# Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis

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***Background:*** The impact of dupilumab, an anti–interleukin (IL) 4 receptor $\alpha$ antibody that inhibits IL-4 and IL-13 signaling, on vaccine responses of patients with atopic dermatitis (AD) is unknown.

***Objectives:*** To assess T-cell–dependent and T-cell–independent humoral immune responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination, and dupilumab efficacy and safety.

***Methods:*** In a randomized, double-blinded, placebo-controlled study (NCT02210780), adults with moderate-to-severe AD received dupilumab (300 mg) or placebo weekly for 16 weeks, and single doses of Tdap and quadrivalent meningococcal polysaccharide vaccines at week 12. Primary endpoint was proportion of patients achieving satisfactory IgG response to tetanus toxoid at week 16.

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Dr Evans is a previous employee of Regeneron Pharmaceuticals Inc.

Conflicts of interest: Dr Blauvelt has served as an investigator and consultant for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly and Co, Genentech/Roche, GlaxoSmithKline, Janssen, Leo Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron Pharmaceuticals Inc, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac and as a paid speaker for Eli Lilly and Co, Janssen, Regeneron Pharmaceuticals Inc, and Sanofi Genzyme. Dr Simpson has received grants or research support from Anacor Pharma, Eli Lilly and Co, GlaxoSmithKline, MedImmune, Novartis, Regeneron Pharmaceuticals Inc, Roivant Sciences, Tioga Pharmaceuticals Inc, and Vanda Pharmaceuticals Inc and has served as a consultant for AbbVie, Anacor Pharma, Celgene, Dermira Inc, Eli Lilly and Co, Galderma, Genentech, GlaxoSmithKline, LEO Pharmaceutical Inc, Menlo Therapeutics, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, and Valeant Pharmaceutical Co. Dr Tyring has served as an investigator for Regeneron Pharmaceuticals Inc. Drs Purcell, Shumel, Petro, Akinlade, Gadkari, and Graham are employees and shareholders of Regeneron Pharmaceuticals Inc. Drs Eckert and Pirozzi are employees of Sanofi and may hold stock or stock options in the company. Dr Evans was an employee of Regeneron Pharmaceuticals Inc at the time of the study and a shareholder of Regeneron Pharmaceuticals Inc.

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***Results:*** In total, 178 patients completed the study. Similar positive immune responses (≥4-fold increase in antibody titer, or an antibody titer of ≥8) were achieved in the dupilumab and placebo groups to tetanus (83.3% and 83.7%, respectively) and meningococcal polysaccharide (86.7% and 87.0%, respectively). Dupilumab significantly decreased total serum IgE; most dupilumab-treated patients were Tdap-IgE seronegative at week 32 (62.2% dupilumab and 34.8% placebo). Dupilumab improved key AD efficacy endpoints ($P < .001$). Injection-site reactions and conjunctivitis were more common with dupilumab; AD exacerbations more frequent with placebo.

***Limitation:*** Patients' prior vaccination status was not available before enrollment.

***Conclusion:*** Dupilumab did not affect responses to the vaccines studied, significantly decreased IgE, and improved measures of AD severity versus placebo, with an acceptable safety profile. ( J Am Acad Dermatol 2019;80:158-67.)

***Key words:*** atopic dermatitis; dupilumab; IgE; meningococcal polysaccharide; tetanus toxoid; vaccine.

**CAPSULE SUMMARY**

- The type 2—skewed cytokine milieu in atopic dermatitis has been linked to vaccination-hyporesponsiveness in infancy.
- Dupilumab in adults with moderate-to-severe atopic dermatitis did not influence correlate of nonlive vaccine—induced responses, was well-tolerated, and decreased total and vaccine-specific serum IgE.
- Vaccination after 12-week dupilumab therapy was not associated with adverse clinical effects.

Atopic dermatitis (AD), a chronic inflammatory skin disease, affects ≤20% of children and 10% of adults.[1-4] Immune dysregulation and skin-barrier dysfunction play key roles in AD pathogenesis.[5-7] Immune abnormalities include cutaneous T-cell expansion and elevated expression of type 2 cytokines, interleukin (IL) 4 and IL-13, central drivers of type 2 inflammatory diseases, such as AD, asthma, chronic sinusitis with nasal polyposis, and eosinophilic esophagitis.[8-11]

