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

Andrew Blauvelt, MD, MBA, Eric L. Simpson, MD, MCR, Stephen K. Tying, MD, PhD, Lisa A. Purcell, PhD, Brad Shumel, MD, Christopher D. Petro, PhD, Bolanle Akinlade, MD, Abhijit Gadkari, PhD, Laurent Eckert, PhD, Neil M.H. Graham, MBBS, MD, MPH, Gianluca Pirozzi, MD, PhD, Robert Evans, PharmD



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

Andrew Blauvelt, MD, MBA,^a Eric L. Simpson, MD, MCR,^b Stephen K. Tying, MD, PhD,^c Lisa A. Purcell, PhD,^d Brad Shumel, MD,^d Christopher D. Petro, PhD,^d Bolanle Akinlade, MD,^d Abhijit Gadkari, PhD,^d Laurent Eckert, PhD,^e Neil M.H. Graham, MBBS, MD, MPH,^d Gianluca Pirozzi, MD, PhD,^f Robert Evans, PharmD^g

^aOregon Medical Research Center, Portland, OR, USA; ^bDepartment of Dermatology, Oregon Health & Science University, Portland, OR, USA; ^cCenter for Clinical Studies and Department of Dermatology, University of Texas Health Science Center at Houston, Houston, TX, USA; ^dRegeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; ^eSanofi, Chilly-Mazarin, France; ^fSanofi, Bridgewater, NJ, USA; ^gPrevious employee of Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

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Corresponding author: Andrew Blauvelt, MD, MBA, Oregon Medical Research Center, 9495 SW Locust St, Suite G, Portland, OR 97223, USA.
E-mail: ablauvelt@oregonmedicalresearch.com

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ABSTRACT (200/max. 200 words)

Background: The impact of dupilumab, an anti-interleukin (IL)-4R α antibody that inhibits IL-4/IL-13 signaling, on vaccine responses in atopic dermatitis (AD) patients is unknown.

Objectives: To assess T-cell-dependent and -independent humoral 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.

Results: 178 patients completed the study. Similar positive responses with dupilumab/placebo to tetanus (83.3%/83.7%) and meningococcal polysaccharide (86.7%/87.0%) were achieved. Dupilumab significantly decreased total serum IgE; most dupilumab-treated patients were Tdap IgE-seronegative at Week 32 (62.2%/34.8%; dupilumab/placebo). Dupilumab improved key AD efficacy endpoints ($P<0.001$). 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.

Conclusions: 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.

CAPSULE SUMMARY (50/max. 50 words):

- The Type 2/Th2-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 non-live 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.

Key words: [6 (as many as necessary permitted)]

Atopic dermatitis, dupilumab, vaccine, tetanus toxoid, meningococcal polysaccharide, IgE

LIST OF ABBREVIATIONS

- AD: atopic dermatitis
- AE: adverse event
- BSA: body surface area
- CI: confidence interval
- CMH: Cochran–Mantel–Haenszel (test)
- CSwNP: chronic sinusitis with nasal polyposis
- EASI: Eczema Area and Severity Index
- EASI-50: $\geq 50\%$ reduction in Eczema Area and Severity Index score
- EASI-75: $\geq 75\%$ reduction in Eczema Area and Severity Index score
- GISS: Global Individual Sign Score
- HIV: human immunodeficiency virus
- IGA: Investigator's Global Assessment
- IgE: immunoglobulin E
- IgG: immunoglobulin G
- IgM: immunoglobulin M
- IL: interleukin
- IL-4R α : interleukin-4 receptor alpha
- IQR: interquartile range
- ISR: Injection site reaction
- MFI: mean fluorescent intensity
- MPSV4: quadrivalent meningococcal polysaccharide vaccine
- NRS: Numerical Rating Scale
- PTM: pertussis toxin mutant
- POEM: Patient-Oriented Eczema Measure
- SBA: serum bactericidal assay
- TCI: topical calcineurin inhibitors
- TCS: topical corticosteroids
- Tdap: tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine
- Th1: type 1 helper T-cell
- Th2: type 2 helper T-cell

