ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

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ABSTRACT

BACKGROUND

Dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, inhibits signaling of interleukin-4 and interleukin-13, type 2 cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis.

METHODS

In two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2), we enrolled adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16.

RESULTS

We enrolled 671 patients in SOLO 1 and 708 in SOLO 2. In SOLO 1, the primary outcome occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo (P<0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo (P<0.001 for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo (P<0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.

CONCLUSIONS

In two phase 3 trials of identical design involving patients with atopic dermatitis, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo. Trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab. (Funded by Sanofi and Regeneron Pharmaceuticals; SOLO 1 ClinicalTrials.gov number, NCT02277743; SOLO 2 ClinicalTrials.gov number, NCT02277769.)

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Atopic dermatitis is a chronic, relapsing inflammatory skin disease that is characterized by the up-regulation of type 2 immune responses (including those involving type 2 helper T cells),[1,2] an impaired skin barrier, and increased *Staphylococcus aureus* colonization.[3,4] In patients with moderate-to-severe atopic dermatitis, skin lesions can encompass a large body-surface area and are frequently accompanied by intense, persistent pruritus, which leads to sleep deprivation, symptoms of anxiety or depression, and a poor quality of life.[5-7] For patients with moderate-to-severe atopic dermatitis, topical therapies have limited efficacy, and systemic treatments are associated with substantial toxic effects. Thus, there is an unmet need for effective and safe long-term medications for these patients.[8,9]

Dupilumab is a fully human monoclonal antibody that binds specifically to the shared alpha chain subunit of the interleukin-4 and interleukin-13 receptors, thereby inhibiting the signaling of interleukin-4 and interleukin-13, which are type 2 inflammatory cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis and asthma.[10-14] In support of this premise, early-phase trials of dupilumab showed efficacy in patients with atopic dermatitis,[10,11,14,15] those with asthma,[16,17] and those with chronic sinusitis with nasal polyposis[18] — all of which are conditions that have type 2 immunologic signatures.[13] Clinical improvements were associated with improvement of inflammatory pathways, including type 2 pathways, and normalization of epidermal-barrier abnormalities.[10,11] Here we present the results of two phase 3 trials of dupilumab monotherapy (SOLO 1 and SOLO 2) in adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable.

Methods

Study Design and Oversight

We conducted two independent, randomized, double-blind, placebo-controlled, parallel-group trials of identical design to evaluate dupilumab in adults with moderate-to-severe atopic dermatitis in North America, Europe, and Asia. The two-trial concept was designed to provide replication of results. We enrolled patients from October 28, 2014, to July 8, 2015, in SOLO 1 and from December 3, 2014, to June 17, 2015, in SOLO 2. Data were not analyzed until after the statistical analysis plans were finalized on January 26, 2016.

Dupilumab or placebo was injected subcutaneously weekly or every other week for 16 weeks after a 35-day screening and washout period. Patients who were assigned to receive dupilumab every other week were given matching placebo on the off weeks in order to preserve the blinding (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were required to apply moisturizers twice daily for at least 7 consecutive days before randomization and throughout the trial period.

Topical or systemic rescue treatment to control unacceptable symptoms of atopic dermatitis could be used at the investigators' discretion. Dupilumab or placebo was discontinued in patients who received systemic rescue treatment.

During the treatment period, patients had weekly clinical and safety assessments and collection of blood samples. After the treatment period, eligible patients could enter an ongoing maintenance trial (LIBERTY AD SOLO-CONTINUE; ClinicalTrials.gov number, NCT02395133) or an open-label extension trial (LIBERTY AD MAINTAIN; NCT01949311). (Details about the follow-up studies are provided in the Supplementary Appendix.) For patients who were ineligible or unwilling to enter either trial, safety follow-up continued through week 28. The maintenance and open-label extension studies are not yet complete, so data from those studies are not included in this report.

These trials were conducted in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted unblinded monitoring of patient safety. All the patients provided written informed consent before participation in the trial. The local institutional review board or ethics committee at each trial center oversaw trial conduct and documentation.

All the authors participated in interpretation of the data and provided input into the drafting of the manuscript, critical feedback, and final approval for submission of the manuscript for publication. The investigators had confidentiality agreements with the sponsors, Sanofi and Regeneron Pharma-

ceuticals. Editorial support was provided by medical writers who were paid by the sponsors. The authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of the trials to the protocols, available at NEJM.org.

PATIENTS

Patients were eligible to participate in the trial if they were at least 18 years of age, had moderate-to-severe atopic dermatitis — including a score of 3 (moderate) or 4 (severe) on the Investigator's Global Assessment (IGA; scores range from 0 to 4, with higher scores indicating more severe disease) — for which topical treatment provided inadequate control or was medically inadvisable, and had chronic atopic dermatitis (according to the consensus criteria of the American Academy of Dermatology[19]) for at least 3 years before screening. (Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.)

TREATMENT

Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, weekly subcutaneous injections of dupilumab (300 mg) or placebo or the same dose of dupilumab every other week alternating with placebo. Patients in the dupilumab groups received a 600-mg loading dose of dupilumab on day 1. Randomization was conducted by means of a central interactive voice-response system and was stratified according to disease severity (IGA score, 3 vs. 4) and region. Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment.

Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Rescue treatment for atopic dermatitis could be provided to patients if medically necessary (i.e., to control unacceptable symptoms of atopic dermatitis). If the rescue medication was topical, the patient could continue the assigned regimen; however, if the rescue medication was systemic (e.g., systemic glucocorticoids or nonsteroidal systemic immunosuppressive drugs), the trial regimen was immediately discontinued. (Detailed information about rescue treatment and prohibited concomitant medications is provided in the Supplementary Appendix.)

