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Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2)

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ABSTRACT

Background: Two phase 3 trials with identical design, LIBERTY AD SOLO 1 (NCT02277743) and LIBERTY AD SOLO 2 (NCT02277769), confirmed dupilumab efficacy and safety versus placebo in adults with moderate-to-severe atopic dermatitis (AD).
Objectives: To report a pooled analysis of these trials to further explore dupilumab's effects on AD clinical parameters, patient-reported outcomes (PROs), symptoms of anxiety/depression, health-related quality of life (HRQoL), and safety.
Methods: A pooled analysis of two 16-week phase 3 studies in adults with moderate-to-severe AD (N = 1379) inadequately controlled with/inadvisable for topical medications, randomized to dupilumab 300 mg once weekly (qw), every 2 weeks (q2w), or placebo.
Results: Dupilumab significantly improved all pre-specified efficacy endpoints versus placebo ($P < 0.0001$), including clinical severity outcomes and PROs, symptoms of anxiety/depression, and HRQoL, consistent with previously published results. In post-hoc analyses, among patients reporting at least some baseline pain/discomfort on the EuroQoL-5D, no pain/discomfort at Week 16 was reported by 43%/46%/14% of dupilumab qw/q2w/placebo-treated patients ($P < 0.0001$). The distribution of dupilumab-treated patients within pre-defined score categories on the Investigator's Global Assessment (0–1/2/3/4) and Eczema Area and Severity Index (≥90%/≥75–<90%/≥50–<75%/<50%) steadily and consistently improved over time versus marginal changes with placebo. Dupilumab significantly improved pruritus within 1–3 days of treatment initiation. No new safety signals were observed. Injection-site reactions and conjunctivitis were more common with dupilumab; AD exacerbation and non-herpetic skin infections more frequent with placebo.
Conclusions: Dupilumab versus placebo significantly improved objective AD signs, subjective PROs, symptoms of anxiety/depression, and HRQoL, with a favorable benefit-risk profile in adults with moderate-to-severe AD.

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Abbreviations: AD, atopic dermatitis; BSA, body surface area; CMH, Cochran–Mantel–Haenszel; CRSwNP, chronic rhinosinusitis with nasal polyposis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, 5-dimension 3-level EuroQol; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS Anxiety; HADS-D, HADS Depression; HRQoL, health-related quality of life; IGA, Investigator's Global Assessment; IL, interleukin; MCID, minimal clinically important difference; NRI, nonresponder imputation; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; QoL, quality of life; qw, once weekly; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SE, standard error; TCS, topical corticosteroid.

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1. Introduction

Atopic dermatitis (AD) is a chronic, predominantly type 2 inflammatory skin disease that affects up to 10% of adults and 20% of children [1–5]. Moderate-to-severe AD is characterized by extensive eczematous lesions, pronounced persistent, severe itch [6–8], substantial pain and discomfort [9–12], and is frequently associated with other type 2 (atopic/allergic) comorbidities, e.g. asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis, and food allergies [8,13–15], and a significant disease burden, e.g. anxiety/depression, sleep disturbances, and reduced health-related quality of life (HRQoL) [8]. There is a large unmet need for effective and safe treatments for moderate-to-severe AD, because topical therapies have limited efficacy and systemic immunotherapies are discouraged for long-term use, due to substantial side effects [16–18].

Dupilumab is the first targeted biologic agent approved in the United States of America for subcutaneous administration every 2 weeks (q2w) for the treatment of patients aged ≥12 years with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable, for the treatment of adult AD patients not adequately controlled with existing therapies in Japan, and for use in adults with moderate-to-severe AD who are candidates for systemic therapy in the European Union. Dupilumab is a fully human *VelocImmune*-derived® monoclonal antibody [19,20] that blocks the shared receptor subunit for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, cytokines that are key drivers of type 2 diseases [15].

Administered as monotherapy or with concomitant topical corticosteroids (TCS) in early-phase and phase 3 studies, dupilumab improved signs and symptoms of AD with an acceptable safety profile in adults with moderate-to-severe AD [21–25]. Two parallel, randomized, double-blind, placebo-controlled, 16-week pivotal phase 3 trials with identical design, LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2, confirmed the efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe AD inadequately controlled by topical medications or for whom their use was inappropriate [11].