INTRODUCTION

Atopic dermatitis (AD), a chronic inflammatory skin disease, affects $\leq 20\%$ 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 helper T-cell (Th2) cytokines, interleukin (IL)-4 and IL-13, central drivers of Type 2/Th2 diseases, such as AD, asthma, chronic sinusitis with nasal polyposis (CSwNP), and eosinophilic esophagitis.⁸⁻¹¹

Dupilumab, a fully human, VelocImmune®-derived monoclonal antibody directed against the IL-4 receptor alpha (IL-4R α) subunit, inhibits signaling of both IL-4 and IL-13.^{8,9,11,12} Dupilumab has been shown to significantly improve signs and symptoms of moderate-to-severe AD,^{8,13-17} asthma,^{9,18-20} CSwNP,²¹ and eosinophilic esophagitis,²² and is approved in the EU, USA, Japan, and 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.²³ 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.²⁴ Vaccination may cause IgE-mediated hypersensitivity and other immediate-type allergic reactions.²⁵ The Type 2/Th2-skewed cytokine milieu of AD patients has been linked to vaccine hyporesponsiveness during infancy;^{26,27} it is unclear whether therapeutic modulation affects vaccine responses.²⁸ Severe AD is associated with increased vaccine-specific IgE responses, with a risk of adverse events (AEs) during subsequent antigen exposure.²⁹ As dupilumab suppresses IL-4/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 that examined

146 whether dupilumab affects antibody responses to two commonly administered vaccines in adults
147 with moderate-to-severe AD, as well as dupilumab efficacy and safety.

148

METHODS

Study design

This was a phase 2, randomized, double-blinded, multicenter, placebo-controlled, parallel-group study conducted in the USA (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 one dose each of tetanus toxoid/reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) and quadrivalent meningococcal polysaccharide vaccine (MPSV4).

Patients

Eligible patients were aged 18–64 years with moderate-to-severe AD (American Academy of Dermatology Consensus Criteria³⁰) for ≥ 3 years; had documented history (within 6 months of screening) of inadequate response to medium-to-high potency topical corticosteroids (TCS) (with/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), an Investigator's Global Assessment (IGA) score ≥ 3 (range 0–4), and $\geq 10\%$ of their body surface area (BSA) affected by AD at screening and baseline. Use of emollients and TCS with/without TCI was permitted at entry if patients had been on a stable regimen for ≥ 14 days.

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 (300mg) or placebo were administered subcutaneously weekly. A 600mg 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, ON, Canada³¹) and standard MPSV4 (0.5 mL, Menomune[®] – A/C/Y/W-135, Sanofi Pasteur, Swiftwater, PA³²) were administered intramuscularly in the deltoid muscle and subcutaneously in the opposite arm, respectively, at Week 12; both were non-live vaccines. Concomitant AD therapies (TCI and/or TCS [≤ 10 mg prednisone or equivalent]) were permitted. Rescue treatment (TCS of higher potency than at baseline, TCI, high-dose systemic corticosteroids) was permitted for intolerable AD symptoms.

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 pre-vaccination tetanus antibody concentrations ≥ 0.1 or ≥ 0.2 IU/mL in patients with pre-vaccination concentrations < 0.1 IU/mL.³³

