Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial

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Background: Children with severe atopic dermatitis (AD) have limited treatment options.

Objective: We report the efficacy and safety of dupilumab + topical corticosteroids (TCS) in children aged 6-11 years with severe AD inadequately controlled with topical therapies.

Methods: In this double-blind, 16-week, phase 3 trial (NCT03345914), 367 patients were randomized 1:1:1 to 300 mg dupilumab every 4 weeks (300 mg q4w), a weight-based regimen of dupilumab every 2 weeks (100 mg q2w, baseline weight <30 kg; 200 mg q2w, baseline weight ≥30 kg), or placebo; with concomitant medium-potency TCS.

Results: Both the q4w and q2w dupilumab + TCS regimens resulted in clinically meaningful and statistically significant improvement in signs, symptoms, and quality of life (QOL) versus placebo + TCS in all prespecified endpoints. For q4w, q2w, and placebo, 32.8%, 29.5%, and 11.4% of patients, respectively, achieved Investigator's Global Assessment scores of 0 or 1; 69.7%, 67.2%, and 26.8% achieved ≥75% improvement in Eczema Area and Severity Index scores; and 50.8%, 58.3%, and 12.3% achieved ≥4-point reduction in worst itch score. Response to therapy was weight-dependent: optimal dupilumab doses for efficacy and safety were 300 mg q4w in children <30 kg and 200 mg q2w in children ≥30 kg.

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Conjunctivitis and injection-site reactions were more common with dupilumab + TCS than with placebo + TCS.

Limitations: Short-term 16-week treatment period; severe AD only.

Conclusion: Dupilumab + TCS is efficacious and well tolerated in children with severe AD, significantly improving signs, symptoms, and QOL. (J Am Acad Dermatol 2020;83:1282-93.)

Key words: atopic dermatitis; children; dupilumab; pediatric; severe.

Atopic dermatitis (AD) is one of the most common skin disorders in children and the leading contributor to the global burden of skin disease.[1,2] In children with moderate-to-severe AD, skin lesions often involve a large body surface area (BSA), and the related pruritus, sleep deprivation, activity restriction, poor school performance, depression, and anxiety have a greater impact on quality-of-life (QOL) for patients and their caregivers than other common skin disorders such as psoriasis and urticaria.[3-5]

CAPSULE SUMMARY

- Children with severe atopic dermatitis inadequately controlled with topical therapies have limited treatment options.
- Dupilumab biologic therapy targeting the shared receptor component for interleukin-4 and interleukin-13 improves outcomes in children with severe atopic dermatitis inadequately controlled with topical corticosteroids, including signs, symptoms, and quality-of-life, with an acceptable safety profile.

AD begins before the age of 5 years in more than 85% of patients and persists into adulthood in half the cases.[6,7] Despite the chronic nature of AD, treatment in children is often limited to short-term topical corticosteroids (TCS), with topical calcineurin inhibitors as second-line therapy.[8,9] Guidelines discourage systemic corticosteroids owing to the risk of rebound after short-term treatment, unfavorable benefit-to-risk

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Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
BSA:	body surface area
CDLQI:	Children's Dermatology Life Quality Index
DFI:	Dermatitis Family Impact
EASI:	Eczema Area and Severity Index
EASI-50:	≥50% improvement in EASI
EASI-75:	≥75% improvement in EASI
EASI-90:	≥90% improvement in EASI
FAS:	full analysis set
IGA:	Investigator's Global Assessment
NRS:	Numerical Rating Scale
POEM:	Patient-Oriented Eczema Measure
QOL:	quality of life
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event

ratio, and multiple adverse events (AEs) associated with their use.[10,11] Although other systemic agents have been used off-label, the risk of serious AEs associated with these agents and the lack of high-level evidence for long-term efficacy makes them especially inappropriate for this age group.[12] Consequently, systemic treatments are offered only as a last resort for the most intractable cases,[8] resulting in a large unmet need for children whose disease is inadequately controlled with topical therapy.

Dupilumab is a fully human, VelocImmune-derived monoclonal antibody[13,14] that blocks the shared receptor component for interleukin-4 and interleukin-13. Dupilumab clinical trials have shown that these cytokines are key and central drivers of multiple type 2 inflammatory diseases. Dupilumab use is approved in the United States and European Union and other countries for adults and adolescents with moderate-to-severe AD, moderate-to-severe asthma with evidence of type 2 inflammation or eosinophilia, and adults with chronic rhinosinusitis and nasal polyps. Dupilumab significantly improves signs, symptoms, and QOL in adults and adolescents with moderate-to-severe AD, with an acceptable safety profile.[15-19] We now report results from a phase 3 trial of dupilumab with concomitant TCS in children age 6-11 years with severe AD inadequately controlled with topical therapies.

METHODS

Study design

LIBERTY AD PEDS was a randomized, double-blind, placebo-controlled, phase 3 trial, registered at Clinicaltrials.Gov (identifier NCT03345914) on November 14, 2017, and conducted at 61 sites in Canada, Czech Republic, Germany, Poland, United Kingdom, and United States. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. The protocol was reviewed and approved by institutional review boards or ethics committees at all study sites. Assent was obtained from each patient, and written informed assent was obtained from their parents or legal guardians before study participation. Patients were enrolled from November 17, 2017, to February 28, 2019. The study concluded on September 9, 2019.

The study design included screening up to 9 weeks, TCS standardization for 2 weeks, treatment for 16 weeks, and follow-up for 12 weeks (only for those patients who declined or were ineligible to participate in a subsequent open-label extension study, NCT02612454).

Patients and treatment

Key inclusion criteria were children age 6-11 years with AD (American Academy of Dermatology consensus criteria[20]) diagnosed ≥1 year before screening; Investigator's Global Assessment (IGA) score of 4, Eczema Area and Severity Index (EASI) score ≥21, affected BSA ≥15%, weekly averaged baseline worst itch score (Peak Pruritus Numerical Rating Scale [NRS]) ≥4; weight ≥15 kg; and documented history of inadequate response to topical AD medication within 6 months of baseline.

Patients were randomized 1:1:1 to dupilumab + TCS every 2 weeks (q2w + TCS; weight-tiered: baseline weight 15 to <30 kg, 100 mg q2w + TCS, 200 mg loading dose; baseline weight ≥30 kg, 200 mg q2w + TCS, 400 mg loading dose); dupilumab + TCS every 4 weeks (300 mg

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IRB approval: This study was approved by multiple institutional review boards and ethics committees.

