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ORIGINAL ARTICLE

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# Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2

Michael J. Cork[a], Laurent Eckert[b], Eric L. Simpson[c], April Armstrong[d], Sébastien Barbarot[e], Luis Puig[f], Giampiero Girolomoni[g], Marjolein de Bruin-Weller[h], Andreas Wollenberg[i], Yoko Kataoka[j], Anita Remitz[k], Stefan Beissert[l], Vera Mastey[m], Marius Ardeleanu[m], Zhen Chen[m], Abhijit Gadkari[m]* and Jingdong Chao[m]*

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**ABSTRACT**

**Background:** Atopic dermatitis (AD) profoundly affects quality of life (QoL). Dupilumab significantly improves clinical outcomes, is well tolerated, and approved to treat inadequately controlled moderate-to-severe AD in adults; however, its effect on patient-reported outcomes (PROs) is not fully characterized.
**Objective:** To evaluate the impact of dupilumab on patient-reported AD symptoms and QoL.
**Methods:** Pooled data were analyzed from two identically designed phase 3 studies, LIBERTY AD SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769), assessing the following PROs: Peak Pruritus Numerical Rating Scale (NRS), Pruritus Categorical Scale, SCORing AD (SCORAD), Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), Hospital Anxiety and Depression Scale (HADS), five-dimension EuroQoL questionnaire (EQ-5D), and patient-assessed disease status and treatment effectiveness.
**Results:** Dupilumab rapidly improved (vs. placebo) Peak Pruritus NRS scores by day 2 ($p < .05$), anxiety and depression (HADS), and QoL (DLQI) by week 2, and maintained through week 16 ($p < .0001$). At week 16, more dupilumab-treated than placebo-treated patients reported improvement in SCORAD itch and sleep, and no pain/discomfort (EQ-5D) ($p < .0001$).
**Limitations:** Cultural differences of translated PROs.
**Conclusion:** Dupilumab had a significant, positive impact on AD symptoms, including itch, sleep, pain, anxiety and depression, and QoL in adults with moderate-to-severe AD.

**ARTICLE HISTORY**
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**KEYWORDS**
Atopic dermatitis; dupilumab; patient-reported outcomes; quality of life

## Introduction

Atopic dermatitis (AD) is a complex, chronic, systemic, inflammatory skin disease characterized by erythematous, eczematous lesions, and intense pruritus (1–4). Innate and adaptive immune responses, and environmental factors, contribute to the clinical presentation of AD (5,6). AD affects patients worldwide; the prevalence in adults is 4.4% in the European Union, 3.5% in Canada, 4.9% in the United States, and 2.1% in Japan (7).

AD adversely affects patients' quality of life (QoL) (8–12). Pruritus, a prominent symptom of AD, can be intense and debilitating (3,4,13) and is associated with reduced health-related QoL (HRQoL) and increased incidence of depression and anxiety (11,12,14,15). Rates of depression and suicidal ideation are higher in patients with AD than in control populations (16–18), and patients with AD report higher rates of pain, fatigue, insomnia, and daytime sleepiness (9,19,20).

Moderate-to-severe AD in adults can be challenging to treat because of the risk/benefit profiles of systemic therapies (21,22). There is a substantial unmet need for safe and effective treatments, especially for patients with inadequate response to currently available topical medications and systemic immunosuppressants (11,23).

Dupilumab is a fully human monoclonal antibody directed against interleukin (IL)-4 receptor alpha (IL-4Rα), which inhibits signaling of IL-4 and IL-13, cytokines that are key drivers of type 2 diseases such as AD, asthma, allergic rhinitis, and food allergies, diseases often associated as comorbidities (24). Dupilumab is

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approved for treatment of inadequately controlled, moderate-to-severe AD in adults. In early and phase 3 clinical trials, including SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769), dupilumab significantly improved, versus placebo, AD signs and symptoms in adults with moderate-to-severe AD, and had a favorable safety profile (12,25–28).

The burden of moderate-to-severe AD is not fully captured by clinical outcome measures. To obtain further insight into the efficacy of dupilumab, we evaluated its impact on patient-reported symptoms of AD, including pruritus and sleep disturbance, anxiety and depression, HRQoL, and global assessments of disease and treatment effect using pooled data from SOLO 1 and 2.

## Methods

### Study design

The design and methodology of SOLO 1 (NCT02277743) and 2 (NCT02277769) have already been published (27). Briefly, SOLO 1 and 2 were randomized, placebo-controlled, double-blind, phase 3 trials. Eligible patients were aged $\geq$18 years and had AD for $\geq$3 years, an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe), an Eczema Area and Severity Index (EASI) score $\geq$16, and a pruritus Numerical Rating Scale (NRS) average score $\geq$3. Patients received subcutaneous dupilumab 300 mg once weekly (qw), or every 2 weeks (q2w), or placebo qw, for 16 weeks (27). Both trials were conducted in accordance with the Declaration of Helsinki International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. All patients provided written informed consent. Study oversight was provided by local institutional review boards or ethics committees at each study site and by an independent data and safety monitoring committee.

