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REVIEW

A Review of Phase 3 Trials of Dupilumab for the Treatment of Atopic Dermatitis in Adults, Adolescents, and Children Aged 6 and Up

Jennifer Cather · Melodie Young · Douglas C. DiRuggiero · Susan Tofte · Linda Williams · Tayler Gonzalez

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ABSTRACT

Atopic dermatitis (AD) is a chronic pruritic skin disease that can have a profound negative impact on patients' quality of life, especially in cases of inadequate disease control. Dupilumab, a dual inhibitor of IL-4 and IL-13 signaling, is approved in the United States for the treatment of moderate-to-severe AD in adults (≥ 18 years old) and in children (≥ 6 years old). In this review, we present results from phase 3 trials evaluating dupilumab's efficacy and safety in adults, adolescents, and children. These trials demonstrate that dupilumab provides rapid improvements (in as little as 1 week) and sustained efficacy (up to 4 years) when used as a treatment for moderate-to-severe AD. Dupilumab not only improves skin signs and symptoms, but also provides multiple health benefits beyond the skin, including improvements in quality of life, itch, sleep disturbances, and pain/discomfort. Dupilumab is generally well tolerated, has a favorable safety profile in adults, adolescents, and children, has no serious drug–drug interactions, does not require routine laboratory testing, and is not an immunosuppressant. Taken together, phase 3 trials demonstrate that dupilumab provides rapid and sustained efficacy and is generally well tolerated for the treatment of moderate-to-severe AD across age groups.

Keywords: Atopic dermatitis; Dupilumab; Efficacy; Safety; Adults; Children; Adolescents

J. Cather · M. Young
Mindful Dermatology and Modern Research Associates, Dallas, TX, USA

D. C. DiRuggiero
Skin Cancer and Cosmetic Dermatology Center, Rome, GA, USA

S. Tofte
Oregon Health and Science University, Portland, OR, USA

L. Williams
Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

T. Gonzalez (✉)
Sanofi, Cambridge, MA, USA
e-mail: Tayler.Gonzalez@sanofi.com

Key Summary Points

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation in multiple diseases; it is the first biologic approved for multiple type 2 inflammatory diseases, including atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis.

Dupilumab provides multidimensional improvements in AD signs and symptoms and offers health benefits beyond the skin in patients aged 6 years and older with moderate-to-severe AD.

Dupilumab provides rapid and sustained benefits, with improvements occurring as early as 1 to 2 weeks following the start of treatment.

Dupilumab is well tolerated with a favorable safety profile in adults, adolescents, and children.

Results from phase 3 trials of dupilumab for the treatment of atopic dermatitis demonstrate that IL-4 and IL-13 are key drivers of type 2 inflammation in AD across all ages.

INTRODUCTION

Atopic dermatitis (AD) is a chronic type 2 inflammatory skin disease that affects people of all ages and can place a significant burden on patients and their families [17, 39, 47, 49]. Moderate-to-severe AD is associated with intense itch and eczematous lesions, which can lead to sleep impairment, elevated psychosocial stress, and chronic absenteeism from work and/or school, and can have an overall profound negative impact on quality of life [20]. Patients with AD also have an elevated risk of developing allergic comorbidities such as asthma, food allergy, allergic rhinitis, and eosinophilic esophagitis, which can further increase overall disease burden [27, 42]. Given that AD is a chronic, relapsing disease, it is important to consider long-term efficacy and safety when making treatment decisions. Topical corticosteroids (TCS) are typically the first-line treatment for AD [21]; however, moderate-to-severe AD is often inadequately controlled with topical therapies and requires the use of systemic agents for effective disease control [46]. While oral corticosteroids, such as prednisolone, are approved by the United States Food and Drug Administration, they are only recommended for short-term use and in specific circumstances, limiting their utility as a long-term treatment option for AD [18]. Similarly, systemic immunosuppressants are only recommended for short-term use due to long-term safety concerns and the need for routine laboratory monitoring [43].

Dupilumab, a fully human VelocImmune®-derived [19, 28, 30] monoclonal antibody, is the first biologic approved for several type 2 inflammatory diseases, including AD, asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP). Dupilumab blocks the shared receptor subunit for interleukin (IL)-4 and IL-13, two cytokines that play a central role in driving type 2 inflammation [24]. Dupilumab is approved in the United States for the treatment of moderate-to-severe AD in adults, adolescents, and children. It is also approved as an add-on maintenance treatment for moderate-to-severe asthma in adults and adolescents, and as an add-on maintenance treatment for CRSwNP in adults (dupilumab PI).

In the following article, we discuss the results of phase 3 clinical trials of dupilumab for the treatment of moderate-to-severe AD in adults (> 18 years old) and adolescents (12–17 years old) and severe AD in children (≥ 6 to < 11 years old). We review dupilumab efficacy (with or without concomitant TCS) across multiple measures of AD severity, including the Investigator's Global Assessment (IGA), the Eczema Area and Severity Index (EASI), the Peak Pruritus Numerical Rating Scale (NRS), the Dermatology Life Quality Index (DLQI; ≥ 16 years of age),

and the Children's Dermatology Life Quality Index (CDLQI; ≥ 4 years to < 16 years of age). We also report long-term safety results up to 4 years. This review article summarizes previously conducted studies and does not involve any new studies with human participants or animals performed by any of the authors. The focus of this review article is on dupilumab doses approved by the FDA in the United States. The FDA-approved doses are as follows: adults: 300 mg q2w; adolescents and children: 300 mg q4w (baseline weight ≥ 15 to < 30 kg), 200 mg q2w (baseline weight ≥ 30 to < 60 kg), 300 mg q2w (baseline weight ≥ 60 kg). Efficacy data are presented for approved doses only, while safety data are presented for all doses included in the clinical trials.

PHASE 3 TRIALS OF DUPILUMAB FOR THE TREATMENT OF MODERATE-TO-SEVERE AD

Phase 3 Trials of Dupilumab in Adults with Moderate-to-Severe AD

Four major phase 3 clinical trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD SOLO-CONTINUE, and LIBERTY AD CHRONOS) were conducted worldwide in adults with moderate-to-severe AD [10, 41, 48, 52, 59]. Since SOLO 1 and SOLO 2 had an identical study design, data from these studies were pooled and referred to as SOLO-pooled throughout. Patients who received dupilumab treatment and achieved an IGA score of 0 or 1 or a 75% improvement in the EASI-75 at week 16 in SOLO 1 or 2 were rerandomized in SOLO-CONTINUE to continue their original regimen of dupilumab (300 mg dupilumab qw or q2w) or to receive dupilumab 300 mg every 4 weeks (q4w) or 8 weeks (q8w) or placebo for 36 weeks. An additional ongoing open-label extension (OLE) study, LIBERTY AD OLE (NCT01949311), was conducted to examine dupilumab's long-term efficacy and safety [6, 7]. The doses included in each study are shown in Table 1. Baseline patient demographics were similar across treatment groups and trials (Table 1). Detailed efficacy and safety analyses have been reported previously [4, 6, 10, 22, 23, 32, 41, 47–49, 51, 51, 52, 52–59].

Phase 3 Trials of Dupilumab in Adolescents and Children with Moderate-to-Severe AD

Two major phase 3 clinical trials, LIBERTY AD ADOL (NCT03054428) and LIBERTY AD PEDS (NCT03345914), were conducted to determine the efficacy and safety of dupilumab in adolescents (12–17 years old) and children (6–11 years old) with moderate-to-severe AD [35, 50]. To examine dupilumab's long-term efficacy and safety in adolescents and children, data from an ongoing phase 3 OLE, LIBERTY AD PED-OLE (NCT02612454), were reported by Cork et al. [13, 14]. The doses included in each study are shown in Table 2. Baseline patient demographics were similar across treatment groups and trials (Table 2). Detailed efficacy and safety analyses have been reported previously [13, 14, 33, 50]. A history of atopic comorbidities at study baseline was common across all studies; the most common comorbidities (≥ 5% incidence) included asthma, allergies (other than food allergies), allergic rhinitis, food allergies, allergic conjunctivitis, hives, and chronic rhinosinusitis.

DUPILUMAB EFFICACY

Adult Efficacy

The primary endpoint in SOLO-pooled was the proportion of patients who achieved an IGA score of 0 or 1 (score range: 0 [clear] to 4 [severe]) and at least a 2-point reduction from baseline at week 16; a key secondary endpoint was the proportion of patients who achieved at least a 75% improvement (i.e., reduction) from baseline in the EASI (EASI-75; score range: 0 [clear] to 72 [severe]) at week 16. Coprimary endpoints for SOLO-CONTINUE were the percent change in EASI score from the SOLO-CONTINUE baseline and the proportion of

Table 1 Baseline and clinical characteristics in adults with moderate-to-severe AD

