Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD)

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Background: Moderate to severe atopic dermatitis (AD) is associated with substantial patient burden despite current therapies.

Objective: We sought to evaluate dupilumab treatment on patient-reported outcomes in adults with moderate to severe AD.

Methods: Adults (N = 380) with moderate to severe AD inadequately controlled by topical medications were randomized to 16 weeks of double-blind, subcutaneous treatment with dupilumab 100 mg every 4 weeks, 200 mg every 2 weeks, 300 mg every 2 weeks, 300 mg once weekly, or placebo. Patient-reported outcomes included pruritus numeric rating scale; patient-reported sleep item on Scoring AD scale; Patient-Oriented Eczema Measure; Hospital Anxiety and Depression Scale; Dermatology Life Quality Index; and 5-dimension 3-level EuroQol.

Results: Dupilumab reduced peak itch at 16 weeks relative to placebo by 1.1 to 3.2 points on numeric rating scale (P < .0001 all doses, except 100 mg every 4 weeks P < .05); improved sleep and health-related quality of life on Dermatology Life Quality Index and 5-dimension 3-level EuroQol (P < .05 all doses, except 100 mg every 4 weeks); and reduced anxiety and depression symptoms (P < .05 all doses).
Dupilumab's effects appeared early and achieved clinically relevant improvements without significant safety concerns.

**Limitations:** There are potential cultural differences affecting patient-reported outcome responses. Outcomes were secondary or exploratory end points.

**Conclusion:** Dupilumab produced early and sustained patient-reported and clinically relevant improvements in sleep, mental health, and health-related quality of life; the two 300-mg dose regimens resulted in greatest benefits. (J Am Acad Dermatol 2016;75:506-15.)

**Key words:** adults; atopic dermatitis; disease burden; dupilumab; patient-reported outcomes; pruritus; quality of life.

Atopic dermatitis (AD) is a chronic disease characterized by T-helper (Th)-2-mediated skin inflammation and intense, persistent, and debilitating itch, particularly in patients with moderate to severe disease. In addition, patients are burdened by sleep loss, anxiety and depression, and diminished health-related quality of life (HRQoL), including decreases in daily activities and productivity at work or school.

Use of dupilumab, a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor-α and inhibits signaling of the Th2 cytokines IL-4 and IL-13, resulted in symptomatic and clinical improvements in AD. A subsequent phase IIb randomized, controlled trial in patients with moderate to severe AD further supported a favorable safety profile and treatment benefits, including significant improvements relative to placebo on objective clinical measures of disease activity. Given the patient burden associated with AD and the increasing importance of incorporating the patient perspective in clinical trials, patient-reported outcomes (PROs) were included in this phase IIb study as secondary or exploratory end points to evaluate treatment effects of dupilumab on symptoms and HRQoL.

**METHODS**

**Study design**

This was an international, randomized, placebo-controlled, double-blind, parallel group dose-ranging study; complete details of study design and methods along with primary results of changes in objective disease and full safety analysis have been previously reported. ClinicalTrials.gov registration number is NCT01859988 and EudraCT number is 2012-003651-11. The protocol was approved by the appropriate institutional review boards/ethics committees at each study site. All patients provided written informed consent.

**Patients**

Patients were adults (age ≥18 years) with moderate to severe AD, defined by Investigator Global Assessment score 3 or higher, with disease not adequately controlled by topical medications (documented history within 6 months) or for whom topical treatment was inadvisable. Patients were required to have chronic AD, defined by consensus criteria, present for 3 or more years before screening; an Eczema Area and Severity Index score of 12 or higher at screening and 16 or higher at baseline; an Investigator Global Assessment score of 3 or higher at screening and baseline; and AD involvement 10% or more of body surface area at screening and baseline. Key exclusion criteria were: active acute or chronic infections; use of topical medications for AD (other than bland emollients) within 1 week of baseline; systemic immunosuppressive/immunomodulating drugs within 4 weeks of baseline; or significant comorbidities or laboratory abnormalities.

