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Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Adolescents with atopic dermatitis (AD) have high disease burden negatively affecting quality of life, with limited treatment options. The efficacy and safety of dupilumab, a monoclonal antibody, approved for treatment in adolescent patients with inadequately controlled AD, remain unknown in this patient population.

OBJECTIVE To assess the efficacy and safety of dupilumab monotherapy in adolescents with moderate to severe inadequately controlled AD.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, parallel-group, phase 3 clinical trial was conducted at 45 US and Canadian centers between March 21, 2017, and June 5, 2018. A total of 251 adolescents with moderate to severe AD inadequately controlled by topical medications or for whom topical therapy was inadvisable were included.

INTERVENTIONS Patients were randomized (1:1:1; interactive-response system; stratified by severity and body weight) to 16-week treatment with dupilumab, 200 mg (n = 43; baseline weight <60 kg), or dupilumab, 300 mg (n = 39; baseline weight ≥60 kg), every 2 weeks; dupilumab, 300 mg, every 4 weeks (n = 84); or placebo (n = 85).

MAIN OUTCOMES AND MEASURES Proportion of patients with 75% or more improvement from baseline in Eczema Area and Severity Index (EASI-75) (scores range from 0 to 72, with higher scores indicating greater severity) and Investigator's Global Assessment (IGA) 0 or 1 on a 5-point scale (scores range from 0 to 4, with higher scores indicating greater severity) at week 16.

RESULTS A total of 251 patients were randomized (mean [SD] age, 14.5 [1.7] years; 148 [59.0%] male). Of 250 patients with data available on concurrent allergic conditions, most had comorbid type 2 diseases (asthma, 134 [53.6%]; food allergies, 60.8%; allergic rhinitis, 65.6%). A total of 240 patients (95.6%) completed the study. Dupilumab achieved both coprimary end points at week 16. The proportion of patients with EASI-75 improvement from baseline increased (every 2 weeks, 41.5%; every 4 weeks, 38.1%; placebo, 8.2%) with differences vs placebo of 33.2% (95% CI, 21.1%-45.4%) for every 2 weeks and 29.9% (95% CI, 17.9%-41.8%) for every 4 weeks ($P < .001$). Efficacy of the every-2-week regimen was generally superior to the every-4-week regimen. Patients in the dupilumab arms had higher percentage values of conjunctivitis (every 2 weeks, 9.8%; every 4 weeks, 10.8%; placebo, 4.7%) and injection-site reactions (every 2 weeks, 8.5%; every 4 weeks, 6.0%; placebo, 3.5%), and lower nonherpetic skin infections (every 2 weeks, 9.8%; every 4 weeks, 9.6%; placebo, 18.8%).

CONCLUSIONS AND RELEVANCE In this study, dupilumab significantly improved AD signs, symptoms, and quality of life in adolescents with moderate to severe AD, with an acceptable safety profile. Placebo-corrected efficacy and safety of dupilumab were similar in adolescents and adults.

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Atopic dermatitis (AD) is a chronic, predominantly type 2 inflammatory skin disease characterized by intense pruritus and often associated with atopic and nonatopic comorbidities,[1-3] reflecting the systemic nature of the disease. Contrary to the common misperception that AD is a mild, spontaneously resolving childhood disease, the prevalence of AD in adolescents (age, 13-17 years) is estimated to range from 0.2% to 24.6% worldwide and from 7.0% to 8.6% in the United States.[4,5] Up to one-third of these patients are estimated to have moderate to severe disease,[6] along with a higher risk of atopic comorbidities and a higher disease burden.[7] Itching, associated sleep loss, and the chronic, relapsing nature of AD negatively affect quality of life (QoL) of patients and family members.[8,9] Atopic dermatitis in adolescents is associated with poorer performance in school, difficulties in forming social relationships and participating in sports, and increased rates of anxiety, depression, and suicidal ideation.[9-11]

Topical therapies adequately treat mild AD, but moderate to severe AD often requires systemic treatment. Until recently, the only systemic medications approved by the US Food and Drug Administration to treat pediatric AD were systemic corticosteroids. Moreover, available guidelines discourage use of systemic corticosteroids.[12,13] Systemic immunosuppressants, such as cyclosporine, have been used off-label, restricted by long-term adverse effects.[14]

Dupilumab is a fully human VelocImmune-derived monoclonal antibody (Regeneron Pharmaceuticals Inc)[15,16] that reduces type 2 inflammation by blocking the shared receptor subunit for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both cytokines.[17,18] The IL-4/IL-13 cytokines are key mediators of type 2 diseases, including AD and associated atopic diseases (eg, asthma, allergic rhinitis, food allergies, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis).[17] In phase 3 trials, dupilumab significantly improved AD signs and symptoms, including pruritus, anxiety and depression, and QoL in adults with moderate to severe AD, with an acceptable safety profile.[19-21] Dupilumab is approved for subcutaneous administration for the treatment of patients aged 12 years or older with a 400-mg loading dose followed by 200 mg every 2 weeks in adolescents (age, ≥12 to <18 years) with baseline body weight less than 60 kg or a 600-mg loading dose followed by 300 mg every 2 weeks in adolescents weighing 60 kg or more in the United States with moderate to severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable.[22] In addition, dupilumab is approved for use in patients aged 12 years or older with moderate to severe AD who are candidates for systemic therapy in the European Union and for certain patients with other type 2 inflammatory diseases, including asthma and chronic rhinosinusitis with nasal polyps, in multiple countries.[19-28] Dupilumab has also shown efficacy and safety in other type 2 immune diseases, such as eosinophilic esophagitis,[29] and is being investigated as a potential novel treatment in adolescents with eosinophilic esophagitis[30] and in younger children with AD,[31] asthma,[32] and food allergy.[33] We report results from a phase 3 trial on the efficacy and safety of dupilumab monotherapy in adolescents with moderate to severe AD inadequately controlled by topical therapies. The primary results from the phase 3 trial reported herein led to FDA approval of dupilumab in this patient population.[22]

Key Points

Question What is the efficacy and safety of dupilumab monotherapy in adolescents with moderate to severe inadequately controlled atopic dermatitis?

Findings In this randomized phase 3 clinical trial including 251 adolescents with moderate to severe atopic dermatitis, dupilumab 200 or 300 mg every 2 weeks and 300 mg every 4 weeks resulted in a significant treatment response vs placebo following 16-week treatment, with an acceptable safety profile.

Meaning The findings appear to support the use of dupilumab for the treatment of adolescents with moderate to severe atopic dermatitis.

Methods

Study Design and Oversight

This randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial (R668-AD-1526, LIBERTY AD ADOL) was conducted between March 21, 2017, and June 5, 2018, in 45 study centers (hospitals, clinics, and academic institutions) in the United States and Canada. The trial protocol is available in Supplement 1. The trial was conducted in accordance with the Declaration of Helsinki,[34] International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. The protocol was reviewed and approved by institutional review boards/ethics committees at all centers. An independent data and safety monitoring committee monitored patient safety (unblinded) and integrity of study results. For all patients, at least 1 parent or legal guardian provided written informed consent, and patients provided written informed assent. Participants were reimbursed for travel expenses.