END POINTS

End points were analyzed according to a prespecified hierarchy (see the Statistical Analysis section). The primary end point was the proportion of patients with an IGA score of 0 or 1 (clear or almost clear)[20] and a reduction from baseline of at least 2 points in the score at week 16. The proportion of patients who had an improvement from baseline at week 16 of at least 75% on the Eczema Area and Severity Index (EASI-75) was a key secondary end point (and was identified as a coprimary end point by regulators in the European Union and Japan). The EASI score assesses the severity and extent of erythema; induration, papulation, and edema; excoriations; and lichenification.[21,22] EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of atopic dermatitis. (End-point descriptions are provided in Table S1 in the Supplementary Appendix.)

Other key secondary end points in the hierarchy were the proportions of patients with an improvement of at least 4 points at weeks 2, 4, and 16 or of at least 3 points at week 16 in the weekly average of peak scores for pruritus on a numerical rating scale that ranged from 0 to 10, with higher scores indicating more severe pruritus, and the mean percent change in the peak score on the numerical rating scale for pruritus from baseline to week 16.[23,24] Peak scores on the pruritus numerical rating scale were self-assessed by patients daily and were averaged over a week to create a weekly measurement; patients used an interactive voice-response system to record the peak score at screening and daily through week 16.

Additional secondary end points in the hierarchy were the mean percent change from baseline to week 16 on the EASI score, the Scoring Atopic Dermatitis (SCORAD) score,[25] and the Global Individual Signs Score (GISS) and the mean percent change from baseline to week 2 on the pruritus numerical rating scale; the proportion of patients with an improvement on the EASI of at least 50% (EASI-50) or at least 90% (EASI-90) at week 16; and the mean change from baseline to week 16 on the pruritus numerical rating scale, percent body-surface area affected, the score on the Dermatology Life Quality Index (DLQI),[26,27] the score on the Patient-Oriented Eczema Measure (POEM),[22,28] and the total score on the Hospital Anxiety and Depression Scale

(HADS).[29,30] Additional prespecified end points were the proportion of patients with an improvement of at least 4 points (i.e., the minimal clinically important difference) from baseline to week 16 in the scores on the DLQI (scores range from 0 to 30, with higher scores indicating greater effect on quality of life) and the POEM (scores range from 0 to 28, with higher scores indicating a greater symptom burden) and the proportion of patients with HADS anxiety (HADS-A) and depression (HADS-D) subscores of less than 8 (on a scale from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms) at week 16 among patients who had had a baseline HADS-A or HADS-D subscore of 8 or more, which is the cutoff for identifying patients with anxiety or depression.[29] (A list of all efficacy end points is provided in the Supplementary Appendix.)

Over the 16-week treatment period, we evaluated safety outcomes, including adverse events, serious adverse events, and adverse events leading to treatment discontinuation. Adverse events were defined as the occurrence of any untoward medical condition during the treatment period.

STATISTICAL ANALYSIS

For binary outcomes, we used the Cochran–Mantel–Haenszel test after adjustment for randomization strata (disease severity and region). For the primary analysis of binary variables, we categorized data at time points after the use of rescue medication (either topical or systemic), withdrawal from the trial, or other missing data as indicating no response at all subsequent time points, including week 16. For continuous end points, we treated data that were collected after the use of rescue medication as missing, and subsequently we performed multiple imputation of missing data using the Markov-chain Monte Carlo algorithm and a regression model to generate multiple complete data sets at each time point. We then used analysis of covariance (ANCOVA) to evaluate data sets, with a model that included the assigned treatment, stratification factors (region and disease severity), and relevant baseline values. Results were then combined to generate statistical inferences.

We performed three prespecified sensitivity analyses for binary outcomes using the Cochran–Mantel–Haenszel test, with various methods to handle missing data. In the first sensitivity analysis, patients who had received rescue treatment or had withdrawn from the trial were considered to have had no response, and other missing values were imputed by means of the last-observation-carried-forward method. In the second sensitivity analysis, we included all observed values regardless of the use of rescue medication, with patients who had missing data treated as having had no response. In the third sensitivity analysis, we included all observed values regardless of the use of rescue medication, with no imputation of missing data.

We performed prespecified sensitivity analyses for continuous end points using the following methods to account for missing data: multiple imputation in which all observed data were included regardless of the use of rescue medication; use of a mixed-effect repeated-measures model, with data collected after the use of rescue medication treated as missing; treating data that were collected after the use of rescue medication as missing, followed by the last-observation-carried-forward method and ANCOVA; treating data that were collected after the use of rescue medication as missing, followed by the worst-observation-carried-forward method and ANCOVA; and ANCOVA on all observed values without imputation. (Additional statistical methods are provided in the Supplementary Appendix.)

To control for the overall type I error rate at 0.05 for primary and secondary end points across dose regimens, we used a significance level of 0.025 for comparisons of each dose of dupilumab with placebo according to the prespecified hierarchical order. If there were no significant between-group differences for a particular end point, testing would stop at that end point. All reported P values are two-sided. The significance of differences between dose groups was not investigated.

RESULTS

TRIAL PATIENTS

A total of 671 patients underwent randomization in SOLO 1 and 708 in SOLO 2 (Figs. S1 and S2 in the Supplementary Appendix). The randomized groups were well balanced with respect to baseline characteristics (Table 1, and Table S2 in the Supplementary Appendix). Approximately half of all patients had moderate atopic dermatitis (IGA score, 3), and half had severe atopic dermatitis (IGA score, 4). In each of the groups, a me-

dian of approximately 50% of the patients' body-surface area was affected (Table 1). Before enrollment, 32.9% of the patients in SOLO 1 and 33.0% of those in SOLO 2 had received systemic glucocorticoids, and 25.9% and 31.4%, respectively, had received systemic immunosuppressant agents (Table S3 in the Supplementary Appendix).

