ORIGINAL ARTICLE

# Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

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## ABSTRACT

### BACKGROUND

Dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, has shown efficacy in patients with asthma and elevated eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)–mediated inflammation could help in the treatment of related diseases, including atopic dermatitis.

### METHODS

We performed randomized, double-blind, placebo-controlled trials involving adults who had moderate-to-severe atopic dermatitis despite treatment with topical glucocorticoids and calcineurin inhibitors. Dupilumab was evaluated as monotherapy in two 4-week trials and in one 12-week trial and in combination with topical glucocorticoids in another 4-week study. End points included the Eczema Area and Severity Index (EASI) score, the investigator's global assessment score, pruritus, safety assessments, serum biomarker levels, and disease transcriptome.

### RESULTS

In the 4-week monotherapy studies, dupilumab resulted in rapid and dose-dependent improvements in clinical indexes, biomarker levels, and the transcriptome. The results of the 12-week study of dupilumab monotherapy reproduced and extended the 4-week findings: 85% of patients in the dupilumab group, as compared with 35% of those in the placebo group, had a 50% reduction in the EASI score (EASI-50, with higher scores in the EASI indicating greater severity of eczema) ($P<0.001$); 40% of patients in the dupilumab group, as compared with 7% in the placebo group, had a score of 0 to 1 (indicating clearing or near-clearing of skin lesions) on the investigator's global assessment ($P<0.001$); and pruritus scores decreased (indicating a reduction in itch) by 55.7% in the dupilumab group versus 15.1% in the placebo group ($P<0.001$). In the combination study, 100% of the patients in the dupilumab group, as compared with 50% of those who received topical glucocorticoids with placebo injection, met the criterion for EASI-50 ($P=0.002$), despite the fact that patients who received dupilumab plus glucocorticoids used less than half the amount of topical glucocorticoids used by those who received placebo plus the topical medication ($P=0.16$). Adverse events, such as skin infection, occurred more frequently with placebo; nasopharyngitis and headache were the most frequent adverse events with dupilumab.

### CONCLUSIONS

Patients treated with dupilumab had marked and rapid improvement in all the evaluated measures of atopic dermatitis disease activity. Side-effect profiles were not dose-limiting. (Funded by Regeneron Pharmaceuticals and Sanofi; ClinicalTrials.gov numbers, NCT01259323, NCT01385657, NCT01639040, and NCT01548404.)

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Atopic dermatitis, which is characterized by a disturbed skin barrier, robust type 2 helper T-cell (Th2)–mediated immune responses to numerous environmental antigens, susceptibility to cutaneous infections, and intractable pruritus, is a common chronic skin condition with a worldwide prevalence of 1 to 20%.[1] Approximately 20% of patients with atopic dermatitis have moderate-to-severe disease,[1] and treatments approved by the Food and Drug Administration for atopic dermatitis, which include emollients, topical glucocorticoids, and calcineurin inhibitors,[2,3] have limited efficacy in moderate-to-severe disease.[4,5]

The Th2 cytokines interleukin-4 and interleukin-13 are believed to play roles in the pathogenesis of atopic dermatitis,[6,7] but the clinical effect of blocking both interleukin-4 and interleukin-13 in atopic dermatitis has not been tested in clinical trials. Recently, a clinical study of dupilumab, a fully human monoclonal antibody that is directed against the shared alpha subunit of the interleukin-4 receptors and that blocks signaling from both interleukin-4 and interleukin-13, showed efficacy in patients with moderate-to-severe asthma and elevated eosinophil levels,[8] raising the possibility that blocking this signaling could benefit patients with other Th2-related diseases. To address the importance of Th2-related biologic factors in atopic dermatitis, we evaluated dupilumab in four randomized, double-blind, placebo-controlled trials involving adults with moderate-to-severe disease.

## Methods

### Study Design and Oversight

We conducted four separate studies, three of which were early-phase studies designed primarily to assess the safety of dupilumab, administered subcutaneously, for the treatment of patients with atopic dermatitis. However, clinical end points were part of the design of each of the four trials. Two of the trials had dose-escalation designs, and two had parallel-group designs (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Safety was assessed by means of evaluation of the incidence of adverse events, assessment of vital signs, physical examination, clinical laboratory testing, and electrocardiography. The full protocols and statistical analysis plans are provided at NEJM.org.

The study protocols were developed by the study sponsors (Regeneron Pharmaceuticals and Sanofi) with input from three of the academic authors. Data were collected by the study investigators and analyzed by the sponsors; the study investigators had confidentiality agreements with the sponsors. All the authors take responsibility for the accuracy and completeness of the data and analyses reported and for the fidelity of the studies to the protocols. The first draft of the manuscript was written by the first author, with input from all the authors; subsequent drafts were prepared with the assistance of a medical writer paid by the sponsors. The first author made the decision to submit the manuscript for publication.