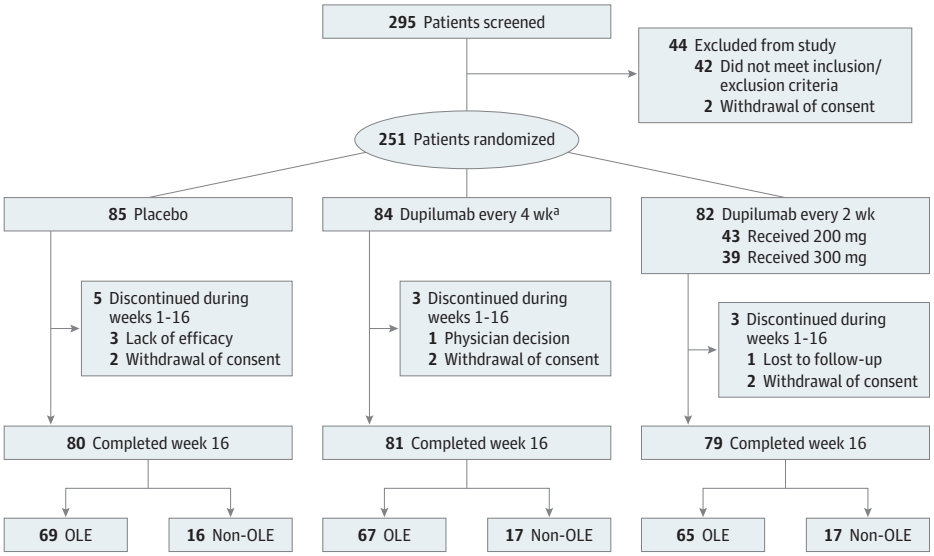
Patients

Eligible patients were 12 years or older to younger than 18 years with moderate to severe AD inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable. Patients had chronic AD, as per American Academy of Dermatology criteria[35] for 1 year or more before screening (detailed inclusion and exclusion criteria are given in the eMethods in Supplement 2). Patient eligibility was assessed during a 35-day screening period that involved washout of prior medications.

Randomization and Blinding

Eligible patients were randomized (1:1:1) by an interactive voice response system and stratified by baseline Investigator's Global Assessment (IGA) score (3 vs 4) and body weight (<60 kg vs ≥60 kg) to 16-week treatment with subcutaneous dupilumab every 2 or every 4 weeks or placebo every 2 weeks (**Figure 1**). This regimen was based on data from a phase 2b dose-ranging study and 2 phase 3 studies in adults[19,36] and a study in patients aged

Figure 1. CONSORT Diagram



OLE indicates open-label extension trial (NCT02612454).

[a] One patient in the every-4-week dupilumab group who was randomized but did not receive treatment was included in the efficacy, but not the safety, analysis.

6 to younger than 18 years.[37] To account for differences in body size from adults, a tiered weight-based regimen was studied. In the dupilumab every-2-week group, patients weighing less than 60 kg received 200 mg after a 400-mg loading dose on day 1; patients weighing 60 kg or more received 300 mg after a 600-mg loading dose on day 1. In the dupilumab every-4-week group, all patients received 300 mg after a 600-mg loading dose. To maintain blinding, all patients received injections every 2 weeks (dupilumab or placebo) from day 1; patients in the dupilumab every-4-week group received placebo in the weeks that dupilumab was not given (eMethods in Supplement 2 gives additional information on the blinding procedure).

Procedures

Patients applied moisturizers twice daily for 7 or more days before randomization and throughout the study. A 35-day screening period preceded initiation of the study drug. Systemic nonsteroidal immunosuppressants, systemic or topical corticosteroids, topical calcineurin inhibitors, and topical crisaborole could be used only as rescue treatment by patients with intolerable AD symptoms at the discretion of the investigator (additional details in eMethods in Supplement 2). Patients who completed the 16-week treatment period were eligible to participate in an open-label extension study (R668-AD-1434, LIBERTY AD PED-OLE, NCT02612454); patients not enrolling in the open-label extension study were followed up for 12 additional weeks.

Outcomes

Coprimary end points per European Medicines Agency feedback were the proportion of patients with IGA scores of 0 or 1 (as in other dupilumab trials,[19] scores range from 0 to 4, with higher scores indicating greater severity; the clinically meaningful within-person change or response definition for this scale has not been determined) and 2 or more points improvement from baseline or 75% or more improvement from baseline in Eczema Area and Severity Index (EASI-75) scale at week 16. Scores on the EASI range from 0 to 72, with higher scores indicating greater severity, and a change of 6.6 has been estimated as the clinically meaningful within-person change or response definition. The EASI-75 score was a key secondary end point in the United States. Other key secondary end points at week 16 were the percentage changes from baseline in EASI and Peak Pruritus Numerical Rating Scale (NRS), and proportion of patients with a 3-point or more or 4-point or more improvement from baseline in Peak Pruritus NRS (assesses the maximum itch intensity in the previous 24 hours on a scale ranging from 0 to 10, with higher values indicating worse itching; clinically meaningful within-person change or response definition is 4 points). Other secondary end points included 50% or more or 90% or more improvement from baseline in EASI (EASI-50/EASI-90) at week 16, percentage change in SCORing Atopic Dermatitis (combined score of investigator-reported disease severity and affected body surface area and patient-reported symptoms of itch and sleep loss; scores range from 0 to 103, with higher scores indicating greater severity; a change of 8.7 has been estimated as the clinically meaningful within-person change or response definition) and changes in Children's Dermatology Life Quality Index (scores range from 0 to 30, with higher scores indicating greater effect on QoL; a clinically meaningful within-person change or response definition is 6 points), Patient-Oriented Eczema Measure (composite measure of patient-reported symptoms including the effect of symptoms on sleep, evaluates frequency of symptoms, including itch, and the effect of AD on sleep on a scale of 0 to 28, with higher scores indicating greater severity; clinically meaningful within-person change or response definition is 6 points), and Hospital Anxiety and Depression Scale (HADS) scores from baseline to week 16 (measures patient-reported symptoms of anxiety and depression on a scale from 0 to 42;

scores on HADS-A [measuring anxiety] and HADS-D [measuring depression] subscales range from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms; clinically meaningful within-person change or response definition for this scale has not been determined; recommended cutoff score for identifying patients with anxiety or depression is 8) (eMethods in Supplement 2 gives a full list of end points). Because adolescent patients with AD have high rates of comorbid type 2 diseases, we also explored the potential benefit of dupilumab in asthma, allergic rhinitis, and food allergy in prespecified analyses. The effect of dupilumab on asthma control in adolescent patients with ongoing comorbid asthma was assessed by the 5-question version of the Juniper Asthma Control Questionnaire, whereas the effect of dupilumab on symptoms of allergic rhinitis in adolescent patients with ongoing allergic rhinitis was assessed by the Total Nasal Symptoms Score; the summed Total Nasal Symptoms Score included the following 4 nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, each rated on a 0 to 3 scale of severity.