Dupilumab, a fully human, VelocImmune-derived monoclonal antibody directed against the IL-4 receptor $\alpha$ subunit, inhibits signaling of both IL-4 and IL-13.[8,9,11-13] Dupilumab has been shown to significantly improve signs and symptoms of moderate-to-severe AD,[8,14-18] asthma,[9,19-21] chronic sinusitis with nasal polyposis,[22] and eosinophilic esophagitis[23] and is approved in the European Union, United States, and Japan as well as other countries for the treatment of adults with inadequately controlled moderate-to-severe AD. Although multiple immune responses interact to provide vaccine protection, antibody titers are often surrogates or correlates of vaccine-induced immunity.[24] T-cell—dependent vaccines elicit the production of functional IgG antibodies through T-cell activation; T-cell—independent vaccines result in IgM responses by B-cell activation independent of T cells.[25] Vaccination might cause IgE-mediated hypersensitivity and other immediate-type allergic reactions.[26] The type 2—skewed cytokine milieu of AD patients has been linked to vaccine hyporesponsiveness during infancy[27,28]; it is unclear whether therapeutic modulation affects vaccine responses.[29] Severe AD is associated with increased vaccine-specific IgE responses, with a risk for adverse events during subsequent antigen exposure.[30] As dupilumab suppresses IL-4 and IL-13 signaling, there is a need to assess immune responses to vaccination in patients receiving this drug. Here, we report results from a study examining whether dupilumab affects antibody responses to 2 commonly administered vaccines in adults with moderate-to-severe AD and examines dupilumab efficacy and safety.

## METHODS

### Study design

This investigation was a phase 2, randomized, double-blinded, multicenter, placebo-controlled, parallel-group study conducted in the United States (August 2014-September 2015; LIBERTY AD EVALUATE; ClinicalTrials.gov identifier: NCT02210780). Patients were randomized (1:1) via an interactive response technology system to subcutaneous dupilumab or placebo weekly for 16 weeks. At week 12, patients received 1 dose each of tetanus toxoid with reduced diphtheria toxoid and acellular pertussis vaccine (Tdap), and quadrivalent meningococcal polysaccharide vaccine (MPSV4).

*Abbreviations used:*

| | |
|---|---|
| AD: | atopic dermatitis |
| CI: | confidence interval |
| EASI: | Eczema Area and Severity Index |
| EASI-50: | ≥50% reduction in Eczema Area and Severity Index score |
| EASI-75: | ≥75% reduction in Eczema Area and Severity Index score |
| IGA: | Investigator's Global Assessment |
| IL: | interleukin |
| IQR: | interquartile range |
| MPSV4: | quadrivalent meningococcal polysaccharide vaccine |
| SBA: | serum bactericidal assay |
| TCI: | topical calcineurin inhibitor |
| TCS: | topical corticosteroids |
| Tdap: | tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine |
| TEAE: | treatment-emergent adverse event |

## Patients

Eligible patients were aged 18-64 years, had moderate-to-severe AD (American Academy of Dermatology Consensus Criteria[31]) for ≥3 years, had a documented history (within 6 months of screening) of inadequate response to medium-to-high potency topical corticosteroids (TCS) (with or without topical calcineurin inhibitors [TCI]) despite treatment for ≥28 days or were patients for whom topical AD therapies were inadvisable, had an Eczema Area and Severity Index (EASI) score ≥16 (range 0-72), had an Investigator's Global Assessment (IGA) score ≥3 (range 0-4), and ≥10% of their body surface area was affected by AD at screening and baseline. Use of emollients and TCS with or without TCI was permitted at entry if patients had been on a stable regimen for ≥14 days (complete exclusion criteria available from the authors upon request).

Patients were stratified by baseline AD severity (moderate [IGA 3] vs severe [IGA 4]). Patients and personnel involved were blinded to all randomization assignments.

Ethical principles of the Declaration of Helsinki, consistent with those of the International Council on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements were followed. Informed consent was obtained from each patient before any procedure.

## Treatments

Dupilumab (300 mg) or placebo were administered subcutaneously weekly. A 600-mg loading dose of dupilumab or matching placebo was administered on day 1. One dose of commercially available Tdap vaccine (0.5 mL, Adacel [Sanofi Pasteur, Toronto, Canada][32]) and standard MPSV4 (0.5 mL, Menomune − A/C/Y/W-135 [Sanofi Pasteur, Swiftwater, PA][33]) were administered intramuscularly in the deltoid muscle and subcutaneously in the opposite arm, respectively, at week 12; both were nonlive vaccines. Concomitant AD therapies (TCI, TCS [≤10 mg prednisone or equivalent], or both) were permitted. Rescue treatment (TCS of higher potency than at baseline, TCI, high-dose systemic corticosteroids) was permitted for intolerable AD symptoms (prohibited concomitant medications and procedures materials available from the authors upon request).