PRIMARY OUTCOME

For both dupilumab regimens in the two trials, there were significant differences in all comparisons with placebo regarding the prespecified efficacy end points in the hierarchy (Table 2 and Figs. 1 and 2, and Figs. S4 through S7 in the Supplementary Appendix). At week 16, significantly more patients receiving dupilumab than receiving placebo had an IGA score of 0 or 1 and an improvement of 2 points or more on the IGA from the baseline score (primary end point). In SOLO 1, the primary outcome occurred in 85 patients (38%) receiving dupilumab every other week and in 83 (37%) receiving weekly dupilumab, as compared with 23 (10%) receiving placebo (P<0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) receiving dupilumab every other week and in 87 (36%) receiving weekly dupilumab, as compared with 20 (8%) receiving placebo (P<0.001 for both comparisons) (Table 2 and Fig. 1A).

CLINICAL SEVERITY

In the two trials, an improvement of at least 75% on the EASI (EASI-75) at week 16 was reported in significantly more patients receiving each regimen of dupilumab than among those receiving placebo (P<0.001 for all comparisons) (Table 2 and Fig. 1B). The least-squares mean (±SE) percent change in the EASI score from baseline to week 16 was significantly greater among patients receiving dupilumab than among those receiving placebo, with reductions of 72.3±2.6 among those receiving dupilumab every other week and 72.0±2.6 among those receiving weekly dupilumab, as compared with a reduction of 37.6±3.3 among those receiving placebo in SOLO 1; there were least-squares mean percent reductions of 67.1±2.5, 69.1±2.5, and 30.9±3.0, respectively, in SOLO 2 (P<0.001 for all comparisons) (Table 2 and Fig. 2A and 2B). Results in the two dupilumab groups in the two trials were significantly better than those in the placebo groups in additional measures of clinical severity, including EASI-50, EASI-90, body-surface area affected, and scores on SCORAD and GISS (P<0.001 for all comparisons) (Table 2).

MEASURES OF PRURITUS

At week 16, an improvement of at least 3 points or at least 4 points in the peak score on the pruritus numerical rating scale occurred in significantly more patients receiving dupilumab than in those receiving placebo (P<0.001 for all comparisons) (Table 2). By week 2, patient-reported scores with respect to itching were significantly better among patients receiving dupilumab than among those receiving placebo (Table 2 and Fig. 2C and 2D).

PATIENT-REPORTED SYMPTOMS AND QUALITY OF LIFE

In the two trials, dupilumab significantly reduced patient-reported symptoms of atopic dermatitis and its effect on sleep, symptoms of anxiety or depression, and quality of life (Table 2, and Table S4 and Figs. S6 and S7 in the Supplementary Appendix). For both the DLQI and POEM scores, significantly more patients in the two dupilumab groups than in the placebo groups had a reduction of at least 4 points (considered to be the minimal clinically important difference[22,27]) in the total score (Table S4 in the Supplementary Appendix). Among patients who had had symptoms of anxiety or depression (HADS-A or HADS-D score, ≥8) at baseline, significantly more dupilumab-treated patients than those receiving placebo had HADS-A and HADS-D scores of less than 8 at week 16 (Table S4 in the Supplementary Appendix).

USE OF RESCUE MEDICATION

In the two trials, more patients in the placebo group than in either dupilumab group received rescue treatment. In SOLO 1, the rates of rescue treatment were 21% among those receiving dupilumab every other week and 23% among those receiving dupilumab every week, as compared with 51% among those receiving placebo; in SOLO 2, the rates were 15%, 21%, and 52%, respectively (Table S5 in the Supplementary Appendix). Patients in the placebo groups were more likely to receive systemic rescue therapies (glucocorticoids or immunosuppressant agents) (Table S5 in the Supplementary Appendix) and tended to receive rescue treatments earlier than dupilumab-treat-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	SOLO 1			SOLO 2		
	Placebo (N = 224)	Dupilumab Every Other Week (N = 224)†	Dupilumab Every Week (N = 223)	Placebo (N = 236)	Dupilumab Every Other Week (N = 233)†	Dupilumab Every Week (N = 239)
Median age (IQR) — yr	39.0 (27.0–50.5)	38.0 (27.5–48.0)	39.0 (27.0–51.0)	35.0 (25.0–47.0)	34.0 (25.0–46.0)	35.0 (25.0–46.0)
Male sex — no. (%)	118 (53)	130 (58)	142 (64)	132 (56)	137 (59)	139 (58)
Race — no. (%)‡						
White	146 (65)	155 (69)	149 (67)	156 (66)	165 (71)	168 (70)
Black	16 (7)	10 (4)	20 (9)	20 (8)	13 (6)	15 (6)
Asian	56 (25)	54 (24)	51 (23)	50 (21)	44 (19)	45 (19)
Other or missing data	6 (3)	5 (2)	3 (1)	10 (4)	11 (5)	11 (5)
Median disease duration (IQR) — yr	28.0 (19.0–40.0)	26.0 (17.0–40.0)	26.0 (16.0–42.0)	26.0 (18.0–39.0)	24.5 (18.0–36.0)	24.0 (17.0–37.0)
Median affected body-surface area (IQR) — %	57.0 (37.4–77.0)	53.4 (37.4–72.5)	54.5 (39.0–73.0)	53.3 (34.0–72.8)	50.0 (36.0–68.0)	50.0 (34.0–69.0)
Median EASI score (IQR)§	31.8 (22.2–43.8)	30.4 (21.5–40.8)	29.8 (22.0–41.2)	30.5 (22.1–41.7)	28.6 (21.0–40.1)	29.0 (21.2–41.8)
IGA score of 4 — no. (%)¶	110 (49)	108 (48)	106 (48)	115 (49)	115 (49)	112 (47)
Median peak score on numerical rating scale for pruritus (IQR)‖	7.7 (6.2–8.6)	7.6 (5.9–8.7)	7.7 (6.0–8.7)	7.7 (6.5–9.0)	7.8 (6.7–8.9)	7.8 (6.3–8.9)
Median total SCORAD score (IQR)**	67.0 (58.0–77.6)	65.1 (56.5–77.4)	65.9 (57.2–75.8)	68.9 (58.6–78.5)	67.8 (57.3–76.7)	67.4 (58.4–77.9)
Median POEM score (IQR)††	21.0 (16.0–25.0)	21.0 (16.0–25.0)	22.0 (17.0–26.0)	23.0 (17.0–26.0)	21.0 (18.0–25.0)	21.0 (18.0–26.0)
Median DLQI score (IQR)‡‡	14.0 (9.0–20.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)	15.0 (9.0–22.0)	15.0 (10.0–21.0)	16.0 (10.0–22.0)
Median total HADS score (IQR)§§	12.0 (6.0–17.0)	11.0 (6.0–17.0)	12.0 (6.0–17.5)	12.0 (7.0–19.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)
HADS-A or HADS-D score ≥8 — no. (%)§§	97 (43)	100 (45)	102 (46)	115 (49)	129 (55)	136 (57)
Median GISS score (IQR)¶¶	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–11.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Previous history of eczema herpeticum — no. (%)	4 (2)	4 (2)	6 (3)	3 (1)	7 (3)	0