Serum was collected for pharmacokinetic evaluation and biomarker analyses at various times during treatment. Safety assessments included evaluation of treatment-emergent adverse events, laboratory test measurements, and vital signs. Safety end points included incidences of serious treatment-emergent adverse events and nonherpetic skin infection.

Statistical Analysis

Randomization of 240 patients was planned (eMethods in Supplement 2 indicates power calculations). The efficacy population included all randomized patients. For the coprimary and binary secondary end points, the Cochran-Mantel-Haenszel test was used with adjustment for randomization strata (disease severity and weight group). Patients who withdrew from the study or received rescue medication, as well as those with other missing data, were counted as nonresponders at all subsequent times, including week 16. For continuous end points, data collected after rescue medication use were set as missing; subsequent missing data were imputed by multiple imputation. Sensitivity analyses were conducted for both binary and continuous end points (eMethods in Supplement 2). A multiplicity adjustment approach (hierarchical procedure; eMethods in Supplement 2) was used to control the overall type I error rate at .05 for the primary and secondary end points for the 2 dupilumab regimens vs placebo. Each hypothesis was formally tested only if the preceding one was significant at the 2-sided .05 significance level.

The safety population was defined as all randomized patients who received 1 or more injection of the study drug. Pharmacokinetic analysis included descriptive statistics of functional dupilumab serum concentration at each measurement point by dose. The association between functional dupilumab serum concentration and clinical response (IGA and EASI scales) was assessed; eMethods in Supplement 2 gives additional details. All statistical tests were 2-tailed with a 5% level of statistical significance. All analyses were performed using SAS, version 9.2 or higher (SAS Institute, Inc).

Results

Patients

Between April 7, 2017, and December 13, 2017, a total of 251 patients of 295 screened were randomized to dupilumab, 200 or 300 mg, every 2 weeks (n = 82; 43 received 200 mg and 39 received 300 mg); dupilumab, 300 mg, every 4 weeks (n = 84); or placebo (n = 85). A high proportion of these patients (240 [95.6%]) completed the study treatment (Figure 1). Treatment groups had similar baseline characteristics that reflected a substantial disease burden (eg, influence on QoL and mental health) (**Table 1**). Overall, high proportions of 250 patients with available data (230 [92.0%]) had 1 or more comorbid type 2 diseases. Of the 250 individuals with data on specific conditions, 164 had allergic rhinitis (65.6%), 134 had asthma (53.6%), 152 had food allergy (60.8%), and 106 had received prior systemic therapy for AD (42.4%) (Table 1).

Coprimary Outcomes

Dupilumab achieved both coprimary end points. A significantly higher proportion of patients reached EASI-75 at week 16 in both the every-2-week (34 [41.5%]) and every-4-week (32 [38.1%]) groups vs placebo (7 [8.2%]). Differences vs placebo were 33.2% (95% CI, 21.1%-45.4%) for every 2 weeks and 29.9% (95% CI, 17.9%-41.8%) for every 4 weeks (both regimens, $P < .001$) (**Table 2**, **Figure 2**A). The proportions of patients reaching IGA 0 or 1 at week 16 was also significantly higher with every 2 weeks (20 [24.4%]) and every 4 weeks (15 [17.9%]) vs placebo (2 [2.4%]). Differences vs placebo were 22.0% (95% CI, 12.2%-31.9%) for every 2 weeks and 15.5% (95% CI, 6.7%-24.3%) for every 4 weeks (both $P < .001$) (Table 2, Figure 2B).

Key Secondary Outcomes

Both dupilumab regimens significantly improved the first key secondary end point: least-squares mean percentage change from baseline to week 16 in EASI (every 2 weeks, −65.9; every 4 weeks, −64.8; placebo, −23.6). The least-squares mean percentage differences vs placebo were −42.3 (95% CI, −55.6 to −29.0) for every 2 weeks and −41.2 (95% CI, −54.4 to −28.0) for every 4 weeks (both regimens, $P < .001$) (Table 2, **Figure 3**A). Significant improvement was also seen for the second key secondary end point: least-squares mean percentage change from baseline to week 16 in Peak Pruritus NRS (every 2 weeks, −47.9; every 4 weeks, −45.5; placebo, −19.0). The least-squares mean percentage differences vs placebo were −29.0 (95% CI, −39.5 to −18.4) for every 2 weeks and −26.5 (95% CI, −37.5 to −15.6) for every 4 weeks (both regimens, $P < .001$) (Table 2, Figure 3B). The proportion of patients with 3 points or more or 4 points or more improvement from baseline in Peak Pruritus NRS was significantly higher with dupilumab than placebo at week 16. Proportions of patients with at least 3-point improvement from baseline at week 16 were the following: every 2 weeks, 48.8%; every 4 weeks, 38.6%; and placebo, 9.4%. Proportions of patients with at least 4-point improvement from baseline at week 16 were the following: every 2 weeks, 36.6%; every 4 weeks, 26.5%; and placebo, 4.8% (Table 2, eFigure 1 in Supplement 2).