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q4w + TCS; 600 mg loading dose regardless of weight); or matching placebo + TCS.

All patients received concomitant once-daily medium-potency TCS starting 2 weeks before baseline. Rescue treatment with high-potency TCS or systemic therapy was permitted for patients with an IGA score of 4 or intolerable symptoms during the treatment period. Very-high-potency TCS were prohibited, even as rescue.

Randomization was performed using a centralized scheme, provided by an interactive response system assigned to the designated study pharmacist or qualified designee, and stratified by baseline weight (<30 kg vs ≥30 kg) and region (North America vs Europe). Patients and all other personnel were blinded to all randomization procedures.

Outcomes

The primary endpoint was the proportion of patients with an IGA score of 0 or 1 (clear or almost clear) at week 16; the co-primary endpoint in the European Union and EU reference countries was ≥75% improvement in EASI (EASI-75) from baseline to week 16. Key secondary endpoints included percent change in EASI and weekly average of Peak Pruritus NRS from baseline to week 16.

Statistical analysis

A sample size of 240 patients was calculated to have sufficient power to discriminate between placebo + TCS and the dupilumab + TCS groups at a 2-sided, 0.05 significance level. Because of an operational error, 68 patients were potentially unblinded, and the sample size was increased to maintain study balance and power.

The primary analysis was performed on the full analysis set (FAS), which included all randomized patients. A modified FAS, defined as all randomized patients but excluding the 68 potentially unblinded patients, was added as a sensitivity analysis for the co-primary and selected secondary endpoints.

Efficacy was assessed in the FAS. The primary analysis for all efficacy variables compared the 2 dupilumab treatment groups (100/200 mg q2w + TCS and 300 mg q4w + TCS) with the placebo + TCS group. The co-primary endpoints and categorical secondary endpoints were assessed using a Cochran–Mantel–Haenszel test adjusted by randomization strata (baseline weight group and region), with patients who received rescue medication or with missing values considered nonresponders. Continuous secondary endpoints were analyzed using multiple imputation with analysis of covariance. Efficacy data after rescue medication use were treated as missing and imputed using multiple imputation. Time-to-event endpoints were analyzed using the Cox proportional hazard model.

A hierarchical procedure was used to control the overall type-1 error rate at 0.05 for the primary endpoint and secondary endpoints across the 2 dupilumab + TCS dose regimens versus placebo.

Safety was assessed in all treated patients who received ≥1 dose of study drug (safety analysis set). All analyses were performed using SAS version 9.4.

RESULTS

Patients

Of 474 patients screened, 367 patients were enrolled, randomized, and included in the FAS, of whom 362 (98.6%) received ≥1 dose of study treatment and were included in the safety analysis set. Among the 5 patients (1.4%) randomized and not treated, 3 patients were randomized in error and 2 patients withdrew consent. As a result, 351 patients (95.6%) completed the study treatment.

Baseline demographics and disease characteristics were balanced among treatment groups and were consistent with severe disease (Table I). Patients had high rates of atopic comorbidities, including asthma, allergic rhinitis, and food allergies; 91.7% (332/362) had ≥1 atopic comorbidity. One third of patients had received prior systemic treatment for AD. At baseline, Children's Dermatology Life Quality Index (CDLQI) and Dermatitis Family Impact (DFI) scores showed a significant impact of AD on children and their families.

Efficacy

Both of the dupilumab + TCS regimens (weight-tiered 100/200 mg q2w + TCS and non–weight-tiered 300 mg q4w + TCS) versus placebo + TCS significantly improved all prespecified efficacy endpoints (Table II). At week 16, significantly more patients receiving dupilumab q2w + TCS and q4w + TCS versus placebo + TCS achieved the primary endpoint of an IGA score of 0 or 1 (q2w + TCS, 29.5% [$P = .0004$]; q4w + TCS, 32.8% [$P < .0001$]; placebo + TCS, 11.4%; Fig 1).

Significantly more patients receiving dupilumab + TCS achieved EASI-75 at week 16 than those receiving placebo + TCS (q2w + TCS, 67.2%; q4w + TCS, 69.7%; placebo + TCS, 26.8%; $P < .0001$). Both IGA scores of 0 or 1 and EASI-75 showed ongoing improvement at week 16 (Fig 1), suggesting that the maximal effect had not yet been achieved. Both of the dupilumab + TCS regimens showed significantly better efficacy than placebo + TCS in additional disease severity measures, including ≥50% or ≥90% improvement from baseline in EASI scores (EASI-50 or EASI-90), BSA,