The objective of this analysis was to pool data from the SOLO 1 and SOLO 2 trials to further explore dupilumab's effects on AD clinical parameters and symptoms, including patient-reported pain and discomfort, and to obtain more precise estimates of safety outcomes, findings that are particularly useful for subset and subdomain analyses.

2. Materials and methods

Detailed descriptions have been published [11] and are summarized below.

2.1. Study design

This was a pooled analysis of two phase 3, randomized, multicenter, double-blinded, placebo-controlled, parallel-group, 16-week trials of dupilumab in adults with moderate-to-severe AD (LIBERTY AD SOLO 1: R668-AD-1334, NCT02277743 and LIBERTY AD SOLO 2: R668-AD-1416, NCT02277769). The studies had identical design but were conducted independently, in parallel, at approximately 160 study sites in North America, Europe, and Asia. Patients were enrolled from October 2014 to July 2015 in SOLO 1, and from December 2014 to June 2015 in SOLO 2 [11]. A 35-day screening and washout period preceded study drug administration. Both studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines, good clinical practice, and applicable regulatory requirements. All patients provided written informed consent prior to participation.

2.2. Patients

Patients were adults (age ≥18 years) with moderate-to-severe AD inadequately controlled by topical medications or for whom topical treatment was medically inadvisable. Key inclusion criteria included chronic AD diagnosed ≥3 years before screening; Eczema Area and Severity Index (EASI) score ≥16, Investigator's Global Assessment (IGA) score ≥3, and AD involvement in ≥10% of body surface area (BSA) at screening and baseline; pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥3 at baseline; and documented recent history (within 6 months before screening) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable.

2.3. Treatment

Patients were randomized 1:1:1 to receive subcutaneous dupilumab 300 mg once weekly (qw) or q2w, with alternating q2w placebo or placebo qw using a central interactive response system. Randomization was stratified according to disease severity (IGA 3 versus 4) and region. A washout period (up to 7 days for topical treatments and 28 days for systemic AD drugs) preceded study drug administration. A 600 mg loading dose of dupilumab was administered on Day 1 to patients in the active treatment groups. Patients in the placebo group received placebo on Day 1 to match the dupilumab loading dose.

To maintain blinding, coded kits containing dupilumab or placebo were used to mask treatments assigned. Patients who received dupilumab q2w were given matching placebo at alternating weeks to preserve blinding. Concomitant use of medications for conditions other than AD was permitted. Prohibited medications included TCS or calcineurin inhibitors and systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (including cyclosporine, methotrexate, mycophenolate mofetil, or azathioprine), which could be administered during the study only as rescue medications. Rescue treatment for AD could be provided if medically necessary (i.e. to control intolerable symptoms of AD). Topical rescue treatment was administered with study treatment, but if the rescue treatment was systemic, study treatment was discontinued.

2.4. Study endpoints

Analysis of study endpoints was performed according to a pre-specified hierarchy. A full list of study endpoints and endpoint descriptions have been published [11] and are included in the supplementary material.

In addition to the pre-specified endpoints, the following post-hoc analyses are reported:

- Percentage change from baseline in daily Peak Pruritus NRS score
- Proportion of patients with ≥3-point improvement (reduction) in daily Peak Pruritus NRS score
- Proportion of patients with ≥4-point improvement (reduction) in daily Peak Pruritus NRS score
- Proportion of patients who reported no pain/discomfort at Week 16 among patients who reported at least some pain/discomfort at baseline on the generic 5-dimension 3-level EuroQol (EQ-5D) [26]
- Distribution of patients achieving an IGA score of 0 or 1, 2, 3, or 4 over time

- Distribution of patients achieving <50%, ≥50 to <75%, or ≥75 to <90% improvement from baseline in EASI scores over time.

2.5. Safety

Safety was assessed by the overall incidence of adverse events and serious adverse events, the incidence of adverse events leading to treatment discontinuation, and the incidences of overall infections, non-herpetic skin infections, and herpes viral infections during the study.

