analyses on the data. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

Disclosures. Jonathan I. Silverberg is an investigator for AbbVie, BMS, Eli Lilly, GlaxoSmithKline, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Realm Therapeutics, Regeneron Pharmaceuticals, Inc.; a consultant for AbbVie, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, MedImmune (AstraZeneca), Menlo Therapeutics, Pfizer, Realm Therapeutics, Regeneron Pharmaceuticals, Inc.; a speaker for Regeneron Pharmaceuticals, Inc. Mark Boguniewicz has received research grants, consulting fees from Regeneron Pharmaceuticals, Inc., Sanofi. Jon Hanifin – no disclosures. Kim A. Papp has received research grants, consulting fees, honoraria for lectures from Regeneron Pharmaceuticals, Inc., Sanofi. Noah A. Levit, Haixin Zhang are employees and shareholders of Regeneron Pharmaceuticals, Inc. Ana B. Rossi is an employee of Sanofi, and may hold stock and/or stock options in the company.

Compliance with Ethics Guidelines. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trials. Pediatric patients provided assent according to the Ethics Committee (Institutional Review Board [IRB]/Independent Ethics Committee)-approved standard practice for pediatric patients at each participating center.

Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

REFERENCES

1. Abuabara K, Silverberg JI, Simpson EL, et al. International observational atopic dermatitis cohort to follow natural history and treatment course: TARGET-DERM AD study design and rationale. BMJ Open. 2020;10(11): e039928.

2. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132–8.

3. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. J Invest Dermatol. 2015;135(1):56–66.

4. Silverberg JI, Vakharia PP, Chopra R, et al. Phenotypical differences of childhood- and adult-onset atopic dermatitis. J Allergy Clin Immunol Pract. 2018;6(4):1306–12.

5. Silverberg JI, Kantor R. The role of interleukins 4 and/or 13 in the pathophysiology and treatment of atopic dermatitis. Dermatol Clin. 2017;35(3): 327–34.

6. Zhou L, Leonard A, Pavel AB, et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2019;144(1):144–56.

7. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. J Am Acad Dermatol. 2019;80(6):1526-32.e7.

8. Ha DL, Park GH, Kim HS, et al. Clinical and laboratory differences between early-onset and late-onset adult atopic dermatitis. J Cutan Med Surg. 2020;24(4):360–6.

9. Nomura T, Wu J, Kabashima K, Guttman-Yassky E. Endophenotypic variations of atopic dermatitis by age, race, and ethnicity. J Allergy Clin Immunol Pract. 2020;8(6):1840–52.

10. Girolomoni G, de Bruin-Weller M, Aoki V, et al. Nomenclature and clinical phenotypes of atopic dermatitis. Ther Adv Chronic Dis. 2021;12: 20406223211002980.

11. Chan AR, Sandhu VK, Drucker AM, Fleming P, Lynde CW. Adult-onset atopic dermatitis: presentations and progress. J Cutan Med Surg. 2020;24(3): 267–72.

12. Rupnik H, Rijavec M, Korošec P. Filaggrin loss-of-function mutations are not associated with atopic dermatitis that develops in late childhood or adulthood. Br J Dermatol. 2015;172(2):455–61.

13. Smieszek SP, Welsh S, Xiao C, et al. Correlation of age-of-onset of atopic dermatitis with filaggrin loss-of-function variant status. Sci Rep. 2020;10(1):2721.

14. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol. 2017;13(5):425–37.

15. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy. 2020;75(5):1188–204.

16. Renert-Yuval Y, Del Duca E, Pavel AB, et al. The molecular features of normal and atopic dermatitis skin in infants, children, adolescents, and adults. J Allergy Clin Immunol. 2021;148(1):148–63.

17. Tavecchio S, Angileri L, Pozzo Giuffrida F, Germiniasi F, Marzano AV, Ferrucci S. Efficacy of dupilumab on different phenotypes of atopic dermatitis: one-year experience of 221 patients. J Clin Med. 2020;9(9):2684.

18. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.

19. EMA. European Medicines Agency. DUPIXENT® (dupilumab). Summary of product characteristics. 2021. https://ec.europa.eu/health/documents/community-register/2019/20190801145601/anx_145601_en.pdf. Accessed 8 July 2022.

20. FDA. US Food and Drug Administration. DUPIXENT® (dupilumab). Highlights of prescribing information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed 8 July 2022.

21. Stingeni L, Bianchi L, Antonelli E, DADA - Dupilumab for Atopic Dermatitis of the Adolescence Study Group, et al. Moderate-to-severe atopic dermatitis in adolescents treated with dupilumab: a multicentre Italian real-world experience. J Eur Acad Dermatol Venereol. 2022;36(8):1292–9.

22. Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. J Am Acad Dermatol. 2019;80(2):390–401.

23. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy. 2018;73(6):1284–93.

24. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1–11.

25. Czarnowicki T, He H, Canter T, et al. Evolution of pathologic T-cell subsets in patients with atopic dermatitis from infancy to adulthood. J Allergy Clin Immunol. 2020;145(1):215–28.

26. Paller AS, Bansal A, Simpson EL, et al. Clinically meaningful responses to dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: post-hoc analyses from a randomized clinical trial. Am J Clin Dermatol. 2020;21(1):119–31.

27. Cork MJ, Thaçi D, Eichenfield LF, 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.

28. de Bruin-Weller M, Thaçi D, Smith CH, 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 CAFE). Br J Dermatol. 2018;178(5):1083–101.

29. Blauvelt A, de Bruin-Weller M, Gooderham M, 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.

30. Pagan AD, David E, Ungar B, Ghalili S, He H, Guttman-Yassky E. Dupilumab improves clinical scores in children and adolescents with moderate to severe atopic dermatitis: a real-world, single-center study. J Allergy Clin Immunol Pract. 2022;10(9):2378–85.

31. Sears AV, Woolf RT, Gribaleva E, et al. Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: a single-centre, prospective 1-year observational cohort study of the first 100 patients treated. Br J Dermatol. 2021;184(4):755–7.

32. Patruno C, Napolitano M, Argenziano G, DADE - Dupilumab for Atopic Dermatitis of the Elderly study group, et al. Dupilumab therapy of atopic dermatitis of the elderly: a multicentre, real-life study. J Eur Acad Dermatol Venereol. 2021;35(4):958–64.

33. Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med. 2015;163(6):461–4.