Table I. Baseline demographics and clinical characteristics

Demographics and characteristics	Overall			Baseline weight <30 kg			Baseline weight ≥30 kg		
	Placebo + TCS (n = 123)	Dupilumab 300 mg q4w + TCS (n = 122)	Dupilumab 100 mg or 200 mg q2w + TCS (n = 122)	Placebo + TCS (n = 61)	Dupilumab 300 mg q4w + TCS (n = 61)	Dupilumab 100 mg q2w + TCS (n = 63)	Placebo + TCS (n = 62)	Dupilumab 300 mg q4w + TCS (n = 61)	Dupilumab 200 mg q2w + TCS (n = 59)
Age, mean (SD), years	8.3 (1.8)	8.5 (1.7)	8.5 (1.7)	7.1 (1.3)	7.5 (1.4)	7.6 (1.4)	9.5 (1.3)	9.5 (1.5)	9.5 (1.4)
Race, n (%)									
White	77 (62.6)	89 (73.0)	88 (72.1)	40 (65.6)	45 (73.8)	43 (68.3)	37 (59.7)	44 (72.1)	45 (76.3)
Black/African American	23 (18.7)	19 (15.6)	20 (16.4)	9 (14.8)	9 (14.8)	12 (19.0)	14 (22.6)	10 (16.4)	8 (13.6)
Asian	13 (10.6)	5 (4.1)	10 (8.2)	7 (11.5)	4 (6.6)	6 (9.5)	6 (9.7)	1 (1.6)	4 (6.8)
Other	9 (7.3)	8 (6.6)	2 (1.6)	4 (6.6)	3 (4.9)	1 (1.6)	5 (8.1)	5 (8.2)	1 (1.7)
Not reported/missing	1 (0.8)	1 (0.8)	2 (1.6)	1 (1.6)	0	1 (1.6)	0	1 (1.6)	1 (1.7)
Sex, male, n (%)	61 (49.6)	57 (46.7)	65 (53.3)	30 (49.2)	27 (44.3)	32 (50.8)	31 (50.0)	30 (49.2)	33 (55.9)
Weight, kg, mean (SD)	31.5 (10.8)	31.0 (9.4)	32.1 (10.8)	23.3 (3.4)	23.8 (3.0)	24.5 (3.5)	39.5 (9.5)	38.1 (8.0)	40.2 (10.0)
Weight group, n (%)									
<30 kg	61 (49.6)	61 (50.0)	63 (51.6)	61 (100)	61 (100)	63 (100)	0	0	0
≥30 kg	62 (50.4)	61 (50.0)	59 (48.4)	0	0	0	62 (100)	61 (100)	59 (100)
BMI, kg/m^2, mean (SD)	17.9 (3.9)	17.6 (2.9)	18.0 (3.7)	16.0 (2.5)	15.7 (1.3)	16.1 (1.7)	19.8 (4.1)	19.5 (2.9)	20.2 (4.0)
Duration of AD, years, mean (SD)	7.2 (2.2)	7.4 (2.4)	7.2 (2.3)	6.3 (1.7)	6.8 (1.7)	6.4 (2.1)	8.0 (2.2)	8.0 (2.9)	8.1 (2.3)
EASI score, mean (SD)	39.0 (12.0)	37.4 (12.5)	37.3 (10.9)	38.9 (12.6)	36.9 (12.4)	37.5 (10.0)	39.0 (11.5)	37.8 (12.6)	37.1 (11.8)
Weekly average of daily NRS, mean (SD)	7.7 (1.5)	7.8 (1.6)	7.8 (1.5)	7.6 (1.6)	7.9 (1.5)	7.9 (1.5)	7.8 (1.5)	7.7 (1.7)	7.6 (1.5)
Percent BSA affected, mean (SD)	60.2 (21.5)	54.8 (21.6)	57.8 (20.0)	62.0 (20.9)	54.6 (21.9)	61.5 (19.4)	58.4 (22.1)	54.9 (21.4)	53.9 (20.2)
SCORAD, mean (SD)	72.9 (12.0)	75.6 (11.7)	72.3 (10.8)	73.0 (12.6)	75.5 (12.6)	73.3 (10.4)	72.8 (11.5)	75.8 (10.9)	71.2 (11.3)
CDLQI, mean (SD)	14.6 (7.4)	16.2 (7.9)	14.5 (6.8)	16.1 (6.9)	16.9 (8.1)	16.0 (7.0)	13.2 (7.7)	15.5 (7.7)	13.0 (6.3)
POEM, mean (SD)	20.7 (5.5)	21.3 (5.5)	20.5 (5.5)	21.1 (4.9)	21.5 (6.0)	21.1 (5.6)	20.4 (6.0)	21.1 (5.1)	19.9 (5.3)
DFI, mean (SD)	15.0 (7.5)	16.9 (8.7)	14.9 (7.1)	16.1 (7.6)	17.7 (8.9)	16.2 (6.8)	14.0 (7.4)	16.1 (8.4)	13.5 (7.1)
PROMIS anxiety, mean (SD)	57.3 (11.6)	59.8 (13.7)	58.6 (11.3)	58.9 (11.8)	60.3 (13.6)	60.6 (10.5)	55.8 (11.4)	59.3 (13.8)	56.5 (11.8)
PROMIS depression, mean (SD)	55.0 (12.1)	58.1 (12.8)	56.3 (11.2)	54.4 (12.3)	58.8 (13.1)	57.8 (10.6)	55.6 (11.9)	57.4 (12.5)	54.7 (11.7)
History of atopic morbidities not including AD, n/N1 (%)	111/120 (92.5)	107/120 (89.2)	114/122 (93.4)				NA		
Food allergy	83/120 (69.2)	75/120 (62.5)	75/122 (61.5)				NA		
Other allergies	81/120 (67.5)	67/120 (55.8)	79/122 (64.8)				NA		
Allergic rhinitis	72/120 (60.0)	73/120 (60.8)	73/122 (59.8)				NA		
Asthma	54/120 (45.0)	55/120 (45.8)	60/122 (49.2)				NA		
Allergic conjunctivitis (keratoconjunctivitis)	16/120 (13.3)	14/120 (11.7)	14/122 (11.5)				NA		
Hives	8/120 (6.7)	14/120 (11.7)	14/122 (11.5)				NA		
Chronic rhinosinusitis	4/120 (3.3)	5/120 (4.2)	2/122 (1.6)				NA		
Eosinophilic esophagitis	0	1/120 (0.8)	1/122 (0.8)				NA		
Nasal polyps	0	0	2/122 (1.6)				NA		
History of systemic medication for AD, n/N1 (%)	36/120 (30.0)	42/120 (35.0)	40/122 (32.8)				NA		
Patients receiving prior corticosteroids	17/120 (14.2)	25/120 (20.8)	30/122 (24.6)				NA		
Patients receiving prior systemic nonsteroidal immunosuppressants	22/120 (18.3)	23/120 (19.2)	16/122 (13.1)				NA		
Azathioprine	0	2/120 (1.7)	2/122 (1.6)				NA		
Cyclosporine	12/120 (10.0)	17/120 (14.2)	11/122 (9.0)				NA		
Methotrexate	11/120 (9.2)	7/120 (5.8)	3/122 (2.5)				NA		
Mycophenolate	2/120 (1.7)	2/120 (1.7)	1/122 (0.8)				NA		
Eosinophils, median (Q1–Q3), ×10^9/L	0.7 (0.4–1.1)	0.8 (0.4–1.1)	0.6 (0.4–1.2)				NA		

AD, Atopic dermatitis; *BMI*, body mass index; *BSA*, body surface area; *CDLQI*, Children's Dermatology Life Quality Index; *DFI*, Dermatitis Family Impact; *EASI*, Eczema Area and Severity Index; *N1*, number of patients in the safety analysis set; *NA*, not available; *NRS*, Numerical Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *PROMIS*, Patient-Reported Outcomes Measurements Information Systems; *Q1*, first quartile; *Q3*, third quartile; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *SCORAD*, SCORing Atopic Dermatitis; *SD*, standard deviation; *TCS*, topical corticosteroids.