	SOLO 1 & 2 (pooled)			SOLO-CONTINUE				CHRONOS[a]			OLE[b]
	Placebo (*N* = 460)	300 mg q2w (*N* = 457)	300 mg qw (*N* = 462)	Placebo (*N* = 83)	300 mg q8w (*N* = 84)	300 mg q4w (*N* = 86)	300 mg q2w/ qw (*N* = 169)	Placebo + TCS (*N* = 315)	300 mg q2w + TCS (*N* = 106)	300 mg qw + TCS (*N* = 319)	300 mg qw (*N* = 2677)
Baseline characteristics											
Age, mean (SD), years	38.4 (14.03)	38.3 (14.37)	38.2 (14.48)	37 (27.0–46.0)[a]	35 (26.0–46.5)[a]	36 (24.0–49.0)[a]	36 (26.0–48.0)[a]	36.6 (13.01)	39.6 (13.98)	36.9 (13.67)	39.2 (13.4)
Race, *n* (%)											
White	302 (65.7)	320 (70.0)	317 (68.6)	54 (65.1)	56 (66.7)	64 (74.4)	124 (73.4)	208 (66)	74 (70)	208 (65)	1936 (72.3)
Black/African American	36 (7.8)	23 (5.0)	35 (7.6)	7 (8.4)	8 (9.5)	4 (4.7)	7 (4.1)	19 (6)	2 (2)	13 (4)	147 (5.5)
Asian	106 (23.0)	98 (21.4)	96 (20.8)	17 (20.5)	18 (21.4)	16 (18.6)	31 (18.3)	83 (26)	29 (27)	89 (28)	541 (20.2)
Other (or missing data)	9 (2.0)	10 (2.2)	10 (2.2)	5 (6.0)	2 (2.4)	2 (2.3)	7 (4.1)	5 (2)	1 (1)	9 (3)	53 (2.0)
Sex, *n* (%)											
Male	250 (54.3)	267 (58.4)	281 (60.8)	51 (61.4)	51 (60.7)	43 (50.0)	82 (48.5)	193 (61)	62 (58)	191 (60)	1611 (60.2)
Female	210 (45.7)	190 (41.6)	181 (39.2)	32 (38.6)	33 (39.3)	43 (50.0)	87 (51.5)	122 (39)	44 (42)	128 (40)	1066 (39.8)
Clinical characteristics											
Duration of AD, mean (SD), yrs	28.8 (14.43)	27.9 (15.20)	27.6 (15.38)	37 (44.6)[b] 44 (53.0)[c] 2 (2.4)[d]	53 (63.1)[b] 30 (35.7)[c] 1 (1.2)[d]	44 (51.2)[b] 42 (48.8)[c] 0[d]	81 (47.9)[b] 87 (51.5)[c] 1 (0.6)[d]	27.5 (14.34)	30.1 (15.53)	27.9 (14.46)	29.9 (14.8)
Patients with IGA score, *n* (%)											
3	234 (50.9)	234 (51.2)	244 (52.8)	1 (1.2)	2 (2.4)	6 (7.0)	3 (1.8)	168 (53)	53 (50)	172 (54)	1288 (48.1)
4	225 (48.9)	223 (48.8)	218 (47.2)	0 (0)	0 (0)	0 (0)	0 (0)	147 (47)	53 (50)	147 (46)	459 (17.1)
Peak Pruritus NRS, mean (SD)	7 (2)	7 (2)	7 (2)	2.8 (2.11)	2.7 (2.27)	3.1 (2.16)	2.8 (1.92)	7 (2)	7 (2)	7 (2)	5.0 (2.5)
EASI, mean (SD)	34 (14)	32 (13)	33 (13)	2.5 (2.31)	2.3 (2.33)	2.8 (3.31)	2.6 (2.92)	33 (13)	34 (13)	32 (13)	16.4 (14.6)

Table 1 continued

	SOLO 1 & 2 (pooled)			SOLO-CONTINUE				CHRONOS[a]			OLE[b]
	Placebo (*N* = 460)	300 mg q2w (*N* = 457)	300 mg qw (*N* = 462)	Placebo (*N* = 83)	300 mg q8w (*N* = 84)	300 mg q4w (*N* = 86)	300 mg q2w/ qw (*N* = 169)	Placebo + TCS (*N* = 315)	300 mg q2w + TCS (*N* = 106)	300 mg qw + TCS (*N* = 319)	300 mg qw (*N* = 2677)
POEM, mean (SD)	21 (6)	21 (6)	20 (6)	6.1 (5.43)	6.8 (5.88)	6.1 (5.11)	6.4 (5.30)	20 (6)	20 (6)	20 (6)	14.7 (8.00)
DLQI, mean (SD)	15 (7)	15 (7)	15 (7)	3.4 (4.25)	3.0 (3.76)	3.2 (3.93)	3.4 (4.21)	15 (7)	15 (7)	14 (7)	8.5 (7.11)
History of atopic comorbidities *n* (%)[c]											
Number of patients, *N*[d]	460	457	462	82	84	87	167	315	110	315	2677
Asthma	167 (36.6)	199 (42.8)	176 (38.7)	31 (37.8)	38 (45.2)	34 (39.1)	72 (43.1)	130 (41)	45 (41)	116 (37)	1105 (41.3)
Allergies[e]	280 (61.4)	290 (62.4)	291 (64.0)	52 (63.4)	49 (58.3)	56 (64.4)	108 (64.7)	200 (63)	68 (62)	211 (67)	1749 (65.3)
Allergic rhinitis	213 (46.7)	226 (48.6)	230 (50.5)	42 (51.2)	35 (41.7)	37 (42.5)	81 (48.5)	134 (43)	53 (48)	130 (41)	133 (49.8)
Food allergy	171 (37.5)	174 (37.4)	170 (37.4)	37 (45.1)	26 (31.0)	29 (33.3)	59 (35.3)	96 (30)	39 (35)	112 (36)	1010 (37.7)
Allergic conjunctivitis	119 (26.1)	123 (26.5)	120 (26.4)	23 (28.0)	13 (15.5)	20 (23.0)	41 (24.6)	68 (22)	31 (28)	73 (23)	740 (27.6)
Hives	60 (13.2)	72 (15.5)	66 (14.5)	7 (8.5)	10 (11.9)	10 (11.5)	33 (19.8)	34 (11)	14 (13)	34 (11)	368 (13.7)
Chronic rhinosinusitis	21 (4.6)	25 (5.4)	30 (6.6)	8 (9.8)	2 (2.4)	5 (5.7)	10 (6.0)	26 (8)	7 (6)	12 (4)	173 (6.5)
Nasal polyps	7 (1.5)	11 (2.4)	11 (2.4)	1 (1.2)	0 (0.0)	1 (1.1)	2 (1.2)	7 (2)	2 (2)	5 (2)	63 (2.4)
Eosinophilic esophagitis	3 (0.7)	5 (1.1)	0	1 (1.2)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0)	1 (1)	0 (0)	13 (0.5)

DLQI Dermatology Life Quality Index; *EASI* Eczema Area and Severity Index; *IGA* Investigator's Global Assessment; *NRS* Numerical Rating Scale; *POEM* Patient-Oriented Eczema Measure; *SD* standard deviation; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *q8w* every 8 weeks; *TCS* topical corticosteroids; *yrs* years

[a]Median (IQR), years

[b] < 26 years of age

[c] ≥ 26 years of age

[d]Missing data

[e]CHRONOS patients received concomitant TCS

[f]Data for OLE reflect current study (OLE) baseline

[g]Includes any history of atopic comorbidities at baseline

[h]Number of patients reflects safety analysis sets for SOLO-pooled, SOLO-CONTINUE, and CHRONOS

[i]Other than food allergies

Table 2 Baseline and clinical characteristics in adolescents with moderate-to-severe AD and children with severe AD

	ADOL			PEDS[a]			PED-OLE (ADOL)[b]		PED-OLE (PEDS)[a]	
	Placebo (*N* = 85)	300 mg q4w (*N* = 84)	200/300 mg q2w (*N* = 82)	Placebo + TCS (*N* = 123)	300 mg q4w + TCS (*N* = 122)	100 mg or 200 mg q2w + TCS (*N* = 122)	2 mg/kg qw (*N* = 17)	4 mg/kg qw (*N* = 19)	2 mg/kg qw (*N* = 17)	4 mg/kg qw (*N* = 16)
Baseline characteristics										
Age, mean (SD), years	14.5 (1.8)	14.4 (1.6)	14.5 (1.7)	8.3 (1.8)	8.5 (1.7)	8.5 (1.7)	15 (2)	14 (2)	9 (2)	8 (2)
Race, *n* (%)										
White	48 (56.5)	55 (65.5)	54 (65.9)	77 (62.6)	89 (73.0)	88 (72.1)	N/A	N/A	16 (94)	15 (94)
Black/African American	15 (17.6)	8 (9.5)	7 (8.5)	23 (18.7)	19 (15.6)	20 (16.4)	N/A	N/A	0	1 (6)
Asian	13 (15.3)	13 (15.5)	12 (14.6)	13 (10.6)	5 (4.1)	10 (8.2)	N/A	N/A	N/A	N/A
Other (or missing data)	N/A	N/A	N/A	10 (8.1)	9 (7.4)	4 (3.2)	N/A	N/A	1 (6)	0 (0)
Sex, *n* (%)										
Male	53 (62.4)	52 (61.9)	43 (52.4)	61 (49.6)	57 (46.7)	65 (53.3)	6 (35)	11 (58)	8 (47)	9 (56)
Female	32 (37.6)	32 (38.1)	39 (47.6)	62 (50.4)	65 (53.3)	57 (46.7)	11 (65)	8 (42)	9 (53)	7 (45)
Clinical characteristics										
Duration of AD, mean (SD), yrs	12.3 (3.4)	11.9 (3.2)	12.5 (3.0)	7.2 (2.2)	7.4 (2.4)	7.2 (2.3)	12 (4)	13 (2)	7 (3)	8 (2)
Patients with IGA score, *n* (%)										
3	39 (45.9)	38 (45.2)	39 (47.6)	N/A	N/A	N/A	11 (65)	11 (58)	9 (53)	7 (44)
4	46 (54.1)	46 (54.8)	43 (52.4)	N/A	N/A	N/A	5 (29)	4 (21)	4 (24)	8 (50)
Peak Pruritus NRS, mean (SD)	7.7 (1.6)	7.5 (1.8)	7.5 (1.5)	7.7 (1.5)	7.8 (1.6)	7.8 (1.5)	5 (2)	5 (3)	6 (3)	6 (2)
EASI, mean (SD)	35.5 (14.0)	35.8 (14.8)	35.3 (13.8)	39.0 (12.0)	37.4 (12.5)	37.3 (10.9)	26 (17)	21 (18)	21 (18)	32 (20)
POEM, mean (SD)	21.1 (5.4)	21.1 (5.5)	21.0 (5.0)	20.7 (5.5)	21.3 (5.5)	20.5 (5.5)	15 (7)	16 (8)	17 (8)	20 (5)