Secondary endpoints were proportions of patients at Week 16 with: (1) positive response to tetanus toxoid (≥ 2 -fold increase from baseline anti-tetanus IgG concentration in patients with pre-vaccination tetanus antibody concentrations ≥ 0.1 IU/mL, or ≥ 0.2 IU/mL in patients with pre-vaccination concentrations of < 0.1 IU/mL); (2) positive response to MPSV4 (meningococcal serogroup C serum bactericidal assay [SBA] titer ≥ 8);³⁴ (3) IGA score of 0 or 1; (4) $\geq 50\%$ reduction in EASI (EASI-50); (5) $\geq 75\%$ reduction in EASI (EASI-75); and changes from baseline at Week 16 in: (6) peak pruritus Numerical Rating Scale (NRS); (7) BSA; (8) erythema, (9) infiltration/papulation, (10) excoriations; (11) lichenification of Global Individual Sign Score (GISS); and (12) Patient-Oriented Eczema Measure (POEM). Total IgE levels and proportions of patients who were tetanus- 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 expressed as reciprocal of the final dilution providing $\geq 50\%$ 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

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.³⁵ Sera were treated with GullSORB[™] (Meridian Bioscience, Inc., Cincinnati, OH) to remove potentially competing IgG and incubated with purified pertussis toxin mutant (PTM), 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 IgE was detected via anti-IgE-phycoerythrin antibody (Clone BE5, Thermo Fisher Scientific, Waltham, MA). Samples were analyzed on a Luminex[®] FLEXMAP 3D instrument (Luminex Corporation) and PTM, pertactin, or tetanus toxoid IgE-positive beads were reported as mean fluorescent intensity (MFI). Detection limit was defined as three standard deviations above the MFI 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 AEs [TEAEs] and serious TEAEs) coded per Medical Dictionary for Regulatory Activities, v18.0. The investigator (or designee) recorded all AEs from signing of informed consent until study end. Information about injection-site reactions (ISRs) 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 (CMH) test stratified by randomization strata (moderate [IGA=3] versus 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/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 CMH 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’s test adjusted for multiple comparisons. Percent 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.

RESULTS

Patients

Of 243 patients screened, 194 were enrolled and randomized; 178 (91.8%) completed the study (**Fig. 1**). Patients in both treatment groups had similar baseline demographics and disease characteristics (**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% with 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%, placebo 83.7% (90% confidence interval [CI] of difference vs placebo: -9.41, 8.69). Proportions of patients achieving anti-tetanus IgG response (≥ 2 -fold increase) at Week 16 (secondary endpoint) were also similar: dupilumab 95.6%, placebo 94.6% (90% CI difference vs placebo: -4.29, 6.27), with no differences at baseline, Week 12 or 16 in tetanus toxoid titers between treatment groups ($P > 0.9999$, all comparisons; **Fig. 2A**). Overall median tetanus toxoid titers significantly increased in both groups at Week 16 versus Weeks 0 and 12 ($P < 0.0001$; placebo: Week 0=1.12, Week 12=1.11, and Week 16=15.25 IU/mL; dupilumab: Week 0=1.09, Week 12=1.21, and Week 16=13.91 IU/mL; **Fig. 2A**).

Similar proportions of patients had a positive response to serotype C of the meningococcal polysaccharide vaccine at Week 16: dupilumab 86.7%, placebo 87.0% groups (90% CI

difference vs placebo: -8.54, 7.96), with no differences in SBA titers between treatment groups ($P>0.9999$ for all comparisons; **Fig. 2B**), but both groups had significantly increased median SBA titers at Week 16 versus Weeks 0 and 12 ($P<0.0001$; placebo: Week 0= <4 , Week 12= <4 , and Week 16=1024; dupilumab: Week 0= <4 , Week 12= <4 , and Week 16=1024 IU/mL; **Fig. 2B**).

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%, placebo 65.2% ($P=0.001$) (**Table II**).

Changes in total IgE concentrations

Placebo-treated patients showed no changes in median total IgE levels (**Fig. 3A**); dupilumab-treated patients had significant reductions in median total IgE levels (baseline 798 IU/mL, interquartile range [IQR]: 214–2,784) to Weeks 12, 16, and 32 (468.5 IU/mL, IQR: 129–1,366, 363.5 IU/mL, IQR: 97.3–1,172 and 323.5 IU/mL, IQR: 85.8–969.3, respectively; **Fig. 3B**). At Week 32, median percent decrease from baseline in total IgE: dupilumab -57%, placebo -7.3% (**Fig. 3C**).