### Dupilumab Monotherapy for 4 Weeks

The U.S. and multinational phase 1 studies had sequential, dose-escalation cohorts. Both trials enrolled adults with moderate-to-severe atopic dermatitis that was not adequately controlled with topical medications (glucocorticoids and calcineurin inhibitors). In the U.S. study, Study M4A, patients were randomly assigned in a 1:4 ratio to receive placebo (6 patients) or dupilumab at a dose of 75 mg (8 patients), 150 mg (8 patients), or 300 mg (8 patients), with all study drugs administered subcutaneously once a week. In the multinational study, Study M4B, patients were randomly assigned in a 1:3 ratio to receive placebo (10 patients) or dupilumab at a dose of 150 mg (14 patients) or 300 mg (13 patients), with all study drugs administered subcutaneously once a week.

Both studies were designed to assess safety as the primary end point. Prespecified exploratory efficacy end points included the proportion of patients who had an investigator's global assessment score of 0 (clear) or 1 (almost clear), the percentage reduction in the affected body-surface area, the score on the Eczema Area and Severity Index (EASI, on which scores range from 0 to 72, with higher scores indicating greater severity; a score change of 6.6 has been estimated as the minimal clinically important difference),[9,10] the score on the 5-D pruritus scale (on which scores range from 5 to 25, with higher scores indicating greater itch),[11] the score on the pruritus numerical-rating scale (on which scores range from 0 to 10, with higher numbers indicating worse itch),[12] and levels of biomarkers (i.e., thymus and activation-regulated chemokine [TARC] and IgE).

### DUPILUMAB MONOTHERAPY FOR 12 WEEKS

A monotherapy trial, Study M12, was conducted in Europe to assess the clinical efficacy (primary end point) and safety (secondary end point) of weekly subcutaneous dupilumab at a dose of 300 mg in adults who had moderate-to-severe atopic dermatitis that was poorly controlled with topical agents. A total of 109 patients were randomly assigned in a 1:1 ratio to dupilumab (55 patients) or placebo (54 patients), with stratification according to a cutoff in the baseline IgE level of 150 kU per liter (360 $\mu$g per liter), with a level of less than 150 kU per liter indicating intrinsic atopic dermatitis and a level of 150 kU per liter or more indicating extrinsic atopic dermatitis.[13,14] Key efficacy end points at week 12 included the percentage change in the EASI score (primary end point), the percentage reduction in the affected body-surface area, the Scoring Atopic Dermatitis (SCORAD) score (on a scale from 0 to 103, with higher scores indicating greater severity; a score change of 8.7 has been estimated as the minimal clinically important difference),[10,15] the score on the pruritus numerical-rating scale, the score on the 5-D pruritus scale, the proportion of patients with a reduction of 50% or more in the EASI score (EASI-50), and the proportion of patients with an investigator's global assessment score of 0 or 1.

### COMBINATION THERAPY FOR 4 WEEKS

Study C4, a phase 2a study conducted in Europe, evaluated dupilumab in combination with topical glucocorticoids in adults with moderate-to-severe atopic dermatitis. Patients were randomly assigned in a 2:1 ratio to receive four weekly doses of subcutaneous dupilumab at a dose of 300 mg (21 patients) or placebo (10 patients), with both groups receiving a standardized regimen of topical glucocorticoids. The primary end points were the incidence and severity of adverse events. Prespecified exploratory efficacy end points included the percentage changes in the EASI score, the investigator's global assessment score, the SCORAD score, and the score on the pruritus numerical-rating scale and the proportions of patients with an investigator's global assessment score of 0 or 1 and with EASI-50 at day 29.

### PATIENTS

In all the studies, eligible patients were 18 years of age or older, with moderate-to-severe atopic dermatitis, as defined by an investigator's global assessment score of 3 or more. The proportion of body-surface area involved with atopic dermatitis that was required for inclusion varied among the studies: 15% or higher was required in Study M4A and 10% or higher in Studies M4B, M12, and C4. Also required were a SCORAD score of more than 20 (Study C4) or an EASI score of 12 or higher (Studies M4A and M4B) or 16 or higher (Study M12). The duration of disease had to have been 3 or more years for inclusion in the monotherapy studies and 2 or more years for inclusion in the combination study (Table S1 in the Supplementary Appendix).[16]

### BIOMARKER AND SKIN-BIOPSY EVALUATIONS

Pharmacodynamic response was based on the median percentage change from baseline in the serum levels of the Th2-associated biomarkers TARC and total IgE. Serum TARC was measured by means of an enzyme-linked immunosorbent assay (R&D Systems). Total serum IgE was measured with the use of the ImmunoCAP assay (Thermo Fisher Scientific). For microarray analyses, skin-biopsy specimens were obtained at baseline and at week 4 from the patients in Studies M4A and M4B who consented to participation in an optional substudy. Details of the methodologic evaluations of biomarker levels and microarray evaluation of skin-biopsy specimens are provided in the Supplementary Appendix.