Table 2 continued

	ADOL			PEDS[a]			PED-OLE (ADOL)[b]		PED-OLE (PEDS)[a]	
	Placebo (*N* = 85)	**300 mg q4w (*N* = 84)**	**200/300 mg q2w (*N* = 82)**	**Placebo + TCS (*N* = 123)**	**300 mg q4w + TCS (*N* = 122)**	**100 mg or 200 mg q2w + TCS (*N* = 122)**	**2 mg/kg qw (*N* = 17)**	**4 mg/kg qw (*N* = 19)**	**2 mg/kg qw (*N* = 17)**	**4 mg/kg qw (*N* = 16)**
CDLQI, mean (SD)	13.1 (6.7)	14.8 (7.4)	13.0 (6.2)	14.6 (7.4)	16.2 (7.9)	14.5 (6.8)	9 (5)	9 (8)	12 (8)	12 (4)
History of atopic comorbidities, *n* (%)[c]										
Number of patients, *N*[d]	85	84	82	120	120	122	17	19	17	16
Asthma	46 (54.1)	42 (50.6)	46 (56.1)	54 (45.0)	55 (45.8)	60 (49.2)	7 (41)	8 (42)	N/A	N/A
Allergies[e]	62 (72.9)	53 (63.9)	58 (70.7)	81 (69.2)	67 (55.8)	79 (64.8)	11 (65)	14 (74)	N/A	N/A
Allergic rhinitis	57 (67.1)	48 (57.8)	59 (72.0)	72 (60.0)	73 (60.8)	73 (59.8)	10 (59)	9 (47)	N/A	N/A
Food allergy	48 (56.5)	52 (62.7)	52 (63.4)	83 (69.2)	75 (62.5)	75 (61.5)	8 (47)	11 (58)	N/A	N/A
Allergic conjunctivitis	16 (18.8)	21 (25.3)	20 (24.4)	16 (13.3)	14 (11.7)	14 (11.5)	6 (35)	7 (37)	N/A	N/A
Hives	22 (25.9)	28 (33.7)	22 (26.8)	8 (6.7)	14 (11.7)	14 (11.5)	1 (6)	1 (5)	N/A	N/A
Chronic rhinosinusitis	7 (8.2)	6 (7.2)	6 (7.3)	4 (3.3)	5 (4.2)	2 (1.6)	0 (0)	3 (16)	N/A	N/A
Nasal polyps	2 (2.4)	1 (1.2)	2 (2.4)	0	0	2 (1.6)	N/A	N/A	N/A	N/A
Eosinophilic esophagitis	0 (0)	0 (0)	1 (1.2)	0	1 (0.8)	1 (0.8)	N/A	N/A	N/A	N/A

DLQI Dermatology Life Quality Index; *EASI* Eczema Area and Severity Index; *CDLQI* Children's Dermatology Life Quality Index; *IGA* Investigator's Global Assessment; *IQR* interquartile range; *TCS* topical corticosteroids; *NRS* Numerical Rating Scale; *POEM* Patient-Oriented Eczema Measure; *SD* standard deviation; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *q8w* every 8 weeks; *TCS* topical corticosteroids; *yrs* years

[a]PEDS patients received concomitant TCS

[b]Data for PED-OLE studies reflect the current study (OLE) baseline

[c]Includes any history of atopic comorbidities at baseline

[d]Number of patients reflects the safety analysis set for PEDS

[e]Other than food allergies

patients with EASI-75 at week 36 among patients with EASI-75 at the SOLO-CONTINUE baseline; a key secondary endpoint was the proportion of patients with an IGA of 0 or 1 (and a ≥ 2-point reduction) at week 36. Coprimary endpoints in CHRONOS were the proportion of patients with an IGA of 0 or 1 (and a ≥ 2-point reduction) and EASI-75 at week 16 and week 52.

SOLO-pooled, SOLO-CONTINUE, and CHRONOS all demonstrated improvements in AD signs and symptoms for patients receiving dupilumab compared with placebo (Table 3). At week 16 in SOLO-pooled, 37.0% of patients receiving dupilumab 300 mg q2w achieved an IGA of 0 or 1 (and a ≥ 2-point reduction), compared with 9.3% receiving placebo, and 47.7% of patients receiving dupilumab achieved EASI-75, compared with 13.3% receiving placebo. At week 36 in SOLO-CONTINUE, 54.0% of patients receiving dupilumab 300 mg q2w or qw maintained an IGA of of 0 or 1 (and a ≥ 2-point reduction), compared with 14.3% receiving placebo, and 71.6% of patients receiving dupilumab maintained EASI-75, compared with 30.4% receiving placebo. At week 16 in CHRONOS, 39% of patients receiving dupilumab 300 mg q2w + TCS achieved an IGA of 0 or 1 (and a ≥ 2-point reduction), compared with 12% receiving placebo, and 69% of patients receiving dupilumab achieved EASI-75, compared with 23% receiving placebo. At week 52 in CHRONOS, 36% of patients receiving dupilumab 300 mg q2w + TCS achieved an IGA of 0 or 1 (and a ≥ 2-point reduction), compared with 13% receiving placebo, and 65% of patients receiving dupilumab achieved EASI-75, compared with 22% receiving placebo. While EASI scores improved for the duration of the treatment in both the dupilumab and placebo groups in all trials, scores improved more greatly in the dupilumab groups compared with placebo (Figs. 1 and 2).

In addition to improving IGA and EASI, dupilumab improved a number of secondary endpoints, including the Patient-Oriented Eczema Measure (POEM), the Dermatology Life Quality Index (DLQI), and the Peak Pruritus Numerical Rating Scale (NRS, Figs. 3, 4, 5, 6). At week 16 in SOLO-pooled and CHRONOS, dupilumab treatment was associated with a significantly greater least squares (LS) mean change in POEM, DLQI, and Peak Pruritus NRS compared with placebo. This effect was also seen in CHRONOS through week 52. Improvements in Peak Pruritus NRS were seen as early as 2 days following treatment initiation among patients receiving dupilumab compared with placebo in SOLO-pooled and CHRONOS, suggesting that dupilumab treatment has a rapid effect [44]. Rapid improvements in sleep quality were observed in SOLO-pooled and CHRONOS, with significant reductions in sleep disturbances occurring as early as week 1 of dupilumab treatment compared with placebo [6]. Statistically significant clinical benefits were also observed among patients who did not achieve an IGA of 0 or 1. In patients with an IGA > 1 at week 16, dupilumab significantly improved several outcome measures compared with placebo: EASI (− 48.9% vs. − 11.3%, $P < 0.001$), pruritus NRS (− 35.2% vs. − 9.1%, $P < 0.001$), affected BSA (− 23.1% vs. − 4.5%, $P < 0.001$), POEM score ≥ 4-point improvement (57.4% vs. 21.0%, $P < 0.001$), and DLQI ≥ 4-point improvement (59.3% vs. 24.4%, $P < 0.001$) [41].

Efficacy in Adolescents and Children

In both ADOL and PEDS, the coprimary endpoints were the proportion of patients achieving an IGA of 0 or 1 and the proportion of patients achieving EASI-75 at week 16. Consistent with results from adult clinical trials, ADOL and PEDS demonstrated marked improvements in AD measures in patients receiving dupilumab compared with placebo in adolescents with moderate-to-severe AD and in children with severe AD (Table 4). In ADOL, at week 16, 24.4% of patients receiving dupilumab 200/300 mg q2w achieved an IGA of 0 or 1, compared with 2.4% of patients receiving placebo, and 41.5% of patients receiving dupilumab 200/300 mg q2w achieved EASI-75, compared with 8.2% of patients receiving placebo. In PEDS, at week 16, 29.5% of patients receiving dupilumab 300 mg q4w + TCS (weight < 30 kg) achieved an IGA of 0 or 1 compared with 13.1% receiving placebo, while 39% of patients receiving dupilumab

Table 3 Efficacy results in adults with moderate-to-severe AD

	SOLO 1 & 2 (pooled)		SOLO-CONTINUE[f]		CHRONOS[g]			
	Placebo, week 16 (*N* = 460)	**300 mg q2w, week 16 (N = 457)**	**Placebo, week 36 (*N* = 83)**	**300 mg q2w/qw[a], week 36 (*N* = 169)**	**Placebo + TCS, week 16 (*N* = 315)**	**300 mg q2w + TCS, week 16 (*N* = 106)**	**Placebo + TCS, week 52 (*N* = 264)**	**300 mg q2w + TCS, week 52 (*N* = 89)**
Proportion of patients achieving IGA 0/1, n (%)	43 (9.3)	169 (37.0)	9/63[b] (14.3)	68/126[b] (54.0)	39 (12)	41 (39)	33 (13)	32 (36)
% change in EASI, LS mean (SE)	− 34.3 (2.3)	− 70.0 (1.8)	− 6.61 (0.80)	− 0.09 (0.51)	− 43.2 (2.26)	− 76.7 (3.77)	− 45.8 (2.70)	− 78.3 (4.44)
Proportion of patients achieving EASI-50, n (%)	107 (23.3)	306 (67.0)	33/83 (39.8)	124/169 (73.4)	118 (37)	85 (80)	79 (30)	70 (79)
Proportion of patients achieving EASI-75, n (%)	61 (13.3)	218 (47.7)	24/79 (30.4)	116/162 (71.6)	73 (23)	73 (69)	57 (22)	58 (65)
Proportion of patients achieving EASI-90, n (%)	34 (7.4)	150 (32.8)	N/A	N/A	35 (11)	42 (40)	41 (16)	45 (51)
POEM, change from baseline, LS mean (SE)	− 4.2 (0.4)	− 10.9 (0.4)	− 7.0 (0.90)	0.3 (0.56)	− 4.7 (0.38)	− 12.4 (0.63)	− 5.3 (0.46)	− 13.7 (0.75)
Proportion of patients with ≥ 4-point reduction in Peak Pruritus NRS, n/*N1* (%)	47/433 (10.9)	168/438 (38.4)	10/78 (12.8)[c]	78/159 (49.1)[c]	59/229 (20)	60/102 (59)	32/249 (13)	44/86 (51)
Proportion of patients with ≥ 3-point reduction in Peak Pruritus NRS, *n*/*N2* (%)	67/447 (15.0)	220/451 (48.8)	15/82 (18.3)[d]	95/166 (57.2)[d]	85/306 (28)	69/105 (66)	40/256 (16)	49/88 (56)
DLQI, change from baseline, LS mean (SE)	− 4.3 (0.3)	− 9.3 (0.3)	− 3.1 (0.52)	0.2 (0.33)	− 5.3 (0.31)	− 9.7 (0.51)	− 5.6 (0.36)	− 10.9 (0.59)