* There were no significant differences between the dupilumab groups and the placebo groups in any of the listed categories. IQR denotes interquartile range. Percentages may not total 100 because of rounding.

† In this regimen, dupilumab was administered every other week and placebo every other week to maintain blinding.

‡ The protocol did not specify how data on race should be collected.

§ Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating greater severity; a change of 6.6 has been estimated as the minimal clinically important difference (MCID).

¶ Scores on the Investigator's Global Assessment (IGA) scale range from 0 to 4, with higher scores indicating greater severity; the MCID for this scale has not been determined.

‖ The peak score on the numerical rating scale for pruritus is a 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.

** Scoring Atopic Dermatitis (SCORAD) is a combined score of investigator-reported disease severity and affected body-surface area and patient-reported symptoms of itch and sleep dysfunction; scores range from 0 to 103, with higher scores indicating greater severity; a change of 8.7 has been estimated as the MCID.

†† The Patient-Oriented Eczema Measure (POEM), a composite measure of patient-reported symptoms including the effect of symptoms on sleep, evaluates the frequency of symptoms (including itching) and the effect of atopic dermatitis on sleep on a scale of 0 to 28, with higher scores indicating greater severity; a change of 4 has been estimated as the MCID.

‡‡ The Dermatology Life Quality Index (DLQI) evaluates health-related quality of life on a scale of 0 to 30, with higher scores indicating greater effect on quality of life. A change of 4 has been estimated as the MCID.

§§ The Hospital Anxiety and Depression Scale (HADS) 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 MCID for this scale has not been determined. The recommended cutoff score for identifying patients with anxiety or depression is 8.

¶¶ The Global Individual Signs Score (GISS) is a cumulative score of ratings for individual components of lesions associated with atopic dermatitis (erythema, infiltration or papulation, excoriations, and lichenification); the cumulative score ranges from 0 to 12, with higher scores indicating greater severity; the MCID for this scale has not been determined.

ed patients (Fig. S3 in the Supplementary Appendix).

Overall, among patients receiving dupilumab, similar results were observed in the primary analysis and with all observed values regardless of the use of rescue medication (Figs. S4 and S5 in the Supplementary Appendix). Outcomes of sensitivity analyses were similar to those of the primary analysis (Table S6 in the Supplementary Appendix).

SAFETY

The overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the two trials (Table 3). Serious adverse events and adverse events leading to treatment discontinuation were uncommon in the two trials (Table 3, and Tables S7 and S8 in the Supplementary Appendix). The only serious adverse event that was reported in more than 2 patients in any treatment group was a serious exacerbation of atopic dermatitis, which was reported in 2 patients receiving dupilumab every other week and 3 receiving placebo in SOLO 1 and in 1 patient receiving weekly dupilumab and 5 patients receiving placebo in SOLO 2 (Table S7 in the Supplementary Appendix).

Adverse events that were categorized as "infections and infestations" in the *Medical Dictionary for Regulatory Activities* (MedDRA) system organ class (which includes any type of infectious adverse event, regardless of cause or organ system) developed in 35% of the patients receiving dupilumab every other week and in 34% of those receiving dupilumab every week, as compared with 28% of those receiving placebo in SOLO 1 and in 28%, 29%, and 32%, respectively, in SOLO 2. (Common adverse events that are categorized as MedDRA preferred terms in this class included nasopharyngitis, upper respiratory tract infection, and conjunctivitis, including conjunctivitis of unspecified cause.) Skin infections were observed in 6% of patients receiving each dose of dupilumab in the two trials and in 8% of those receiving placebo in SOLO 1 and 11% in SOLO 2. All "infections and infestations" that were not reported as skin infections could be classified as "non-skin" infections; these were reported in 30% of the patients receiving dupilumab every other week, in 31% of those receiving dupilumab every week, and in 22% of those receiving placebo in SOLO 1 and in 25%, 26%, and 24%, respectively, in SOLO 2 (Table 3, and Table S9 in the Supplementary Appendix). Herpes infections were reported in 7%, 4%, and 4% of patients, respectively, in SOLO 1 and in 4%, 5%, and 3% of patients, respectively, in SOLO 2 (Table 3, and Table S9 in the Supplementary Appendix). Additional details regarding serious, severe, and opportunistic infections are provided in Table S10 in the Supplementary Appendix.