### Patient-reported outcomes

Patient-reported outcomes (PROs) reported include least squares (LS) mean percentage change from baseline to week 2 and percentage of patients with $\geq$3-point reduction from baseline through week 16 in daily Peak Pruritus NRS score (29,30), (a pre-specified secondary endpoint); percentage of patients reporting 'absence of'/'mild' pruritus as well as 'severe' pruritus from baseline through week 16 in Pruritus Categorical Scale (PCS) score (31); LS mean change from baseline at week 2 and percentage of patients at week 16 reporting absence of symptoms in the past week in each Patient-Oriented Eczema Measure (POEM) item (32,33); LS mean change from baseline at week 16 for patient-reported Scoring AD (SCORAD) itch and sleep (34,35); LS mean change from baseline at week 2 and week 16 in Hospital Anxiety and Depression Scale (HADS) score (36,37); LS mean change from baseline at week 2 and the percentage of patients reporting 'not at all' at week 16 in Dermatology Life Quality Index (DLQI) score (38,39); percentage of patients reporting 'good,' 'very good,' or 'excellent' through week 16 in Patient Global Assessment of Disease Status (PGADS) and Patient Global Assessment of Treatment Effect (PGATE); and on the five-dimension, three-level EuroQoL questionnaire (EQ-5D) (40), the percentage of patients reporting no pain or discomfort at week 16.

Peak Pruritus NRS measures the intensity of worst itch in the previous 24 hours on a scale of 0–10; higher scores indicate more severe pruritus. PCS measures intensity of itching, scratching, and/or discomfort due to pruritus in the previous 24 hours on a four-point scale (30). POEM assesses frequency of AD symptoms (itching, soreness, or pain; redness of the skin, bleeding, weeping, or oozing of the skin; dryness or roughness of the skin; flaking of the skin; cracking of the skin; tightness of the skin) and impact of AD on sleep (32). The HADS assesses symptoms of anxiety and depression with seven questions for each, on a 0–3 scale (36). The DLQI has 10 questions about the effect of AD on patients' QoL during the previous week, using a scale of (0–3) (39). The PGADS and PGATE are global assessments of disease severity and treatment satisfaction, both on a five-point scale. SCORAD visual analog scale (VAS) itch is a patient-reported component of SCORAD. For VAS itch, patients report average itch for the past 3 days or nights. Sleep loss is assessed by SCORAD VAS sleep—average sleep loss for the past 3 days or nights. The EQ-5D is a standardized instrument for measuring QoL, with one question for each of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (40).

### Statistics

SOLO 1 and 2 data were pooled within each treatment group, therefore all $p$ values $\leq$.05 are considered nominally significant. All statistical tests were two-sided. For categorical endpoints, data obtained after rescue medication use and missing data were considered 'nonresponder' data. For continuous endpoints, data obtained after use of rescue medication and missing data were accounted for using the last-observation-carried-forward method.

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). For comparisons of each dupilumab dose with placebo according to the pre-specified hierarchical order, a significance level of 0.025 was used, controlling for the overall type I error rate at 0.05 for primary and secondary endpoints. All reported $p$ values are nominal, two-sided. Detailed descriptions of the statistical analyses for the individual studies are published elsewhere (27).

## Results

### Patients

In total, 1,379 patients were enrolled in the two studies. 457 patients received dupilumab 300 mg q2w, 462 received dupilumab 300 mg qw, and 460 received placebo. In this pooled analysis, treatment groups had similar baseline demographics and disease characteristics (Table 1).

### Pruritus

Compared with placebo, dupilumab improved Peak Pruritus NRS scores as early as day 2, regardless of dose regimen, with −4.5% LS mean percentage change from baseline for dupilumab q2w, $p$ = .0033 vs. placebo; −4.0% for dupilumab qw, $p$ = .0110 vs. placebo, and −0.6% for placebo; (Figure 1). More patients in the dupilumab q2w and dupilumab qw groups had a $\geq$3-point improvement in Peak Pruritus NRS score by day 4, compared with patients in the placebo group (7.4% and 8.0%, respectively, vs. 3.3%; $p$ = .0044 and $p$ = .0019, respectively, vs. placebo) and at weeks 2 and 16 (at week 2: 17.1% and 20.2%, respectively, vs. 5.1%; week 16: 48.8% and 50.3%, respectively, vs. 15.0% of placebo recipients; $p$ < .0001 vs. placebo, either regimen at both time points; Table 2, Figure 1).