Table 3 continued

	SOLO 1 & 2 (pooled)		SOLO-CONTINUE[f]		CHRONOS[g]			
	Placebo, week 16 (*N* = 460)	**300 mg q2w, week 16 (N = 457)**	**Placebo, week 36 (*N* = 83)**	**300 mg q2w/qw[a], week 36 (*N* = 169)**	**Placebo + TCS, week 16 (*N* = 315)**	**300 mg q2w + TCS, week 16 (*N* = 106)**	**Placebo + TCS, week 52 (*N* = 264)**	**300 mg q2w + TCS, week 52 (*N* = 89)**
Peak Pruritus-NRS, change from baseline, LS mean (SE)	− 1.6 (0.1)	− 3.5 (0.1)	− 35.6 (4.3)[e]	0.1 (3.1)[e]	− 2.1 (0.13)	− 4.1 (0.21)	− 2.1 (0.16)	− 4.2 (0.26)

DLQI DermatologyLife Quality Index; *EASI* Eczema Area and Severity Index; *EASI-50* improvement from baseline of at least 50% in EASI; *EASI-75* improvement from baseline of at least 75% in EASI; *EASI-90* improvement from baseline of at least 90% in EASI; *IGA* Investigator's Global Assessment; N1 number of patients with baseline NRS score C 4 and nonmissing values at eachvisit; N2 number of patients with baseline NRS score C 3 and nonmissing values at each visit; N/A data not available/reported; *NRS* Numerical Rating Scale; *POEM* Patient-Oriented Eczema Measure; *q2w* every 2 weeks; *q4w* every 4 weeks; ; *TCS* topical corticosteroids

[a]Data for SOLO-CONTINUE are pooled and combine the approved dose (300 mg q2w) and unapproved dose (300 mg qw)

[b]Denominator reflects the number of patients with an IGA score of 0 or 1 at SOLO-CONTINUE baseline

[c]Denominator reflects the number of patients with a Peak Pruritus NRS score ≤ 4 at SOLO-CONTINUE baseline

[d]Denominator reflects the number of patients with a Peak Pruritus NRS score ≤ 3 at SOLO-CONTINUE baseline

[e]Percent change in Peak Pruritus NRS score from SOLO baseline: difference between SOLO-CONTINUE baseline and week 35, LS mean (SE)

[f]All changes from baseline data for SOLO-CONTINUE use SOLO-CONTINUE baseline

[g]CHRONOS patients received concomitant TCS

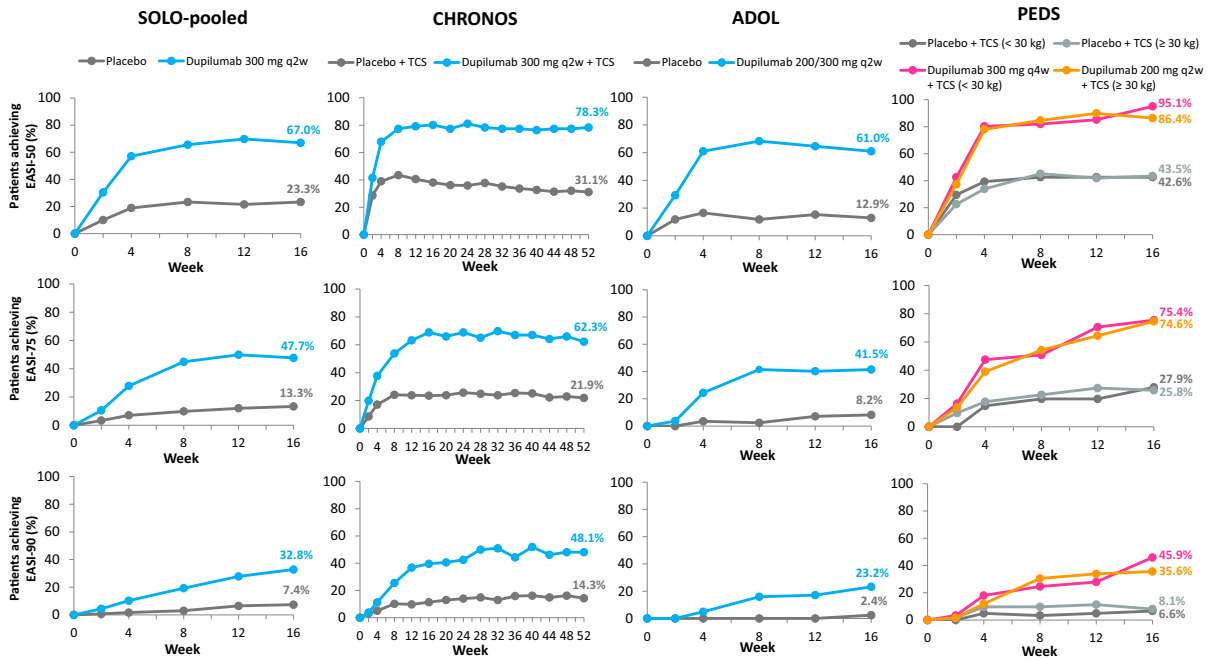


Fig. 1 Proportions of patients achieving EASI-50, EASI-75, and EASI-90 over time. *EASI* Eczema Area and Severity Index; *EASI-50* ≥ 50% reduction in EASI from baseline; *EASI-75* ≥ 75% reduction in EASI from baseline; *EASI-90* ≥ 90% reduction in EASI from baseline; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids

200 mg q2w + TCS (weight ≥ 30 kg) achieved an IGA of 0 or 1, compared with 9.7% receiving placebo. In addition, 75.4% of patients receiving dupilumab 300 mg q4w + TCS (weight < 30 kg) achieved EASI-75, compared with 27.9% of patients receiving placebo, and 74.6% of patients receiving dupilumab 200 mg q2w + TCS (weight ≥ 30 kg) achieved EASI-75 compared with 25.8% receiving placebo. EASI scores improved in adolescents and children across the 16-week treatment period in both the dupilumab and placebo groups in both trials, with significantly lower scores in the dupilumab groups compared with placebo (Figs. 1 and 2).

Like in adults, dupilumab also improved a number of AD signs and symptoms beyond IGA and EASI in adolescents and children (Figs. 2, 3). Specifically, at week 16 in ADOL and PEDS, dupilumab treatment was associated with significantly greater LS mean changes in POEM, CDLQI, and Peak Pruritus NRS compared with placebo.

DUPILUMAB SAFETY

Adult Safety

The overall rate of treatment-emergent adverse events (TEAEs) in phase 3 clinical trials of dupilumab in adults was similar in patients treated with dupilumab and in those treated with placebo (Table 5). Most TEAEs were mild or moderate and TEAEs leading to drug discontinuation were rare. Common TEAEs (> 5% incidence) included nasopharyngitis, exacerbation of AD, upper respiratory tract infections, headaches, conjunctivitis, injection-site reactions, herpes viral infections, and non-herpetic skin infections. Although rare (prevalence < 1%), hypersensitivity reactions were reported during dupilumab clinical trials. These reactions include generalized urticaria rash, erythema nodosum, and serum sickness or serum sickness-like reactions (dupilumab PI). Some cases of eosinophilia were reported during clinical trials of dupilumab for the treatment of

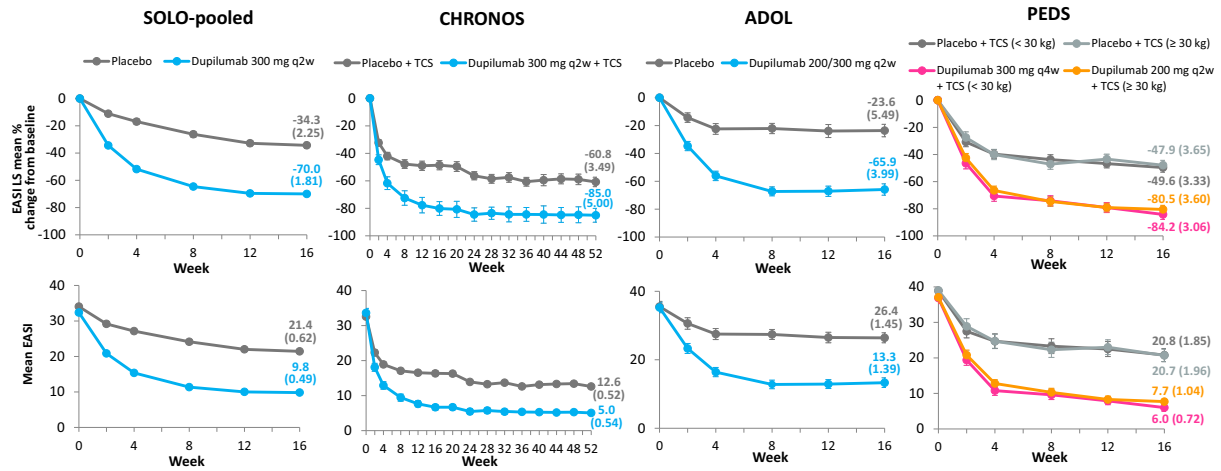


Fig. 2 LS mean percent change in EASI and mean EASI over time. *EASI* Eczema Area and Severity Index; *LS* least squares; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids

asthma; however, eosinophilia was less frequent in trials of dupilumab for AD [6, 12, 37, 55, 56]

One adverse event of particular interest in dupilumab clinical trials is conjunctivitis. Patients with AD are at a heightened risk of ocular disorders, including conjunctivitis. In the trials of dupilumab for the treatment of moderate-to-severe AD in adults, a higher incidence of conjunctivitis was observed among patients taking dupilumab compared with placebo [1]. However, the majority of conjunctivitis cases in dupilumab clinical trials were mild to moderate in severity, and treatment discontinuation resulting from conjunctivitis was infrequent. Moreover, the exposure-adjusted incidence rate for conjunctivitis in OLE was lower at 4 years (15.66 events [nE]/100 patient-years [PY]) compared with 3 years (16.14 nE/100 PY) and 76 weeks (20.8 nE/100 PY), and compared with week 52 in CHRONOS (30.60 nE/100 PY), suggesting that conjunctivitis may improve with continued dupilumab treatment (Table 5) [4, 7, 8, 10]. The heightened incidence of conjunctivitis with dupilumab also appears to be specific to AD, as clinical trials of dupilumab for other allergic diseases, such as