There were two deaths in SOLO 2: a 49-year-old woman who was not receiving an asthma-control medication died of an asthma attack 84 days after the last dose of dupilumab, and a 31-year-old man with a history of depression, including hospitalization for depression, and suicidal ideation committed suicide, an event that occurred 8 days after the most recent dose of dupilumab. (Detailed narratives are provided in the Supplementary Appendix.)

The most common adverse events in the two trials were exacerbations of atopic dermatitis, injection-site reactions, and nasopharyngitis (Table 3). The incidence of nasopharyngitis was generally balanced across dupilumab and placebo groups. Dupilumab-treated patients had a higher incidence of injection-site reactions, most of which were mild or moderate. Exacerbations of atopic dermatitis and most types of skin infections were more common in the placebo groups. The rates of conjunctivitis with an unspecified cause and allergic conjunctivitis were higher in the dupilumab groups than in the placebo groups (Table 3); bacterial or viral conjunctivitis (MedDRA preferred term) was reported in less than 2% of the patients in any group (Table S9 in the Supplementary Appendix).

Laboratory values, vital signs, and electrocardiographic assessments did not indicate noteworthy differences among treatment groups. Small transient increases in eosinophil levels from baseline were observed in the dupilumab groups at weeks 4 and 8, with subsequent decreases toward or below baseline levels by week 16 (Table S11 and Fig. S8 in the Supplementary Appendix).

DISCUSSION

In SOLO 1 and SOLO 2, both dose regimens of dupilumab resulted in better results than placebo over 16 weeks of treatment across multiple outcome measures that reflected objective signs of atopic dermatitis, subjective symptoms (e.g., pruritus), important aspects of mental

Table 2. Efficacy Outcomes.*

Outcome	SOLO 1†			SOLO 2†		
	Placebo (N = 224)	Dupilumab Every Other Week (N = 224)	Dupilumab Every Week (N = 223)	Placebo (N = 236)	Dupilumab Every Other Week (N = 233)	Dupilumab Every Week (N = 239)
IGA score of 0 or 1 and reduction of ≥2 points from baseline at week 16: primary outcome — no. (%)	23 (10)	85 (38)	83 (37)	20 (8)	84 (36)	87 (36)
Key secondary outcomes						
EASI-75 at wk 16 — no. (%)‡	33 (15)	115 (51)	117 (52)	28 (12)	103 (44)	115 (48)
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 16	−26.1±3.0	−51.0±2.5	−48.9±2.6	−15.4±3.0	−44.3±2.3	−48.3±2.4
Improvement in peak score on numerical rating scale for pruritus — no./total no. (%)						
≥4 points from baseline to wk 16§	26/212 (12)	87/213 (41)	81/201 (40)	21/221 (10)	81/225 (36)	89/228 (39)
≥3 points from baseline to wk 16 ¶	38/221 (17)	103/220 (47)	109/211 (52)	29/226 (13)	117/231 (51)	115/234 (49)
≥4 points from baseline to wk 4§	13/212 (6)	34/213 (16)‖	47/201 (23)	14/221 (6)	51/225 (23)	63/228 (28)
≥4 points from baseline to wk 2§	7/212 (3)	20/213 (9)**	19/201 (9)††	2/221 (1)	24/225 (11)	29/228 (13)
Other secondary outcomes						
Peak least-squares mean change from baseline in peak score on numerical rating scale for pruritus at wk 16	−2.03±0.21	−3.78±0.16	−3.72±0.17	−1.21±0.22	−3.30±0.16	−3.68±0.16
Least-squares mean percent change from baseline in EASI score at wk 16	−37.6±3.3	−72.3±2.6	−72.0±2.6	−30.9±3.0	−67.1±2.5	−69.1±2.5
EASI-50 at wk 16 — no. (%)	55 (25)	154 (69)	136 (61)	52 (22)	152 (65)	146 (61)
EASI-90 at wk 16 — no. (%)	17 (8)	80 (36)	74 (33)	17 (7)	70 (30)	73 (31)
Least-squares mean change from baseline in affected body-surface area at wk 16	−15.4±1.9	−33.4±1.4	−34.3±1.4	−12.6±1.6	−30.6±1.3	−32.1±1.3
Least-squares mean percent change from baseline in SCORAD score at wk 16	−29.0±3.2	−57.7±2.1	−57.0±2.1	−19.7±2.5	−51.1±2.0	−53.5±2.0
Least-squares mean change from baseline in DLQI score at wk 16	−5.3±0.5	−9.3±0.4	−9.0±0.4	−3.6±0.5	−9.3±0.4	−9.5±0.4
Least-squares mean change from baseline in POEM score at wk 16	−5.1±0.7	−11.6±0.5	−11.0±0.5	−3.3±0.6	−10.2±0.5	−11.3±0.5
Least-squares mean change from baseline in HADS total score at wk 16	−3.0±0.7	−5.2±0.5	−5.2±0.5	−0.8±0.4	−5.1±0.4	−5.8±0.4
Least-squares mean percent change from baseline in GISS score at wk 16	−26.4±3.3	−53.4±2.4	−52.0±2.4	−17.9±2.5	−45.6±2.1	−46.8±2.1
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 2	−3.5±1.8	−19.9±1.7	−18.5±1.7	−5.3±1.6	−23.1±1.6	−20.3±1.6

* Plus–minus values are means ±SE. Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. Within each dose regimen, the primary and secondary end points were tested with a hierarchical testing procedure with a prespecified order — in other words, inferential conclusions about successive end points required statistical significance of the previous end point at a 0.025 significance level. Most outcomes were assessed at scheduled trial visits.