### STATISTICAL ANALYSIS

No formal sample-size calculations were performed for Studies M4A and M4B, and observations from these two studies were pooled because the studies had a similar design and similar patient populations. In Study M12, we calculated that an enrollment of 50 patients per group would provide the study with 97% power to detect a between-group difference of 40 percentage points in the percentage change from baseline in the EASI scores, assuming a standard deviation of 50% for the percentage change from baseline to week 12, with the use of a two-sided test at the 0.049 significance level. In Study C4, categorical variables were analyzed with the use of Fisher's exact test, continuous variables with the use of analysis of covariance with treatment as the main factor and baseline values as covariates, and time-to-event variables with the use of a log-rank test. Nominal P values were estimated.

Details of the statistical analyses are provided in the Supplementary Appendix.

## RESULTS

### PATIENTS

The enrollment and disposition of the patients are shown in Table S2 in the Supplementary Appendix. Withdrawal from the study occurred approximately twice as frequently in the placebo groups as in the dupilumab groups, and were due primarily to lack of efficacy. The demographic and clinical characteristics of the patients at baseline were similar between the study groups and across the studies (Table 1, and Table S3 in the Supplementary Appendix).

### EFFICACY

*Monotherapy at 4 Weeks and 12 Weeks*

In Studies M4A and M4B, dupilumab was associated with rapid and dose-dependent improvements in all clinical indexes (Fig. 1A and 1B and Table 2), as well as reductions in the serum levels of TARC (Fig. S2A and Table S4 in the Supplementary Appendix). Similar responses were observed at the 4-week time point in Study M12 (Fig. 1C and 1D and Table 2, and Fig. S2B and Table S4 in the Supplementary Appendix). Study M12 showed that continued treatment resulted in further improvements (e.g., the proportion of patients with EASI-50 increased to 85%, and the mean score on the pruritus numerical-rating scale decreased by 55.7% at 12 weeks [Table 2]), and the number of patients with an investigator's global assessment score of 0 (clear) or 1 (almost clear) more than doubled between 4 and 12 weeks (Table 2, and Fig. S3 in the Supplementary Appendix). The percentage reduction in the EASI score over the duration of the study was consistently greater with dupilumab than with placebo, in analyses in which three different statistical methods were used to control for missing data (Fig. S4 in the Supplementary Appendix). By the end of 12 weeks, the proportions of patients with EASI-50 and EASI-75 (a 75% reduction in the EASI score) were greater in the dupilumab group than in the placebo group (Table 2).

Dupilumab monotherapy was associated with a reduction in serum levels of TARC and total IgE in all the monotherapy studies (Table S4 and

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

| Characteristic | 4-Wk Monotherapy | | 12-Wk Monotherapy | | 4-Wk Combination Therapy | |
|---|---|---|---|---|---|---|
| | Placebo (N=16) | Dupilumab (N=51) | Placebo (N=54) | Dupilumab (N=55) | Placebo and Topical Glucocorticoids (N=10) | Dupilumab and Topical Glucocorticoids (N=21) |
| Age — yr | 37.4±4.3 | 42.6±1.9 | 39.4±1.7 | 33.7±1.4 | 37.8±5.3 | 36.0±2.5 |
| Male sex — no. (%) | 11 (69) | 28 (55) | 27 (50) | 31 (56) | 5 (50) | 8 (38) |
| White race — no. (%) | 13 (81) | 39 (76) | 54 (100) | 55 (100) | 10 (100) | 20 (95) |
| Body-mass index† | 25.7±1.5 | 26.6±0.9 | 24.5±0.6 | 25.9±0.7 | 23.9±1.1 | 25.3±0.7 |
| EASI score‡ | 22.8±3.0 | 30.0±2.0 | 30.8±1.9 | 28.4±1.8 | 24.1±4.0 | 23.1±2.7 |
| Investigator's global assessment score§ | 3.6±0.2 | 3.8±0.1 | 4.0±0.1 | 3.9±0.1 | 3.4±0.2 | 3.4±0.1 |
| Body-surface area affected — % | 40.3±6.5 | 51.4±3.5 | 50.8±3.3 | 46.8±3.3 | 38.9±7.6 | 40.4±4.6 |
| 5-D pruritus scale score¶ | 16.9±1.0 | 19.3±0.5 | 18.7±0.5 | 18.4±0.4 | NA | NA |
| Pruritus numerical-rating scale score‖ | 5.8±0.5 | 6.0±0.2 | 5.8±0.3 | 6.1±0.2 | 5.0±0.4 | 6.4±0.4 |

* Plus–minus values are means ±SE. The 4-week monotherapy studies included the study conducted in the United States (Study M4A) and the study conducted multinationally (Study M4B). The 12-week monotherapy study was Study M12, and the 4-week study of combination therapy was Study C4. NA denotes not assessed.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ 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.[9,10]

§ The investigator's global assessment of the severity of atopic dermatitis was scored on a scale of 0 (clear) to 5 (very severe).