Dupilumab also rapidly improved itch severity as assessed on the PCS. At week 2, more patients in the dupilumab q2w and dupilumab qw groups reported 'absent or mild' pruritus, compared with patients in the placebo group (29.1% and 30.7%, respectively, vs. 13.9%; $p$ < .0001 vs. placebo for either dose regimen; Table 2). At week 16, more dupilumab-treated patients reported 'absent or mild' pruritus, compared with placebo (51.9%

**Table 1.** Baseline demographics and disease characteristics of patients in SOLO 1 and SOLO 2 (pooled data).

| Characteristic | Placebo ($n = 460$) | Dupilumab 300 mg q2w ($n = 457$) | Dupilumab 300 mg qw ($n = 462$) |
|---|---|---|---|
| Mean age, years (SD) | 38.4 (14.0) | 38.3 (14.4) | 38.2 (14.5) |
| Male, *n* (%) | 250 (54.3) | 267 (58.4) | 281 (60.8) |
| Race, *n* (%) | | | |
| White | 302 (65.7) | 320 (70.0) | 317 (68.6) |
| Black or African American | 36 (7.8) | 23 (5.0) | 35 (7.6) |
| Asian | 106 (23) | 98 (21.4) | 96 (20.8) |
| Other | 8 (1.7) | 8 (1.8) | 8 (1.7) |
| AD duration, years (%) | 28.8 (14.4) | 27.9 (15.2) | 27.6 (15.4) |
| BSA (%), mean (SD) | 55.8 (23.3) | 53.7 (22.2) | 54.1 (22.3) |
| EASI total score, mean (SD) | 34.0 (14.4) | 32.4 (13.3) | 32.5 (13.3) |
| IGA = 4, *n* (%) | 225 (48.9) | 223 (48.8) | 218 (47.2) |
| Peak weekly averaged pruritus NRS score, mean (SD) | 7.4 (1.8) | 7.4 (1.8) | 7.3 (1.9) |
| PCS score *n* (%) | | | |
| 'absence of'/'mild' pruritus | 40 (8.7) | 32 (7.0) | 37 (8.4) |
| 'moderate' pruritus | 197 (42.8) | 218 (47.7) | 193 (41.8) |
| 'severe' pruritus | 222 (48.3) | 206 (45.1) | 227 (49.1) |
| SCORAD total score, mean (SD) | 68.8 (14.5) | 67.1 (13.7) | 67.5 (13.3) |
| POEM score, mean (SD) | 20.6 (5.9) | 20.3 (6.0) | 20.7 (5.9) |
| DLQI score, mean (SD) | 15.1 (7.5) | 14.7 (7.3) | 15.1 (7.5) |
| HADS total score, mean (SD) | 13.2 (8.3) | 13.0 (7.4) | 13.7 (8.2) |
| GISS total score, mean (SD) | 9.1 (1.8) | 9.0 (1.8) | 8.9 (1.7) |

AD: atopic dermatitis; BSA: body surface area; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; GISS: Global Individual Signs Score; HADS: Hospital Anxiety and Depression Scale; IGA: Investigator's Global Assessment; NRS: Numerical Rating Scale; PCS: Pruritus Categorical Scale; POEM: Patient-Oriented Eczema Measure; qw: weekly; q2w: every 2 weeks; SCORAD: SCORing Atopic Dermatitis; SD: standard deviation.

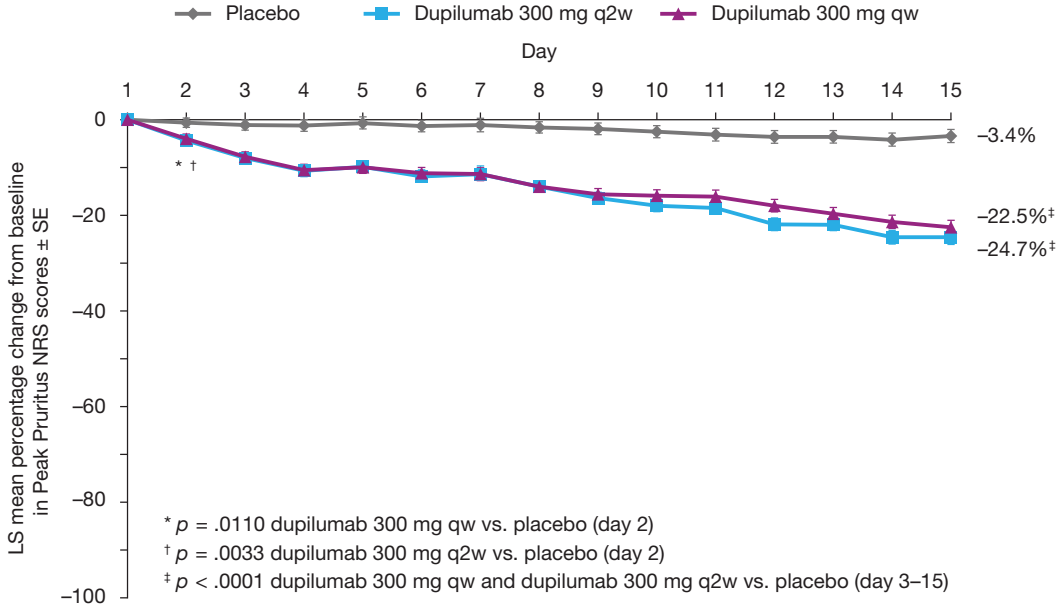


**Figure 1.** LS mean percentage change from baseline to week 2 in daily Peak Pruritus NRS score. Placebo, $n = 460$; dupilumab 300 mg q2w, $n = 457$; dupilumab 300 mg qw, $n = 462$. LS: least squares; NRS: Numerical Rating Scale; qw: weekly; q2w: every 2 weeks; SE: standard error.

and 53.7%, respectively, vs. 19.3%; $p < .0001$ vs. placebo for either dose regimen; Table 2). In addition, fewer dupilumab-treated patients reported 'severe pruritus' at week 16, compared with placebo (20.8% and 21.9%, respectively, vs. 36.7%; $p < .0001$ vs. placebo for either dose regimen; Table 2).