† Unless otherwise indicated, P<0.001 for the comparison between each regimen of dupilumab and placebo.

‡ The EASI-75 at week 16 was the coprimary outcome in the European Union and Japan.

§ Included in this analysis were patients with a baseline peak score of at least 4 on the numerical rating scale for pruritus.

¶ Included in this analysis were patients with a baseline peak score of at least 3 on the numerical rating scale for pruritus.

‖ P=0.001 versus placebo.

** P=0.010 versus placebo.

†† P=0.009 versus placebo.

health (i.e., anxiety and depression), and quality of life. The mean efficacy results were similar for both dupilumab regimens. SOLO 1 and SOLO 2 were designed to provide replication of results, and patient populations and results were highly consistent in the two trials.

Our findings confirm and expand on the results of previous early-phase trials of dupilumab in patients with moderate-to-severe atopic dermatitis.[10,11,14,15] Improvement in the primary outcome was supported by improvement in all other measures of clinical severity and extent of involvement. The between-group difference was significant for all prespecified efficacy end points that were listed in the statistical hierarchy. In addition, significant improvement was observed with respect to patient-reported symptoms of atopic dermatitis (including the effect on pruritus and sleep), symptoms of anxiety or depression, and health-related quality of life, with a significant reduction in itching apparent by week 2. These data suggest that the amelioration of signs and symptoms of atopic dermatitis by treatment with dupilumab may reduce the disease burden associated with moderate-to-severe atopic dermatitis across multiple domains that are important to patients.

Sensitivity analyses showed that the primary efficacy outcome was not driven by the categorization of the use of rescue medication as no response. Indeed, the between-group difference in this outcome remained significant when patients who received rescue medication were included in the analysis, even though considerably more patients in the placebo groups than in the dupilumab groups received rescue treatment.

The incidence of conjunctivitis was higher among patients receiving dupilumab than among those receiving placebo. The cause of conjunctivitis in patients with atopic dermatitis is not yet fully understood. In contrast to our findings in the current trials, the incidence of conjunctivitis was not increased in dupilumab-treated patients in early studies of dupilumab involving patients with asthma[16,17] or with chronic sinusitis with nasal polyposis,[18] which suggests that characteristics specific to atopic dermatitis may contribute to its cause. Further studies on the causes of conjunctivitis are warranted.

In phase 1 and phase 2a studies of dupilumab in patients with moderate-to-severe atopic dermatitis, the most frequent serious adverse events were exacerbation of atopic dermatitis and skin infections, both of which were more frequent in the placebo groups, whereas in the phase 2b trial, there was no apparent imbalance in the rates of serious adverse events across treatment groups.[10,14] In SOLO 1 and SOLO 2, infections were reported in 28 to 35% of patients receiving dupilumab and in 28 to 33% of those receiving placebo. Her-

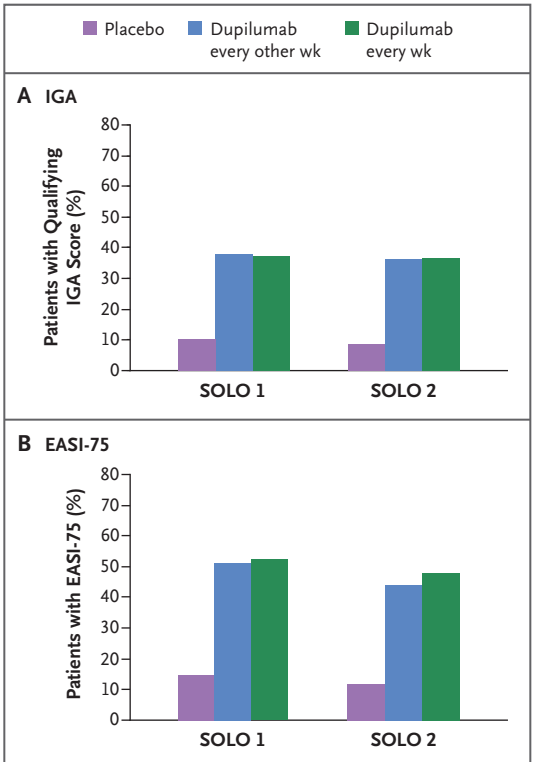

Figure 1. Primary End Point and Key Secondary End Point.

Panel A shows the proportions of patients with the primary end point (both a score of 0 or 1 [clear or almost clear] on the Investigator's Global Assessment [IGA; scores range from 0 to 4, with higher scores indicating more severe disease] and a reduction from baseline of 2 points or more on the IGA at week 16) among patients who received dupilumab every week, dupilumab every other week, or placebo in SOLO 1 and SOLO 2. Panel B shows the proportions of patients with the key secondary end point (which was considered to be a coprimary end point by regulators in the European Union and Japan) of an improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI-75) at week 16 in the two trials. P<0.001 for all comparisons between dupilumab and placebo. For binary end points, patients who received rescue medications or withdrew from the study were categorized as having had no response, as were those with all other missing values.