**Study treatments**

Patients were randomized to treatment with subcutaneous dupilumab 300 mg once weekly (qw), 300 mg every 2 weeks (q2w), 200 mg q2w, 300 mg every 4 weeks (q4w), or 100 mg q4w, or placebo qw. The first treatment was a loading dose of two 2-mL subcutaneous injections containing 600 mg dupilumab.

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**CAPSULE SUMMARY**

- The substantial patient burden associated with moderate to severe atopic dermatitis demonstrates need for effective therapies.
- Dupilumab resulted in significant and clinically relevant improvements in patient-reported outcomes assessing symptoms and health-related quality of life.
- Dupilumab effects on patient-reported outcomes complemented clinical measures, demonstrating efficacy for atopic dermatitis across multiple domains important to patients.
Abbreviations used:

AD: atopic dermatitis
DLQI: Dermatology Life Quality Index
EQ-5D-3L: 5-dimension 3-level EuroQol
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
IL: interleukin
MCID: minimal clinically important difference
NRS: numeric rating scale
POEM: Patient-Oriented Eczema Measure
PRO: patient-reported outcome
qw: once weekly
q2w: every 2 weeks
q4w: every 4 weeks
SCORAD: Scoring Atopic Dermatitis
TEAE: treatment-emergent adverse event

Outcomes

Outcomes measures are described in Table I. Dermatology-related PROs in the current analysis were the pruritus numeric rating scale (NRS) using the weekly averaged peak value\(^1\); the Scoring AD (SCORAD) sleep item\(^2\); the Patient-Oriented Eczema Measure (POEM)\(^3\); and the Dermatology Life Quality Index (DLQI)\(^4\). Other PROs included the Hospital Anxiety and Depression Scale (HADS)\(^5\) and the 5-dimension 3-level EuroQol (EQ-5D-3L)\(^6\), which relied on United Kingdom-based preferences to estimate the utility index.\(^7\) Values of the minimal clinically important difference (MCID), reflecting the smallest change in score that represents a clinically relevant change, have been estimated for POEM (3.4)\(^8\), DLQI (5)\(^9\), and EQ-5D-3L health index (0.074).\(^10\)

Changes in pruritus NRS and POEM total scores were secondary end points; all other assessments were exploratory. The safety profile was based on incidence of treatment-emergent adverse events (TEAEs).\(^11\)

Statistical analyses

Evaluation of efficacy end points was based on the full analysis set, defined as all randomized patients who received 1 or more doses of study drug, with last observation carried forward for imputation of missing continuous variables. Analysis of covariance was used for PROs with continuous variables, controlling for treatment with the relevant baseline value as the covariate. PROs with categorical variables were analyzed using a Cochran-Mantel-Haenszel test. For binary variables, missing values were treated as nonresponders. Least squares mean estimates by treatment group were generated and were used to compare the improvement from baseline for each of the dupilumab groups versus placebo. A mixed model repeated measures analysis was also performed that included treatment, baseline, visit, region, baseline Investigator Global Assessment strata, treatment by visit, and baseline by visit. All statistical tests were 2-sided at the 5% level. The study was not powered for statistical comparisons among dupilumab doses.

The cumulative percentage of patients experiencing an improvement at least equal to the value of absolute change in peak pruritus NRS score from baseline to week 16 was plotted post hoc by treatment group. Responder analyses were performed ad hoc to evaluate the proportion of patients who reported changes in scores that met or exceeded the MCID on POEM and DLQI. In a post hoc analysis to estimate lost productivity among patients who were employed or enrolled in school full-time, the number of missed work/school days was cumulated at each visit through week 16 and negative binomial regression compared the cumulated mean values between dupilumab and placebo groups at week 16. In addition, the proportion of patients with no missed days was cumulated, and group comparisons at week 16 were derived from logistic regression.

All analyses were performed using Statistical Analysis Software (SAS, Version 9.2, SAS Institute, Cary, NC).