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Placebo (n = 85)	Dupilumab 300 mg Every 4 wk (n = 84)	Dupilumab 200/300 mg Every 2 wk (n = 82)	All Patients (n = 251)
Age, mean (SD), y	14.5 (1.8)	14.4 (1.6)	14.5 (1.7)	14.5 (1.7)
Age, No. (%), y				
≥12 to <15	41 (48.2)	45 (53.6)	43 (52.4)	129 (51.4)
≥15 to <18	44 (51.8)	39 (46.4)	39 (47.6)	122 (48.6)
Male, No. (%)	53 (62.4)	52 (61.9)	43 (52.4)	148 (59.0)
Ethnicity, No. (%)				
Not Hispanic or Latino	72 (84.7)	64 (76.2)	69 (84.1)	205 (81.7)
Hispanic or Latino	13 (15.3)	20 (23.8)	13 (15.9)	46 (18.3)
Race, No. (%)				
White	48 (56.5)	55 (65.5)	54 (65.9)	157 (62.5)
Black or African American	15 (17.6)	8 (9.5)	7 (8.5)	30 (12.0)
Asian	13 (15.3)	13 (15.5)	12 (14.6)	38 (15.1)
Weight, mean (SD), kg	64.4 (21.5)	65.8 (20.1)	65.6 (24.5)	65.2 (22.0)
Weight, No. (%)				
<60 kg	43 (50.6)	42 (50.0)	43 (52.4)	128 (51.0)
≥60 kg	42 (49.4)	42 (50.0)	39 (47.6)	123 (49.0)
BMI, mean (SD)	23.9 (6.0)	24.1 (5.9)	24.9 (7.9)	24.3 (6.6)
Duration of AD, mean (SD), y	12.3 (3.4)	11.9 (3.2)	12.5 (3.0)	12.2 (3.2)
EASI score, mean (SD)[a]	35.5 (14.0)	35.8 (14.8)	35.3 (13.8)	35.5 (14.2)
Patients with IGA score, No. (%)[b]				
3	39 (45.9)	38 (45.2)	39 (47.6)	116 (46.2)
4	46 (54.1)	46 (54.8)	43 (52.4)	135 (53.8)
Peak Pruritus NRS score, mean (SD)[c]	7.7 (1.6)	7.5 (1.8)	7.5 (1.5)	7.6 (1.7)
Percent BSA involvement, mean (SD)	56.4 (24.1)	56.9 (23.5)	56.0 (21.4)	56.5 (23.0)
SCORAD score, mean (SD)[d]	70.4 (13.3)	69.8 (14.1)	70.6 (13.9)	70.3 (13.7)
CDLQI score, mean (SD)[e]	13.1 (6.7)	14.8 (7.4)	13.0 (6.2)	13.6 (6.8)
POEM score, mean (SD)[f]	21.1 (5.4)	21.1 (5.5)	21.0 (5.0)	21.0 (5.3)
Total HADS score, mean (SD)[g]	11.6 (7.8)	13.3 (8.2)	12.6 (8.0)	12.5 (8.0)
Serum TARC, median (Q1-Q3), pg/mL	2160.0 (1120.0-6000.0)	2095.0 (1110.0-5350.0)	2940.0 (974.0-7320.0)	2320.0 (1080.0-6280.0)
Serum total IgE, median (Q1-Q3), kU/mL	3983.0 (813.0-10931.0)	3482.0 (728.0-10000.0)	3739.5 (1699.0-9517.0)	3785.0 (967.0-10000.0)
Serum LDH concentration, median (Q1-Q3), U/L	259.0 (223.0-321.0)	275.5 (227.0-362.0)	277.0 (213.0-344.0)	271.0 (223.0-346.0)
Blood eosinophil count/μL	660 (320-1130)	680 (345-980)	600 (380-1120)	650 (370-1100)
Patients with ≥1 concurrent allergic condition, No. (%)	78 (91.8)	73 (88.0)[h]	79 (96.3)	230 (92.0)[i]

(continued)

Table 1. Baseline Demographics and Disease Characteristics (continued)

Characteristic	Placebo (n = 85)	Dupilumab 300 mg Every 4 wk (n = 84)	Dupilumab 200/300 mg Every 2 wk (n = 82)	All Patients (n = 251)
Allergic rhinitis	57 (67.1)	48 (57.8)	59 (72.0)	164 (65.6)
Asthma	46 (54.1)	42 (50.6)	46 (56.1)	134 (53.6)
Food allergy	48 (56.5)	52 (62.7)	52 (63.4)	152 (60.8)
Allergic conjunctivitis	16 (18.8)	21 (25.3)	20 (24.4)	57 (22.8)
Hives	22 (25.9)	28 (33.7)	22 (26.8)	72 (28.8)
Chronic rhinosinusitis	7 (8.2)	6 (7.2)	6 (7.3)	19 (7.6)
Nasal polyps	2 (2.4)	1 (1.2)	2 (2.4)	5 (2.0)
Eosinophilic esophagitis	0	0	1 (1.2)	1 (0.4)
Other allergies[j]	62 (72.9)	53 (63.9)	58 (70.7)	173 (69.2)
Patients receiving prior systemic medications for AD, No. (%)	33 (38.8)	38 (45.8)[h]	35 (42.7)	106 (42.4)[i]
Corticosteroids	21 (24.7)	27 (32.5)	21 (25.6)	69 (27.6)
Nonsteroidal immunosuppressants	17 (20.0)	15 (18.1)	20 (24.4)	52 (20.8)
Azathioprine	1 (1.2)	1 (1.2)	0	2 (0.8)
Cyclosporine	12 (14.1)	6 (7.2)	14 (17.1)	32 (12.8)
Methotrexate	6 (7.1)	10 (12.0)	10 (12.2)	26 (10.4)
Mycophenolate	0	1 (1.2)	2 (2.4)	3 (1.2)

Abbreviations: AD, atopic dermatitis; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; LDH, lactate dehydrogenase; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; Q1, first quartile; Q3, third quartile; QoL, quality of life; SCORAD, SCORing Atopic Dermatitis; TARC, thymus and activation-regulated chemokine.

SI conversion factors: To convert eosinophils to 10^9 per liter, multiply by 0.001; LDS to microkatals per liter, multiply by 0.0167.

[a] Scores range from 0 to 72, with higher scores indicating greater severity; a change of 6.6 has been estimated as the clinically meaningful within-person change or response definition.

[b] Scores range from 0 to 4, with higher scores indicating greater severity; the clinically meaningful within-person change or response definition for this scale has not been determined.

[c] Patient-reported measure that assesses the maximum itch intensity in the previous 24 hours on a scale ranging from 0 to 10, with higher values indicating worse itching. The clinically meaningful within-person change or response definition is 4 points.

[d] Combined score of investigator-reported disease severity and affected BSA and patient-reported symptoms of itch and sleep loss; scores range from 0 to 103, with higher scores indicating greater severity; a change of 8.7 has been estimated as the clinically meaningful within-person change or response definition.

[e] Evaluates health-related QoL on a scale of 0 to 30, with higher scores indicating greater effect on QoL. The clinically meaningful within-person change or response definition is 6 points.

[f] Composite measure of patient-reported symptoms, evaluates the frequency of symptoms (including itching) and the effect of AD on sleep on a scale of 0 to 28, with higher scores indicating greater severity; the clinically meaningful within-person change or response definition is 6 points.

[g] Measures patient-reported symptoms of anxiety and depression on a scale from 0 to 42; scores on HADS-A (measuring anxiety) and HADS-D (measuring depression) subscales range from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms; the clinically meaningful within-person change or response definition for this scale has not been determined. The recommended cutoff score for identifying patients with anxiety or depression is 8.

[h] Data available on 83 patients.

[i] Data available on 250 patients.

[j] Includes allergies to, for example, medications, animals, plants, mold, and dust mites.