## Endpoints

Primary endpoint was proportion of patients with a positive response to the tetanus component of Tdap at week 16, defined as ≥4-fold increase from baseline anti-tetanus IgG concentration in patients with prevaccination tetanus antibody concentrations ≥0.1 or ≥0.2 IU/mL in patients with prevaccination tetanus antibody concentrations <0.1 IU/mL.[34]

Secondary endpoints were proportions of patients at week 16 with a) a positive response to tetanus toxoid (≥2-fold increase from baseline anti-tetanus IgG concentration in patients with prevaccination tetanus antibody concentrations ≥0.1 IU/mL or ≥0.2 IU/mL in patients with prevaccination concentrations of <0.1 IU/mL); b) a positive response to MPSV4 (meningococcal serogroup C serum bactericidal assay [SBA] titer ≥8)[35]; c) an IGA score of 0 or 1; d) an ≥50% reduction in EASI (EASI-50); and e) an ≥75% reduction in EASI (EASI-75). Other secondary endpoints were changes from baseline at week 16 in peak pruritus Numerical Rating Scale, body surface area, erythema, infiltration and papulation, excoriations, lichenification of Global Individual Sign Score, and Patient-Oriented Eczema Measure (prespecified endpoints available from the authors upon request). Total IgE levels and proportions of patients who were tetanus-antigen−specific and pertussis-antigen−specific IgE seropositive at weeks 12, 16, and 32 were analyzed post-hoc.

## Tetanus toxoid-specific IgG antibodies and meningococcal serogroup C SBA titers

Tetanus toxoid−specific IgG antibodies were measured using VaccZyme Anti-Tetanus Enzyme Immunoassay (Binding Site Group, Birmingham, UK). The quantitative sandwich enzyme immunoassay was performed by Covance Central Laboratory Services (Indianapolis, IN). The baby rabbit complement meningococcal SBA assay was performed by the Vaccine Evaluation Unit of Public Health England (Manchester, UK) using a validated method, and SBA titers were expressed as the

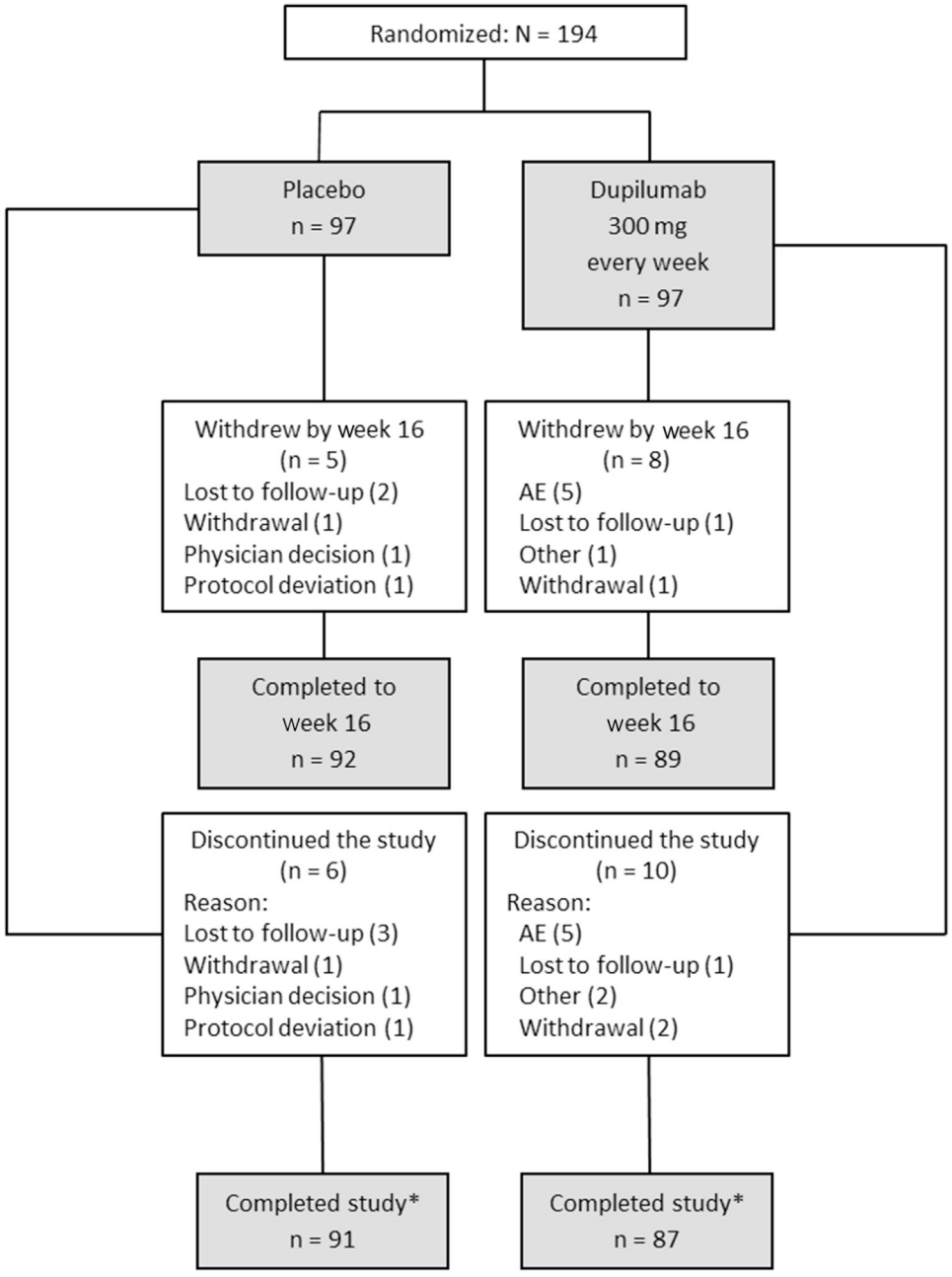


**Fig 1.** Atopic dermatitis trial profile. *Patients who completed all scheduled study visits underwent screening, completed the treatment period, and had at least 1 follow-up visit. *AE,* Adverse event.