Table II. Efficacy outcomes

Endpoints	Overall			Baseline weight <30 kg			Baseline weight ≥30 kg		
	Placebo + TCS (n = 123)	Dupilumab 300 mg q4w + TCS (n = 122)	Dupilumab 100 mg or 200 mg q2w + TCS (n = 122)	Placebo + TCS (n = 61)	Dupilumab 300 mg q4w + TCS (n = 61)	Dupilumab 100 mg q2w + TCS (n = 63)	Placebo + TCS (n = 62)	Dupilumab 300 mg q4w + TCS (n = 61)	Dupilumab 200 mg q2w + TCS (n = 59)
Co-primary endpoints									
Proportion of patients with IGA 0 or 1, n (%)	14 (11.4)	40 (32.8)*,7	36 (29.5)†,1	8 (13.1)	18 (29.5)‡,§	13 (20.6)	6 (9.7)	22 (36.1)†,§	23 (39.0)†,‡
Proportion of patients with EASI-75, n (%)	33 (26.8)	85 (69.7)*,8	82 (67.2)*,2	17 (27.9)	46 (75.4)*,‡	38 (60.3)†,‡	16 (25.8)	39 (63.9)*,‡	44 (74.6) *,‡
Secondary endpoints in the statistical testing hierarchy									
% change in EASI, LS mean (SE)	−48.6 (2.5)	−82.1 (2.4)*,9	−78.4 (2.4)*,3	−49.1 (3.3)	−84.3 (3.0)*,‡	−76.7 (3.0)*,‡	−48.3 (3.6)	−79.9 (3.6)*,‡	−80.4 (3.6)*,‡
Proportion of patients with EASI-50, n (%)	53 (43.1)	111 (91.0)*,10	101 (82.8)*,4	26 (42.6)	58 (95.1)*,‡	50 (79.4)*,‡	27 (43.5)	53 (86.9)*,‡	51 (86.4)*,‡
% change in weekly average of daily Peak Pruritus NRS, LS mean (SE)	−25.9 (2.9)	−54.6 (2.9)*,11	−57.0 (2.8)*,5	−27.0 (4.2)	−55.1 (3.9)*,‡	−56.1 (3.9)*,‡	−25.0 (4.0)	−54.3 (4.2)*,‡	−58.2 (4.0)*,‡
Proportion of patients with ≥4-point reduction in weekly average of daily Peak Pruritus NRS, n/N1 (%)	15/122 (12.3)	61/120 (50.8)*,12	70/120 (58.3)*,6	7/60 (11.7)	33/61 (54.1)*,‡	35/63 (55.6)*,‡	8/62 (12.9)	28/59 (47.5)*,‡	35/57 (61.4)*,‡
Proportion of patients with ≥3-point reduction in weekly average of daily Peak Pruritus NRS, n/N2 (%)	26/123 (21.1)	73/121 (60.3)*,15	81/120 (67.5)*,13	11/61 (18.0)	38/61 (62.3)*,‡	43/63 (68.3)*,‡	15/62 (24.2)	35/60 (58.3)†,‡	38/57 (66.7)*,‡
Proportion of patients with EASI-90, n (%)	9 (7.3)	51 (41.8)*,16	37 (30.3)*,14	4 (6.6)	28 (45.9)*,‡	16 (25.4)‡,‖	5 (8.1)	23 (37.7)*,‡	21 (35.6)†,‡
Change in POEM, LS mean (SE)	−5.3 (0.7)	−13.6 (0.7)*,20	−13.4 (0.7)*,17	−5.9 (1.0)	−14.0 (1.0)*,‡	−13.3 (0.9)*,‡	−4.7 (0.9)	−13.2 (0.9)*,‡	−13.6 (0.9)*,‡
Change in CDLQI, LS mean (SE)	−6.4 (0.5)	−10.6 (0.5)*,21	−10.7 (0.5)*,18	−7.2 (0.8)	−11.5 (0.7)*,‡	−11.6 (0.7)*,‡	−5.6 (0.7)	−9.7 (0.6)*,‡	−9.8 (0.6)*,‡
% change in SCORAD, LS mean (SE)	−29.8 (2.3)	−62.4 (2.1)*,22	−60.2 (2.1)*,19	−28.9 (3.1)	−65.3 (2.9)*,‡	−58.1 (2.8)*,‡	−30.7 (3.3)	−59.3 (3.1)*,‡	−62.7 (3.1)*,‡
Other secondary endpoints									
Change in weekly average of daily Peak Pruritus NRS, LS mean (SE)	−2.1 (0.2)	−4.2 (0.2)*,‡	−4.5 (0.2)*,‡			NA			
Change in percent BSA affected, LS mean (SE)	−21.7 (1.7)	−40.5 (1.6)*,‡	−39.4 (1.6)*,‡	−23.9 (2.3)	−43.2 (2.2)*,‡	−40.6 (2.1)*,‡	−19.8 (2.5)	−38.2 (2.5)*,‡	−38.4 (2.5)*,‡
Change in DFI, LS mean (SE)	−6.8 (0.5)	−10.8 (0.5)*,‡	−10.9 (0.5)*,‡			NA			
Change in PROMIS anxiety, LS mean (SE)	−10.2 (0.9)	−13.2 (0.9)‡,§	−13.5 (0.9)‡,‖			NA			
Change in PROMIS depression, LS mean (SE)	−7.4 (0.8)	−12.8 (0.8)*,‡	−11.9 (0.8)*,‡			NA			
Mean proportion of TCS-free days (SD)	0.1 (0.2)	0.2 (0.2)‡,‖	0.2 (0.2)‡,‖			NA			
Mean weekly use of low- or medium-potency TCS, LS mean (SE), g	20.1 (1.4)	15.0 (1.4)‡,‖	14.4 (1.4)‡,‖			NA			
Change in SCORAD sleep component VAS, LS mean (SE)¶	−2.0 (0.3)	−4.3 (0.2)*,‡	−4.5 (0.2)*,‡	−2.0 (0.4)	−4.6 (0.3)*,‡	−4.5 (0.3)*,‡	−2.1 (0.4)	−3.9 (0.3)†,‡	−4.5 (0.3)*,‡
Change in POEM sleep item, LS mean (SE)#	−1.0 (0.1)	−2.1 (0.1)*,‡	−2.1 (0.1)*,‡	−1.0 (0.2)	−2.2 (0.2)*,‡	−1.9 (0.2)†,‡	−0.9 (0.2)	−2.0 (0.2)*,‡	−2.3 (0.2)*,‡
Change in CDLQI sleep item, LS mean (SE)**	−0.6 (0.1)	−1.4 (0.1)*,‡	−1.4 (0.1)*,‡	−0.7 (0.1)	−1.5 (0.1)*,‡	−1.4 (0.1)*,‡	−0.6 (0.1)	−1.2 (0.1)*,‡	−1.3 (0.1)*,‡