RESULTS

Patients

Of 452 patients assessed for eligibility, 380 were randomized and 379 received 1 or more doses of study treatment (placebo, n = 61; dupilumab, n = 318). Among these patients, 86.9% and 92.2% in the placebo and dupilumab groups, respectively, completed the 16-week treatment period. Baseline demographic and clinical characteristics were similar among treatments (Table II).

Itch and other skin symptoms

Relative to placebo, dupilumab significantly reduced itch (daily peak pruritus NRS weekly average) from baseline at week 16 in a dose-dependent manner (Fig 1, A, and Table III). The 300-mg qw dose showed the greatest reductions relative to placebo, least squares mean change −3.2 versus −0.1 points (P < .0001), representing least squares mean percent changes of −46.9% versus 5.1% (P < .0001).\(^12\) Significant improvements relative to placebo (P < .05) were observed at all doses as
<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Description; items/domains</th>
<th>Recall period</th>
<th>Range/interpretation</th>
<th>Assessment frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus NRS&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Used in this analysis to evaluate change from baseline at wk 16 in peak itch intensity</td>
<td>Past 24 h</td>
<td>0 = No itch to 10 = worst imaginable itch</td>
<td>Daily</td>
</tr>
<tr>
<td>SCORAD patient-reported sleep item&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Assesses sleep loss</td>
<td>Past 3 d</td>
<td>VAS of 0 = no sleep loss, 10 = worst imaginable sleep loss</td>
<td>Baseline, wk 1-4, 6, 8, 10, 12, 14-16</td>
</tr>
<tr>
<td>POEM&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Evaluates time spent in the past week with AD signs and symptoms; individual items of itchy, bleeding, oozing, cracked, flaking, and dry/rough skin, and their impact on sleep</td>
<td>Past week</td>
<td>Items rated on a 5-point scale of 0 = no days to 4 = every day; score range 0-28 with higher scores indicating greater severity</td>
<td>Baseline, wk 2, 4, 8, 12, 16</td>
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<tr>
<td>DLQI&lt;sup&gt;22&lt;/sup&gt;</td>
<td>10-Item questionnaire evaluating the impact of skin condition on HRQoL during the past week; 6 domains of symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment</td>
<td>Past week</td>
<td>Score range 0-30; higher scores indicate greater impact</td>
<td>Baseline, wk 2, 4, 8, 12, 16</td>
</tr>
<tr>
<td>HADS&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Screens for symptoms of anxiety and depression; anxiety and depression subscales each with 7 items</td>
<td>Past week</td>
<td>Items rated on a 4-point scale with a score range of 0-21 for each subscale; scores ≤7 are considered normal, 8-10 borderline, and ≥11 indicate clinical anxiety or depression</td>
<td>Baseline and end of treatment (16 wk)</td>
</tr>
<tr>
<td>EQ-5D-3L&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Assesses health status; dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a VAS health state thermometer</td>
<td>Today</td>
<td>Dimensions rated using responses of no problem, some/moderate problems, or extreme problems/unable to do; VAS of 0 = worst health to 100 = best health; an overall health index is generated (−0.59 = worst health to 1 = best health using the United Kingdom—based preferences&lt;sup&gt;25&lt;/sup&gt;)</td>
<td>Baseline and end of treatment (16 wk)</td>
</tr>
</tbody>
</table>

<sup>AD</sup>, Atopic dermatitis; <sup>DLQI</sup>, Dermatology Life Quality Index; <sup>EQ-5D-3L</sup>, 5-dimension 3-level EuroQoL; <sup>HADS</sup>, Hospital Anxiety and Depression Scale; <sup>HRQoL</sup>, health-related quality of life; <sup>NRS</sup>, numeric rating scale; <sup>POEM</sup>, Patient-Oriented Eczema Measure; <sup>SCORAD</sup>, Scoring Atopic Dermatitis; <sup>VAS</sup>, visual analog scale.
early as week 1 and remained significant throughout the study (Fig 1, A).