reciprocal of the final dilution providing ≥50% killing compared with the number of colony-forming units at 60 minutes. Baseline was day 1, and week 12 measurements (not shown) were collected to ensure that no patient received vaccination between baseline and week 12.

### Antigen-specific IgE

A low abundance of serum antigen–specific IgE meant a modified, multiplexed Luminex assay (Luminex Corporation, Austin, TX) was employed to measure tetanus and acellular pertussis antigen–specific IgE responses.[36] Sera were treated with GullSORB (Meridian Bioscience Inc, Cincinnati, OH) to remove potentially competing IgG and incubated with purified pertussis toxin mutant, pertactin, or tetanus toxoid (all from List Biological Laboratory, Campbell, CA) coupled to fluorescent-barcoded MagPlex microspheres (Luminex Corporation). The beads were washed, and bound

**Table I.** Baseline demographics and disease characteristics

| Characteristic | Dupilumab, N = 97 | Placebo, N = 97 |
|---|---|---|
| Age, y | 39 ± 14 | 40 ± 14 |
| Male sex, % | 51 | 47 |
| Race, % | | |
| White | 62 | 69 |
| Black/Asian/other | 24/12/2 | 18/11/2 |
| Weight, kg | 81 ± 19 | 81 ± 19 |
| AD duration, y | 28 ± 15 | 27 ± 17 |
| EASI (range 0-72) | 29 ± 13 | 31 ± 14 |
| IGA score (range 0-4) | 3.4 ± 0.5 | 3.4 ± 0.5 |
| BSA affected, % | 46 ± 23 | 49 ± 25 |
| Peak pruritus NRS score (range 0-10) | 7.4 ± 2.2 | 7.3 ± 2.2 |
| GISS total score | 8.8 ± 1.76 | 8.8 ± 1.80 |
| Erythema score (range 0-3) | 2.2 ± 0.58 | 2.3 ± 0.58 |
| Infiltration and papulation score ± SD (range 0-3) | 2.3 ± 0.55 | 2.2 ± 0.54 |
| Excoriation score (range 0-3) | 2.1 ± 0.65 | 2.1 ± 0.63 |
| Lichenification score (range 0-3) | 2.2 ± 0.72 | 2.1 ± 0.73 |
| POEM (range 0-28) | 21.5 ± 6.04 | 20.6 ± 5.59 |
| Total serum IgE (IU/mL), median (Q1, Q3) | 978 (215.0, 4734.0) | 1933 (397.0, 7200.0) |
| Patients with systemic steroid treatment for AD at baseline, % | 3.1 | 5.2 |
| Patients with systemic treatments for AD in previous year, % | | |
| Corticosteroid use | 98 | 96 |
| Methotrexate use | 5 | 9 |

Values are means ± SD unless otherwise specified.
*AD*, Atopic dermatitis; *BSA*, body surface area; *EASI*, Eczema Area and Severity Index; *GISS*, Global Individual Signs Score; *IGA*, Investigator's Global Assessment; *NRS*, Numerical Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *Q1*, first quartile; *Q3*, third quartile; *SD*, standard deviation.

IgE was detected via anti-IgE–phycoerythrin antibody (Clone BE5, Thermo Fisher Scientific, Waltham, MA). Samples were analyzed on a Luminex FLEXMAP 3D instrument, and pertussis toxin mutant, pertactin, or tetanus toxoid IgE–positive beads were reported as mean fluorescent intensities. The detection limit was defined as 3 standard deviations above the mean fluorescent intensity of a negative control serum. Total serum IgE was measured by ImmunoCAP Fluorescent Enzyme Immunoassay (Thermo Scientific, Phadia AB, Uppsala, Sweden).

### Safety

Safety was assessed through week 32 (incidence of treatment-emergent adverse events [TEAEs] and serious TEAEs) coded per Medical Dictionary for Regulatory Activities, v18.0. The investigator (or designee) recorded all adverse events that occurred from the signing of informed consent until study end. Information about injection-site reactions was recorded by site staff or patient, if occurring outside the clinic.

### Statistics

All categorical variables, including vaccine-related endpoints and efficacy analyses, were analyzed using a Cochran–Mantel–Haenszel test stratified by randomization strata (moderate [IGA 3] vs severe [IGA 4]). Analyses included all randomized patients who received any study drug or vaccine injection and had measured responses to the tetanus toxoid vaccine. Patients who had missing values at or withdrew before week 16 were defined as nonresponders. For efficacy analyses, patients who received rescue treatment were defined as nonresponders from that timepoint onwards. Nominal *P* values were derived from the Cochran–Mantel–Haenszel test stratified by randomization strata.