Dupilumab efficacy

Dupilumab demonstrated clinically and statistically significant improvements in all AD efficacy measures. IGA score of 0/1 at Week 16: dupilumab 44.3%, placebo 10.3% (**Table III**);

significantly more patients with dupilumab than placebo attained EASI-50 (72.2%, 32.0%) or EASI-75 (53.6%, 19.6%) (**Table III**). Dupilumab-treated patients had significantly greater improvements in peak pruritus NRS than placebo-treated patients, and experienced significantly greater reductions in percent BSA affected by AD, GISS components, and POEM scores (**Supplementary Table**).

Safety

TEAE rates were similar between groups (**Table IV**); 55.7% and 61.9% of patients in the dupilumab and placebo groups, respectively, reported ≥ 1 TEAE; most were mild or moderate. No deaths were reported. Three serious TEAEs were reported in the dupilumab group (one patient each): 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. TEAEs led to withdrawal of five patients on dupilumab: mycosis fungoides and serum sickness-like reaction, a photosensitivity reaction, dizziness and fatigue, and conjunctivitis of moderate severity; no withdrawals because of TEAEs in the placebo group. Upper respiratory tract infection was the most frequently reported TEAE in both groups, with similar rates. Conjunctivitis and ISRs to dupilumab or placebo were mild or moderate, and more frequent with dupilumab than placebo. AD exacerbations and non-herpetic skin infections occurred more frequently with placebo versus dupilumab (**Table IV**). ISRs to Tdap occurred only in the placebo group (3.1%); there were no ISRs to MPSV4.

DISCUSSION

Vaccine immune responses with 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 300mg weekly, and were robust and comparable in patients receiving dupilumab or placebo. Dupilumab also reduced vaccine-specific IgE and total IgE levels versus placebo. Vaccination after 12-week dupilumab therapy was not associated with any adverse clinical effects. Dupilumab also improved multiple AD efficacy measures versus placebo, consistent with previous phase 1-3 studies.^{8,13-17} 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 co-stimulatory signaling to produce antigen-specific antibodies.²⁴ For vaccine responses to tetanus toxoid, IgG production is T-cell-dependent.³⁶⁻³⁸ Since dupilumab acts on IL-4/IL-13, both Type 2/Th2 cytokines, dupilumab was not expected to affect total tetanus toxoid IgG levels, as observed here. Achievement of primary endpoint was consistent with a randomized clinical trial of healthy adults receiving Tdap vaccination,³⁹ and titer levels at any timepoint were similar to placebo, demonstrating that dupilumab does not impair tetanus vaccine response. In contrast to tetanus, polysaccharide vaccines, such as MPSV4, are thought to elicit T-cell-independent immune responses.²⁵ In this study, the proportions of patients attaining SBA titers ≥ 8 following vaccination with MPSV4 and the overall SBA titers at each timepoint were similar in dupilumab and placebo groups, indicating that dupilumab has no adverse effects on immune responses to a T-cell-independent vaccine. Given the effect of dupilumab on Type 2/Th2 cytokines, it is possible that treatment with dupilumab shifts Type 2/Th2-skewed vaccines

in a Th1 direction, not by increasing total IgG production, but by changing the IgG subtypes from IgG4 (Th2) to IgG1 (Th1), thereby potentially improving the functional response to vaccines.

The reduction in vaccine-specific IgE responses is consistent with the mechanism of action of dupilumab, which would be expected to decrease IgE production, and with other reports showing reduced total and allergen-specific IgE following dupilumab treatment.^{8,21,40} Patients with severe AD have an increased vaccine-specific IgE response, which may be associated with an increased risk of AEs during future vaccine or antigen exposure;²⁹ additional studies are needed to determine whether dupilumab reduces the risk of subsequent AEs by limiting vaccine-specific IgE responses.