Superscript numbers (*1-22*) show the order in the statistical testing hierarchy; all *P*-values in the hierarchy were controlled for multiplicity.
BSA, Body surface area; *CDLQI*, Children's Dermatology Life Quality Index; *DFI*, Dermatitis Family Index (10-item questionnaire assessing the impact of having a child with atopic dermatitis on family quality of life); *EASI*, Eczema Area and Severity Index; *EASI-50/-75/-90*, ≥50%/75%/90% improvement from baseline in EASI scores; *IGA*, Investigator's Global Assessment; *LS*, least-squares; *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; *NA*, not available; *NRS*, Numerical Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *PROMIS*, Patient-Reported Outcomes Measurements Information Systems; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *SCORAD*, SCORing Atopic Dermatitis; *SE*, standard error; *TCS*, topical corticosteroids; *VAS*, visual analog scale.
*$P < .0001$.
†$P < .001$.
‡Nominal *P* value.
§$P < .05$.
‖$P < .01$.
Sleeplessness was assessed with the ¶SCORAD sleep component (a visual analog scale with a maximum score of 10, indicating the worst imaginable sleeplessness), the #POEM sleep item ("Over the last week, on how many nights has your sleep been disturbed because of the eczema?"), and the **CDLQI sleep item ("Over the last week, how much has your sleep been affected by your skin problem?").

and SCORing Atopic Dermatitis (SCORAD; $P < .0001$, all comparisons). The least-squares mean (±standard error) percent change in EASI from baseline to week 16 was significantly greater among patients treated with dupilumab + TCS, with reductions of 78.4 ± 2.4% for q2w + TCS and 82.1 ± 2.4% for q4w + TCS versus 48.6 ± 2.5% for placebo + TCS (Table II; Fig 1).

At week 16, significantly more patients receiving dupilumab + TCS than placebo + TCS showed ≥3- and ≥4-point improvement in weekly average of Peak Pruritus NRS ($P < .0001$, all comparisons; Fig 2), with consistently higher proportions in the dupilumab + TCS groups achieving ≥4-point reduction as early as week 4 (q2w + TCS, $P = .0044$; q4w + TCS, $P < .0001$).

Dupilumab + TCS significantly reduced patient-reported symptoms of AD, effects on QOL, and symptoms of anxiety and depression, as assessed by mean change from baseline in Patient-Oriented Eczema Measure (POEM), CDLQI, DFI, and Patient-Reported Outcomes Measurements Information Systems anxiety and depression scores[21] (Table II). Dupilumab + TCS also improved sleeplessness as assessed with the SCORAD sleep component, the POEM sleep item, and the CDLQI sleep item (Table II).

The placebo + TCS regimen had a higher proportion of patients requiring rescue medication (19.2%) than either dupilumab regimen (q2w + TCS, 4.9%; q4w + TCS, 2.5%). Sensitivity analyses (all observed values regardless of rescue treatment use) were consistent with the primary analyses. Analyses in the modified FAS were consistent with the FAS, indicating no introduction of bias due to the potential unblinding.

Efficacy and pharmacokinetic analyses by weight strata

Prespecified analyses by weight strata indicated differences between treatment groups on key efficacy parameters (Table II; Fig 1). In the <30-kg stratum, a numerically greater proportion of patients receiving dupilumab 300 mg q4w + TCS achieved an IGA score of 0 or 1 and EASI-50/75/90 versus 100 mg q2w + TCS; notably, mean percent change EASI improvement was greater for 300 mg q4w + TCS than for 100 mg q2w + TCS in the <30-kg stratum at all time points (Fig 1). In the ≥30-kg stratum, a numerically greater proportion of patients randomized to dupilumab 200 mg q2w + TCS than 300 mg q4w + TCS achieved an IGA score of 0 or 1, EASI-75, and ≥4- and ≥3-point reductions in worst itch score.

Consistent with the efficacy analyses, the dupilumab 300 mg q4w + TCS regimen maintained substantially higher trough blood levels than did the 100 mg q2w + TCS regimen in the <30-kg stratum (week 16 mean C_{trough} 98.7 mg/L vs 62.6 mg/L). In the ≥30-kg group, the dupilumab 200 mg q2w + TCS regimen maintained consistently higher trough blood levels than did the 300 mg q4w + TCS regimen (86.0 mg/L vs 53.9 mg/L). Exposure–response relationships over time, assessed by quartile analyses of exposure for percent change from baseline in EASI and percentage of patients achieving an IGA score of 0 or 1 and logistic regression for binary endpoints (EASI-50, EASI-75, EASI-90, and IGA 0 or 1), indicated a trend for increasing drug effect with increasing C_{trough} (data not shown).

Safety

Overall incidence of treatment-emergent AEs (TEAEs) was lower in the dupilumab + TCS groups (Table III). Two patients receiving placebo + TCS and two receiving dupilumab 300 mg q4w + TCS reported serious TEAEs—none related to the study drug. Treatment discontinuations due to AEs were uncommon (placebo + TCS, n = 2; dupilumab 100/200 mg q2w + TCS, n = 2). No deaths or treatment-related events of hypersensitivity or anaphylaxis occurred during the study. As in previous dupilumab trials, injection-site reactions were more common with dupilumab (none were severe or led to discontinuation), as was conjunctivitis; all but 1 conjunctivitis event were of mild-to-moderate severity. One patient receiving dupilumab 200 mg q2w + TCS discontinued treatment because of bacterial conjunctivitis of moderate severity. Most patients with conjunctivitis recovered or were recovering with standard ophthalmic treatments during study drug treatment. The highest incidence of conjunctivitis (20.6%) occurred in the treatment group with the lowest exposure (100 mg q2w + TCS).