Continuous dupilumab efficacy variables were analyzed using a mixed-effect model repeated-measure approach. Efficacy data were set to missing after rescue treatment was used or a patient discontinued. Analysis of the IgE endpoints included all treated patients at weeks 0, 12, 16, and 32; patients with missing values were excluded. Vaccine titers at weeks 0, 12, and 16 and total IgE levels between visits in both treatment groups were analyzed using Friedman test adjusted for multiple comparisons. Percentage change of total IgE levels from baseline to week 32 between treatment groups was analyzed by a Mann–Whitney U test. Tdap-specific IgE seropositivity was a categorical variable and was analyzed by Fisher's exact test.

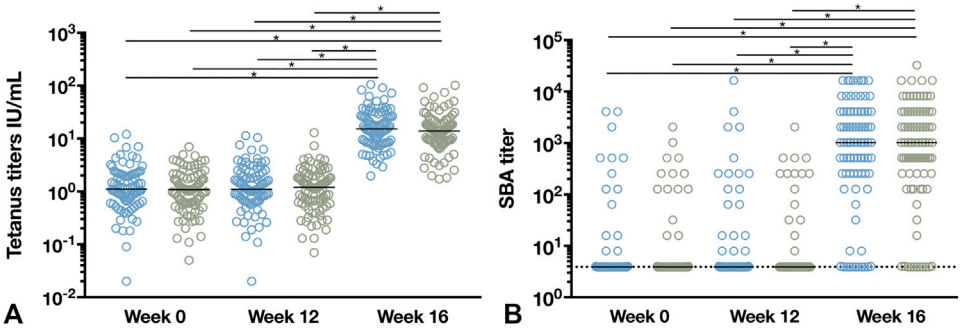


**Fig 2.** Vaccine immune responses of placebo-treated (*blue circles*) and dupilumab-treated (*green circles*) patients with moderate-to-severe atopic dermatitis at baseline (week 0), week 12, and week 16. Black bars represent median values per group. Tetanus toxoid antibody levels (IU/mL) (**A**) and SBA titers (**B**). Limit of detection of SBA indicated by *dotted line*. Values were compared by using Friedman test with a Dunn post-hoc. *$P < .0001$. *SBA*, Serum bactericidal assay.

## RESULTS

### Patients

Of 243 patients screened, 194 were enrolled and randomized, and 178 (91.8%) completed the study (Fig 1). Patient demographics and baseline disease characteristics were similar in both groups (Table I). During the study, most patients used concomitant TCS: 66.0% and 73.3% in dupilumab and placebo groups, respectively. Overall, 9.8% of patients received rescue treatment for intolerable AD symptoms: 15.5% and 4.1% for placebo and dupilumab, respectively, indicating better control of AD symptoms in the dupilumab group.

### Immune responses to vaccinations

Similar proportions of patients had positive responses (≥4-fold increase in titer) to tetanus vaccination at week 16 (primary endpoint): dupilumab 83.3% and placebo 83.7% (90% confidence interval [CI] of difference, dupilumab vs placebo −9.41 to 8.69). The proportions of patients achieving antitetanus IgG responses (≥2-fold increase) at week 16 (secondary endpoint) were also similar: dupilumab 95.6% and placebo 94.6% (90% CI difference, dupilumab vs placebo −4.29 to 6.27). No differences were observed at baseline, week 12, or week 16 with tetanus toxoid titers between treatment groups ($P > .9999$, all comparisons; Fig 2, *A*). Overall median tetanus toxoid titers significantly increased in both groups at week 16 versus weeks 0 and 12 ($P < .0001$; placebo week 0 = 1.12 IU/mL, week 12 = 1.11 IU/mL, and week 16 = 15.25 IU/mL; dupilumab week 0 = 1.09 IU/mL, week 12 = 1.21 IU/mL, and week 16 = 13.91 IU/mL; Fig 2, *A*).

Similar proportions of patients had a positive response to serotype C of the meningococcal polysaccharide vaccine at week 16: dupilumab 86.7% and placebo 87.0% groups (90% CI difference, dupilumab vs placebo −8.54 to 7.96). No differences were observed for SBA titers between treatment groups ($P > .9999$ for all comparisons; Fig 2, *B*), but both groups had significantly increased median SBA titers at week 16 versus weeks 0 and 12 ($P < .0001$; placebo week 0 = <4 IU/mL, week 12 = <4 IU/mL, and week 16 = 1024 IU/mL; dupilumab week 0 = <4 IU/mL, week 12 = <4 IU/mL, and week 16 = 1024 IU/mL; Fig 2, *B*).