The cumulative distribution function plot (Fig 2) for the pruritus NRS provides information about the percentages of patients from each treatment group who achieved a change of at least a certain value in peak pruritus NRS score from baseline to week 16. The curves demonstrate discrimination between placebo and all doses of dupilumab across almost the entire improvement range. The percentages of patients achieving response thresholds of 2+, 3+, and 4-point reductions in NRS score (ie, itch reduction) were substantially higher in patients treated with dupilumab at each dose compared with placebo, including the lowest dupilumab dose (Fig 2).

All dupilumab doses except 100 mg q4w also significantly improved other skin symptoms at 16 weeks relative to placebo (P < .001) as measured by POEM total score (Fig 1, B, and Table III), and individual items of itchy, bleeding, oozing, cracked, flaking, and dry/rough skin (P < .05; data not shown). Improvements in POEM total score were observed at the first POEM assessment 2 weeks after treatment initiation (all P < .0001), also exceeding the MCID for POEM, and were maintained over treatment duration except for the 100-mg q4w dose (Fig 1, B). Except for the 100-mg q4w dose, the majority of patients receiving dupilumab reported a change in POEM total score at week 16 equal to or greater than MCID (63.9%-88.9%) (Table III) that was significantly greater than placebo (26.0%; P < .0001).

Among the subset of patients who reported moderate or severe pain/discomfort on the EQ-5D-3L at baseline (n = 263), improvements were largest for the dupilumab 200-mg q2w, 300-mg q2w and 300-mg qw doses; 53.8%, 51.2%, and 57.4% of these patients, respectively, reported no pain/discomfort at week 16, compared with 20.5% of placebo-treated patients (P < .005 vs placebo for all 3 doses based on change from baseline; data not shown).

### Sleep
Patients reported better sleep on the sleep items from the SCORAD and POEM measures that was significant relative to placebo (P < .05) at all doses except 100 mg q4w (Table III). Significant sleep improvements relative to placebo (P < .05) were consistently reported with dupilumab at the earliest evaluated time points, 1 week for SCORAD (all doses except 100 mg q4w) (Fig 1, C) and 2 weeks for POEM (all doses; data not shown) and were maintained over the treatment duration except for the 100-mg q4w dose.

### Anxiety, depression, HRQoL, and lost productivity
Patients treated with dupilumab reported significant improvements in psychological symptoms at 16 weeks as indicated by reductions in HADS total score (Table III). The 300-mg qw and 300-mg q2w doses demonstrated significance compared with placebo (P < .05) on both the HADS anxiety and depression subscales (Table III). In addition, among the subset of patients who reported HADS anxiety and depression subscale scores indicative of anxiety or depression (≥11) at baseline (n = 94), 29.2% (300 mg q2w) and 25.0% (300 mg qw) of patients had scores of 11 or more at week 16 compared with 77.8% of patients taking placebo, representing reductions of 70.8% and 75.0%, respectively, versus 22.2% with placebo (P < .05 both doses; data not shown). Similarly, among patients who reported being moderately or extremely anxious or depressed on the EQ-5D-3L at baseline (n = 178), the largest improvement was with the 300-mgqw dose; only 19.4% remained anxious or depressed compared with 76.0% of patients taking placebo (P < .001 based on change from baseline score; data not shown).