Consistent with long-term experience with dupilumab,[22] infection (including skin infections and herpes viral infections) was lower with dupilumab + TCS than with placebo + TCS. In this patient population with a high burden of comorbid type 2 inflammatory diseases, and as would be expected given the demonstrated efficacy of dupilumab for these conditions, incidence of type 2 inflammatory AEs was lower with higher dupilumab exposure. Among patients <30 kg, there was a trend toward a lower incidence of AEs of AD exacerbation, asthma, and allergic rhinitis in the dupilumab 300 mg q4w + TCS group than in the 100 mg q2w + TCS group (Table III). A similar trend was noted in patients ≥30 kg, with a lower incidence for 200 mg q2w + TCS than for 300 mg q4w + TCS.

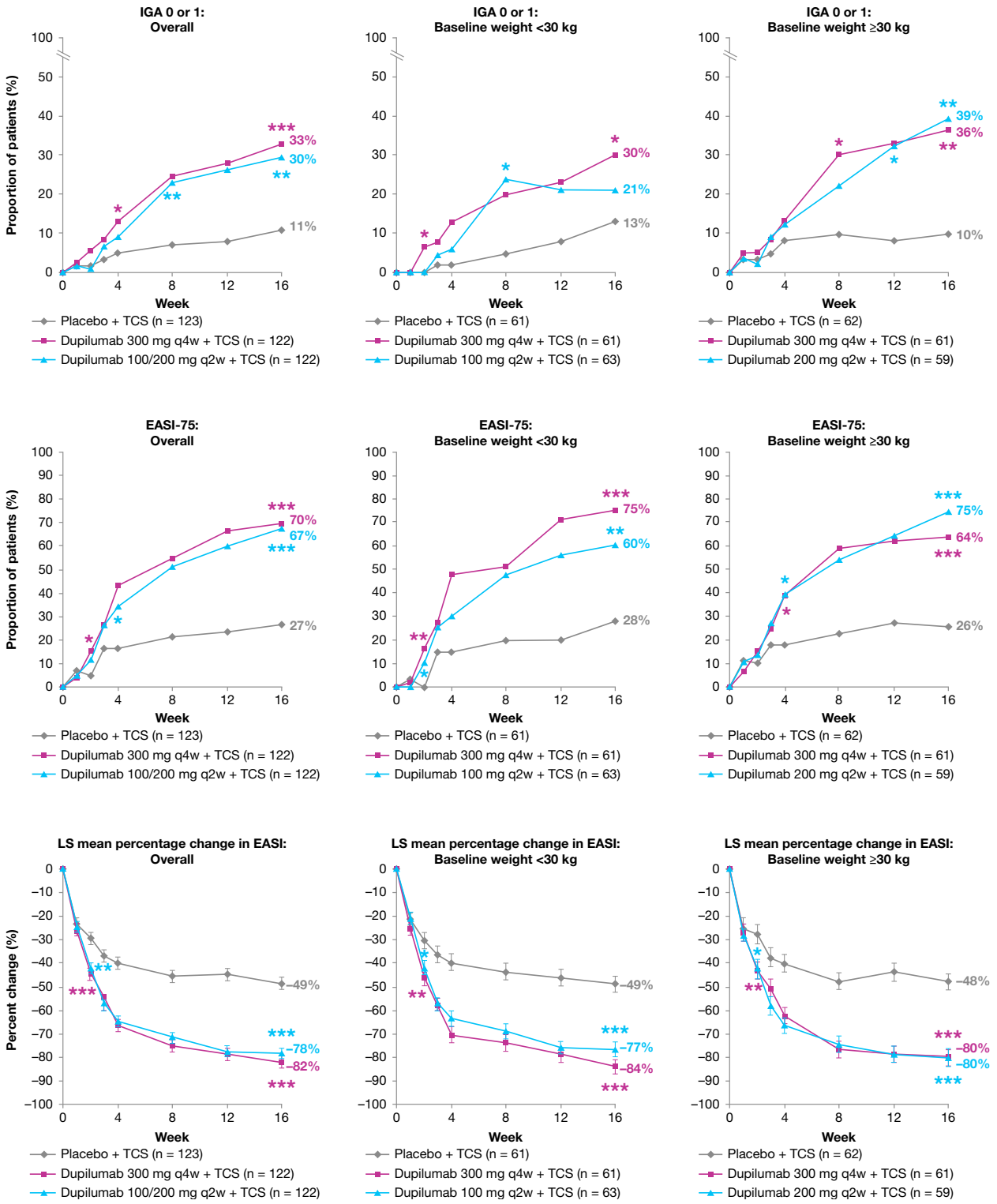

Fig 1. Atopic dermatitis. Proportion of patients achieving co-primary endpoints of an IGA score of 0 or 1 and EASI-75, and the LS mean percentage change in EASI over time in the overall population and the baseline weight <30-kg and ≥30-kg subgroups. *EASI*, Eczema Area and Severity Index; *EASI-75*, ≥75% improvement from baseline in EASI scores; *IGA*, Investigator's Global Assessment; *LS*, least-squares; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *TCS*, topical corticosteroids. **P* < .05; ***P* < .001; ****P* < .0001; all *P* values in the weight strata are nominal.