**Table II.** Tdap IgE seropositivity at weeks 12, 16, and 32

| Patient IgE positivity | Dupilumab, N = 74* | Placebo, N = 69* | *P* value† |
|---|---|---|---|
| Week 12, n (%) | | | |
| 1 antigen | 11 (14.9) | 13 (18.8) | |
| 2 antigens | 7 (9.5) | 9 (13.0) | |
| 3 antigens | 5 (6.8) | 12 (17.4) | |
| Total positive | 23 (31.1) | 34 (49.3) | .040 |
| Week 16, n (%) | | | |
| 1 antigen | 12 (16.2) | 7 (10.1) | |
| 2 antigens | 6 (8.1) | 17 (24.6) | |
| 3 antigens | 8 (10.8) | 16 (20.3) | |
| Total positive | 26 (35.2) | 40 (58.0) | .007 |
| Week 32, n (%) | | | |
| 1 antigen | 9 (12.2) | 14 (20.3) | |
| 2 antigens | 6 (8.1) | 8 (11.6) | |
| 3 antigens | 13 (17.6) | 23 (33.3) | |
| Total positive | 28 (37.8) | 45 (65.2) | .001 |

*Tdap*, Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine.
*Patients included for analysis were curated on the basis of sample availability.
†Tdap IgE positivity between placebo-treated and dupilumab-treated individuals was compared by Fisher's exact test.

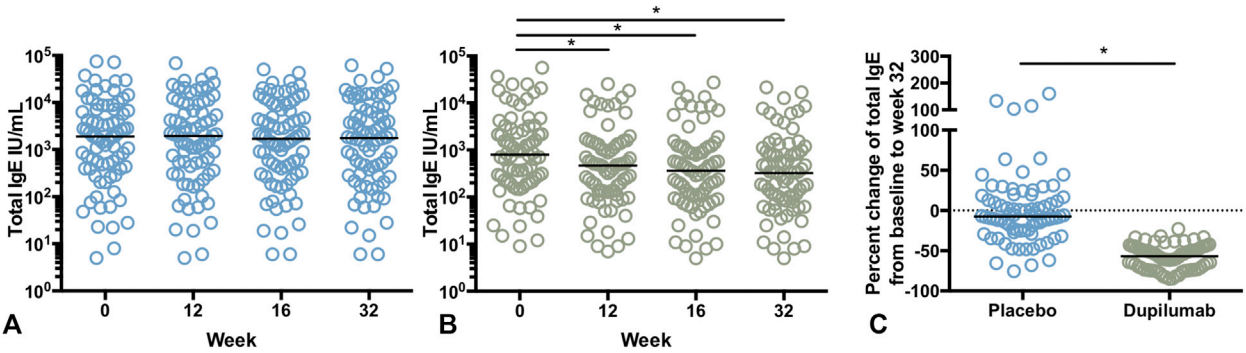


**Fig 3.** Total serum IgE levels in placebo-treated (**A**) and dupilumab-treated (**B**) patients with moderate-to-severe atopic dermatitis at baseline (week 0), week 12, week 16, and week 32. Values were compared by using Friedman test. **C**, Percent change in total IgE levels from baseline to end of study (week 32). For all graphs, black bars represent median values per group. Values were compared by using Mann–Whitney U test (**A** and **B**) and Friedman's test (**C**). *$P < .0001$.

**Table III.** Efficacy of dupilumab in achievement of AD disease score endpoints at week 16

| Efficacy endpoint | Dupilumab, N = 97 | Placebo, N = 97 | *P* value |
|---|---|---|---|
| Patients attaining IGA score 0 or 1, n (%) | 43 (44.3) | 10 (10.3) | |
| Difference dupilumab vs placebo (90% CI) | 34.0 (24.29-43.75) | | <.001 |
| Patients attaining EASI-50, n (%) | 70 (72.2) | 31 (32.0) | |
| Difference dupilumab vs placebo (90% CI) | 40.2 (29.40-51.01) | | <.001 |
| Patients attaining EASI-75, n (%) | 52 (53.6) | 19 (19.6) | |
| Difference dupilumab vs placebo (90% CI) | 34.0 (23.38-44.66) | | <.001 |
| Peak pruritus NRS score change from baseline, LS mean (SE) | −4.46 (0.256) | −2.33 (0.274) | |
| Difference dupilumab vs placebo, LS mean (SE) | −2.13 (0.371) | | <.001 |

*AD*, Atopic dermatitis; *CI*, confidence interval; *EASI-50*, ≥50% reduction in Eczema Area and Severity Index score; *EASI-75*, ≥75% reduction in Eczema Area and Severity Index score; *IGA*, Investigator's Global Assessment; *LS*, least squares; *NRS*, Numerical Rating Scale; *SE*, standard error.

### Vaccine-specific IgE

Samples from weeks 12 (baseline vaccine administration), 16, and 32 were available for antigen-specific IgE analyses. Dupilumab-treated patients were less likely to develop Tdap-specific IgE (pertussis toxin, pertactin, and tetanus toxoid antigens) by week 32: dupilumab 37.8% and placebo 65.2% ($P = .001$) (Table II).