¶ Scores on the 5-D pruritus scale range from 5 to 25, with higher scores indicating a greater effect of itch.[11]

‖ Scores on the pruritus numerical-rating scale range from 0 (no itch) to 10 (worst imaginable itch).[12]

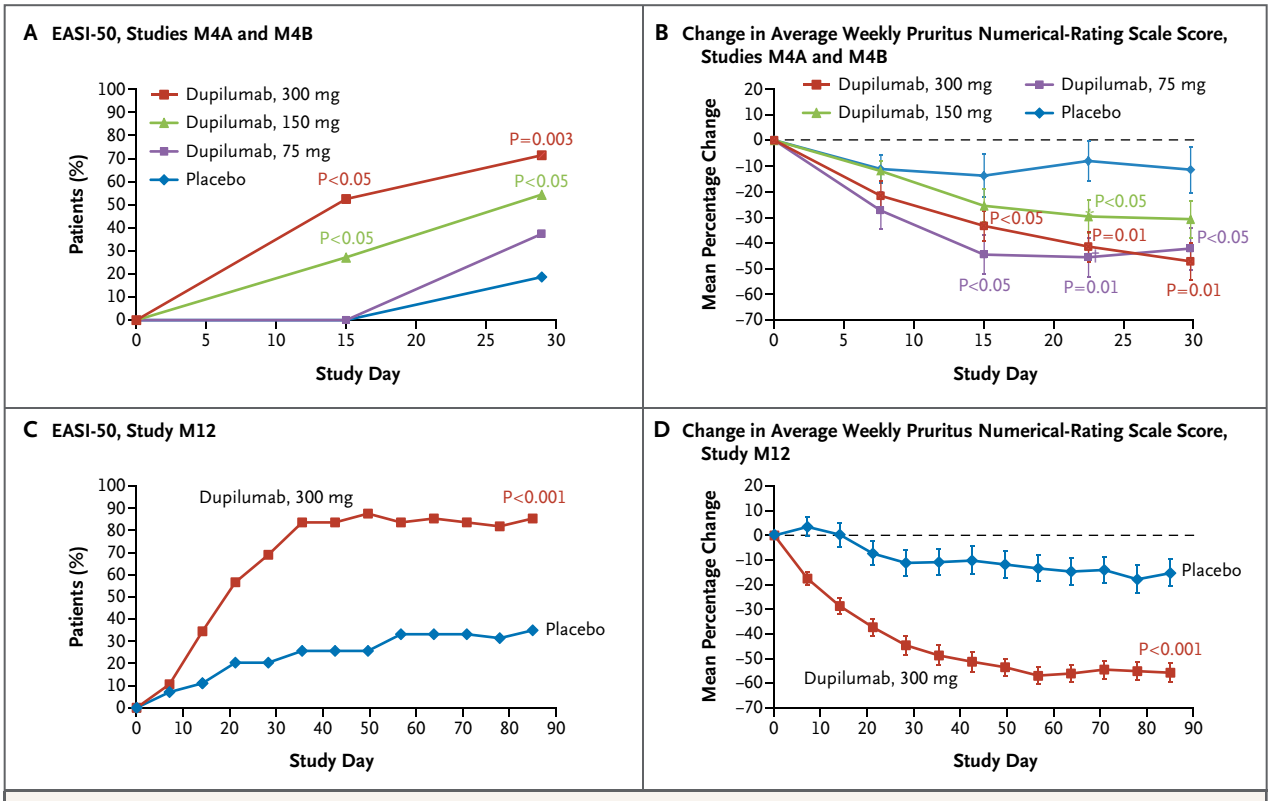


**Figure 1. Key Efficacy End Points in Studies M4A and M4B Combined and in Study M12.**

In Studies M4A and M4B (4-week studies of dupilumab monotherapy conducted in the United States and multinationally, respectively), treatment with dupilumab resulted in a dose-dependent increase in the proportion of patients who had a 50% improvement in the Eczema Area and Severity Index score (EASI-50) at day 29 (Panel A) and also a reduction in pruritus, as shown by the mean percentage change in the score on the pruritus numerical-rating scale (on which higher numbers indicate worse itch) over time (Panel B). At day 85 in Study M12 (a 12-week trial of dupilumab monotherapy), treatment with 300 mg of dupilumab, as compared with placebo, resulted in a significantly greater proportion of patients who met the criterion for EASI-50 (Panel C) and had a significant reduction in the score on the pruritus numerical-rating scale over time (Panel D). All analyses with missing data were based on the last-observation-carried-forward method. I bars in Panels B and D represent standard errors, and the dashed line indicates baseline.

Fig. S5A and S5B in the Supplementary Appendix), although the reductions in IgE occurred more slowly than the reductions in TARC, presumably owing to the longer half-life of IgE. The 300-mg dose of dupilumab was associated with the greatest clinical and biomarker responses (Fig. 1, and Fig. S2A and S5A in the Supplementary Appendix).