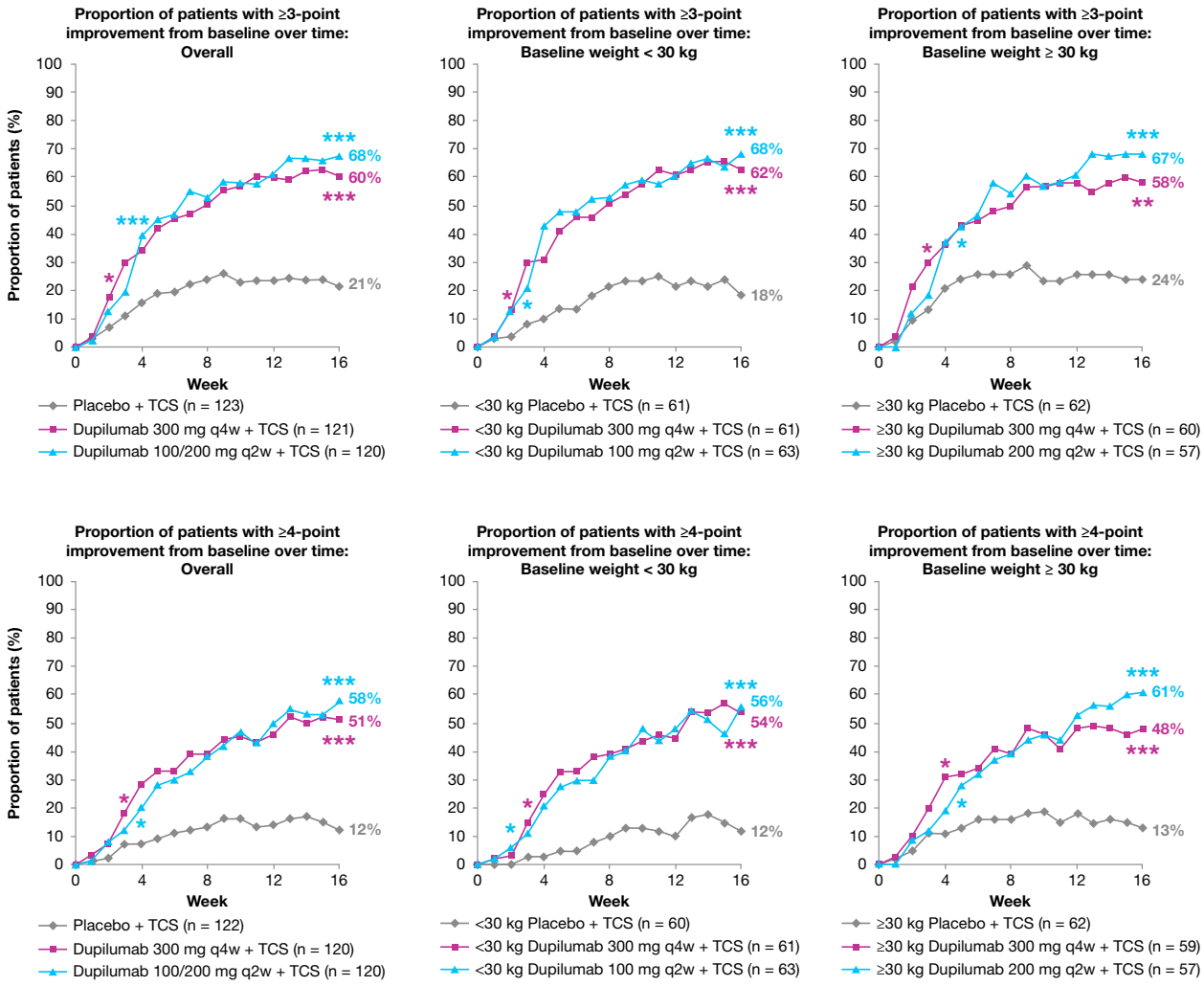

Fig 2. Atopic dermatitis. Proportions of patients with ≥3- and ≥4-point improvement in weekly average of Peak Pruritus NRS over time, in the overall population and the baseline weight <30 kg and ≥30 kg subgroups. *n*, Number of patients with baseline NRS ≥3 or ≥4; *NRS*, Numerical Rating Scale; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *TCS*, topical corticosteroids. $^{*}P < .05$; $^{***}P < .0001$; all *P* values in the weight strata are nominal.

DISCUSSION

In children age 6-11 years with severe AD inadequately controlled with topical medications, 16 weeks of dupilumab + TCS resulted in statistically significant, clinically meaningful, and rapid improvements in AD signs and symptoms, including itch, anxiety, depression, sleep, and QOL. As most efficacy measures were continuing to show improvement at week 16, it is possible that further benefit would accrue with longer treatment. Overall, efficacy of both dupilumab regimens (q2w + TCS and q4w + TCS) in children with severe AD was similar to that reported in adults[15-17] and adolescents with moderate-to-severe AD.[18,19]

In this phase 3 study, a monthly regimen of dupilumab (300 mg q4w + TCS) was compared with a weight-based dosing regimen (100 mg q2w + TCS, patients <30 kg; 200 mg q2w + TCS, patients ≥30 kg). In analyses by prespecified baseline weight strata, optimal doses for efficacy and safety were 300 mg q4w + TCS in <30-kg and 200 mg q2w + TCS in ≥30-kg children. These 2 dose regimens have recently been approved by the US Food and Drug Administration.[23]

Data were consistent with the known dupilumab safety profile. As with previous studies of dupilumab in AD, injection-site reactions and conjunctivitis were the only 2 TEAEs for which incidence notably increased for dupilumab + TCS versus placebo + TCS; most cases were of mild-to-moderate severity and resolved during the trial. Overall incidence of TEAEs was lower with