Dupilumab had an acceptable safety profile, with ISRs and conjunctivitis occurring more often with dupilumab, and non-herpetic skin infections more frequently with placebo, similar to previous dupilumab AD trials.¹⁵⁻¹⁷

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,¹⁵ despite comparable design and outcomes with the LIBERTY AD CHRONOS trial.¹⁶

In conclusion, in adults with moderate-to-severe AD, vaccination during dupilumab treatment did not affect IgG 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 -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 non-live vaccines such as Tdap and MPSV4 can be

365 indicated safely and are immunogenic in adult patients with moderate-to-severe AD treated with
366 dupilumab.

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380 **TABLES**381 **Table I.** Baseline demographics and disease characteristics^a

Characteristic	Dupilumab (n = 97)	Placebo (n = 97)
Age (y)	39 ± 14	40 ± 14
Male sex (%)	51	47
Race (%)		
White	62	69
African American/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/papulation score (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

^aValues are means $\pm$ 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; *IgE*, immunoglobulin E; *IU*, international unit; *NRS*, Numerical Rating Scale; *POEM*, Patient-Oriented Eczema Measure; *Q1*, first quartile; *Q3*, third quartile *SD*, standard deviation.

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

	Dupilumab (n = 74) ^a	Placebo (n = 69) ^a	P value ^b
Week 12, n (%) of patients IgE-positive for			
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)	0.040
Week 16, n (%) of patients IgE-positive for			
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)	0.007
Week 32, n (%) of patients IgE-positive for			
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)	0.001

390 ^aPatients included for analysis were curated on the basis of sample availability.

391 ^bTdap IgE positivity between placebo- and dupilumab-treated individuals was compared by
 392 Fishers exact test.

393 *IgE*, immunoglobulin E; *Tdap*, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis
 394 vaccine.

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

	Dupilumab (n = 97)	Placebo (n = 97)	P value
Patients attaining IGA score 0 or 1, n (%)	43 (44.3)	10 (10.3)	
Difference vs placebo (90% CI)	34.0 (24.29–43.75)		<0.001
Patients attaining EASI-50, n (%)	70 (72.2)	31 (32.0)	
Difference vs placebo (90% CI)	40.2 (29.40–51.01)		<0.001
Patients attaining EASI-75, n (%)	52 (53.6)	19 (19.6)	
Difference vs placebo (90% CI)	34.0 (23.38–44.66)		<0.001
LS mean change (SE) from baseline in peak pruritus NRS score	–4.46 (0.256)	–2.33 (0.274)	
LS mean difference (SE) vs placebo	–2.13 (0.371)		<0.001

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

402 **Table IV.** Safety assessment

	Dupilumab (n = 97)	Placebo (n = 97)
TEAEs (n)	167	136
Serious TEAEs (n)	3 ^a	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 (%) ^b	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)
Non-herpetic skin infections, n (%) ^c	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)

403 ^aSerious TEAEs were (one patient each) mycosis fungoides stage IV, squamous cell carcinoma,
 404 and serum-sickness-like reaction.

405 ^bDoes not include TEAEs related to vaccination, except for injection-site reactions.

406 ^cAdjudicated.

407 *HLT*, high-level term (Medical Dictionary for Regulatory Activities); *PT*, preferred term
 408 (Medical Dictionary for Regulatory Activities); *Tdap*, tetanus toxoid, reduced diphtheria toxoid,
 409 acellular pertussis vaccine; *TEAE*, treatment-emergent adverse event.