Dupilumab also significantly improved HRQoL on the DLQI at week 16 at all doses except 100 mg qw (Table III). Changes in DLQI total score were...
observed at 2 weeks after treatment initiation (Fig 1, D), the earliest DLQI assessment, and except for the 100-mg q4w dose, exceeded the MCID over the treatment duration, indicating a clinically relevant improvement in HRQoL. Higher proportions of patients taking dupilumab reported a change in DLQI total score equal to or greater than MCID at week 16 (38.5%-71.4%) than placebo (27.9%), with all doses except 100 mg q4w showing significance (P < .05) (Table III). In addition, all dupilumab doses except 100 mg q4w resulted in consistent and significant (P < .05) improvements on each of the 6 DLQI domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment) relative to placebo at week 16 (data not shown). Likewise, among patients who reported some problems with performing or inability to perform usual activities on the EQ-5D-3L at baseline...
Table III. Patient-reported efficacy outcomes, baseline to week 16 (full analysis set, last observation carried forward analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo qw, n = 61</th>
<th>Dupilumab 100 mg q4w, n = 65</th>
<th>Dupilumab 300 mg q4w, n = 65</th>
<th>Dupilumab 200 mg q2w, n = 61</th>
<th>Dupilumab 300 mg q2w, n = 64</th>
<th>Dupilumab 300 mg qw, n = 63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak weekly averaged pruritus NRS score</td>
<td></td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>6.3 (1.8)</td>
<td>6.7 (1.9)</td>
<td>6.8 (1.9)</td>
<td>7.0 (2.3)</td>
<td>6.7 (2.1)</td>
<td>6.5 (1.5)</td>
</tr>
<tr>
<td>LS mean change from baseline (SE)</td>
<td>−0.1 (0.3)</td>
<td>−1.1 (0.3)</td>
<td>−2.4 (0.3)</td>
<td>−2.3 (0.3)</td>
<td>−2.8 (0.3)</td>
<td>−3.2 (0.3)</td>
</tr>
<tr>
<td>P vs placebo</td>
<td>.0090</td>
<td>.0001</td>
<td>.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<tr>
<td>POEM total score</td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>20.3 (5.3)</td>
<td>21.3 (5.6)</td>
<td>20.4 (5.7)</td>
<td>21.7 (5.7)</td>
<td>20.7 (6.4)</td>
<td>20.7 (5.7)</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
<td>−1.1 (0.9)</td>
<td>−3.3 (0.9)</td>
<td>−9.9 (0.9)</td>
<td>−10.4 (0.9)</td>
<td>−9.8 (0.9)</td>
<td>−12.1 (0.9)</td>
</tr>
<tr>
<td>P vs placebo</td>
<td>.0570</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<tr>
<td>POEM total score change ≥MCID</td>
<td>Patients</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>26.2%</td>
<td>40.0%</td>
<td>72.3%</td>
<td>63.9%</td>
<td>76.6%</td>
<td>88.9%</td>
</tr>
<tr>
<td>LS mean change from baseline (SE)</td>
<td>−0.5 (0.2)</td>
<td>−0.7 (0.2)</td>
<td>−1.6 (0.2)</td>
<td>−1.5 (0.2)</td>
<td>−1.5 (0.2)</td>
<td>−2.0 (0.2)</td>
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<tr>
<td>P vs placebo</td>
<td>.1776</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<tr>
<td>HADS total score</td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>12.1 (7.5)</td>
<td>13.9 (7.8)</td>
<td>11.7 (7.7)</td>
<td>13.6 (8.7)</td>
<td>14.0 (7.8)</td>
<td>12.6 (7.1)</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
<td>−0.0 (0.8)</td>
<td>−2.4 (0.8)</td>
<td>−2.7 (0.8)</td>
<td>−4.0 (0.8)</td>
<td>−4.3 (0.8)</td>
<td>−4.6 (0.8)</td>
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<tr>
<td>P vs placebo</td>
<td>.0282</td>
<td>.0103</td>
<td>.0002</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<tr>
<td>HADS anxiety subscale</td>
<td></td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>6.7 (3.8)</td>
<td>7.4 (4.2)</td>
<td>6.5 (4.3)</td>
<td>7.6 (5.1)</td>
<td>7.9 (4.4)</td>
<td>6.8 (3.6)</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
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<td>−1.4 (0.4)</td>
<td>−1.3 (0.4)</td>
<td>−1.9 (0.4)</td>
<td>−2.2 (0.4)</td>
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<tr>
<td>P vs placebo</td>
<td>.0758</td>
<td>.0808</td>
<td>.0062</td>
<td>.0011</td>
<td>.0009</td>
<td></td>
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<tr>
<td>HADS depression subscale</td>
<td></td>
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<td></td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>5.4 (4.3)</td>
<td>6.5 (4.8)</td>
<td>5.3 (4.3)</td>
<td>6.0 (4.4)</td>
<td>6.0 (4.1)</td>
<td>5.8 (4.2)</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
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<td>1.0 (0.5)</td>
<td>−1.4 (0.4)</td>
<td>−2.0 (0.5)</td>
<td>−2.0 (0.4)</td>
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<tr>
<td>P vs placebo</td>
<td>.0303</td>
<td>.0036</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<tr>
<td>DLQI total score</td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>12.8 (6.2)</td>
<td>15.7 (6.6)</td>
<td>13.3 (7.3)</td>
<td>15.0 (7.1)</td>
<td>14.5 (7.2)</td>
<td>15.0 (7.8)</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
<td>−1.3 (0.9)</td>
<td>−2.2 (0.8)</td>
<td>−6.2 (0.8)</td>
<td>−6.8 (0.9)</td>
<td>−6.9 (0.8)</td>
<td>−9.3 (0.9)</td>
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<tr>
<td>P vs placebo</td>
<td>.4108</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<td>DLQI change ≥MCID</td>
<td>Patients</td>
<td></td>
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<tr>
<td>Baseline, mean (SD)</td>
<td>27.9%</td>
<td>38.5%</td>
<td>55.4%</td>
<td>50.8%</td>
<td>65.6%</td>
<td>71.4%</td>
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<tr>
<td>LS mean change from baseline (SE)</td>
<td>.0282</td>
<td>.0005</td>
<td>.0016</td>
<td>&lt;.0001</td>
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<td>P vs placebo</td>
<td>.0782</td>
<td></td>
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</table>