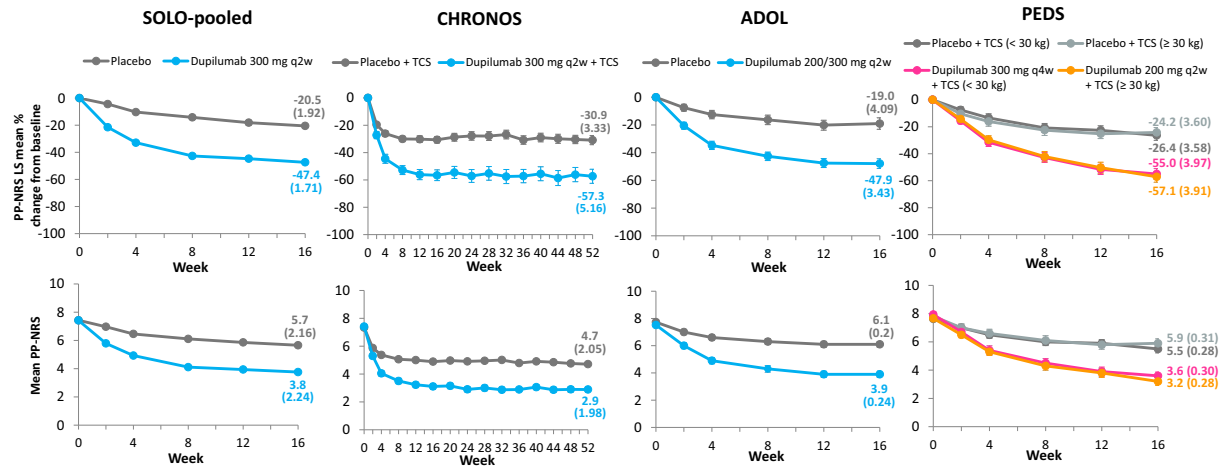


Fig. 3 LS mean percent changes in Peak Pruritus NRS and mean Peak Pruritus NRS over time. *LS* least squares; *NRS* Numerical Rating Scale; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids

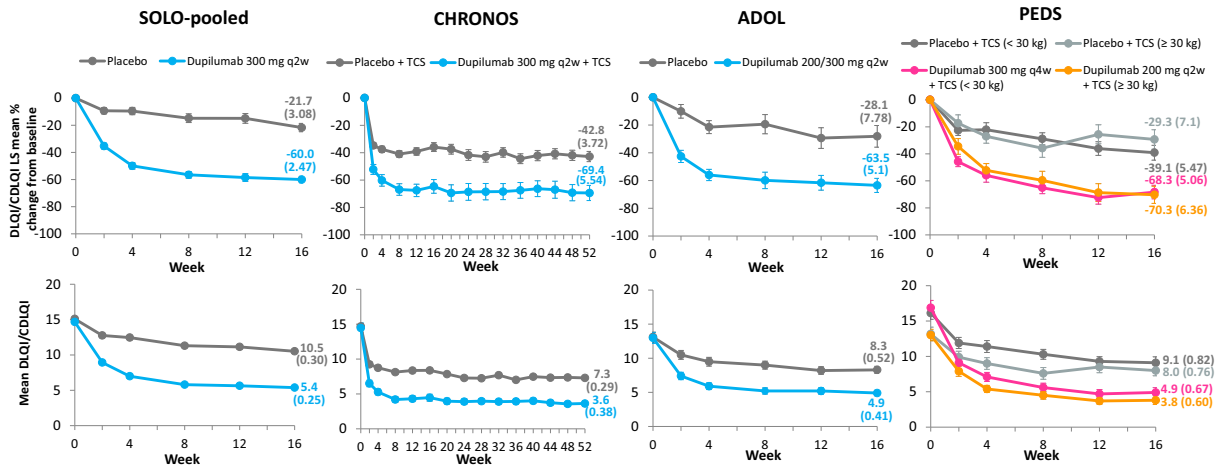


Fig. 4 LS mean percent changes in DLQI or CDLQI and mean DLQI or CDLQI over time. *CDLQI* Children's Dermatology Life Quality Index; *DLQI* Dermatology Life Quality Index; *LS* least squares; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids

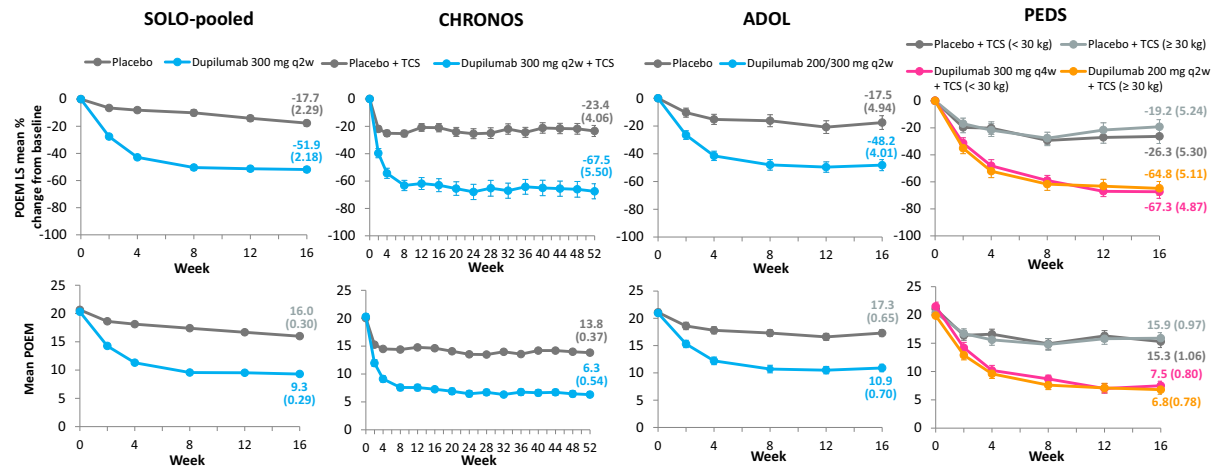


Fig. 5 LS mean percent changes in POEM and mean POEM over time. *LS* least squares; *POEM* Patient-Oriented Eczema Measure; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids

asthma and CRSwNP, did not reveal higher rates of conjunctivitis among patients treated with dupilumab compared with placebo [1].

Another adverse event of particular interest in dupilumab clinical trials is skin infections. Patients with AD have a greater risk of developing viral and/or bacterial skin infections, and some systemic treatments for AD increase infection risk [2, 5, 25, 26, 31, 45, 53]. However, phase 3 clinical trials of dupilumab in adults showed that dupilumab reduced the rate of serious or severe infections and also reduced the rate of non-herpetic skin infections, but not herpetic infections, compared with placebo (Fig. 7; Table 5) [22, 32]

The long-term use of some AD treatments can lead to treatment-associated changes in laboratory parameters such as neutrophil, platelet, and blood eosinophil counts, as well as organ toxicity [29]. As a result, patients taking these drugs require frequent and ongoing laboratory testing, which can be burdensome for

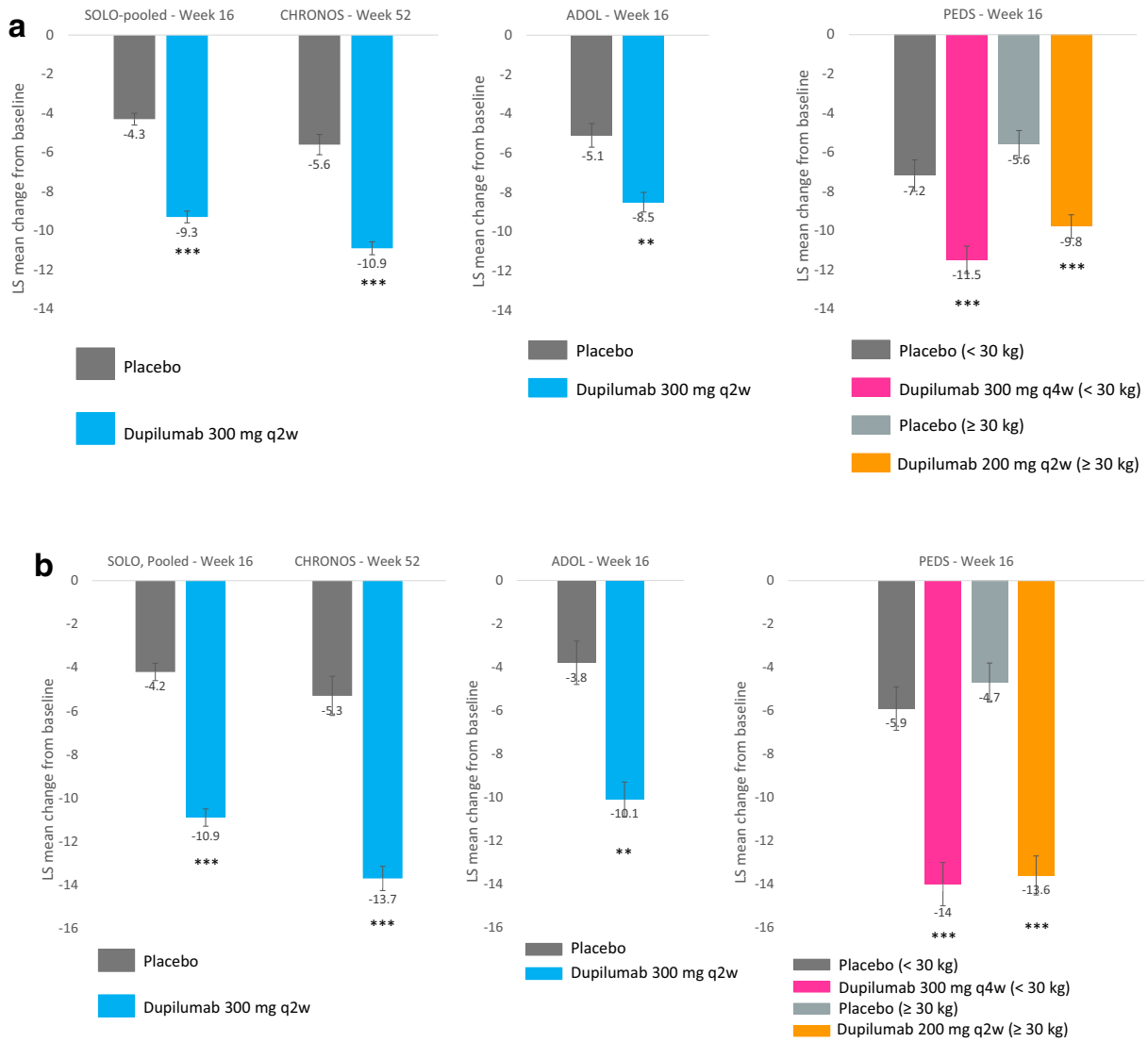


Fig. 6 **A** LS mean change in DLQI/CDLQI. **B** LS mean change in POEM. *DLQI* Dermatology Life Quality Index; *CDLQI* Children's Dermatology Life Quality Index; *POEM* Patient-Oriented Eczema Measure; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks

patients. Phase 3 trials of dupilumab in adults, however, revealed a favorable laboratory safety profile up to 3 years [6, 57]. While transient changes in neutrophils, platelets, and blood eosinophils were observed in a small number of patients taking dupilumab, these changes were not related to any clinically important adverse events (AEs). Moreover, no clinically meaningful changes were observed in any other laboratory parameters. These results suggest that routine laboratory monitoring is not necessary for patients taking dupilumab.