For SCORAD VAS itch score, dupilumab-treated patients had a higher LS mean change from baseline at week 16 than placebo-treated patients (−4.00 for dupilumab q2w, −4.06 for dupilumab qw, and −1.26 for placebo; $p < .0001$, either regimen vs. placebo) (Table 2).

### Pain

Among patients reporting at least 'some pain/discomfort' on the EQ-5D at baseline, more dupilumab- than placebo-treated patients reported 'no pain/discomfort' at week 16 (45.7% for dupilumab q2w, 43.2% for dupilumab qw, and 13.5% for placebo; $p < .0001$ vs. placebo, either dose regimen; Table 2). Overall, by week 16, 62.0–62.2% of dupilumab-treated patients reported 'no pain/discomfort,' vs. 39.2% of placebo-treated patients, and 37.8–37.9% of dupilumab-treated patients reported 'some/extreme pain/discomfort,' in contrast to 60.8% of placebo-treated patients.

### Sleep

Dupilumab-treated patients (either regimen) had greater LS mean change from baseline at week 16 in SCORAD sleep than placebo-treated patients (−3.3 for dupilumab q2w, −3.4 for dupilumab qw, and −0.82 for placebo; $p < .0001$, either dose regimen vs. placebo; Table 2). At week 16 more dupilumab- than placebo-treated

**Table 2.** Patient-reported outcomes in SOLO 1 and SOLO 2 (pooled data).

| | Placebo ($n = 460$) | Dupilumab 300 mg q2w ($n = 457$) | Dupilumab 300 mg qw ($n = 462$) |
|---|---|---|---|
| Peak Pruritus NRS: improvement, *n*/*N* (%)[a] | | | |
| ≥ 3 points from baseline at day 4 | 15/447 (3.3) | 34/451 (7.4)[b] | 37/445 (8.0)[c] |
| ≥ 3 points from baseline at week 2 | 23/447 (5.1) | 77/451 (17.1)[d] | 90/445 (20.2)[d] |
| ≥ 3 points from baseline at week 16 | 67/447 (15.0) | 220/451 (48.8)[d] | 224/445 (50.3)[d] |
| PCS score: *n* (%)[e] | | | |
| Week 2 | | | |
| 'absence of' or 'mild' pruritus | 64 (13.9) | 133 (29.1)[d] | 142 (30.7)[d] |
| 'moderate' pruritus | 184 (40.0) | 211 (46.2)[f] | 200 (43.3) |
| 'severe' pruritus | 169 (36.7) | 95 (20.8)[d] | 101 (21.9)[d] |
| Week 16 | | | |
| 'absence of' or 'mild' pruritus | 89 (19.3) | 237 (51.9)[d] | 248 (53.7)[d] |
| 'moderate' pruritus | 74 (16.1) | 102 (22.3) | 78 (16.9) |
| 'severe' pruritus | 39 (8.5) | 26 (5.7) | 18 (3.9)[g] |
| POEM score: LS mean change from baseline at week 2 (SE) | −1.6 (0.27) | −5.8 (0.27)[d] | −6.2 (0.26)[d] |
| DLQI score: LS mean change from baseline at week 2 (SE) | −1.9 (0.25) | −5.6 (0.25)[d] | −5.7 (0.25)[d] |
| HADS score: LS mean change from baseline at week 2 (SE) | −0.8 (0.23) | −2.9 (0.23)[d] | −3.0 (0.23)[d] |
| HADS score: LS mean change from baseline at week 16 (SE) | −1.0 (0.28) | −4.7 (0.28)[d] | −5.0 (0.28)[d] |
| SCORAD VAS itch score: LS mean change from baseline at week 16 (SE)[h] | −1.26 (0.14) | −4.00 (0.14)[d] | −4.06 (0.14)[d] |
| SCORAD VAS sleep score: LS mean change from baseline at week 16 (SE)[i] | −0.82 (0.14) | −3.30 (0.14)[d] | −3.40 (0.14)[d] |
| EQ-5D: patients reporting no pain or discomfort at week 16, *n*/*N* (%)[j] | 49/362 (13.5) | 169/370 (45.7)[d] | 163/377 (43.2)[d] |
| PGADS: patients reporting their status as 'good' at week 16 *n* (%) | 60 (13.0) | 98 (21.4)[k] | 102 (22.1)[l] |
| PGADS: patients reporting their status as 'very good' or 'excellent' at week 16 *n* (%) | 53 (11.5) | 174 (38.1)[d] | 169 (36.6)[d] |
| PGATE: patients reporting their status as 'good' at week 16 *n* (%) | 52 (11.3) | 98 (21.4)[d] | 85 (18.4)[m] |
| PGATE: patients reporting their status as 'very good' or 'excellent' at week 16 *n* (%) | 45 (9.8) | 199 (43.5)[d] | 204 (44.2)[d] |