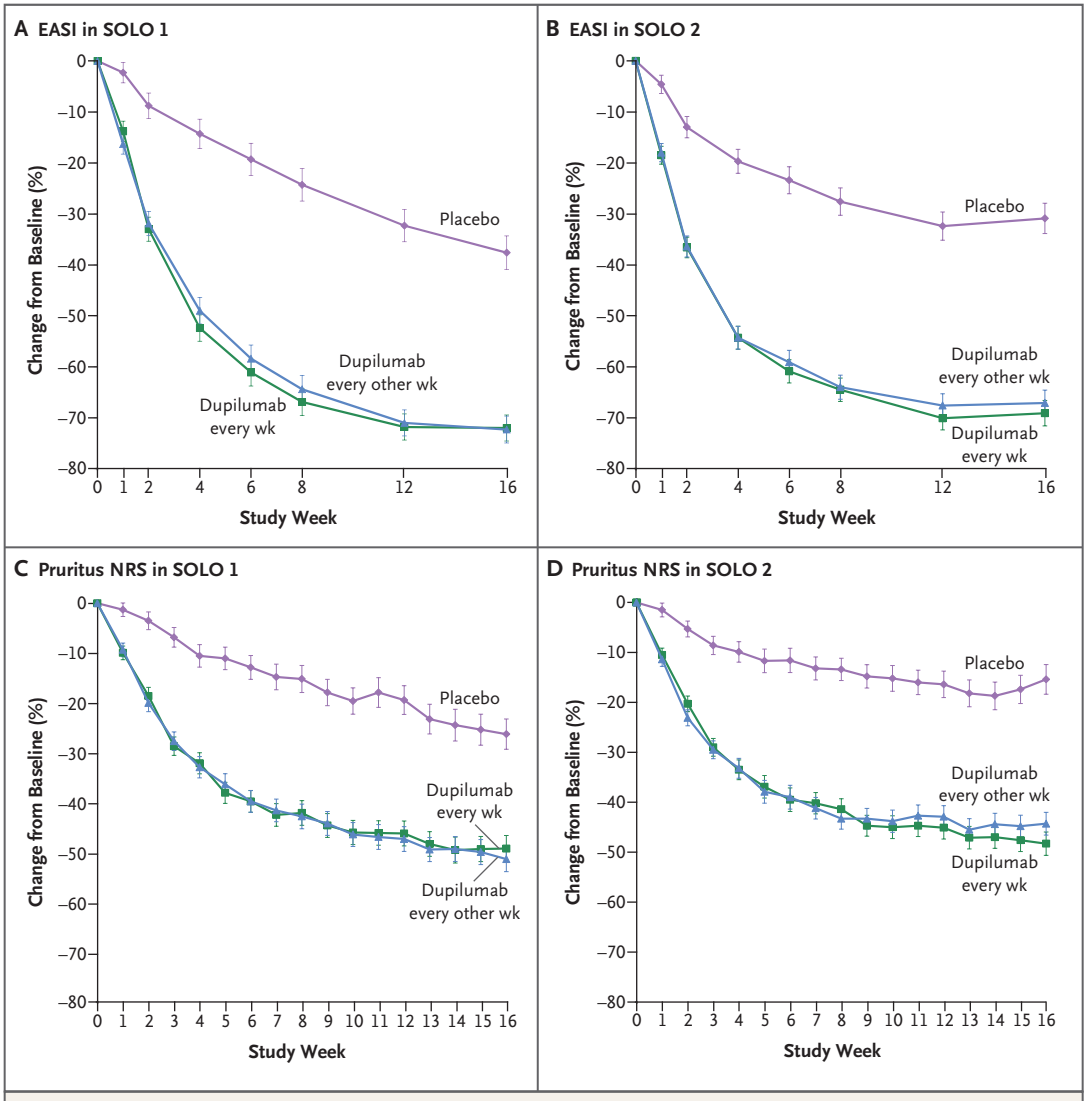

Figure 2. Secondary End Points.

Shown are the least-squares mean percent changes from baseline in the Eczema Area and Severity Index (EASI) score (Panels A and B) and in the weekly average of peak scores on the numerical rating scale (NRS) for pruritus (a key secondary end point) (Panels C and D) in SOLO 1 and SOLO 2 at 16 weeks ($P<0.001$ for all comparisons with placebo). The I bars represent standard errors. For the pruritus NRS, the baseline peak score was the average of the daily scores for maximum itch intensity during the 7 days immediately preceding randomization (minimum of four scores required). For continuous end points, data from patients who received rescue medications were categorized as missing at all time points after the receipt of the rescue medication; missing data were imputed with the use of a multiple-imputation method.

pes viral infections of any type were reported in 4 to 7% of patients receiving dupilumab and in 3 to 4% of those receiving placebo. The patients receiving placebo had a higher incidence of skin infections (8 to 11%) than did dupilumab-treated patients (approximately 6%), a finding that was consistent with an improvement in skin-barrier integrity and function associated with dupilumab,[10,11] whereas non-skin infections were observed in 25 to 31% of patients receiving dupilumab and in 22 to 24% of those receiving placebo. There is evidence that reducing type 2 skin inflammation helps normalize skin antimicrobial responses.[31-36] Two deaths were reported in the dupilumab groups. These trials were not long enough or large enough to exclude uncom-