Table III. Safety assessment

	Overall			Baseline weight <30 kg			Baseline weight ≥30 kg		
Safety assessments	**Placebo + TCS (n = 120)**	**Dupilumab 300 mg q4w + TCS (n = 120)**	**Dupilumab 100/200 mg q2w + TCS (n = 122)**	**Placebo + TCS (n = 60)**	**Dupilumab 300 mg q4w + TCS (n = 60)**	**Dupilumab 100 mg q2w + TCS (n = 63)**	**Placebo + TCS (n = 60)**	**Dupilumab 300 mg q4w + TCS (n = 60)**	**Dupilumab 200 mg q2w + TCS (n = 59)**
Patients with ≥1 TEAE, n (%)	88 (73.3)	78 (65.0)	82 (67.2)	43 (71.7)	39 (65.0)	46 (73.0)	45 (75.0)	39 (65.0)	36 (61.0)
Patients with ≥1 serious TEAE, n (%)*	2 (1.7)	2 (1.7)	0	0	2 (3.3)	0	2 (3.3)	0	0
Patients with ≥1 TEAE leading to permanent treatment discontinuation†	2 (1.7)	0	2 (1.6)	2 (3.3)	0	1 (1.6)	0	0	1 (1.7)
Deaths	0	0	0	0	0	0	0	0	0
TEAEs (PT) reported in ≥5% of patients, n (%)									
Dermatitis atopic, exacerbation	17 (14.2)	8 (6.7)	10 (8.2)	7 (11.7)	4 (6.7)	8 (12.7)	10 (16.7)	4 (6.7)	2 (3.4)
Asthma	12 (10.0)	2 (1.7)	4 (3.3)	7 (11.7)	0	4 (6.3)	5 (8.3)	2 (3.3)	0
Rhinitis allergic	5 (4.2)	3 (2.5)	4 (3.3)	2 (3.3)	1 (1.7)	3 (4.8)	3 (5.0)	2 (3.3)	1 (1.7)
Nasopharyngitis	8 (6.7)	15 (12.5)	8 (6.6)	2 (3.3)	6 (10.0)	6 (9.5)	6 (10.0)	9 (15.0)	2 (3.4)
Upper respiratory tract infection	12 (10.0)	13 (10.8)	10 (8.2)	5 (8.3)	9 (15.0)	5 (7.9)	7 (11.7)	4 (6.7)	5 (8.5)
Viral upper respiratory tract infection	6 (5.0)	2 (1.7)	1 (0.8)	5 (8.3)	1 (1.7)	1 (1.6)	1 (1.7)	1 (1.7)	0
Vomiting	8 (6.7)	6 (5.0)	6 (4.9)	4 (6.7)	3 (5.0)	2 (3.2)	4 (6.7)	3 (5.0)	4 (6.8)
Cough	9 (7.5)	3 (2.5)	5 (4.1)	5 (8.3)	0	2 (3.2)	4 (6.7)	3 (5.0)	3 (5.1)
Headache	10 (8.3)	6 (5.0)	7 (5.7)	3 (5.0)	1 (1.7)	1 (1.6)	7 (11.7)	5 (8.3)	6 (10.2)
Other adverse events, n (%)									
Infections and infestations (SOC)	61 (50.8)	52 (43.3)	49 (40.2)	30 (50)	26 (43.3)	28 (44.4)	31 (51.7)	26 (43.3)	21 (35.6)
Conjunctivitis cluster‡	5 (4.2)	8 (6.7)	18 (14.8)	2 (3.3)	4 (6.7)	13 (20.6)	3 (5.0)	4 (6.7)	5 (8.5)
Keratitis cluster§	0	0	1 (0.8)	0	0	1 (1.6)	0	0	0
Skin infection (adjudicated)‖	16 (13.3)	7 (5.8)	10 (8.2)	8 (13.3)	4 (6.7)	5 (7.9)	8 (13.3)	3 (5.0)	5 (8.5)
Injection-site reactions (HLT)	7 (5.8)	12 (10.0)	13 (10.7)	4 (6.7)	6 (10.0)	5 (7.9)	3 (5.0)	6 (10.0)	8 (13.6)
Herpes viral infections (HLT)	6 (5.0)	2 (1.7)	4 (3.3)	3 (5.0)	0	3 (4.8)	3 (5.0)	2 (3.3)	1 (1.7)

HLT, MedDRA High Level Term; *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *SOC*, MedDRA System Organ Class; *TCS*, topical corticosteroids; *TEAE*, treatment-emergent adverse event.

*Includes 1 event of asthma and 1 event of dermatitis atopic (placebo) and 1 event of food allergy and 1 event of conjunctivitis bacterial (dupilumab 100/200 mg q2w + TCS).

†Includes 1 event of asthma and 1 event of dermatitis atopic (placebo) and 1 event of food allergy and 1 event of urinary tract infection (dupilumab 300 mg q4w + TCS). Adverse events were reported according to MedDRA PTs unless otherwise specified.

‡Conjunctivitis cluster includes the PTs conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis.

§Keratitis cluster includes the PTs keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

‖Skin infections were adjudicated on a case-by-case basis, and they included bacterial, viral, and fungal infections.

dupilumab + TCS than with placebo + TCS, which might be related to the effect of dupilumab on comorbid type 2 inflammatory conditions and on skin infections.[22] Of importance, this pediatric study population with severe AD has a high burden of comorbid type 2 or allergic conditions: almost half of these children have asthma, about 60% have allergic rhinitis, and about 65% report food allergies. In addition, children with severe AD are at markedly increased risk of skin infections.[24]

Consistent with the concept that patients with severe AD have a systemic perturbation in their immune axis—resulting from Th-2 polarization—that can be addressed with dupilumab,[25,26] dupilumab + TCS not only improved all measures of AD in these patients, but resulted in a decrease in type 2 AEs. In addition, because infections in patients with AD result from a breakdown in skin integrity, and because dupilumab treatment can restore skin integrity,[27] as expected, dupilumab + TCS was associated with lower rates of skin and herpes virus infections.[22] Dupilumab + TCS-associated decreases in type 2 comorbidities and infections were correlated with pharmacokinetic exposure. The benefit of dupilumab in regard to infections runs counter to experience with immunomodulatory therapies—such as corticosteroids, cyclosporine, Janus kinase inhibitors, tumor necrosis factor inhibitors, azathioprine, and FK506 inhibitors—that tend to be profoundly immunosuppressive. There is an obvious benefit in this pediatric population for AD treatment that can also address associated comorbid atopic conditions while avoiding immunosuppression.

As observed previously in adults and adolescents with AD,[18,28] conjunctivitis incidence in this trial was higher in patients treated with dupilumab + TCS. The highest incidence of conjunctivitis (24%) occurred in the treatment group with the lowest exposure (100 mg q2w + TCS), which is consistent with previous analyses suggesting that conjunctivitis associated with dupilumab results from relative undertreatment within the eye compartment.[28]

Study strengths are the randomized, prospective, double-blinded, placebo-controlled design and the use of validated assessments. Limitations include the relatively short 16-week treatment period and the restriction, per agreement with regulatory authorities, to children with severe disease. A pediatric open-label extension study is ongoing.

This study, the first, to our knowledge, of a targeted biologic agent in children aged 6-11 years with severe AD, demonstrated clear efficacy of dupilumab + TCS in all disease measures, including extent and severity of signs, intensity of symptoms, sleep, and QOL. The safety profile was consistent with that observed in adults and adolescents. Both the 300 mg q4w + TCS and the 100/200 mg q2w + TCS regimens of dupilumab provided substantial clinical benefit for signs and symptoms of AD.

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SUPPLEMENTARY DATA

Supplementary data are available on Mendeley at https://data.mendeley.com/datasets/6k45whwfcp/draft?a=631d9608-f498-4edf-8d94-45d0beb47ba5.

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