Table 2. Efficacy Outcomes[a]

Outcome	Placebo (n = 85)	Dupilumab 300 mg Every 4 wk (n = 84)	Dupilumab 200/300 mg Every 2 wk (n = 82)
Patients with IGA 0 or 1 score at week 16, No. (%)	2 (2.4)	15 (17.9)[b]	20 (24.4)[b]
Difference vs placebo, % (95% CI)	NA	15.5 (6.7-24.3)	22.0 (12.2-31.9)
Patients with EASI-75 score at week 16, No. (%)	7 (8.2)	32 (38.1)[b]	34 (41.5)[b]
Difference vs placebo, % (95% CI)	NA	29.9 (17.9-41.8)	33.2 (21.1-45.4)
EASI score at baseline, mean (SD)[c]	35.5 (14.0)	35.8 (14.8)	35.3 (13.8)
EASI score at week 16, mean (SD)[c]	24.1 (15.5)	12.3 (11.1)	13.0 (12.6)
Percent change from baseline to week 16 in EASI score, LS mean (SE)	−23.6 (5.5)	−64.8 (4.5)[b]	−65.9 (4.0)[b]
Percent difference vs placebo, LS mean (95% CI)	NA	−41.2 (−54.4 to −28.0)	−42.3 (−55.6 to −29.0)
Weekly average of daily Peak Pruritus NRS score at baseline, mean (SD)[c]	7.7 (1.6)	7.5 (1.8)	7.5 (1.5)
Weekly average of daily Peak Pruritus NRS score at week 16, mean (SD)[c]	6.0 (2.3)	4.0 (2.7)	3.9 (2.2)
Percent change from baseline to week 16 in weekly average of daily Peak Pruritus NRS score, LS mean (SE)	−19.0 (4.1)	−45.5 (3.5)[b]	−47.9 (3.4)[b]
Percent difference vs placebo, LS mean (95% CI)	NA	−26.5 (−37.5 to −15.6)	−29.0 (−39.5 to −18.4)
Proportion of patients with ≥3-point improvement (reduction) from baseline to week 16 in weekly average of daily Peak Pruritus NRS, No./No. available (%)	8/85 (9.4)	32/83 (38.6)[b]	40/82 (48.8)[b]
Difference vs placebo, % (95% CI)	NA	29.1 (17.0-41.3)	39.4 (26.9-51.8)
Proportion of patients with ≥4-point improvement (reduction) from baseline to week 16 in weekly average of daily Peak Pruritus NRS, No./No. available (%)	4/84 (4.8)	22/83 (26.5)[b]	30/82 (36.6)[b]
Difference vs placebo, % (95% CI)	NA	21.7 (11.2-32.3)	31.8 (20.5-43.2)
Patients with EASI-50 score at week 16, No. (%)	11 (12.9)	46 (54.8)[b]	50 (61.0)[b]
Difference vs placebo (95% CI)	NA	41.8 (29.0-54.6)	48.0 (35.3-60.8)
Patients with EASI-90 score at week 16, No. (%)	2 (2.4)	16 (19.0)[b]	19 (23.2)[b]
Difference vs placebo (95% CI)	NA	16.7 (7.7-25.7)	20.8 (11.1-30.5)
Time to onset of end point			
Peak Pruritus NRS score improvement ≥3 points	NA		
Median (95% CI), wk	NC	6.0 (5-11)[d]	5.4 (4-8)[b]
Hazard ratio (95% CI)	NA	1.9 (1.2-2.8)	2.2 (1.5-3.4)
Peak Pruritus NRS score improvement ≥4 points			
Median (95% CI), wk	NC	11.0 (6-NC)	11.4 (9-NC)
Hazard ratio (95% CI)	NA	2.3 (1.4-3.9)[e]	2.40 (1.5-4.0)[b]
Percent BSA at baseline, mean (SD)[c]	56.4 (24.1)	56.9 (23.5)	56.0 (21.4)
Percent BSA at week 16, mean (SD)[c]	42.1 (25.4)	23.4 (19.9)	26.4 (25.4)
Change in percent BSA from baseline to week 16, LS mean (SE)	−11.7 (2.7)	−33.4 (2.3)[b]	−30.1 (2.3)[b]
Difference vs placebo, LS mean (95% CI)	NA	−21.8 (−29.0 to −14.6)	−18.4 (−25.1 to −11.8)
SCORAD at baseline, mean (SD)[c]	70.4 (13.2)	69.8 (14.1)	70.6 (13.9)
SCORAD at week 16, mean (SD)[c]	53.1 (19.7)	35.8 (17.8)	34.9 (18.6)
Percent change from baseline to week 16 in SCORAD score, LS mean (SE)	−17.6 (3.8)	−47.5 (3.2)[b]	−51.6 (3.2)[b]
Percent difference vs placebo, LS mean (95% CI)	NA	−29.9 (−40.0 to −19.8)	−34.0 (−43.4 to −24.6)
CDLQI score at baseline, mean (SD)[c]	13.1 (6.7)	14.8 (7.4)	13.0 (6.2)
CDLQI score at week 16, mean (SD)[c]	7.9 (6.5)	5.2 (5.1)	5.0 (4.1)
Change from baseline to week 16 in CDLQI score, LS mean (SE)	−5.1 (0.6)	−8.8 (0.5)[b]	−8.5 (0.5)[b]
Difference vs placebo, LS mean (95% CI)	NA	−3.7 (−5.2 to −2.2)	−3.4 (−5.0 to −1.8)
POEM score at baseline, mean (SD)[c]	21.1 (5.4)	21.1 (5.5)	21.0 (5.0)
POEM score at week 16, mean (SD)[c]	16.2 (8.3)	11.2 (7.4)	10.8 (6.9)
Change from baseline to week 16 in POEM score, LS mean (SE)	−3.8 (1.0)	−9.5 (0.9)[b]	−10.1 (0.8)[b]
Difference vs placebo, LS mean (95% CI)	NA	−5.7 (−8.2 to −3.2)	−6.3 (−8.6 to −4.0)
Change from baseline to week 16 in weekly average of daily Peak Pruritus NRS score, LS mean (SE)	−1.5 (0.3)	−3.4 (0.3)[b]	−3.7 (0.3)[b]
Difference vs placebo, LS mean (95% CI)	NA	−1.9 (−2.7 to −1.1)	−2.2 (−2.9 to −1.4)
Percent change from baseline to week 4 in weekly average of daily Peak Pruritus NRS score, LS mean (SE)	−12.5 (3.1)	−33.1 (3.1)[b]	−34.7 (3.0)[b]
Percent difference vs placebo, LS mean (95% CI)	NA	−20.6 (−29.1 to −12.1)	−22.2 (−30.6 to −13.9)
Total HADS score at baseline, mean (SD)[c]	11.6 (7.8)	13.3 (8.2)	12.6 (8.0)
Total HADS score at week 16, mean (SD)[c]	8.4 (7.6)	7.6 (7.2)	8.5 (8.2)

(continued)

Table 2. Efficacy Outcomes[a] (continued)

Outcome	Placebo (n = 85)	Dupilumab 300 mg Every 4 wk (n = 84)	Dupilumab 200/300 mg Every 2 wk (n = 82)
Change from baseline to week 16 in total HADS score, LS mean (SE)	−2.5 (0.8)	−5.2 (0.7)[f]	−3.8 (0.7)[g]
Difference vs placebo, LS mean (95% CI)	NA	−2.7 (−4.8 to −0.6)	−1.3 (−3.3 to 0.8)
Proportion of patients with reduction of weekly average of daily Peak Pruritus NRS score ≥4 points from baseline at week 4, No./No. available, %	4/84 (4.8)	17/83 (20.5)[h]	18/82 (22.0)[i]
Difference vs placebo, LS mean (95% CI)	NA	15.7 (5.9-25.5)	17.2 (7.1-27.2)

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, 50% improvement from baseline in EASI score; EASI-75, 75% improvement from baseline in EASI score; EASI-90, 90% improvement from baseline in EASI score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; LS, least squares; NA, not applicable; NC, not calculable; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis.