2.6. Statistics

2.6.1. Analysis sets

Efficacy and safety data through Week 16 were pooled from the dupilumab 300 mg q2w, dupilumab 300 mg qw, and placebo groups in the two studies. Efficacy analyses were performed using the full analysis set, which included all randomized patients. Safety analyses were performed using the safety analysis set, which included all randomized patients who received at least one dose of any study drug.

2.6.2. Methods

The Cochran–Mantel–Haenszel (CMH) test adjusted by randomization strata (disease severity and region) was used for the primary and coprimary efficacy analyses and binary secondary outcomes. Patients who received rescue medication or who withdrew from the studies were considered nonresponders. The primary analysis of continuous endpoints used the multiple imputation procedure using the Markov Chain Monte Carlo algorithm and a regression model to generate a complete data set at each time point. Data sets were then analyzed using an analysis of covariance model with treatment, stratification factors (region and disease severity), and relevant baseline value included in the model. Data collected after use of rescue medication were treated as missing.

For binary outcomes using the CMH, three pre-specified sensitivity analyses were performed to handle missing data: (1) patients who received rescue treatment or withdrew from the study were considered nonresponders, and other missing values were imputed by last observation carried forward; (2) all observed data regardless of use of rescue medication, and patients with missing data were treated as nonresponders; and (3) all observed values regardless of rescue treatment, and no imputation of missing data was performed [11]. Pre-specified sensitivity analyses for continuous endpoints included (1) multiple imputation using all observed data regardless of rescue medication use, and (2) a mixed-effect repeated measures model, with data collected after use of rescue medication treated as missing [11].

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, which allowed control for the overall type I error rate at 0.05 for primary and secondary endpoints across dose regimens. All reported *P* values are two-sided. The statistical significance of differences in efficacy and safety between the qw and q2w dose groups was not investigated.

3. Results

3.1. Patients

The pooled analysis included 1379 randomized patients (placebo: n = 460; dupilumab q2w: n = 457; dupilumab qw: n = 462) (Fig. S1). Baseline demographics and characteristics were balanced between treatment groups (Table 1); patients had

Table 1
Pooled baseline demographics and clinical characteristics by treatment group.

Variable	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Age, median (IQR), years	37.0 (26.0–49.0)	36.0 (27.0–47.0)	36.0 (26.0–49.0)
Male, n (%)	250 (54.3)	267 (58.4)	281 (60.8)
Race, n (%)[a]			
White	302 (65.7)	320 (70.0)	317 (68.6)
Black	36 (7.8)	23 (5.0)	35 (7.6)
Asian	106 (23.0)	98 (21.4)	96 (20.8)
Other[b]	9 (2.0)	10 (2.2)	10 (2.2)
Disease duration, median (IQR), years	27.0 (19.0–39.0)	25.5 (17.0–38.0)	25.0 (17.0–39.0)
IGA score			
Score = 3[c], n (%)	234 (50.9)	234 (51.2)	244 (52.8)
Score = 4[d], n (%)	225 (48.9)	223 (48.8)	218 (47.2)
EASI score, median (IQR)	31.1 (22.2–42.6)	29.7 (21.1–40.5)	29.4 (21.7–41.7)
Peak pruritus NRS			
Median (IQR)	7.7 (6.4–8.7)	7.7 (6.3–8.8)	7.7 (6.3–8.7)
Proportion of patients with score ≥3, n (%)	447 (97.2)	451 (98.7)	445 (96.3)
Proportion of patients with score ≥4, n (%)	433 (94.1)	438 (95.8)	429 (92.9)
BSA %, median (IQR)	54.5 (36.0–75.0)	51.0 (36.5–71.0)	52.8 (37.0–70.8)
SCORAD total score, median (IQR)	68.5 (58.3–78.1)	66.6 (56.5–76.7)	66.8 (58.1–77.0)
GISS score, median (IQR)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
DLQI score, median (IQR)	15.0 (9.0–21.0)	14.0 (9.0–20.0)	15.0 (9.0–21.0)
POEM score, median (IQR)	22.0 (16.0–26.0)	21.0 (17.0–25.0)	21.0 (17.0–26.0)
HADS total score, median (IQR)	12.0 (7.0–18.0)	13.0 (7.0–18.0)	13.0 (7.0–19.0)
HADS-A ≥8 or HADS-D ≥8, n (%)	212 (46.1)	229 (50.1)	238 (51.5)