Another potential concern with dupilumab is drug–drug interactions. Some studies have shown that certain cytokines can affect the activity of cytochrome P450 (CYP450) enzymes, the main metabolizing enzymes in the liver, and in vitro studies have found that IL-4 and IL-13 can influence CYP450 enzyme expression. However, studies of drug–drug interactions in patients treated with dupilumab show that

Table 4 Efficacy results in adolescents with moderate-to-severe AD and children with severe AD

	ADOL		PEDS[a]			
	Placebo, week 16 (*N* = 85)	**200/300 mg q2w, week 16 (*N* = 82)**	**Placebo + TCS (< 30 kg), week 16 (*N* = 61)**	**300 mg q4w + TCS (< 30 kg), week 16 (*N* = 61)**	**Placebo + TCS (≥ 30 kg), week 16 (*N* = 62)**	**200 mg q2w + TCS (≥ 30 kg), week 16 (*N* = 59)**
Proportion of patients achieving IGA 0/1, *n* (%)	2 (2.4)	20 (24.4)	8 (13.1)	18 (29.5)	6 (9.7)	23 (39.0)
% change in EASI, LS mean (SE)	− 23.6 (5.5)	− 65.9 (4.0)	49.1 (3.3)	84.3 (3.0)	48.3 (3.6)	80.4 (3.6)
Proportion of patients achieving EASI-50, *n* (%)	11 (12.9)	50 (61.0)	26 (42.6)	58 (95.1)	27 (43.5)	51 (86.4)
Proportion of patients achieving EASI-75, *n* (%)	7 (8.2)	34 (41.5)	17 (27.9)	46 (75.4)	16 (25.8)	44 (74.6)
Proportion of patients achieving EASI-90, *n* (%)	2 (2.4)	19 (23.2)	4 (6.6)	28 (45.9)	5 (8.1)	21 (35)
POEM, change from baseline, LS mean (SE)	− 3.8 (1.0)	− 10.1 (0.8)	− 5.9 (1.0)	− 14.0 (1.0)	− 4.7 (0.9)	− 13.6 (0.9)
Proportion of patients with ≥ 4-point reduction in Peak Pruritus NRS, *n*/*N*1 (%)	4/84 (4.8)	30/82 (36.6)	7/60 (11.7)	33/61 (54.1)	8/62 (12.9)	35/57 (61.4)
Proportion of patients with ≥ 3-point reduction in Peak Pruritus NRS, *n*/*N*2 (%)	8/85 (9.4)	40/82 (48.8)	11/61 (18.0)	38/61 (62.3)	15/62 (24.2)	38/57 (66.7)
CDLQI, change from baseline, LS mean (SE)	− 5.1 (0.6)	− 8.5 (0.5)	− 7.2 (0.8)	− 11.5 (0.7)	− 5.6 (0.7)	− 9.8 (0.6)
Peak Pruritus NRS, change from baseline, LS mean (SE)	− 1.5 (0.3)	− 3.7 (0.3)	N/A	N/A	N/A	N/A

CDLQI Children's Dermatology Life Quality Index; *EASI* Eczema Area and Severity Index; *EASI-50* improvement from baseline of at least 50% in EASI; *EASI-75* improvement from baseline of at least 75% in EASI; *EASI-90* improvement from baseline of at least 90% in EASI; *IGA* Investigator's Global Assessment; *POEM* Patient-Oriented Eczema Measure; N1 number of patients with baseline NRS score ≥ 4 and nonmissing values at each visit; *N2* number of patients with baseline NRS score ≥ 3 and nonmissing values at each visit; *N/A* data not available/reported; *NRS* Numerical Rating Scale; *q2w* every 2 weeks; *q4w* every 4 weeks; *TCS* topical corticosteroids
[a]PEDS patients received concomitant TCS

Table 5 Safety assessment in adults with moderate-to-severe AD

	SOLO 1 & 2 (pooled)			SOLO-CONTINUE[a]				CHRONOS[b]			OLE[a,c]
	Placebo (*N* = 456)	300 mg q2w (*N* = 465)	300 mg Qw (*N* = 455)	Placebo (*N* = 82)	300 mg q8w (*N* = 84)	300 mg q4w (*N* = 87)	300 mg q2w/qw (*N* = 167)	Placebo + TCS (*N* = 315)	300 mg q2w + TCS (*N* = 110)	300 mg qw + TCS (*N* = 315)	300 mg Qw (*N* = 2677)
Safety assessments, *n* (%)											
TEAEs	313 (68.6)	321 (69.0)	307 (67.5)	67 (81.7)	63 (75.0)	64 (73.6)	118 (70.7)	266 (84)	97 (88)	261 (83)	2264 (84.6)
Serious TEAEs	24 (5.3)	11 (2.4)	10 (2.2)	1 (1.2)	3 (3.6)	4 (4.6)	6 (3.6)	16 (5)	4 (4)	9 (3)	256 (9.6)
Severe TEAEs	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	246 (9.2)
TEAEs leading to drug discontinuation	7 (1.5)	6 (1.3)	7 (1.5)	3 (3.7)	0 (0)	2 (2.3)	0 (0)	24 (8)	2 (2)	9 (3)	256 (9.6)
Serious TEAEs related to drug	N/A	N/A	N/A	1(1.2)	3 (3.6)	4 (4.6)	6 (3.6)	N/A	N/A	N/A	31 (1.2)
Most common TEAEs by PT[d]											
Nasopharyngitis	39 (9)	42 (9)	45 (10)	11 (13.4)	11 (13.1)	11 (12.6)	32 (19.2)	61 (19)	25 (23)	60 (19)	752 (28.1)
Atopic dermatitis	148 (32)	62 (13)	59 (13)	40 (48.8)	27 (32.1)	30 (34.5)	34 (20.4)	144 (46)	20 (18)	52 (17)	438 (16.4)
URTI	10 (2)	13 (3)	20 (4)	6 (7.3)	7 (8.3)	5 (5. 7)	13 (7.8)	32 (10)	11 (10)	43 (14)	350 (13.1)
Headache	24 (5)	40 (9)	33 (7)	2 (2.4)	3 (3.6)	5 (5. 7)	8 (4.8)	19 (6)	5 (5)	24 (8)	216 (8.1)
Conjunctivitis[e]	10 (2)	45 (10)	33 (7)	4 (4.9)	3 (3.6)	4 (4.6)	9 (5.4)	25 (8)	15 (14)	61 (19)	521 (19.5)
Injection-site reaction[f]	28 (6)	51 (11)	72 (16)	7 (8.5)	6 (7 .1)	6 (6.9)	18 (10.8)	24 (8)	16 (15)	60 (19)	260 (9.7)
Any herpes viral infection[g]	17 (4)	25 (5)	21 (5)	N/A	N/A	N/A	N/A	25 (8)	8 (7)	22 (7)	333 (12.4)
Non-herpetic skin infection[h]	43 (9)	23 (5)	29 (6)	8 (9.8)	5 (6.0)	1(1.1)	4 (2.4)	56 (18)	12 (11)	26 (8)	N/A

Table 5 continued

	SOLO 1 & 2 (pooled)			SOLO-CONTINUE[a]				CHRONOS[b]			OLE[a,c]
	Placebo (*N* = 456)	300 mg q2w (*N* = 465)	300 mg Qw (*N* = 455)	Placebo (*N* = 82)	300 mg q8w (*N* = 84)	300 mg q4w (*N* = 87)	300 mg q2w/qw (*N* = 167)	Placebo + TCS (*N* = 315)	300 mg q2w + TCS (*N* = 110)	300 mg qw + TCS (*N* = 315)	300 mg Qw (*N* = 2677)
Eczema herpeticum (PT)	3 (0.7)	3 (0.6)	2 (0.4)	0	0	0	0	6 (1.9)	1 (0.9)	0	12 (0.4)

HLT high-level term; N/A data not available/reported; *PT* preferred term; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *q8w* every 8 weeks; SOC system organ class; TCS topical corticosteroids; TEAE treatment-emergent adverse event; URTI upper respiratory tract infection

[a]SOLO-CONTINUE and OLE do not list the exception for herpes viral infections

[b]CHRONOS patients received concomitant TCS

[c]Data for OLE reflect the current study (OLE) baseline

[d]Includes all MedDRA PTs occurring in: ≥ 2% of patients in any treatment group, except for PTs of herpes viral infections (SOLO and SOLO-CONTINUE); ≥ 5% of patients in any treatment group, except for PTs of herpes viral infections (CHRONOS and OLE)

[e]Reported as a narrow cluster of MedDRA PTs: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis

[f]Reported at the SOC level of the MedDRA hierarchy (CHRONOS) or as the MedDRA HLT for injection-site reaction (SOLO, SOLO-CONTINUE, and OLE), which includes injection-site reaction, erythema, swelling, hemorrhage, pruritus, bruising, discomfort, exfoliation, inflammation, nodule, edema, ulcer, hematoma, and pain (as defined in SOLO-CONTINUE)