**Notes:** MCID, minimal clinically important difference; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SCORAD, Scoring Atopic Dermatitis; VAS, visual analog scale.

(n = 158), improvements were largest for dupilumab 300-mg q2w and 300-mg qw doses; 82.4% and 91.7% of patients, respectively, reported no problems with usual activities at week 16, compared with 35.0% of patients taking placebo (P = .0002 both doses based on change from baseline; data not shown).
At 16 weeks, dupilumab-treated patients reported improvements in health status as measured by the EQ-5D-3L visual analog scale score and index values, respectively (Table III). Changes in the index values exceeded the MCID for all dupilumab doses and were significantly greater than placebo except for 100 mg q4w. The greatest effects relative to placebo were observed at the 2 highest doses, 300 mg qw and q2w, with visual analog scale changes of 13.9 and 14.1, respectively, versus 2.4 (both \( P < .05 \)) and utility score changes of 0.240 and 0.230, respectively, versus 0.028 (both \( P < .0001 \)). Of the 2 EQ-5D-3L dimensions of mobility and self-care, the number of patients in each treatment group who reported problems at baseline (≤12) was too low for accurate comparisons.

Among patients who were employed or in school full-time at week 16 (n = 287), lost productivity as indicated by the cumulative mean number of missed days at week 16 was numerically greater in the placebo group (3.5 days) than in any of the dupilumab groups (0.5–2.1 days). The greatest difference from placebo was with dupilumab 200 mg q2w (\( P = .023 \)) followed by the other groups (\( P > .05 \)). Similarly, a numerically lower cumulative proportion of patients with no missed days at week 16 was observed for placebo (71.4%) relative to each dupilumab group (72.9%-88.5%) with the greatest difference with dupilumab 300 mg qw (\( P = .037 \)) followed by the remaining groups (\( P > .05 \)).

For all mixed model repeated measures analyses (data not shown), the results were consistent with the main analyses (last observation carried forward).