[a] Explanation of test scoring is given in Table 1 footnotes.

[b] $P < .001$.

[c] All observed data values regardless of rescue treatment use.

[d] $P = .003$.

[e] $P = .001$.

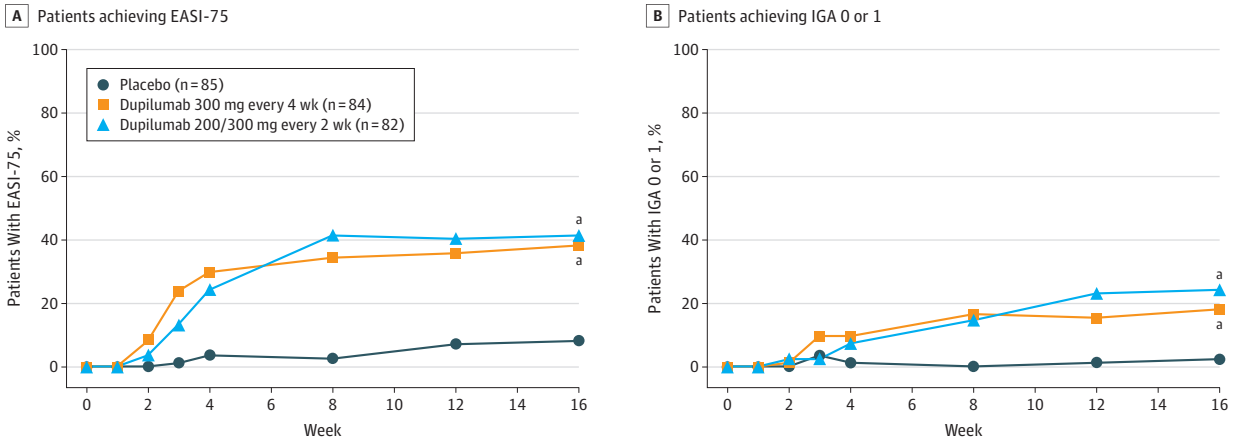
[f] Nominal $P = .01$.

[g] Nominal $P = .22$.

[h] Nominal $P = .003$.

[i] Nominal $P < .001$ vs placebo.

Figure 2. Proportion of Patients Achieving Coprimary End Points Over Time to Week 16



A, Patients achieving 75% or more improvement from baseline in Eczema Area and Severity Index (EASI-75). B, Patients achieving Investigator's Global Assessment (IGA) scores of 0 or 1.

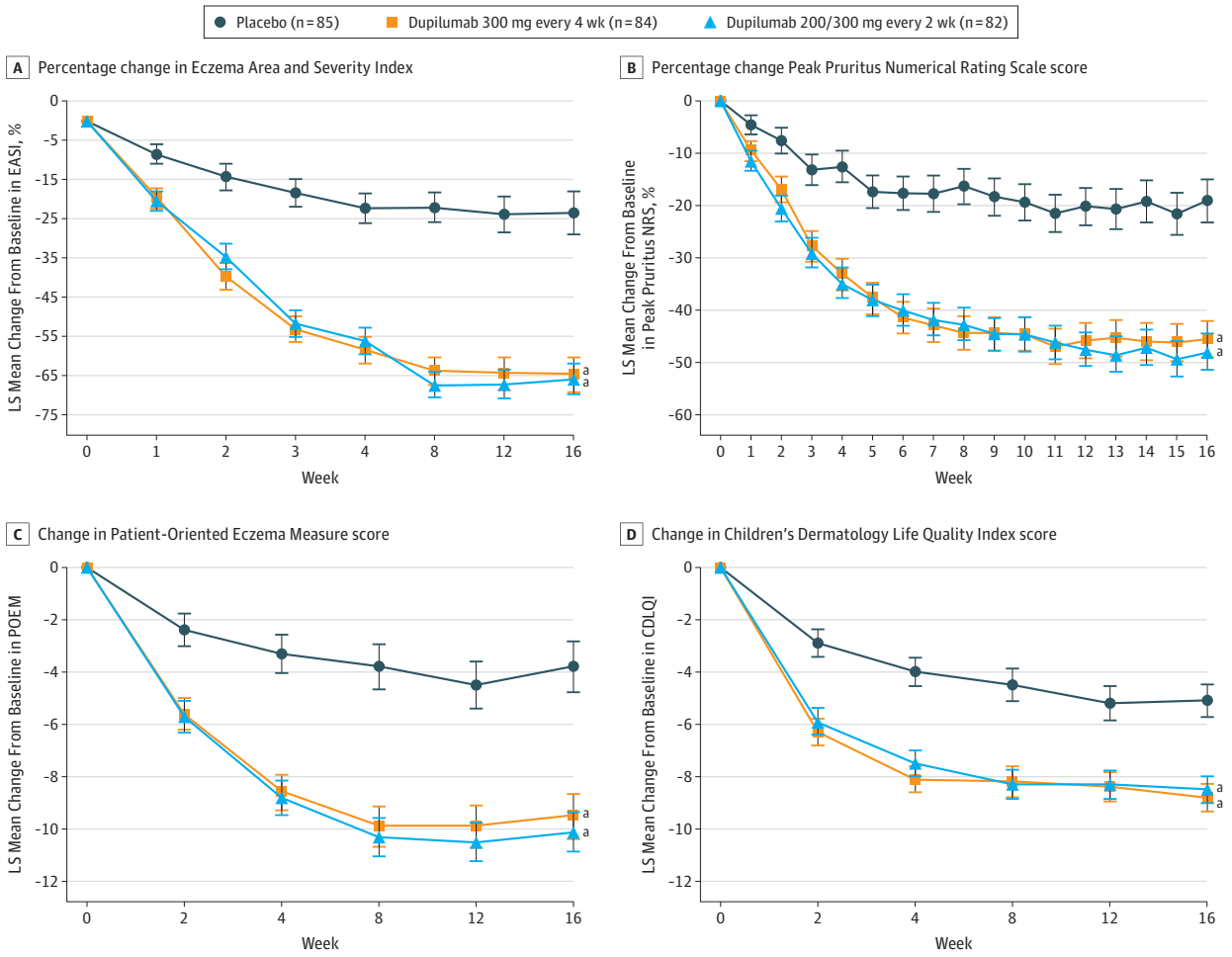
[a] $P < .001$ vs placebo.

For the primary and key secondary outcomes, sensitivity analyses (last observation carried forward for imputation of missing data, or all observed data regardless of rescue treatment use) were consistent with the primary analysis, demonstrating that efficacy was robust irrespective of imputation method used. For example, for patients receiving dupilumab every 2 weeks, differences vs placebo for least-squares mean percentage change from baseline to week 16 in EASI were −34.9 (95% CI, −44.8 to −25.1; $P < .001$) using all observed data regardless of rescue treatment use, and −46.0 (95% CI, −56.8 to −35.3; $P < .001$) using the last observation carried forward for imputation of missing data (eFigure 2, eFigure 3, eTable 1 in Supplement 2).