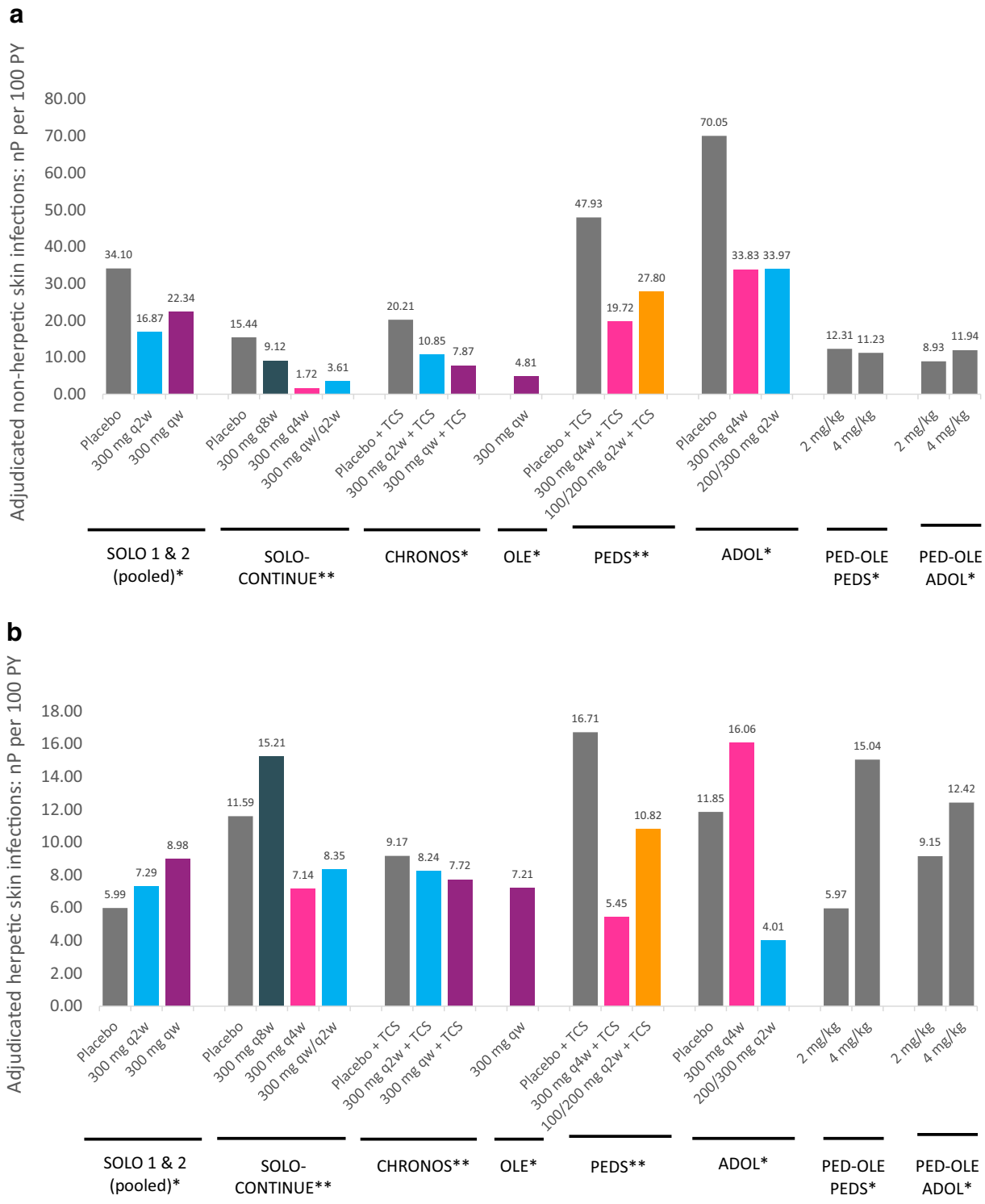
[g]Reported as the MedDRA HLT for any herpes viral infection (SOLO, CHRONOS, and OLE)

[h]Reported as the MedDRA PT for skin infections (OLE) or as non-herpetic skin infection (adjudicated) (SOLO, SOLO-CONTINUE, and CHRONOS), which includes:

SOLO: folliculitis, impetigo, cellulitis, eczema impetiginous, molluscum contagiosum, furuncle, staphylococcal skin infection, subcutaneous abscess, otitis externa, and tinea versicolor

SOLO-CONTINUE: tinea versicolor, folliculitis, impetigo, skin bacterial infection, skin infection, abscess limb, localized infection, staphylococcal skin infection, subcutaneous abscess, and tinea cruris

CHRONOS: folliculitis, molluscum contagiosum, impetigo, cellulitis, subcutaneous abscess, furuncle, infected dermal cyst, skin bacterial infection, skin bacterial infection, staphylococcal skin infection, infected cyst, nipple infection, otitis externa, paronychia, skin infection, superinfection bacterial, tinea pedis, tinea versicolor, abscess limb, bullous impetigo, dermatitis infected, dermaphytosis, eczema impetiginous, eczema infected, erysipelas, fungal skin infection, infection, staphylococcal infection, tinea cruris, tinea infection, and wound infection



dupilumab does not have a meaningful effect on CYP450 enzyme activity [15], suggesting that dupilumab is unlikely to alter the metabolism of concomitantly administered drugs.

◀**Fig. 7** **A** Treatment-emergent (TE) adjudicated non-herpetic skin Infections (nP/100PY). *Includes all adverse events during the 36-week treatment period. **Nonadjudicated. ***CHRONOS data are from the final data cut; all other CHRONOS data reported in tables and other figures are derived from the primary manuscript. List of non-herpetic skin infections (by PT): SOLO 1 & 2: folliculitis, eczema impetiginous, impetigo, skin infection, cellulitis, molluscum contagiosum, furuncle, otitis externa, infected dermal cyst, staphylococcal skin infection, tinea versicolour, abscess limb, abscess sweat gland, acne pustular, body tinea, erysipelas, eyelid infection, otitis externa fungal, rash pustular, staphylococcal impetigo, subcutaneous abscess, wound infection, onychomycosis, paronychia, skin bacterial infection, soft tissue infection, tinea manuum, tinea pedis; skin and subcutaneous tissue disorder (SOC): interigo. SOLO-CONTINUE: tinea versicolour, folliculitis, impetigo, skin bacterial infection, skin infection, abscess limb, localized infection, staphylococcal skin infection, subcutaneous abscess, tinea cruris. CHRONOS: molluscum contagiosum, folliculitis, impetigo, cellulitis, subcutaneous abscess, furuncle, staphylococcal skin infection, skin bacterial infection, infected dermal cyst, otitis externa, skin infection, infected cyst, tinea versicolour, nipple infection, tinea pedis, superinfection bacterial, paronychia, abscess limb, body tinea, bullous impetigo, dermatitis infected, dermatophytosis, eczema impetiginous, eczema infected, erysipelas, fungal skin infection, infection, staphylococcal infection, tinea cruris, tinea infection, wound infection. OLE: folliculitis, impetigo, tinea pedis, tinea versicolour, cellulitis, furuncle, erysipelas, skin infection, subcutaneous abscess, skin bacterial infection, otitis externa, paronychia, localized infection, fungal skin infection, molluscum contagiosum, staphylococcal skin infection, eczema impetiginous, skin candida, superinfection bacterial, tinea cruris, fungal infection, abscess limb, body tinea, staphylococcal infection, rash pustular, post procedural infection, abscess, pyoderma, infected dermal cyst, eczema infected, infected bites, periorbital cellulitis, abscess sweat gland, tinea capitis, perianal streptococcal infection, bacterial infection, wound infection staphylococcal, groin abscess, dermatitis infected, tinea infection. PEDS: molluscum contagiosum, furuncle, folliculitis, impetigo, cutaneous blastomycosis, eczema impetiginous, skin bacterial infection, staphylococcal infection, staphylococcal skin infection, cellulitis, dermatitis infected. ADOL: angular cheilitis, hordeolum, dermatitis infected, molluscum contagiosum, staphylococcal skin infection, tinea infection. PED-OLE, PEDS: dermatitis infected, molluscum contagiosum, abscess limb, body tinea, hand-foot-and-mouth disease, skin infection, subcutaneous abscess. PED-OLE, ADOL: infections and infestations: angular cheilitis, hordeolum, dermatitis infected, molluscum contagiosum, staphylococcal skin infection, tinea infection. **B** Treatment-emergent (TE) adjudicated herpes infections (nP/100PY). HLT high-level term; nP/100 PY number of patients per 100 patient-years; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *q8w* every 8 weeks; *TE* treatment emergent. *Includes all adverse events during the 36-week treatment period. **Nonadjudicated. ***CHRONOS data are from the final data cut; all other CHRONOS data reported in tables and other figures are derived from the primary manuscript. List of herpes infections (by PT, unless otherwise noted): SOLO 1 & 2: oral herpes, eczema herpeticum, genital herpes, herpes ophthalmic, herpes simplex, herpes simplex otitis externa, herpes virus infection, herpes zoster. SOLO-CONTINUE: herpes simplex, oral herpes, herpes ophthalmic, genital herpes, herpes virus infection, herpes zoster, ophthalmic herpes simplex, nasal herpes. CHRONOS (HLT): herpes viral infections. OLE (HLT): oral herpes, herpes simplex, herpes zoster, ophthalmic herpes simplex, eczema herpeticum, nasal herpes, herpes virus infection, herpes ophthalmic, genital herpes, ophthalmic herpes zoster, herpes zoster oticus, herpes dermatitis, varicella, herpes simplex otitis externa, herpes zoster disseminated. PEDS: herpes simplex, herpes virus infection, eczema herpeticum, herpes zoster, oral herpes, varicella. ADOL: herpes simplex, oral herpes, eczema herpeticum. PED-OLE, PEDS (HLT): herpes simplex, herpes zoster, nasal herpes, oral herpes, varicella. PED-OLE, ADOL: oral herpes, herpes simplex, nasal herpes

Safety in Adolescents and Children

Dupilumab safety in phase 3 trials in adolescents and children was similar to that in phase 3 trials in adults (Table 6). The rate of TEAEs in ADOL and PEDS was low, and most TEAEs were mild to moderate in severity. Notably, serious TEAEs and TEAEs leading to drug discontinuation were rare, with a rate of less than 2% in all treatment groups for both studies. TEAEs were more common in PED-OLE, with nearly all patients reporting at least one TEAE (100% and