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; HADS-A, HADS Anxiety; HADS-D, HADS Depression; IGA, Investigator's Global Assessment; IQR, interquartile range; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; qw, once weekly; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis.
Percentages may not total 100 because of rounding.
[a] Race was not reported for 1.5%, 1.3%, and 0.9% of patients in the placebo, dupilumab q2w, and dupilumab qw groups, respectively.
[b] Includes: American Indian or Alaska native, native Hawaiian or other Pacific Islander, and other.
[c] Denotes moderate disease.
[d] Denotes severe disease.

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chronic AD (median disease duration of 26 years at baseline). Prior to enrollment, 32.9% of patients used systemic corticosteroids and 28.4% used systemic nonsteroidal immunosuppressants (Table S1).

3.2. Efficacy

For both dupilumab dose regimens, all pre-specified efficacy endpoints in the hierarchy showed significant improvement versus placebo (Table 2).

3.3. Pre-specified outcomes

A significant proportion of patients achieved an IGA score of 0 or 1 and a reduction of ≥2 points from baseline at Week 16 versus placebo ($P < 0.0001$; Tables 2, S2). In the pooled analysis, dupilumab significantly improved (versus placebo) outcomes of clinical severity, including proportions of patients reaching EASI-50, EASI-75, and EASI-90 from baseline through Week 16 ($P < 0.0001$; Tables 2, S2, Fig. S2a-c) and the percentage change from baseline at Week 16 in EASI score (Table 2; $P < 0.0001$).

Mean EASI scores (standard deviation [SD]) at baseline were similar in each treatment group (range: 32.4 [13.3]–34.0 [14.4]) but decreased over time to Week 16 in both dupilumab groups; reductions in the placebo group were smaller (mean EASI scores at Week 16 [SD]: 9.7 [10.6] and 9.2 [10.3] versus 21.6 [13.4] for dupilumab q2w and qw versus placebo, respectively; Fig. 1a). Dupilumab also significantly improved other measures of clinical severity, including percentage change from baseline to Week 16 in BSA, Global Individual Signs Score (GISS), and total SCORing Atopic Dermatitis (SCORAD) scores (all $P < 0.0001$; Table 2).

Dupilumab rapidly and significantly reduced patient-reported itch, versus placebo ($P < 0.0001$; Table 2, Fig. S3a), showing onset of action as early as Day 2, with clinically meaningful differences versus placebo as early as Day 3 (qw) or Day 4 (q2w) (post-hoc analyses; Table 2). Mean Peak Pruritus NRS scores (SD) at baseline were similar in each treatment group (range: 7.3 [1.9]–7.4 [1.8]) but decreased over time to Week 16 in both dupilumab groups; reductions in the placebo group were smaller (mean Peak Pruritus NRS scores [SD] at Week 16: 3.8 [2.2] and 3.6 [2.2] versus 5.6 [2.2] for q2w and qw versus placebo, respectively; Fig. 1b).

Dupilumab treatment versus placebo resulted in significant improvements in QoL and symptoms of anxiety/depression, as measured by change from baseline to Week 16 in Dermatology Life Quality Index (DLQI) and total Hospital Anxiety and Depression Scale (HADS) scores, respectively ($P < 0.0001$; Table 2, Fig. S3b). For patients who had symptoms of anxiety/depression (HADS-A or HADS-D scores ≥8) at baseline, a significantly greater proportion of those who received dupilumab (versus placebo) achieved HADS-A and HADS-D scores of <8 at Week 16 ($P < 0.0001$; Table 2). Significantly more patients receiving dupilumab than placebo achieved a ≥4-point improvement/reduction from baseline (the minimal clinically important difference [MCID]) in DLQI score at Week 16 ($P < 0.0001$; Table 2, Fig. S3c). Mean DLQI scores (SD) at baseline were similar in each treatment group (range: 14.7 [7.3]–15.1 [7.5]) but decreased over time to Week 16 in both dupilumab groups; reductions in the placebo group were smaller (mean DLQI

Table 2
Efficacy outcomes.