DLQI: Dermatology Life Quality Index; EQ-5D: 5-dimension 3-level EuroQoL; HADS: Hospital Anxiety and Depression Scale; LS: least squares; n/N: number of patients with outcome/total number of patients in this treatment group; NRS: Numerical Rating Scale; PCS: Pruritus Categorical Scale; PGADS: Patient Global Assessment of Disease Status; PGATE: Patient Global Assessment of Treatment Effect; POEM: Patient-Oriented Eczema Measure; qw: weekly; q2w: every 2 weeks; SCORAD: SCORing Atopic Dermatitis; SE: standard error; VAS: visual analog scale.
[a]Analyses for patients with Peak Pruritus NRS score ≥ 3 were conducted on the subset of patients with baseline Peak Pruritus NRS ≥ 3.
[b]$p = .0044$ vs. placebo.
[c]$p = .0019$ vs. placebo.
[d]$p < .0001$ vs. placebo.
[e]Values after first rescue treatment were set to missing (censoring).
[f]$p = .0166$ vs. placebo.
[g]$p = .0035$ vs. placebo.
[h]Analysis for SCORAD itch was performed in patients from whom baseline data were collected: placebo, $n = 440$; dupilumab 300 mg q2w, $n = 444$; dupilumab 300 mg qw, $n = 449$.
[i]Analysis for SCORAD sleep was performed in patients from whom baseline data were collected: placebo, $n = 440$; dupilumab 300 mg q2w, $n = 445$; dupilumab 300 mg qw, $n = 449$.
[j]Among the subset of patients who reported at least some pain or discomfort on the EQ-5D at baseline (placebo, $n = 362$; dupilumab 300 mg q2w, $n = 370$; dupilumab 300 mg qw, $n = 377$).
[k]$p = .0003$ vs. placebo.
[l]$p = .0007$ vs. placebo.
[m]$p = .0026$ vs. placebo.

patients reported absence of sleep disturbance as assessed by POEM (51.2%, 43.5%, and 17.6% for dupilumab q2w, dupilumab qw, and placebo, respectively; $p < .0001$, either dose regimen vs. placebo; Figure 2).

### *Patient-reported symptoms of AD*

Compared with placebo, dupilumab rapidly improved AD symptoms as assessed by POEM. Significant improvement in POEM scores was observed in dupilumab-treated patients as early as week 2, with an LS mean change from baseline of −5.8 for dupilumab q2w, −6.2 for dupilumab qw, and −1.6 for placebo ($p < .0001$ either dose regimen vs. placebo; Table 2). For all POEM items, at week 16 a greater proportion of patients treated with dupilumab, vs. placebo, reported having no symptoms during the past week ($p < .0001$, either dupilumab dose regimen vs. placebo; Figure 2).

### *Symptoms of anxiety and depression*

Both dupilumab dose regimens improved symptoms of anxiety and depression as early as week 2, as assessed by HADS, compared with placebo. Improvement was maintained through week 16 ($p < .0001$ both regimens vs. placebo; Table 2).