Other Secondary Outcomes

The time to onset of improvement in Peak Pruritus NRS was significantly shorter in the dupilumab than placebo groups (Table 2). The least-squares mean percentage change from baseline to week 4 in Peak Pruritus NRS was significantly greater with both dupilumab regimens vs placebo (every 2 weeks, −34.7; every 4 weeks, −33.1; placebo, −12.5) (Table 2, Figure 3B), and a greater proportion of dupilumab-treated patients than placebo-treated patients had 4 points or more improvement in Peak Pruritus NRS at week 4 (prespecified time point) (every 2 weeks, 22.0%; every 4 weeks, 20.5%; placebo, 4.8%) (Table 2, eFigure 1 in Supplement 2). Significantly higher proportions of patients treated with both dupilumab regimens reached EASI-50 and EASI-90 at week 16 (EASI-50: every 2 weeks, 61.0%; every 4 weeks, 54.8%; placebo, 12.9%; EASI-90: every 2 weeks, 23.2%; every 4 weeks, 19.0%; placebo, 2.4%) (Table 2). Both dupilumab regimens also significantly improved SCORing Atopic Dermatitis results at week 16 (Table 2); reduced frequency of patient-reported AD symptoms (including itch and sleep loss) and improved QoL significantly vs placebo measured by Patient-Oriented Eczema Measure (least-squares mean changes from baseline to week 16: every 2 weeks, −10.1; every 4 weeks, −9.5; placebo, −3.8), and Children's Dermatology Life Quality Index scores (least-squares mean changes

Figure 3. Least-Squares (LS) Mean Percentage Changes and LS Mean (SE) Changes From Baseline to Week 16



A, LS mean percentage change in Eczema Area and Severity Index score. B, LS mean percentage change in weekly average of daily Peak Pruritus Numerical Rating Scale score. C, LS mean change in Patient-Oriented Eczema Measure score. D, LS mean change in Children's Dermatology Life Quality Index (CDLQI) score.

[a] $P < .001$ vs placebo.

from baseline to week 16: every 2 weeks, −8.5; every 4 weeks, −8.8; placebo, −5.1) (Table 2, Figure 1C,D). Improvements in total HADS score were numerically greater with dupilumab than placebo and with every-4-week than every-2-week regimens (every 2 weeks, −3.8; every 4 weeks, −5.2; placebo, −2.5) (Table 2). In addition, the proportion of patients requiring rescue medication was higher in the placebo group than the dupilumab groups (every 2 weeks, 20.7%; every 4 weeks, 32.1%; placebo, 58.8% (eFigure 4 in Supplement 2).

Additional Efficacy Analyses

Because the dupilumab every-2-week dose was based on body weight, efficacy was assessed by body weight subgroup (<60 kg vs ≥60 kg). In both subgroups, dupilumab-treated patients were more likely than placebo-treated patients to have IGA 0 or 1, EASI-75, or 4-point or more improvement in Peak Pruritus NRS at week 16 and to achieve greater improvement in least-squares mean percentage change from baseline to week 16 in EASI. For example, in patients receiving dupilumab every 2 weeks, the rates at week 16 for IGA 0 or 1 were 30.2% vs 2.3% for placebo in those weighing less than 60 kg, and 17.9% vs 2.4% in patients weighing 60 kg or more; for EASI-75, rates were 46.5% vs 7.0% for placebo in patients weighing less than 60 kg, and 35.9% vs 9.5% for placebo in patients weighing 60 kg or more (eFigure 5 in Supplement 2). In both weight groups, the every-2-week regimens generally provided numerically superior responses compared with the every-4-week regimen on all prespecified end points except EASI-75 and mean percentage change in EASI, for which each dose regimen provided comparable responses (eFigure 5 in Supplement 2).

Pharmacokinetic Analyses

Pharmacokinetic analysis was conducted on 249 patients. At week 16, steady state mean trough concentrations of func-

Table 3. Adverse Events During the Study Treatment Period

Adverse Events	No. (%)		
	Placebo (n = 85)	Dupilumab 300 mg Every 4 wk (n = 83)	Dupilumab 200/300 mg Every 2 wk (n = 82)
Patients with TEAE	59 (69.4)	53 (63.9)	59 (72.0)
Patients with TEAE leading to discontinuation of study drug permanently	1 (1.2)	0	0
Serious TEAE	1 (1.2)	0	0
Death	0	0	0
Most common TEAEs[a]			
Dermatitis atopic (PT)	21 (24.7)	15 (18.1)	15 (18.3)
Skin infections (adjudicated)	17 (20.0)	11 (13.3)	9 (11.0)
Skin infections excluding herpetic skin infections (adjudicated)	16 (18.8)	8 (9.6)	8 (9.8)
Upper respiratory tract infection (PT)	15 (17.6)	6 (7.2)	10 (12.2)
Headache (PT)	9 (10.6)	4 (4.8)	9 (11.0)
Conjunctivitis[b]	4 (4.7)	9 (10.8)	8 (9.8)
Nasopharyngitis (PT)	4 (4.7)	9 (10.8)	3 (3.7)
Infections and infestations (SOC)[c]	37 (43.5)	38 (45.8)	34 (41.5)
Injection-site reactions (HLT)	3 (3.5)	5 (6.0)	7 (8.5)
Herpes viral infections (HLT)	3 (3.5)	4 (4.8)	1 (1.2)

Abbreviations: HLT, high-level term; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

[a] Adverse events reported according to the Medical Dictionary for Regulatory Activities (MedDRA)[38] preferred term occurring in 5% or more of patients in any treatment group.

[b] Includes MedDRA PTs atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral.

[c] The SOCs according to MedDRA.

tional dupilumab were approximately 3-fold higher in patients receiving dupilumab, 200 or 300 mg, every 2 weeks (54.5 mg/L) than those receiving dupilumab, 300 mg, every 4 weeks (19.8 mg/L) (eFigure 6A in Supplement 2). Many patients receiving the every-4-week regimen, particularly those of greater body weight, had trough concentrations at or near the lower limit of quantification (eFigure 6B in Supplement 2). The dupilumab every-2-week regimen achieved similar exposure in patients with body weight less than 60 kg (200 mg) (mean [SD], 51.3 [24.2] mg/mL); and 60 kg or more (300 mg) (mean [SD], 57.9 [30.0] mg/mL); with dupilumab, 300 mg, every 4 weeks, trough concentrations were lower in patients weighing 60 kg or more (mean [SD], 13.1 [11.9] mg/mL) than in those weighing less than 60 kg (mean [SD], 27.2 [16.1] mg/mL); and in those in the upper weight ranges (eFigure 6B,C in Supplement 2). A positive exposure-response association was observed; higher dupilumab trough concentrations were associated with a higher proportion of patients having IGA 0 or 1 and a greater percentage change from baseline in EASI (eFigure 7 in Supplement 2).