*Combination Therapy at 4 Weeks*

To explore the potential benefits of dupilumab in combination with the standard of care, we compared topical glucocorticoids plus dupilumab with topical glucocorticoids plus placebo. All the patients who received dupilumab plus topical glucocorticoids met the criteria for EASI-50 by 4 weeks, as compared with only 50% of those who received topical glucocorticoids plus placebo (P=0.002) (Fig. S6A in the Supplementary Appendix). Similarly, the combination of dupilumab plus topical glucocorticoids, as compared with topical glucocorticoids plus placebo, was associated with a rapid and sustained reduction in the score on the pruritus numerical-rating scale (P=0.005) (Fig. S6B in the Supplementary Appendix) and in most other clinical and biomarker indexes (Table 2, and Table S4 and Fig. S2C and S5C in the Supplementary Appendix). These changes were observed despite consistent trends at each time point suggesting a 50% reduction in the use of topical glucocorticoids by the patients who received dupilumab, as compared with those who received placebo (P=0.16) (Fig. S7 in the Supplementary Appendix).

**Table 2. Efficacy End Points.***

| End Point | 4-Wk Monotherapy | | 12-Wk Monotherapy | | 4-Wk Combination Therapy | |
|---|---|---|---|---|---|---|
| | Placebo (N=16) | Dupilumab† (N=51) | Placebo (N=54) | Dupilumab (N=55) | Placebo and Topical Glucocorticoids (N=10) | Dupilumab and Topical Glucocorticoids (N=21) |
| ≥EASI-50 — no. of patients (%)‡ | | | | | | |
| Day 29 | 3 (19) | 30 (59)§ | 11 (20) | 38 (69) | 5 (50) | 21 (100)§ |
| Day 85 | NA | NA | 19 (35) | 47 (85)¶ | NA | NA |
| ≥EASI-75 — no. of patients (%)‡ | | | | | | |
| Day 29 | 1 (6) | 15 (29) | 3 (6) | 19 (35) | 4 (40) | 13 (62) |
| Day 85 | NA | NA | 8 (15) | 34 (62) | NA | NA |
| Change in pruritus numerical-rating scale score — %§ | | | | | | |
| Day 29 | −18.6±12.1 | −41.3±4.3§ | −11.2±5.4 | −44.5±3.9 | −24.7±15.0 | −70.7±4.7§ |
| Day 85 | NA | NA | −15.1±5.7 | −55.7±3.8 | NA | NA |
| Investigator's global assessment | | | | | | |
| Score of 0 or 1 — no. of patients (%) | | | | | | |
| Day 29 | 1 (6) | 6 (12) | 2 (4) | 10 (18) | 3 (30) | 11 (52) |
| Day 85 | NA | NA | 4 (7) | 22 (40)¶ | NA | NA |
| Change in score — % | | | | | | |
| Day 29 | −16.0±7.1 | 34.8±3.1§ | −9.9±3.2 | −35.9±2.9 | −30.6±12.3 | −52.5±4.7§ |
| Day 85 | NA | NA | −14.7±3.7 | −49.5±3.5 | NA | NA |
| Change in EASI score — percentage points | | | | | | |
| Day 29 | −25.4±10.1 | −57.7±3.9¶ | −17.4±5.5 | −62.3±3.2 | −52.5±12.5 | −75.6±2.9 |
| Day 85‖ | NA | NA | −23.3±6.7 | −74.0±3.6¶ | NA | NA |
| Change in percentage of body-surface area affected — percentage points | | | | | | |
| Day 29 | −15.3±9.0 | −37.4±4.7§ | −11.4±6.5 | −42.8±5.8 | −36.5±16.1 | −63.6±5.8 |
| Day 85 | NA | NA | −17.8±7.2 | −59.9±6.4 | NA | NA |

* Plus–minus values are means ±SE, except as otherwise noted. The end points listed here are the primary end points for the 12-week monotherapy study and the prespecified exploratory end points for the 4-week monotherapy and combination studies. Percentage-change values are change from baseline.
† Values are for all dupilumab doses combined.
‡ EASI-50 and EASI-75 represent reductions of 50% and 75%, respectively, in the EASI score.
§ P<0.05 for the comparison with placebo.
¶ P<0.001 for the comparison with placebo.
‖ This end point was the primary efficacy end point in the 12-week monotherapy study.

### SKIN-BIOPSY EXPRESSION PROFILING

The 18 patients from the two 4-week monotherapy studies who participated in the substudy of expression profiling in skin-biopsy specimens had clinical responses that were similar to those in the other patients from those studies.[17] Significant dose-dependent changes in the RNA-expression profile were observed in the patients after 4 weeks of treatment with 150 mg or 300 mg of dupilumab. The gene-expression profiles of samples from lesions in dupilumab-treated patients approached the profile of samples from nonlesional sites (Fig. 2A); improvements of 24% and 49% were observed in the lesional transcriptome in the samples from patients who received the 150-mg and 300-mg doses of dupilumab, re-