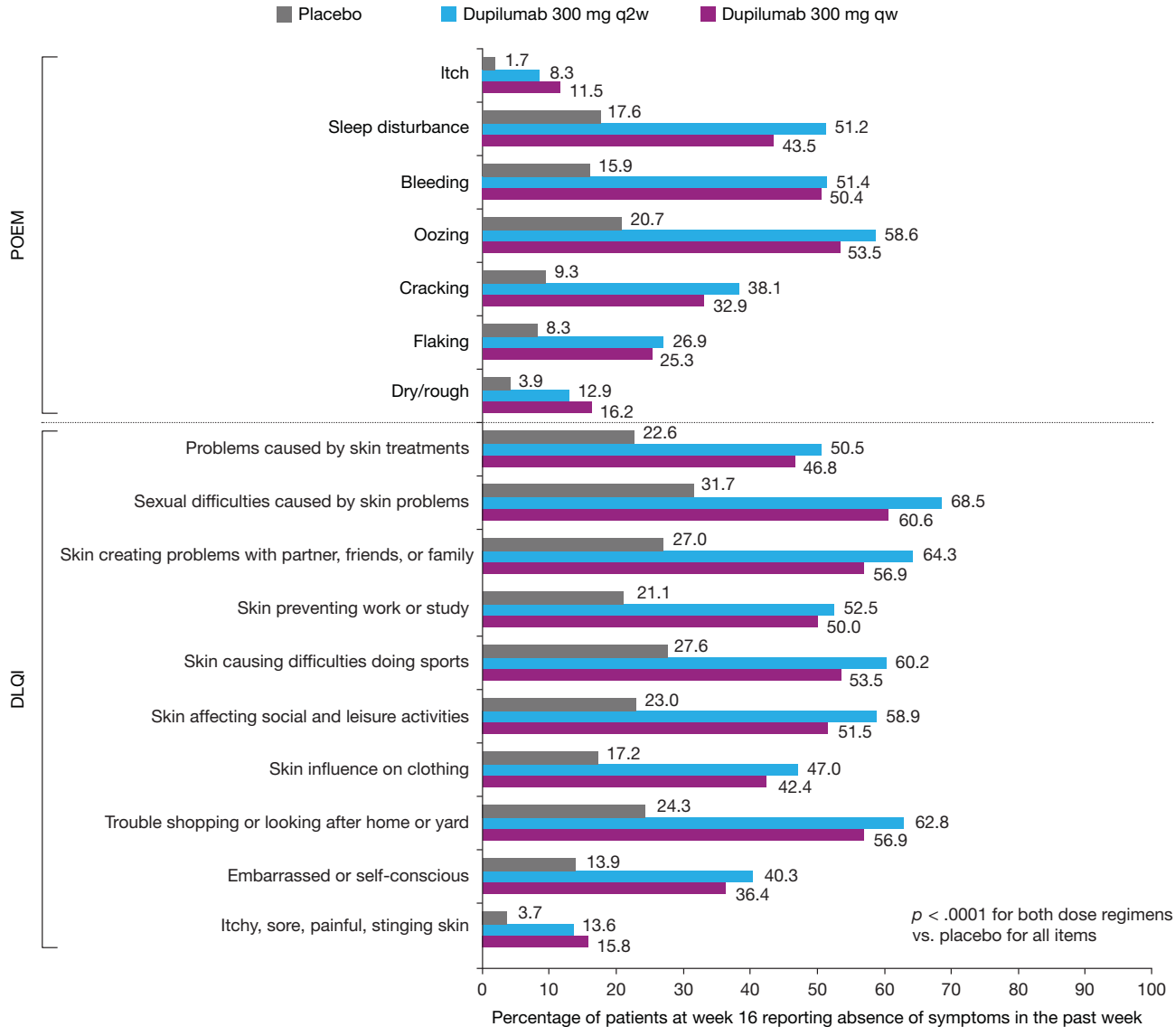


**Figure 2.** Patient-reported symptoms and Qol: percentage of patients reporting absence of symptoms in the past week in each POEM item at week 16 in SOLO 1 and 2 (pooled data), placebo, $n = 460$; dupilumab 300 mg q2w, $n = 457$; dupilumab 300 mg qw, $n = 462$; and percentage of patients reporting 'not at all' on individual DLQI items at week 16 in SOLO 1 and 2 (pooled data), placebo, $n = 460$; dupilumab 300 mg q2w, $n = 457$; dupilumab 300 mg qw, $n = 462$. DLQI: Dermatology Life Quality Index; POEM, Patient-Oriented Eczema Measure; qw: weekly; q2w: every 2 weeks; QoL: quality of life.

### *Health-related quality of life*

Improvement in HRQoL, as assessed by the DLQI, versus placebo occurred as early as week 2, with −5.6 LS mean change from baseline for dupilumab q2w, −5.7 for dupilumab qw, and −1.9 for placebo ($p < .0001$ vs. placebo, either dose regimen; Table 2). At week 16, more dupilumab- than placebo-treated patients responded 'not at all' to each item of the DLQI, indicating minimal impact on QoL ($p < .0001$ vs. placebo, either dose regimen; Figure 2).

### *Global assessment of disease status and treatment effect*

Patients' impressions of their disease status, as measured by PGADS, improved over time, with more patients in the dupilumab q2w and qw groups reporting 'very good or excellent' status at week 16, compared with placebo (38.1% and 36.6%, respectively, vs. 11.5%; $p < .0001$ vs. placebo, either dose regimen; Table 2). Patients whose baseline PGADS rating was 'poor/fair' showed rapid improvement, with 43.9% and 45.3% of patients receiving dupilumab q2w, dupilumab qw reporting 'good,' 'very good,' or 'excellent' status by week 2, vs. 17.7% of placebo recipients, as did 54.4% and 54.2%, respectively, at week 16, versus 17.4% of placebo recipients ($p < .0001$ vs. placebo, either dose regimen; Figure 3). In addition, more dupilumab-treated patients reported a 'good,' 'very good,' or 'excellent' global treatment effect at each visit, as assessed by PGATE; 57.3% and 58.0%, respectively, vs. 24.3% of placebo recipients at week 2, to more than 70% of dupilumab-treated patients at week 6, and with sustained improvement though week 16 ($p < .0001$ vs. placebo, either dose regimen; Figure 3).

### *Safety*

Safety data from the individual studies have been previously published (27). Briefly, the incidence of adverse events was similar in the dupilumab and placebo groups (27).