**Safety profile**

TEAEs were reported in 258 patients (81%) treated with dupilumab and 49 (80%) in the placebo group. Patients with serious TEAEs (3.8% vs 6.6%) and TEAEs leading to study discontinuation (6.6% vs 4.9%) were similar in patients treated with dupilumab compared with placebo. Other than AD flares
(17.0% for all dupilumab doses combined and 18.0% in placebo), the most common TEAEs, defined as occurring in 5% or more of combined dupilumab or placebo group, were nasopharyngitis (28.0% vs 26.2%), upper respiratory tract infection (7.2% vs 18.0%), headache (10.7% vs 3.3%), injection-site reaction (6.6% vs 3.3%), and back pain (2.8% vs 8.2%). A full safety analysis has been previously published.13

DISCUSSION

This analysis complements those previously reported on physician-assessed clinical outcomes13 and provides evidence that dupilumab results in clinically relevant improvements in itch, sleep, mental health, HRQoL, and overall health status in adults with moderate to severe AD. These results are noteworthy because patients in this study had persistent moderate to severe AD despite a high reliance on topical and systemic treatments, and were characterized by a substantial disease burden at study entry.5

Patients treated with dupilumab reported improvements in skin symptoms including itch (the most important symptom for patients) as early as 1 week after treatment initiation. Although early treatment effects may reflect the use of loading doses to more rapidly approach steady-state, this early, sustained, and dose-dependent effect is notable because pruritus likely drives many other outcomes in AD, including sleep and HRQoL.29 Moreover, these data identify the importance of Th2-driven immune pathways in the pathogenesis of itch in AD and reveal that Th2 cytokine signaling blockade yields clinically relevant reduction in itch. A direct effect of dupilumab on itch cannot be ruled out as the phase Ib study of dupilumab found the skin does not need to be completely clear for significant itch relief,13 suggesting that further evaluation of the effects of dupilumab on itch is warranted.

In the current study, dupilumab-treated patients also reported early improvements on sleep disturbance and poor sleep quality. Sleep disturbance plays an important role in many chronic disease states, especially mental health comorbidities.36 and improvements in sleep in patients with AD may positively affect other comorbid states such as anxiety/depression and even systemic inflammation. In fact, dupilumab treatment effects also extended to mental health, as indicated by significant reductions in anxiety and depression symptoms on the HADS and EQ-5D-3L anxiety/depression dimension. The psychological burden associated with AD is well recognized and includes suicidal ideation, which may be exacerbated in patients with severe disease.7,31-34 It is unclear whether inhibiting Th2 inflammatory pathways improves mood by direct neurologic effects or secondary to improved sleep and activity. Studies of tumor necrosis factor inhibition in psoriasis reveal that modulation of inflammation may affect mood via both direct and indirect mechanisms.25,36

Previous studies found that HRQoL correlates with AD disease activity,57-39 and thus it was not surprising that patients reported improvements in HRQoL that were both statistically and clinically significant, using a dermatology-specific (DLQI) and a generic (EQ-5D-3L) measure of HRQoL (with the latter including values that potentially inform economic analyses). Patients at baseline had DLQI scores consistent with a profound impact of skin disease on patients’ lives, and after treatment with most dupilumab doses, their scores showed a minimal disease impact. Domain subscales of the DLQI also showed that patients reported significant improvements, including increased productivity at work or school. Productivity impairment is an outcome that patients recognize in their daily lives that is also of potential economic importance. Although the contribution of lost productivity to the burden of AD has yet to be adequately characterized, a burden-of-illness study using this same population before treatment found that these patients report substantial AD-related impairment at work or school.5

Dupilumab was generally well tolerated in the study; no important deleterious safety signals were identified.13

Limitations include that this was an international study, and although all measures were translated into appropriate languages, it is nevertheless possible that cultural differences may have influenced responses on some PROs. Similarly, use of the United Kingdom algorithm for estimating the EQ-5D-3L may limit interpretability in an international population. Because AD is a chronic disease, these short-term improvements on HRQoL need to be further evaluated in patients with AD on long-term dupilumab therapy. Lastly, although all PROs were prespecified, they were secondary or exploratory end points, and thus the study was neither designed nor powered for analyses of these outcomes.

In conclusion, these results suggest that dupilumab reduces disease activity with concomitant clinically relevant benefits across multiple domains related to the patient burden associated with AD; confirmation awaits completion of phase III trials.

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REFERENCES