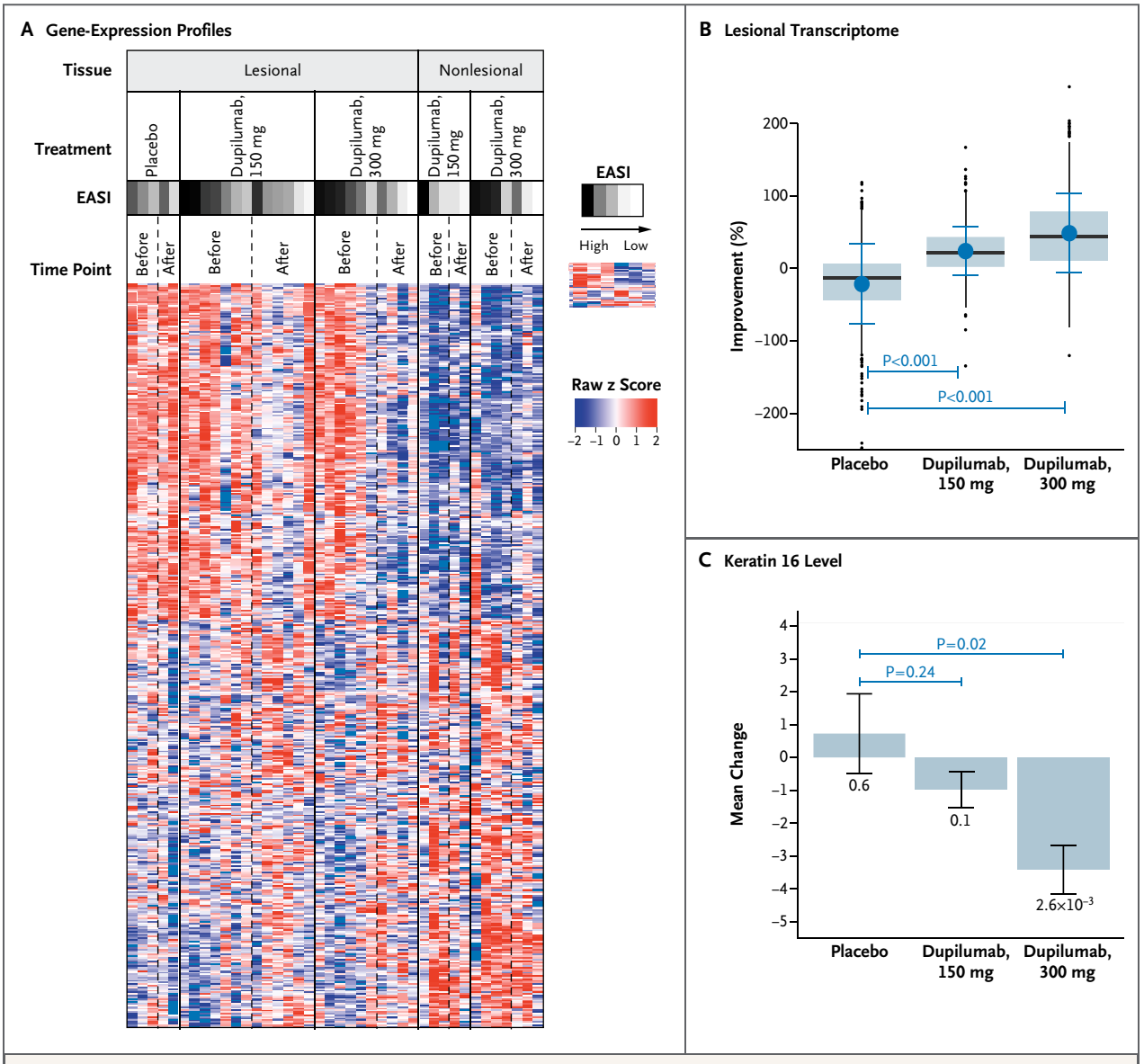


**Figure 2. Molecular Changes in the Atopic Dermatitis Transcriptome in Studies M4A and M4B.**

The heat map in Panel A represents changes in the expression profile of the lesional transcriptome of atopic dermatitis, defined by differentially expressed genes between lesional and nonlesional skin at baseline and after 4 weeks of treatment with 150 or 300 mg of dupilumab or receipt of placebo. A robust, dose-dependent improvement in the lesional transcriptome is evident with dupilumab. Red boxes indicate up-regulated genes, and blue boxes down-regulated genes. The gray-spectrum boxes at the top of each column represent a decrease in the EASI scores from high (black) to low (white), before and after 4 weeks of treatment. The box plots in Panel B show that the percentage improvement in the lesional transcriptome was dose-dependent after 4 weeks of treatment with dupilumab, whereas an exacerbation of the signature was observed in the placebo group. Blue dots indicate means, and the blue I bars 1 SD. The black horizontal lines indicate medians, the vertical black lines values that are within 1.5 times the interquartile range of the median, and the top and bottom of the gray boxes the 75th and 25th percentiles, respectively. The black dots indicate outliers. Panel C shows bar plots representing the mean change after treatment in messenger RNA expression levels ($\log_2$ [post-treatment] − $\log_2$ [pretreatment]) of the proliferation marker keratin 16, as measured by means of a reverse-transcriptase–polymerase-chain-reaction assay. The level of keratin 16 was significantly reduced in the group of patients that received 300 mg of dupilumab, as compared with the group that received placebo (P=0.02), indicating improvement in epidermal pathologic features or hyperplasia after 4 weeks of treatment. A total of 10 patients with complete pretreatment and post-treatment samples were included in this analysis. I bars in Panel C indicate standard errors.