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Pre-specified endpoints in SOLO 1 and SOLO 2			
IGA 0 or 1 and ≥ 2 point reduction from baseline at Week 16, n (%)	43 (9.3)	169 (37.0)***	170 (36.8)***
Difference versus placebo (95% CI)		27.6 (22.5, 32.8)***	27.4 (22.3, 32.6)***
EASI-75 at Week 16, n (%)	61 (13.3)	218 (47.7)***	232 (50.2)***
Difference versus placebo (95% CI)		34.4 (28.9, 40.0)***	37.0 (31.4, 42.5)***
LS mean percentage change from baseline in Peak Pruritus NRS at Week 16	−20.5 ± 1.9	−47.4 ± 1.7***	−48.7 ± 1.7***
LS mean percentage difference versus placebo (95% CI)		−26.8 (−31.7, −22.0)***	−28.1 (−33.1, −23.2)***
Peak Pruritus NRS improvement, n/total n (%):			
≥ 4 points from baseline at Week 16[a]	47/433 (10.9)	168/438 (38.4)***	170/429 (39.6)***
Difference versus placebo (95% CI)		27.5 (22.1, 32.9)***	28.8 (23.3, 34.3)***
≥ 3 points from baseline at Week 16[b]	67/447 (15.0)	220/451 (48.8)***	224/445 (50.3)***
Difference versus placebo (95% CI)		33.8 (28.1, 39.5)***	35.3 (29.6, 41.1)***
≥ 4 points from baseline at Week 2	9/433 (2.1)	44/438 (10.0)***	48/429 (11.2)***
Difference versus placebo (95% CI)		8.0 (4.9, 11.1)***	9.1 (5.8, 12.4)***
LS mean change from baseline ± SE in Peak Pruritus NRS at Week 16	−1.6 ± 0.1	−3.5 ± 0.1***	−3.7 ± 0.1***
LS mean difference versus placebo (95% CI)		−1.9 (−2.2, −1.6)***	−2.1 (−2.4, −1.8)***
LS mean percentage change from baseline ± SE in EASI score at Week 16	−34.3 ± 2.3	−70.0 ± 1.8***	−70.7 ± 1.8***
LS mean percentage difference versus placebo (95% CI)		−35.7 (−41.3, −30.2)***	−36.4 (−41.8, −31.0)***
LS mean change from baseline in EASI score at Week 16	−11.5 ± 0.7	−22.6 ± 0.6***	−23.1 ± 0.6***
LS mean difference versus placebo (95% CI)		−11.1 (−12.8, −9.3)***	−11.6 (−13.3, −9.9)***
EASI-50 at Week 16, n (%)	107 (23.3)	306 (67.0)***	282 (61.0)***
Difference versus placebo (95% CI)		43.7 (37.9, 49.5)***	37.8 (31.9, 43.7)***
EASI-90 at Week 16, n (%)	34 (7.4)	150 (32.8)***	147 (31.8)***
Difference versus placebo (95% CI)		25.4 (20.5, 30.4)***	24.4 (19.6, 29.3)***
LS mean change from baseline ± SE in BSA at Week 16	−13.8 ± 1.2	−32.2 ± 1.0***	−33.5 ± 1.0***
LS mean difference versus placebo (95% CI)		−18.4 (−21.4, −15.4)***	−19.7 (−22.6, −16.8)***
LS mean percentage change from baseline ± SE in total SCORAD score at Week 16	−24.0 ± 1.9	−54.3 ± 1.5***	−55.2 ± 1.5***
LS mean percentage difference versus placebo (95% CI)		−30.3 (−34.7, −25.9)***	−31.2 (−35.6, −26.8)***
LS mean change from baseline ± SE total SCORAD score at Week 16	−16.6 ± 1.2	−36.6 ± 1.0***	−37.5 ± 1.0***
LS mean difference versus placebo (95% CI)		−19.9 (−22.8, −17.1)***	−20.9 (−23.8, −18.0)***
LS mean percentage change from baseline ± SE in GISS total score at Week 16	−22.1 ± 1.8	−49.2 ± 1.5***	−49.4 ± 1.6***
LS mean percentage difference versus placebo (95% CI)		−27.1 (−31.5, −22.8)***	−27.3 (−31.8, −22.8)***
LS mean change from baseline ± SE in DLQI score at Week 16	−4.3 ± 0.3	−9.3 ± 0.3***	−9.2 ± 0.3***
LS mean difference versus placebo (95% CI)		−4.9 (−5.8, −4.1)***	−4.9 (−5.8, −4.1)***
LS mean change from baseline ± SE in POEM score at Week 16	−4.2 ± 0.4	−10.9 ± 0.4***	−11.2 ± 0.4***
LS mean difference versus placebo (95% CI)		−6.7 (−7.7, −5.6)***	−6.9 (−8.0, −5.9)***
LS mean change from baseline ± SE in HADS total score at Week 16	−1.6 ± 0.4	−5.1 ± 0.3***	−5.5 ± 0.3***
LS mean difference versus placebo (95% CI)		−3.5 (−4.3, −2.6)***	−3.8 (−4.7, −3.0)***