## Discussion

In this pooled analysis of data from SOLO 1 and 2, dupilumab treatment resulted in rapid improvement of multiple outcomes

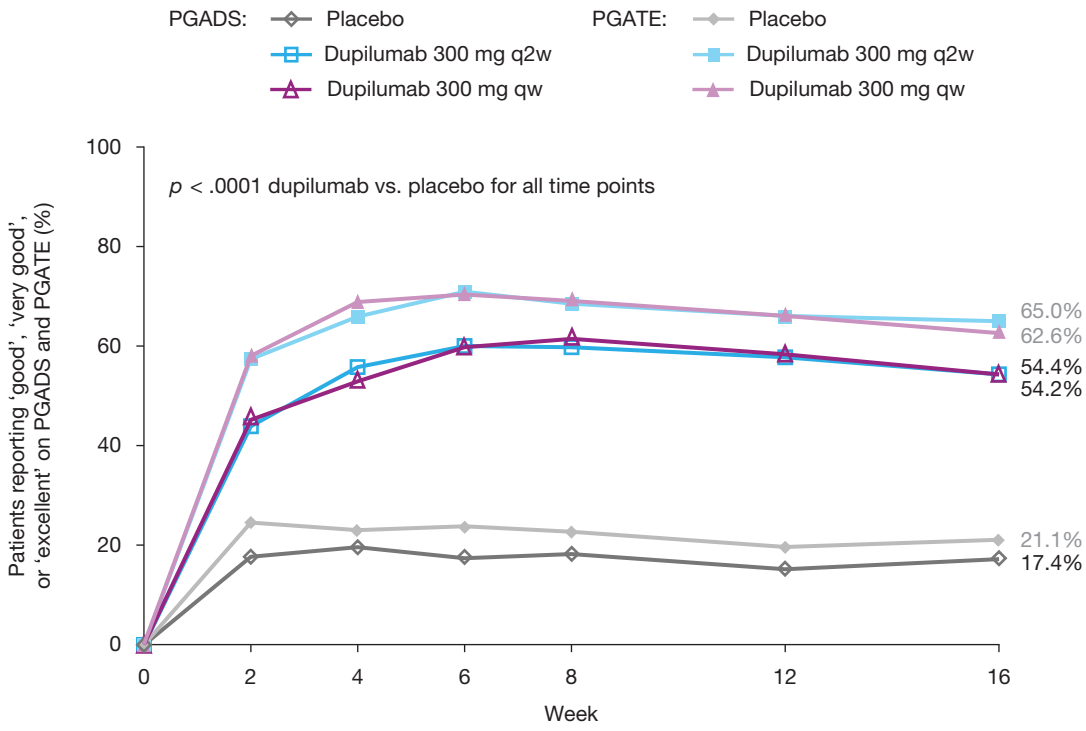


**Figure 3.** Percentage of patients reporting 'good', 'very good', or 'excellent' on the PGADS and PGATE through week 16 after reporting 'poor' or 'fair' at baseline in SOLO 1 and 2 (pooled data). $p < .0001$ for both dupilumab regimens vs. placebo at all time points. Placebo, $n = 460$; dupilumab 300 mg q2w, $n = 457$; dupilumab 300 mg qw, $n = 462$. PGADS data is for patients reporting 'poor' or 'fair' at baseline. PGADS: Patient Global Assessment of Disease Status; PGATE: Patient Global Assessment of Treatment Effect; qw: weekly; q2w: every 2 weeks.

important to patients, including pruritus, sleep disturbance, pain, symptoms of anxiety and depression, and HRQoL.

The results presented here are noteworthy because patients entering SOLO 1 and 2 had a substantial disease burden not controlled by topical treatments. Before enrollment, 32.9% of patients in SOLO 1 and 33.0% in SOLO 2 had received systemic glucocorticoids, and 25.9% and 31.4%, respectively, had received systemic immunosuppressants (27). These pooled analyses confirm findings from previous studies of dupilumab (25–28,41).

Pruritus has a considerable negative effect on patients' HRQoL and sleep (11,14,42,43). In a recent study, nearly 70% of patients with moderate-to-severe AD reported pruritus caused sleep disturbances including delay falling asleep or waking at night (11). Sleep deprivation negatively affects HRQoL and daily productivity (42,43). Stronger itch intensity has been linked to increased stress levels and depression (14).

The rapid improvement in itch observed in this study may have a downstream effect on other aspects of disease burden, as indicated by early responses assessed by POEM, DLQI, and HADS, and previous reports that improvement in itch is positively correlated with QoL improvement, as measured by DLQI (44). Improvements in itch and sleep have been demonstrated by other drugs for treatment of moderate-to-severe AD (45). Significant improvement with dupilumab was seen not only in composite measures but also in the individual components of the DLQI and POEM, including improvement in itchy, painful, sore or stinging skin, feelings of embarrassment, and reduced sleep disturbance. The observed improvement in itch is also clinically meaningful, defined as a within-person change of $\geq$ 3–4 points in Peak Pruritus NRS score (46). This pooled analysis is the first to demonstrate itch improvement as early as day 2 with dupilumab treatment. This study also applied stringent criteria to determine the effectiveness of dupilumab in improving AD symptoms and QoL, measuring the percentage of patients with the absence of symptoms in POEM and DLQI categories.