spectively, as compared with an exacerbation of 21% in the lesional transcriptome in the samples from those who received placebo (P<0.001) (Fig. 2B). These improvements paralleled the reductions in the EASI scores. Significant dose-dependent reductions in the expression of keratin 16 (K16), a marker of keratinocyte proliferation and regulator of innate immunity,[18] suggest that dupilumab reduces the epidermal hyperplasia observed in lesions caused by atopic dermatitis (Fig. 2C).

### CORRELATIONS BETWEEN CLINICAL RESPONSE AND BIOMARKERS

The Th2 biomarker levels measured at study entry (eosinophil counts, TARC, and IgE) showed weak or no correlation with improvements in the EASI or pruritus scores (as assessed by means of the 5-D and numerical-rating scales) after dupilumab treatment (Table S5 in the Supplementary Appendix). However, significant correlations were observed between reductions in the TARC level and changes in pruritus scores (Table S6 in the Supplementary Appendix). At the end of the 12-week monotherapy study, there was a significant correlation between the percentage change in the TARC level and the percentage change in the scores on the pruritus numerical-rating scale (r=0.53; P<0.001) and the 5-D pruritus scale (r=0.40; P=0.004) (Table S6 in the Supplementary Appendix).

### SAFETY

Adverse events occurred with a similar frequency in the placebo and dupilumab groups in all the studies (Table 3). Most adverse events were mild or moderate in severity and were transient. The most common adverse events were nasopharyngitis and headache, which were generally reported at a higher frequency among patients receiving dupilumab than among those receiving placebo. Injection-site reactions were observed at a higher frequency in the dupilumab group in the 12-week monotherapy study than in any treatment group in the other studies. Clinically significant values for clinical laboratory tests, vital signs, and electrocardiographic assessments were balanced between treatment groups in each of the studies, and no trends were observed.

There was a numerical imbalance with respect to serious adverse events, and the proportion of patients with serious adverse events was greater in the placebo group in the 12-week monotherapy study than in any other study group (Table S7 in the Supplementary Appendix). Across all studies, there were 13 serious adverse events in 9 of 80 patients in the placebo groups, as compared with 2 events in 2 of 127 patients in the dupilumab groups; excluding events related to atopic dermatitis, 7 patients in the placebo groups reported 9 serious adverse events (Table S7 in the Supplementary Appendix). A total of 5 patients in the placebo groups discontinued the study owing to adverse events, as compared with 1 in the dupilumab group.

The imbalance in serious adverse events appeared to result from a greater number of skin infections and exacerbations of atopic dermatitis

**Table 3. Adverse Events.***

| Variable | 4-Wk Monotherapy | | 12-Wk Monotherapy | | 4-Wk Combination Therapy | |
|---|---|---|---|---|---|---|
| | Placebo (N=16) | Dupilumab (N=51) | Placebo (N=54) | Dupilumab (N=55) | Placebo and Topical Glucocorticoids (N=10) | Dupilumab and Topical Glucocorticoids (N=21) |
| Any adverse event — no. of patients (%) | 14 (88) | 44 (86) | 43 (80) | 42 (76) | 7 (70) | 12 (57) |
| Mean no. of adverse events per patient | 2.50 | 2.14 | 2.94 | 2.96 | 1.40 | 1.95 |
| Serious adverse event — no. of patients (%) | 1 (6) | 1 (2) | 7 (13) | 1 (2) | 1 (10) | 0 |
| Study discontinuation due to adverse event — no. of patients (%) | 1 (6) | 0 | 3 (6) | 1 (2) | 1 (10) | 0 |
| Skin infection — no. of patients (%) | 2 (12) | 2 (4) | 13 (24) | 3 (5) | 1 (10) | 1 (5) |

* The adverse events included here, which are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities* (version 13.1 for study M4A, version 14.0 for Study M4B, and version 14.1 for Studies M12 and C4), were those that occurred in at least 5% of the patients in any study group.

in the placebo groups. A total of 17 skin infections occurred among the 80 patients in the placebo groups (0.20 infections per patient), as compared with 6 skin infections among the 127 dupilumab-treated patients (0.05 infections per patient), corresponding to a rate of skin infection in the placebo group that was 4 times as high as the rate in the dupilumab group (Table 3, and Table S7 in the Supplementary Appendix). In the 12-week monotherapy study, 14 skin infections occurred in the placebo group, as compared with 4 in the dupilumab group. Among the patients in the placebo group, 7 required hospitalization (for skin infection in 3 patients and for exacerbations of atopic dermatitis in 4), as compared with 1 in the dupilumab group (for a facial fracture). There were no opportunistic infections, serious or otherwise, reported in dupilumab-treated patients, and no deaths in either study group.