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Table 2 (*Continued*)

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
LS mean percentage change from baseline ± SE in Peak Pruritus NRS at Week 2	−4.4 ± 1.2	−21.5 ± 1.2***	−19.4 ± 1.2***
LS mean percentage difference versus placebo (95% CI)		−17.1 (−20.2, −14.0)***	−14.9 (−18.0, −11.9)***
DLQI score ≥ 4 improvement from baseline at Week 16, n (%)[c]	127/438 (29.0)	297/432 (68.8)***	267/443 (60.3)***
Difference versus placebo (95% CI)		39.8 (33.7, 45.9)***	31.3 (25.0, 37.5)***
POEM score ≥ 4 improvement from baseline at Week 16, n (%)[d]	117 (25.4)	317 (69.4)***	293 (63.4)***
Difference versus placebo (95% CI)		43.9 (38.1, 49.7)***	38.0 (32.1, 43.9)***
HADS-A and HADS-D score < 8 at Week 16, n/total n (%)[e]	19/212 (9.0)	92/229 (40.2)***	93/238 (39.1)***
Difference versus placebo (95% CI)		31.2 (23.8, 38.6)***	30.1 (22.8, 37.4)***
Post-hoc analyses			
LS mean percentage change from baseline ± SE in daily Peak Pruritus NRS at Day 2	−0.6 ± 1.0	−4.5 ± 1.0*	−4.0 ± 1.0*
LS mean percentage difference versus placebo (95% CI)		−4.0 (−6.6, −1.3)*	−3.4 (−6.0, −0.8)*
Daily Peak Pruritus NRS improvement, n/total n (%)[f]:			
≥ 3 points from baseline at Day 3	13 (2.8)	23 (5.0)#	33 (7.1)*
Difference versus placebo (95% CI)		2.2 (−0.3, 4.7)#	4.3 (1.5, 7.1)*
≥ 3 points from baseline at Day 4	15 (3.3)	34 (7.4)*	37 (8.0)*
Difference versus placebo (95% CI)		4.2 (1.3, 7.1)*	4.7 (1.8, 7.7)*
≥ 4 points from baseline at Day 3	4 (0.9)	11 (2.4)#	14 (3.0)*
Difference versus placebo (95% CI)		1.5 (−0.1, 3.2)#	2.2 (0.4, 3.9)*
≥ 4 points from baseline at Day 4	4 (0.9)	18 (3.9)*	22 (4.8)**
Difference versus placebo (95% CI)		3.1 (1.1, 5.0)*	3.9 (1.8, 6.0)**
No pain/discomfort on EQ-5D at Week 16, n/total n (%)[g]	49/362 (13.5)	169/370 (45.7)***	163/377 (43.2)***
Difference versus placebo (95% CI)		32.1 (26.0, 38.3)***	29.7 (23.6, 35.8)***