Dupilumab treatment has been reported to reduce pain and discomfort (41). Pain has rarely been evaluated systematically in AD studies, an important gap in characterizing the burden of AD (9). Recent reports highlight pain as an important symptom in patients with moderate-to-severe AD and support pain as a relevant outcome in determining AD-related treatment response (47). Future clinical trials in moderate-to-severe AD should administer appropriate PRO scales to characterize the burden of AD-related pain and enable evaluation of treatment efficacy in different dimensions of pain.

The improvement in anxiety and depression measured by the HADS anxiety and depression subscales reported for the individual SOLO trials (27), in addition to the improvement in overall HADS scores reported here, suggests dupilumab reduces anxiety and depression, symptoms prevalent among patients with AD that increase the disease burden in patients with more severe disease (8). AD-related depression may be not only a secondary comorbidity but also a symptom caused directly by inflammatory cytokines, as suggested by recent evidence for the contribution of inflammatory cytokines to the development of depression in general medicine (48). Improving anxiety and depression in patients with AD may potentially reduce their risk of suicidal ideation.

Global assessments provide a 'real-world' assessment of disease status and treatment effectiveness from the patient's perspective, demonstrated by the rapid increase in satisfaction among dupilumab-treated patients in this study, reported by the PGATE and PGADS. In this analysis, this self-perceived improvement was greater than 70% among dupilumab-treated patients. In SOLO 1 and 2, among patients not reaching an IGA score of 0 or 1 at week 16, a greater proportion of dupilumab- than placebo-treated patients reported 'good,' 'very good,' or 'excellent' on the PGATE (49), demonstrating that physician assessments

such as IGA might not fully capture disease status and treatment efficacy.

A limitation to consider when interpreting these results is this pooled analysis was not pre-specified; therefore, all *p* values should be considered nominal.

In conclusion, dupilumab is not only clinically efficacious in AD (27), but also demonstrates efficacy in a range of outcomes, with significant, early-onset improvements in patient-reported AD symptoms including itch, pain, sleep disturbance, anxiety and depression, HRQoL, and patients' assessment of disease status and treatment effect versus placebo in moderate-to-severe AD. These data expand upon previous reports by showing that dupilumab improves AD in multiple dimensions important to the patient and highlight the importance of PROs in assessing the efficacy of treatments for AD.

## Disclosure statement

Dr. Cork is an investigator and consultant for AbbVie, Astellas Pharma, Boots Pharmaceuticals, Dermavant, Galapagos NV, Galderma, Hyphens Pharma, Johnson & Johnson, Leo Pharma, L'Oréal, Menlo Therapeutics, Inc., Novartis, Oxagen Limited, Pfizer, Procter & Gamble, Regeneron Pharmaceuticals, Inc., Reckitt Benckiser, and Sanofi Genzyme. Dr. Eckert is an employee of and may hold stock and/or stock options in Sanofi. Dr. Simpson has received research funding from AbbVie, Amgen, Celgene, Chugai, Dermira, Galderma, Genentech, Lilly, Menlo Therapeutics, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme, and has received consultancy honoraria from Anacor, Asubio, Celgene, Galderma, Genentech, Medicis, and Merck. Dr. Armstrong is an employee of The University of Southern California and has received consultancy honoraria from AbbVie, Amgen, Eli Lilly, Janssen, Merck, Novartis, and Pfizer; research funding from AbbVie, Eli Lilly and Janssen; and speaker honoraria from AbbVie. Dr. Barbarot is an investigator and consultant with honorarium for Pierre Fabre Laboratories and has received honoraria as a speaker for Bioderma and for participation on advisory boards for Sanofi Genzyme. Dr. Puig has received research funding and consultancy honoraria from Regeneron Pharmaceuticals, Inc. and Sanofi. Dr. Girolomoni has received consultancy honoraria from and/or is an advisory board member for AbbVie, Abiogen, Allmirall, Biogen, Celgene, Eli Lilly, Galderma, Hospira, Leo Pharma, Menlo Therapeutics, Merck, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc, Samsung, Sandoz, Sanofi, and Sun Pharma. Dr. de Bruin-Weller is principal investigator, advisory board member, and consultant for Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme; and principal investigator and advisory board member for AbbVie. Dr. Wollenberg has received lecturer and/or consultancy honoraria from Almirall, Anacor, Astellas, Beiersdorf, Bioderma, Celgene, Chugai, Galderma, GSK, Hans Karrer, Leo Pharma, L'Oreal, MEDA, MedImmune, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi. Dr. Kataoka has received research funding from Sanofi and lecturer honoraria from Sysmex. Dr. Remitz has served as primary investigator, consultant, and lecturer for AbbVie, Eli Lily, Leo Pharma, Novartis, Roche, and Regeneron-Sanofi. Dr. Beissert has received speaker honoraria from Abbvie, Actelion, Bristol Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Pfizer, and La Roche-Posay, and is an advisory board member for Actelion, Amgen, Celgene, Galderma, Janssen-Cilag, Leo Pharma, Lilly, Menlo Therapeutics, Merck Sharp & Dohme, Novartis, and Pfizer. Drs. Mastey, Ardeleanu, Chen, Gadkari, and Chao are employees and shareholders of Regeneron Pharmaceuticals, Inc.

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