## DISCUSSION

Dupilumab treatment in adults with moderate-to-severe atopic dermatitis resulted in marked reductions in signs, symptoms, and associated biomarker levels in two 4-week monotherapy trials (Studies M4A and M4B), one 12-week monotherapy trial (Study M12), and a 4-week combination study with topical glucocorticoids (Study C4). The consistency of these observations across four studies provides strong support for the pathophysiological importance of Th2 cytokines in atopic dermatitis. Dupilumab treatment — as monotherapy or as part of combination therapy — was associated not only with improvement in skin lesions but also with rapid and substantial reductions in pruritus, which is a major contributor to the reduced quality of life experienced by patients with atopic dermatitis.[1]

Overall, side effects and adverse events were balanced between the dupilumab and placebo groups, but the placebo groups had higher rates of study discontinuation, apparently owing to a lack of therapeutic benefit. The placebo groups also had higher rates of skin infection, supporting the possibility that dupilumab improves skin-barrier function. Injection-site reactions occurred more frequently with dupilumab than with placebo, and all were classified as mild. Nasopharyngitis and headache were reported more frequently with dupilumab than with placebo, a finding also reported in a study of dupilumab in patients with asthma and elevated eosinophil levels.[8]

Dupilumab was associated with a reduction in all assayed biomarker levels, as well as with improvement of the lesional transcriptome of atopic dermatitis. The dose-dependent decrease in K16, a marker of keratinocyte proliferation and innate immunity, suggests that the epidermal abnormalities associated with atopic dermatitis might be reduced with dupilumab treatment. We also found a substantial dupilumab-associated reduction in the level of TARC, a key Th2 biomarker. Both the levels of TARC and the change in the levels were significantly correlated with measures of pruritus during the study. Pretreatment levels of serum total IgE, TARC, and peripheral eosinophilia were not highly predictive of a clinical response to dupilumab.

Dupilumab blocks the actions of the Th2 cytokines interleukin-4 and interleukin-13. The results of the studies reported here extend the potential benefit of this new biologic therapy beyond asthma to a second atopic disorder, atopic dermatitis.[19] Dupilumab treatment resulted in highly reproducible improvements across all clinical end points when the drug was administered as monotherapy and, even more so, when it was combined with topical glucocorticoids. Using an integrated translational approach, we found that these clinical improvements were coupled with reductions in levels of serum biomarkers and improvements in the lesional transcriptome.

Our findings provide evidence that allergic asthma and atopic dermatitis might have related drivers — in particular, interleukin-4 and interleukin-13 — and that these diseases may benefit from the same therapeutic approach. Furthermore, this commonality suggests that other atopic diseases may share these drivers, providing a rationale for studying dupilumab in such conditions.

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## REFERENCES


1. DaVeiga SP. Epidemiology of atopic dermatitis: a review. Allergy Asthma Proc 2012;33:227-34.
2. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012;26:1045-60.
3. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. J Eur Acad Dermatol Venereol 2012;26:1176-93.
4. Lübbe J, Friedlander SF, Cribier B, et al. Safety, efficacy, and dosage of 1% pimecrolimus cream for the treatment of atopic dermatitis in daily practice. Am J Clin Dermatol 2006;7:121-31.
5. Frankel HC, Qureshi AA. Comparative effectiveness of topical calcineurin inhibitors in adult patients with atopic dermatitis. Am J Clin Dermatol 2012;13:113-23.
6. De Benedetto A, Kubo A, Beck LA. Skin barrier disruption: a requirement for allergen sensitization? J Invest Dermatol 2012;132:949-63.
7. Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130:1344-54.
8. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013;368:2455-66.
9. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10:11-8.
10. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012;67:99-106.
11. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol 2010;162:587-93.
12. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol 2012;92:502-7.
13. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). Allergy 2001;56:841-9.
14. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. J Dermatol Sci 2010;58:1-7.
15. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997;195:10-9.
16. Eichenfield LF. Consensus guidelines in diagnosis and treatment of atopic dermatitis. Allergy 2004;59:Suppl 78:86-92.
17. Hamilton JD, Suarez-Farinas M, Kostic A, et al. Blocking IL-4Rα signaling with REGN668/SAR231893 rapidly suppresses major pathogenic pathways in severe atopic dermatitis. J Invest Dermatol 2013;133:Suppl:S178. abstract.
18. Lessard JC, Piña-Paz S, Rotty JD, et al. Keratin 16 regulates innate immunity in response to epidermal barrier breach. Proc Natl Acad Sci U S A 2013;110:19537-42.
19. Suárez-Fariñas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol 2013;132:361-70.