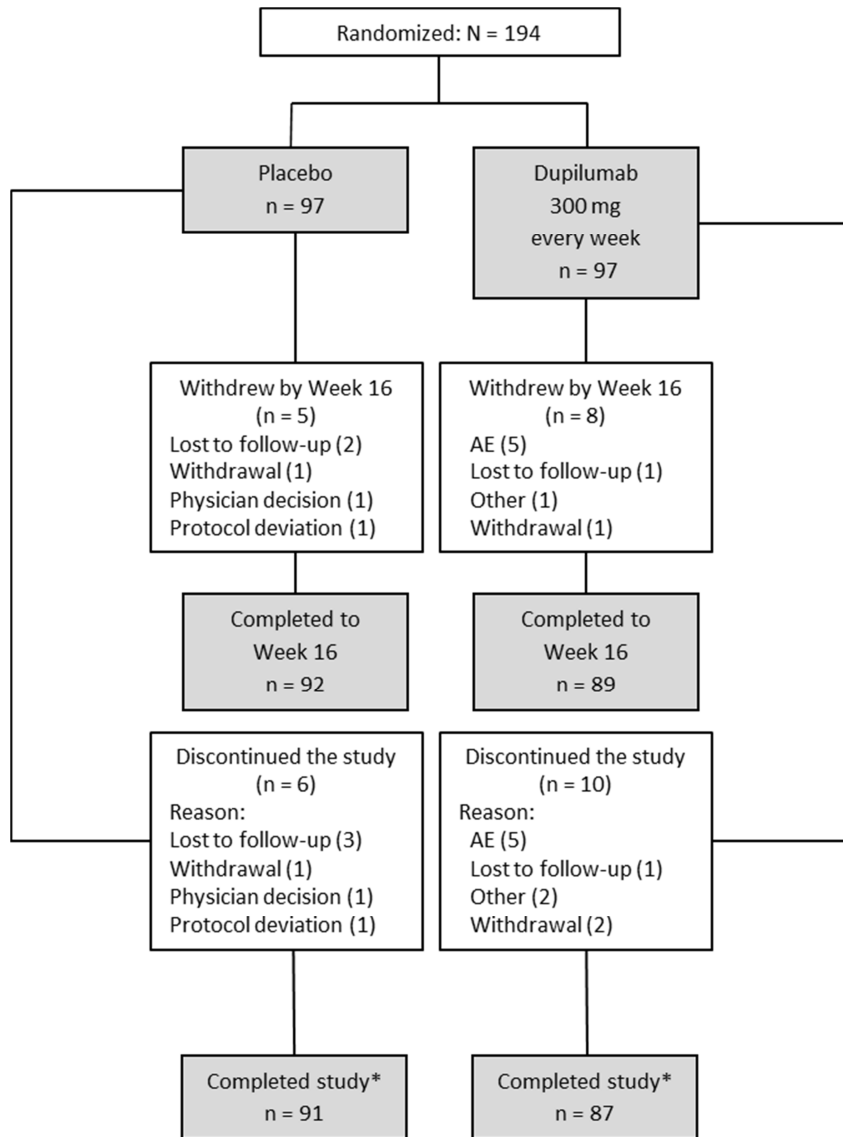
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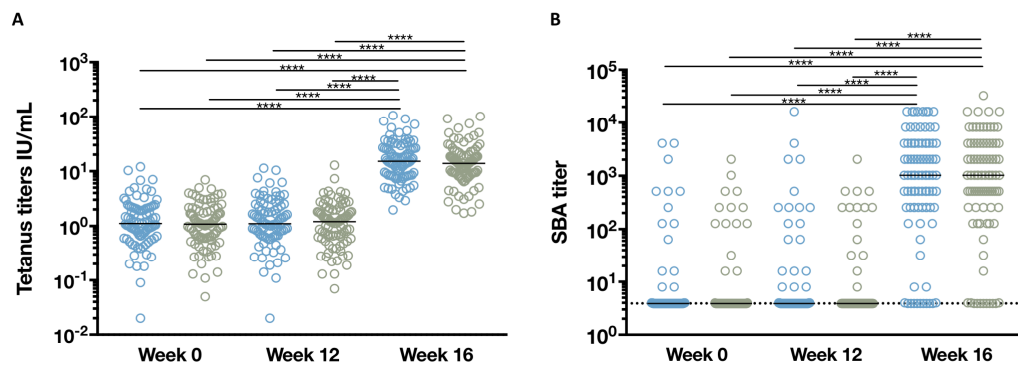
FIGURE LEGENDS