### Changes in total IgE concentrations

Placebo-treated patients showed no changes in median total IgE levels (Fig 3, *A*); dupilumab-treated patients had significant reductions in median total IgE levels at week 12 (468.5 [interquartile range (IQR) 129-1366] IU/mL), week 16 (363.5 [IQR 97.3-1172] IU/mL), and week 32 (323.5 [IQR 85.8-969.3] IU/mL) compared with baseline (798 [IQR 214-2784] IU/mL) (Fig 3, *B*). At week 32, the median percent decrease in total IgE from baseline was −57% in the dupilumab group and −7.3% in the placebo group (Fig 3, *C*).

### Dupilumab efficacy

Dupilumab demonstrated clinically and statistically significant improvements in all AD efficacy measures. The IGA score of 0/1 at week 16 was 44.3% for dupilumab and 10.3% for placebo (Table III); significantly more patients with dupilumab than placebo attained EASI-50 (72.2% vs 32.0%, respectively) or EASI-75 (53.6% vs 19.6%, respectively) (Table III). Dupilumab-treated patients had significantly greater improvements in peak pruritus Numerical Rating Scale and experienced significantly greater reductions in percent body surface area affected by AD, Global Individual Sign Score components, and Patient-Oriented Eczema Measure scores in comparison with placebo-treated patients (Supplemental Table I; available at http://www.jaad.org).

### Safety

TEAE rates were similar between groups (Table IV); 55.7% of patients in the dupilumab group and

**Table IV.** Safety assessment

| Adverse events | Dupilumab, N = 97 | Placebo, N = 97 |
|---|---|---|
| TEAEs, n | 167 | 136 |
| Serious TEAEs, n | 3* | 0 |
| Patients with ≥1 TEAE, n (%) | 54 (55.7) | 60 (61.9) |
| Patients with TEAEs resulting in drug withdrawal, n (%) | 5 (5.2) | 0 |
| Patients with TEAEs related to study drug, n (%)† | 18 (18.6) | 10 (10.3) |
| Injection-site reactions (HLT) by study drug, n (%) | 12 (12.4) | 3 (3.1) |
| Injection-site reactions (HLT) to Tdap, n (%) | 0 (0) | 3 (3.1) |
| Nonherpetic skin infections, n (%)‡ | 6 (6.2) | 8 (8.2) |
| TEAEs by PT in >5% of patients in either group, n (%) | | |
| Upper respiratory tract infection | 11 (11.3) | 14 (14.4) |
| Dermatitis atopic | 1 (1.0) | 11 (11.3) |
| Conjunctivitis | 8 (8.2) | 0 (0) |
| Nasopharyngitis | 4 (4.1) | 5 (5.2) |
| Headache | 5 (5.2) | 3 (3.1) |
| Injection-site reaction | 5 (5.2) | 0 (0) |

*HLT*, High-level term (Medical Dictionary for Regulatory Activities); *PT*, preferred term (Medical Dictionary for Regulatory Activities); *Tdap*, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine; *TEAE*, treatment-emergent adverse event.
*Each serious TEAE (mycosis fungoides stage IV, squamous cell carcinoma, and serum-sickness-like reaction) occurred in a separate patient.
†Does not include TEAEs related to vaccination, except for injection-site reactions.
‡Adjudicated.

61.9% in the placebo reported ≥1 TEAE; most were mild or moderate. No deaths were reported. Three patients in the dupilumab group reported 3 different serious TEAEs: mycosis fungoides stage IV (ongoing at study end), squamous cell carcinoma of the skin (resolved without sequelae), and serum sickness-like reaction (resolved without sequelae); only the latter was considered treatment-related. No serious TEAEs were reported in the placebo group. The following TEAEs led to the withdrawal of 5 patients on dupilumab: mycosis fungoides, serum sickness-like reaction, a photosensitivity reaction, dizziness and fatigue, and conjunctivitis of moderate severity. There were no withdrawals due to TEAEs in the placebo group. Upper respiratory tract infection was the most frequently reported TEAE in both groups, and they occurred at similar rates. Conjunctivitis and injection-site reactions to dupilumab or placebo were mild or moderate and more frequent with dupilumab than placebo. AD exacerbations and nonherpetic skin infections occurred more frequently with placebo than dupilumab (Table IV). Injection-site reactions to Tdap occurred only in the placebo group (3.1%); there were no injection-site reactions to MPSV4.

## DISCUSSION

Vaccine immune responses to tetanus toxoid and meningococcal serogroup C met established correlates of vaccine-induced immunity with an acceptable safety profile in adult patients with moderate-to-severe AD treated with dupilumab 300 mg weekly and were robust and comparable in patients receiving dupilumab or placebo. Dupilumab also reduced vaccine-specific IgE and total IgE levels in comparison with placebo. Vaccination after 12-week dupilumab therapy was not associated with any adverse clinical effects. Dupilumab also improved multiple AD efficacy measures in comparison with placebo, consistent with previous phase 1-3 studies.[8,14-18] Concomitant TCS use did not affect vaccine immune responses.