Table 3. Adverse Events.*

Event	SOLO 1			SOLO 2		
	Placebo (N = 222)	Dupilumab Every Other Week (N = 229)	Dupilumab Every Week (N = 218)	Placebo (N = 234)	Dupilumab Every Other Week (N = 236)	Dupilumab Every Week (N = 237)
	number of patients (percent)					
Adverse or serious adverse event						
At least 1 adverse event	145 (65)	167 (73)	150 (69)	168 (72)	154 (65)	157 (66)
At least 1 serious adverse event	11 (5)	7 (3)	2 (1)	13 (6)	4 (2)	8 (3)
Death†	0	0	0	0	1 (<1)	1 (<1)
Adverse event leading to treatment discontinuation	2 (1)	4 (2)	4 (2)	5 (2)	2 (1)	3 (1)
Noninfectious adverse event‡						
Injection-site reaction	13 (6)	19 (8)	41 (19)	15 (6)	32 (14)	31 (13)
Exacerbation of atopic dermatitis	67 (30)	30 (13)	21 (10)	81 (35)	32 (14)	38 (16)
Headache	13 (6)	21 (9)	11 (5)	11 (5)	19 (8)	22 (9)
Allergic conjunctivitis	2 (1)	12 (5)	7 (3)	2 (1)	2 (1)	3 (1)
Infectious adverse event‡						
Infections and infestations§	63 (28)	80 (35)	74 (34)	76 (32)	65 (28)	68 (29)
Nasopharyngitis	17 (8)	22 (10)	25 (11)	22 (9)	20 (8)	20 (8)
Upper respiratory tract infection	5 (2)	6 (3)	11 (5)	5 (2)	7 (3)	9 (4)
Conjunctivitis¶	2 (1)	11 (5)	7 (3)	1 (<1)	9 (4)	9 (4)
Any herpes viral infection‖	9 (4)	15 (7)	9 (4)	8 (3)	10 (4)	12 (5)
Oral herpes	4 (2)	9 (4)	4 (2)	4 (2)	8 (3)	9 (4)
Herpes simplex	3 (1)	7 (3)	2 (1)	1 (<1)	0	1 (<1)
Eczema herpeticum	2 (1)	1 (<1)	1 (<1)	1 (<1)	2 (1)	0
Herpes virus infection	0	0	1 (<1)	1 (<1)	0	0
Herpes zoster	1 (<1)	1 (<1)	0	1 (<1)	0	0
Ophthalmic herpes simplex	0	0	1 (<1)	0	0	0
Genital herpes	1 (<1)	0	0	0	0	1 (<1)
Herpes ophthalmic	0	0	0	1 (<1)	0	1 (<1)
Herpes simplex otitis externa	0	0	0	0	1 (<1)	0
Adjudicated skin infection	18 (8)	13 (6)	14 (6)	26 (11)	13 (6)	15 (6)
Non-skin infection	49 (22)	69 (30)	67 (31)	57 (24)	58 (25)	61 (26)

* Patients are listed according to the study drug received, which may differ from the randomized group. Adverse events that were reported at the level of preferred terms occurred in at least 5% of the patients in any randomized group, with the exception that all adverse events with preferred terms related to herpes virus infection are reported here. Included in the safety analysis were all the patients who underwent randomization and received at least one dose of dupilumab or placebo.

† Details regarding the two deaths are provided in the Supplementary Appendix.

‡ Adverse events are reported at the preferred term level of the *Medical Dictionary for Regulatory Activities* (MedDRA) hierarchy, unless otherwise indicated.

§ This adverse event is reported at the system organ class level in the MedDRA hierarchy.

¶ This MedDRA preferred term includes conjunctivitis of unspecified cause.

‖ This adverse event is reported at the high-level term in the MedDRA hierarchy.

mon adverse events, and results from larger studies of longer duration are needed to assess the effectiveness and safety of long-term treatment with dupilumab.

Patients with atopic dermatitis, particularly moderate-to-severe disease, are at increased risk for depression.[37,38] Five patients had various serious adverse events related to depression (four in the placebo group and one in the group receiving weekly dupilumab); of these patients, one in the dupilumab group committed suicide. Symptoms of anxiety or depression were reduced to a significantly greater extent with dupilumab than with placebo among patients who had these symptoms at baseline (Table S4 in the Supplementary Appendix). These data underscore the substantial psychosocial effect of moderate-to-severe atopic dermatitis on quality of life and aspects of mental health and the potential for improvement in these areas associated with amelioration of the signs and symptoms of atopic dermatitis with dupilumab.

These trials have several limitations. First, neither trial was planned to allow statistical separation of the two doses of dupilumab. However, in each trial, the two regimens showed similar efficacy and safety. Second, the 16-week treatment period did not address efficacy and safety of longer-term treatment. Third, concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy; another phase 3 trial (LIBERTY AD CHRONOS) has evaluated the efficacy and safety of dupilumab with concomitant topical glucocorticoids with or without topical calcineurin inhibitors.[39] Fourth, we evaluated dupilumab in adults, but not children, in whom atopic dermatitis is more prevalent. A recently completed study evaluated the pharmacokinetics and preliminary efficacy and safety of dupilumab in children.

These results show that the type 2 cytokines interleukin-4 and interleukin-13 are key drivers of atopic dermatitis; they further support the possibility, suggested by earlier studies in related diseases, that interleukin-4 and interleukin-13 are important drivers of atopic or allergic diseases in general, including asthma and chronic sinusitis with nasal polyposis.[16-18]

In conclusion, in two phase 3 trials of identical design involving patients with moderate-to-severe atopic dermatitis that was inadequately controlled with topical medications, both regimens of dupilumab (every other week and weekly) were superior to placebo in ameliorating the signs and symptoms of atopic dermatitis (including pruritus and the effect on sleep), causing clinically meaningful reductions in patient-reported symptoms of anxiety and depression, and improving health-related quality of life. Injection-site reactions and conjunctivitis were more frequent in patients receiving dupilumab than in those receiving placebo. The results of these trials confirm and extend findings on dupilumab from earlier studies involving patients with moderate-to-severe atopic dermatitis.[10,14,15]

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APPENDIX

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