Biomarker Analyses

Both dupilumab groups showed reductions from baseline in blood eosinophil count and significant suppression of blood lactate dehydrogenase level, serum thymus and activation-regulated chemokine (TARC) (also known as CCL17), and total IgE concentrations compared with placebo. For example, for the patients receiving dupilumab every 2 weeks, the difference in median change from baseline to at week 16 in total IgE concentrations vs placebo was −2524.0 kU/L (95% CI, −3579.0 to −1783.6 kU/L) (eFigure 8, eTable 2 in Supplement 2).

Efficacy in Comorbid Conditions

At week 16, patients with comorbid asthma or allergic rhinitis showed numerically greater improvement in asthma control (measured by least-squares mean changes from baseline in the Juniper Asthma Control Questionnaire) (for the patients receiving dupilumab every 2 weeks, least-squares mean difference vs placebo at week 16 was −0.58; 95% CI, −1.07 to −0.10) and numerically greater reduction in symptoms of allergic rhinitis (measured by least-squares mean changes from baseline in the Total Nasal Symptom Score) with dupilumab vs placebo (for the patients receiving dupilumab every 2 weeks, the difference in least-squares mean change from baseline at week 16 vs placebo was −0.81; 95% CI, −2.74 to 1.12) (eTable 3 in Supplement 2). Dupilumab also significantly suppressed IgE concentrations for specific food allergens (cow's milk, egg white, and peanut) and aeroallergens (cat dander and dust mite) at week 16. For example, for patients receiving dupilumab every 2 weeks, the difference in median percentage change from baseline at week 16 vs placebo for suppressed IgE concentrations for peanut allergens was −53.9% (95% CI, −63.2% to −41.5%) and for cat dander was −55.2 (95% CI, −66.8 to −42.7) (eTable 4 in Supplement 2).

Safety

The incidence of treatment-emergent adverse events was similar across treatment groups (**Table 3**).[38] One patient (placebo group) discontinued treatment owing to an adverse event (AD exacerbation) unrelated to the study drug. One serious adverse event (appendicitis) was reported in the placebo group. Incidence of infections was similar across treatment groups; nonherpetic skin infection rates were numerically lower in the

dupilumab vs placebo groups (every 2 weeks, 8 patients [9.8%]; every 4 weeks, 8 [9.6%]; placebo, 16 [18.8%]) (Table 3). Incidence of conjunctivitis was higher in the dupilumab vs placebo groups (every 2 weeks, 8 patients [9.8%]; every 4 weeks, 9 [10.8%]; placebo, 4 [4.7%]), as well as injection-site reactions (every 2 weeks, 7 patients [8.5%]; every 4 weeks, 5 [6.0%]; placebo, 3 [3.5%]), with a dose-dependent increase in injection-site reactions (Table 3, eTable 5 in Supplement 2). None of these events was serious or severe or led to treatment discontinuation. No deaths occurred during the study.

Discussion

In adolescents with moderate to severe AD, 16-week dupilumab monotherapy compared with placebo resulted in statistically significant and clinically meaningful improvements in signs and symptoms of AD, including itch and sleep, and QoL.

While the every-2-week and every-4-week regimens had similar safety, the every-2-week regimen was numerically superior in most categorical efficacy end points, including the proportion of patients with IGA 0 or 1. Pharmacokinetic data support the every-2-week dosing approval, as this dose provided higher dupilumab trough concentrations—a factor associated with greater efficacy. The tiered weight-based every-2-week regimen normalized exposure in patients with body weight less than 60 kg and 60 kg or more; dupilumab was more effective than placebo in both subgroups, and results in patients weighing less than 60 kg were at least comparable to those in patients weighing 60 kg or more in all key efficacy measures. These data, therefore, support tiered weight-based dosing.

Compared with the adult AD population of the LIBERTY AD SOLO 1 and SOLO 2 phase 3 trials,[19] this adolescent population had higher baseline disease severity, rates of atopic comorbidities, and median serum total IgE concentrations (eTable 6 in Supplement 2). The placebo-adjusted response in the adolescent every-2-week group was greater than or comparable to that in the adult every-2-week group for all primary and key secondary end points, except IGA 0 or 1, which was lower in adolescents (eTable 7, eFigure 9 in Supplement 2). A higher placebo response was observed in adults compared with adolescents (eTable 7, eFigure 9 in Supplement 2). The cumulative proportion of patients needing rescue treatment in the dupilumab every-2-week and placebo groups was higher in adolescents than in adults (eFigure 10 in Supplement 2). Safety results were generally similar in adolescents and adults; in both groups, dupilumab was associated with increases in injection-site reaction and conjunctivitis, and with reductions in nonherpetic skin infections (eTable 8 in Supplement 2).

Evaluation of dupilumab efficacy in adolescents with AD, separately from adult patients, was necessary given the possible mechanistic differences in disease mediators between these patient populations. The efficacy and safety results were consistent between the adolescent and adult AD populations, in particular, the marked improvements in mean percentage change in EASI, which is the most powerful continuous measure reflecting disease improvement. Although the unadjusted response rates on categorical measures were lower in adolescents than adults, this difference could be explained by the greater disease severity in adolescents at baseline, which is also reflected in the lower placebo response rates for adolescents and the higher use of rescue medication.

These results suggest that IL-4/IL-13 are fundamental mediators of AD in both patient populations and further distinguish dupilumab as a targeted immunomodulator that lacks broad immunosuppressive effects. This finding is further supported by the marked suppression by dupilumab observed using measures of systemic type 2 inflammation that are known to correlate with AD severity (eg, serum TARC, total IgE, and LDH concentration[39-42]), as was seen in adults. Furthermore, the dupilumab-mediated improvements observed in comorbid conditions, such as asthma and allergic rhinitis, support the role of IL-4/IL-13 in these diseases. We also observed significant suppression of allergen-specific IgE concentrations for aeroallergies by dupilumab, which was consistent with the reported role of IL-4 in allergic asthma.[43] The efficacy of dupilumab on comorbid atopic conditions will be reported in a future study of the adult population with AD.

Limitations

This trial has limitations. These limitations include the relatively short treatment period (16 weeks) and the fact that dupilumab was not assessed in combination with other medications (eg, topical corticosteroids), as was done in some of the dupilumab trials in adults.[20]

Conclusions

Dupilumab monotherapy resulted in statistically significant and clinically meaningful improvements in disease signs and symptoms, including pruritus and sleep loss, and a positive effect on QoL. The every-2-week regimen was numerically superior to the every-4-week regimen on categorical end points. Dupilumab had an acceptable safety profile and the placebo-adjusted efficacy and safety in adolescents with moderate to severe AD were similar to those in adults. To our knowledge, this trial is the largest to date of a systemic treatment for pediatric AD and the first confirmatory trial showing a favorable benefit-to-risk profile of a monoclonal antibody in this patient population with high unmet medical need. The findings provide evidence of the importance of targeted type 2 cytokine blockade, in particular IL-4/IL-13, in reducing the clinical severity and extensive effect of AD in adolescents, with the potential to simultaneously address the high burden of type 2 comorbidities.

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