Table 6 Safety assessment in adolescents with moderate-to-severe AD and children with severe AD

	ADOL			PEDS[a,c]			PED-OLE (ADOL)[b]		PED-OLE (PEDS)[b]	
	Placebo (*N* = 85)	300 mg q4w (*N* = 83)	200/ 300 mg q2w (*N* = 82)	Placebo + TCS (*N* = 120)	300 mg q4w + TCS (*N* = 120)	100 mg or 200 mg q2w + TCS (*N* = 122)	2 mg/kg qw (*N* = 17)	4 mg/kg qw (*N* = 19)	2 mg/kg qw (*N* = 17)	4 mg/kg qw (*N* = 16)
Safety assessments, *n* (%)										
TEAEs	59 (69.4)	53 (63.9)	59 (72.0)	88 (73.3)	78 (65.0)	82 (67.2)	17 (100)	18 (95)	16 (94)	16 (100)
Serious TEAEs	1 (1.2)	0	0	2 (1.7)	2 (1.7)	0	3 (18)	0 (0)	2 (12)	3 (19)
Severe TEAEs	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TEAEs leading to drug discontinuation	1 (1.2)	0	0	2 (1.7)	0	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAEs related to drug	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Most common TEAEs by PT[d]										
Nasopharyngitis	4 (4.7)	9 (10.8)	3 (3.7)	8 (6.7)	15 (12.5)	8 (6.6)	7 (41)	9 (47)	8 (47)	9 (56)
Atopic dermatitis	21 (24.7)	15 (18.1)	15 (18.3)	17 (14.2)	8 (6.7)	10 (8.2)	5 (29)	8 (42)	5 (29)	2 (13)
URTI	15 (17.6)	6 (7.2)	10 (12.2)	12 (10.0)	13 (10.8)	10 (8.2)	4 (24)	4 (21)	2 (12)	4 (25)
Headache	9 (10.6)	4 (4.8)	9 (11.0)	10 (8.3)	6 (5.0)	7 (5.7)	6 (35)	5 (26)	4 (24)	2 (13)
Conjunctivitis[e]	4 (4.7)	9 (10.8)	8 (9.8)	5 (4.2)	8 (6.7)	18 (14.8)	3 (18)	3 (16)	2 (12)	5 (31)
Injection-site reaction[f]	3 (3.5)	5 (6.0)	7 (8.5)	7 (5.8)	12 (10.0)	13 (10.7)	3 (18)	2 (11)	2 (12)	1 (6)

Table 6 continued

	ADOL			PEDS[a,c]			PED-OLE (ADOL)[b]		PED-OLE (PEDS)[b]	
	Placebo (*N* = 85)	**300 mg q4w (*N* = 83)**	**200/ 300 mg q2w (*N* = 82)**	**Placebo + TCS (*N* = 120)**	**300 mg q4w + TCS (*N* = 120)**	**100 mg or 200 mg q2w + TCS (*N* = 122)**	**2 mg/kg qw (*N* = 17)**	**4 mg/kg qw (*N* = 19)**	**2 mg/kg qw (*N* = 17)**	**4 mg/kg qw (*N* = 16)**
Any herpes viral infection[g]	3 (3.5)	4 (4.8)	1 (1.2)	6 (5.0)	2 (1.7)	4 (3.3)	3 (18)	4 (21)	2 (12)	4 (25)
Skin infection[h]	31 (36.5)	19 (22.9)	18 (22.0)	16 (13.3)	7 (5.8)	10 (8.2)	8 (47.1)	12 (63.2)	9 (52.9)	9 (56.3)
Eczema herpeticum (PT)	1 (1.2)	0	0	0	0	1 (0.8)	0	0	0	0

HLT high-level term; N/A data not available/reported; PT preferred term; *qw* every week; *q2w* every 2 weeks; *q4w* every 4 weeks; *q8w* every 8 weeks; SOC system organ class; TCS topical corticosteroids; TEAE treatment-emergent adverse event; URTI upper respiratory tract infection

[a]PEDS patients received concomitant TCS

[b]Data for PED-OLE studies reflect current study (OLE) baselines

[c]Number of patients reflects the safety analysis set for PEDS

[d]Includes all MedDRA PTs occurring in ≥ 5% of patients in any treatment group (ADOL and PEDS) and ≥ 20% of patients in any treatment group (PED-OLE)

[e]Reported as MedDRA PT for conjunctivitis, which includes conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis

[f]Reported as MedDRA HLT (ADOL, PEDS, and PED-OLE, ≥ 6 to < 12 years of age) or MedDRA PT (PED-OLE, ≥ 12 years of age), which includes edema, hemorrhage, induration, irritation, mass, and swelling

[g]Reported as MedDRA HLT for any herpes viral infection, which includes herpes simplex, nasal herpes, and oral herpes (as defined in PED-OLE, > 12 years of age)

[h]Reported as MedDRA PT for skin infection (adjudicated) and non-herpetic skin infection (adjudicated)(ADOL); skin infection (adjudicated) (PEDS); skin infection (HLT) and noherpetic skin infection (adjudicated)(PED-OLE, ≥ 6 to < 12 years of age); skin infection (PED-OLE, > 12 years of age), which includes angular cheilitis, bacterial disease carrier, dermatitis infected, folliculitis, hordeolum, molluscum contagiosum, skin bacterial infection, staphylococcal skin infections, and tinea infections

95% of patients receiving dupilumab 2 mg/kg or 4 mg/kg in PED-OLE [ADOL] and 94% and 100% of patients receiving dupilumab 2 mg/kg or 4 mg/kg in PED-OLE [PEDS], respectively). However, most TEAEs were mild or moderate in severity, and no patients in PED-OLE experienced a TEAE leading to drug discontinuation. Similar to adults, cases of conjunctivitis were more common among adolescents taking dupilumab compared with placebo, but these cases were generally mild to moderate in severity and most cases resolved during the treatment period [3]. Laboratory safety results in pediatric populations were also similar to adults, with no clinically important changes observed in hematologic, serum chemistry, or urinalysis parameters among patients taking dupilumab [34, 38]. Dupilumab was also associated with a reduced rate of skin infections in adolescents and children (Fig. 7, Table 6).

DISCUSSION

Phase 3 clinical trials demonstrate that treatment with dupilumab for moderate-to-severe AD results in rapid and sustained improvements in AD signs and symptoms and is generally well tolerated across age groups. Dupilumab is not an immunosuppressant, does not require ongoing laboratory testing, and is not likely to affect the metabolism of concomitantly administered drugs.

Efficacy results from phase 3 trials highlight dupilumab's multidimensional impact on AD signs and symptoms and suggest that IGA significantly underestimates clinically relevant dupilumab treatment effects. Beyond improving the skin, dupilumab improves patient-reported outcomes, itch severity, and overall quality of life. Additional benefits of dupilumab have also been reported, including a reduction in work/school absenteeism [16], improvements in sleep [6], and improvements in symptoms of anxiety and depression [44]. These improvements are rapid, with significant improvements in itch observed as early as 2 days following treatment initiation and significant improvements in sleep observed by week 1. Treatment adherence with dupilumab is also high in clinical trials and real-world settings, suggesting high patient satisfaction [4, 40]. Dupilumab may also reduce TCS use; in early-phase dupilumab trials, patients receiving dupilumab plus TCS had a 50% reduction in TCS use compared with patients receiving placebo plus TCS [9]. Moreover, concomitant dupilumab with TCS resulted in greater improvements in AD signs and symptoms compared with dupilumab alone [23].

Safety results from phase 3 trials of dupilumab indicate that dupilumab is generally well tolerated and has an acceptable safety profile. Dupilumab is not an immunosuppressant and does not alter correlates of vaccine-induced immunity following vaccination with nonlive vaccines, including T-cell-dependent vaccines (i.e., tetanus toxoid with reduced diphtheria toxoid and acellular pertussis vaccine) or T-cell-independent vaccines (i.e., quadrivalent meningococcal polysaccharide vaccine), or with live-attenuated vaccines (i.e., yellow fever vaccine) [11, 54]. Dupilumab is also associated with a reduced risk of serious or severe infections and non-herpetic skin infections in adults and a reduced risk of overall infections and total skin infections (including non-herpetic and herpesvirus infections) in adolescents and children [23, 32, 33]. Dupilumab does not alter hematology, chemistry, or urinalysis laboratory parameters, suggesting that patients taking dupilumab do not require ongoing laboratory monitoring [6, 34, 38, 57]. Although eosinophilia has been reported in patients receiving dupilumab for asthma, this is less common in patients with AD [6, 12, 37, 55, 56]. Moreover, no severe drug–drug interactions have been reported [15].

Patients receiving dupilumab are at a greater risk of certain adverse events. Conjunctivitis, for example, is an inherent risk for patients with AD and is commonly reported in patients taking dupilumab. However, during phase 3 trials of dupilumab for the treatment of moderate-to-severe AD, cases of conjunctivitis were generally mild or moderate in severity, and most cases resolved with standard ophthalmic treatment [4, 7]. Moreover, conjunctivitis rates were lower at year 4 in OLE compared with week 76 in OLE or week 52 in CHRONOS, suggesting that

conjunctivitis may improve with continued dupilumab treatment. Injection-site reactions are also a concern with injectables, including dupilumab. Similar to conjunctivitis incidence, however, the incidence of injection-site reactions decreased over time, with a lower incidence at week 148 compared with 76 or 52 weeks [4, 7].

In summary, phase 3 clinical trials of dupilumab demonstrate that dupilumab provides a multidimensional benefit in patients ages 6 years and older with moderate-to-severe AD, with rapid and sustained improvements in AD signs and symptoms and an acceptable safety profile. Dupilumab does not increase infection risk, has no severe drug–drug interactions, and does not require regular laboratory monitoring. Overall, these results support dupilumab as a safe and effective long-term treatment option for patients with moderate-to-severe AD.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, 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 reidentification. Regeneron's Pharmaceuticals, Inc. full data sharing policy can be found at: https://vivli.org/ourmember/regeneron/. Submit requests to https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/.

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