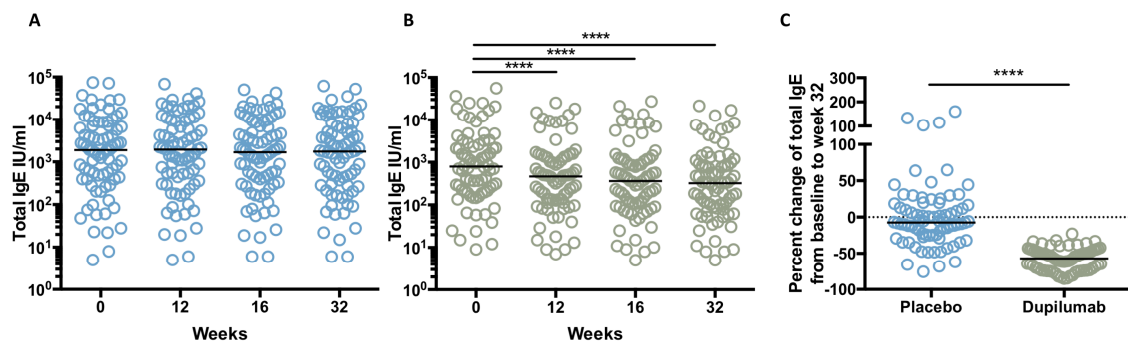
Figure 1. Atopic dermatitis. Trial profile. *Patients who completed all scheduled study visits underwent screening, completed the treatment period, and had at least one follow-up visit. *AE*, adverse event.

Figure 2. Atopic dermatitis. Immune responses to vaccination. (A) Antibody levels to tetanus toxoid (IU/mL) and (B) serum bactericidal assay (SBA) titers in placebo- and dupilumab-treated patients (blue and green symbols, respectively) at baseline (Week 0), Week 12, and Week 16. For all graphs, black bars represent median values per group. *IU*, international unit. Limit of detection of SBA indicated in (B) by dotted line. Values were compared using Friedman's test with a Dunn's post-hoc; **** $P < 0.0001$.

Figure 3. Atopic dermatitis. Total serum immunoglobulin E (IgE) levels in (A) placebo- and (B) dupilumab-treated patients at baseline (Week 0), Week 12, Week 16, and Week 32. (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. *IU*, international unit. For A and B, values were compared using Friedman's test. For C, values were compared using Mann–Whitney *U*-test; **** $P < 0.0001$.







Supplementary Table. Efficacy of dupilumab in achievement of AD clinical and patient-reported endpoints at Week 16*

	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) vs placebo	-18.0 (2.91)		<0.001
Change (SE) from baseline in the erythema component of GISS	-0.9 (0.08)	-0.4 (0.74)	
Difference (SE) vs placebo	-0.6 (0.11)		<0.001
Change (SE) from baseline in the infiltration/papulation component of GISS	-1.1 (0.08)	-0.4 (0.08)	
Difference (SE) vs placebo	-0.6 (0.11)		<0.001
Change (SE) from baseline in the excoriation component of GISS	-1.2 (0.08)	-0.5 (0.09)	
Difference (SE) vs placebo	-0.7 (0.12)		<0.001
Change (SE) from baseline in the lichenification component of GISS	-1.0 (0.09)	-0.4 (0.09)	
Difference (SE) vs placebo	-0.6 (0.12)		<0.001
Change (SE) from baseline in POEM	-13.3 (0.70)	-4.8 (0.73)	
Difference (SE) vs placebo	-8.5 (1.00)		<0.001

*All values are LS means.

AD, atopic dermatitis; BSA, body surface area; GISS, Global Individual Signs Score; LS, least squares; POEM, Patient-Oriented Eczema Measure; SE, standard error.