Humoral responses to T-cell–dependent vaccines normally require successful presentation of antigen via T-cell receptors, production of T-cell and antigen-presenting cell cytokines, and cell-dependent costimulatory signaling to produce antigen-specific antibodies.[25] For vaccine responses to tetanus toxoid, IgG production is T-cell dependent.[37-39] Because dupilumab acts on IL-4 and IL-13, both type 2 cytokines, dupilumab was not expected to affect total tetanus toxoid IgG levels, as observed here. Achievement of the primary endpoint was consistent with a randomized clinical trial of healthy adults receiving Tdap vaccination,[40] and titer levels at every timepoint evaluated were similar to placebo, demonstrating that dupilumab does not impair tetanus vaccine response. In contrast with the tetanus vaccine, polysaccharide vaccines, such as MPSV4, are thought to elicit T-cell–independent immune responses.[26] In this study, the proportions of patients attaining SBA titers ≥8 after vaccination with MPSV4 and the overall SBA titers at each timepoint were similar in the dupilumab and placebo groups, indicating that dupilumab has no adverse effects on immune responses elicited by

T-cell–independent vaccines. Given the effect of dupilumab on type 2 cytokines, it is possible that treatment with dupilumab shifts type 2–skewed vaccines in a type 1 direction, not by increasing total IgG production, but by changing the IgG subtypes from IgG4 (type 2) to IgG1 (type 1), thereby potentially improving the functional response to vaccines.

The reduction in vaccine-specific IgE responses is consistent with the mechanism of action of dupilumab and with other reports showing reduced total and allergen-specific IgE after dupilumab treatment.[8,22,41] Patients with severe AD have an increased vaccine-specific IgE immune response, which might be associated with their increased risk for adverse events during future vaccination or antigen exposure[30]; additional studies are needed to determine whether dupilumab reduces the risk for subsequent adverse events by limiting vaccine-specific IgE responses.

Dupilumab had an acceptable safety profile, with injection-site reactions and conjunctivitis occurring more often with dupilumab and nonherpetic skin infections occurring more frequently with placebo, similar to previous dupilumab AD trials.[16-18]

Study limitations are that prior vaccination status was not available before enrollment and that permitted, but not mandatory, TCS use limits comparison of efficacy data with phase 3 studies,[16] despite comparable design and outcomes with the LIBERTY AD CHRONOS trial.[17]

In conclusion, in adults with moderate-to-severe AD, vaccination during dupilumab treatment did not affect IgG production or functional responses. Dupilumab led to lower levels of vaccine-specific IgE and total IgE than placebo. Vaccination did not affect dupilumab efficacy or safety. Vaccination with T-cell–dependent and T-cell–independent vaccines in dupilumab-treated patients is effective with an acceptable safety profile. These findings are important for the general practicing dermatologist as they demonstrate that nonlive vaccines such as Tdap and MPSV4 can be indicated safely and are immunogenic in adult patients with moderate-to-severe AD treated with dupilumab.

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**Supplemental Table I.** Efficacy of dupilumab in achievement of AD clinical and patient-reported endpoints at week 16

| Efficacy endpoint | Dupilumab, N = 97 | Placebo, N = 97 | *P* value |
|---|---|---|---|
| Change (SE) from baseline in BSA affected by AD | −30.0 (2.04) | −12.0 (2.15) | |
| Difference (SE) dupilumab vs placebo | −18.0 (2.91) | | <.001 |
| Change (SE) from baseline in the erythema component of GISS | −0.9 (0.08) | −0.4 (0.74) | |
| Difference (SE) dupilumab vs placebo | −0.6 (0.11) | | <.001 |
| Change (SE) from baseline in infiltration and papulation component of GISS | −1.1 (0.08) | −0.4 (0.08) | |
| Difference (SE) dupilumab vs placebo | −0.6 (0.11) | | <.001 |
| Change (SE) from baseline in the excoriation component of GISS | −1.2 (0.08) | −0.5 (0.09) | |
| Difference (SE) dupilumab vs placebo | −0.7 (0.12) | | <.001 |
| Change (SE) from baseline in the lichenification component of GISS | −1.0 (0.09) | −0.4 (0.09) | |
| Difference (SE) dupilumab vs placebo | −0.6 (0.12) | | <.001 |
| Change (SE) from baseline in POEM | −13.3 (0.70) | −4.8 (0.73) | |
| Difference (SE) dupilumab vs placebo | −8.5 (1.00) | | <.001 |

All values are least squares means.

*AD*, Atopic dermatitis; *BSA*, body surface area; *GISS*, Global Individual Signs Score; *POEM*, Patient-Oriented Eczema Measure; *SE*, standard error.