BSA, body surface area; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, improvement from baseline of at least 50% in EASI; EASI-75, improvement from baseline of at least 75% in EASI; EASI-90, improvement from baseline of at least 90% in EASI; EQ-5D, 5-dimension 3-level EuroQoL; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS Anxiety; HADS-D, HADS Depression; IGA, Investigator's Global Assessment; LS, least-squares; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; qw, once weekly; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error.
Plus-minus values are means ± SE.
[#] $P > 0.05$.
[*] $P < 0.05$.
[**] $P < 0.001$.
[***] $P < 0.0001$ versus placebo.
[a] Analysis performed for patients with baseline peak pruritus NRS ≥ 4.
[b] Analysis performed for patients with baseline peak pruritus NRS ≥ 3.
[c] In the subset of patients with DLQI ≥ 4 at baseline.
[d] In the subset of patients with POEM ≥ 4 at baseline.
[e] In the subset of patients with HADS-A or HADS-D ≥ 8 at baseline, representing the cut-off for identifying patients with anxiety or depression, respectively.
[f] Patients after rescue treatment or withdrawal from the study were considered as nonresponders and other missing values were imputed by last observation carried forward.
[g] In the subset of patients who reported at least some pain/discomfort on the EQ-5D at baseline.

scores [SD] at Week 16: 5.3 [5.3] and 5.6 [5.5] versus 10.5 [6.4]; dupilumab q2w and qw versus placebo, respectively; Fig. 1c).

Dupilumab (versus placebo) significantly reduced AD symptoms, including pruritus and its impact on sleep, as measured by change from baseline to Week 16 in Patient Oriented Eczema Measure (POEM) score ($P < 0.0001$; Table 2). Mean POEM scores (SD) at baseline were similar in each treatment group (range: 20.3 [6.0]–20.7 [5.9]) but decreased over time to Week 16 in both dupilumab groups; reductions in the placebo group were smaller (mean POEM scores [SD] at Week 16: 9.3 [6.3] and 9.2 [6.5] versus 16.0 [6.5] for dupilumab q2w and qw versus placebo, respectively; Fig. 1d). A significantly higher proportion of patients in both dupilumab groups than in the placebo group achieved a ≥4-point improvement/reduction (the MCID) from baseline at Week 16 in POEM score ($P < 0.0001$; Table 2, Fig. S3d).

3.4. Post-hoc analyses

A post-hoc analysis of the pooled data showed that the distribution of dupilumab-treated patients within the predefined IGA 0 or 1/2/3/4 categories shifted over time, whereas the distribution in the placebo group did not change as much (Figs. 2a, b, S4a). Similar results were observed for the predefined EASI categories (≥90%, ≥75–<90%, ≥50–<75%, and <50%), for which the distribution markedly changed from Weeks 4 to 16 in both dupilumab groups (Figs. 2c, S4b). In the placebo group, the distributions changed only marginally from Weeks 4 to 16 (Fig. 2d).

Patients reported a large disease burden, assessed on the EQ-5D dimension of pain/discomfort at baseline, as indicated by the substantial proportion of patients with 'some/extreme' pain/discomfort (Fig. 3). Of the patients who reported at least some pain/discomfort on the EQ-5D at baseline (placebo, n = 362; qw, n = 377; q2w, n = 370), 43%, 46%, and 14% in the dupilumab qw, q2w, and placebo groups reported no pain/discomfort at Week 16, respectively ($P < 0.0001$ versus placebo; Table 2).

3.5. Rescue medication

Rescue medication was needed by a higher proportion of patients in the placebo versus dupilumab groups (Table S3). Placebo-treated patients were more likely to receive systemic corticosteroids and systemic nonsteroidal immunosuppressants than dupilumab-treated patients (Table S3) and received these medications earlier (Fig. S5). Overall, the treatment response (percentage changes in EASI and Peak Pruritus NRS scores) in dupilumab-treated patients was similar as found by the primary analysis and by analysis of all observed values regardless of rescue medication use (Figs. S6, S7). Sensitivity analyses outcomes were similar to those of the primary analysis (Table S2).

3.6. Safety

The overall incidence of adverse events was similar in the dupilumab and placebo groups in this pooled analysis (Table 3).

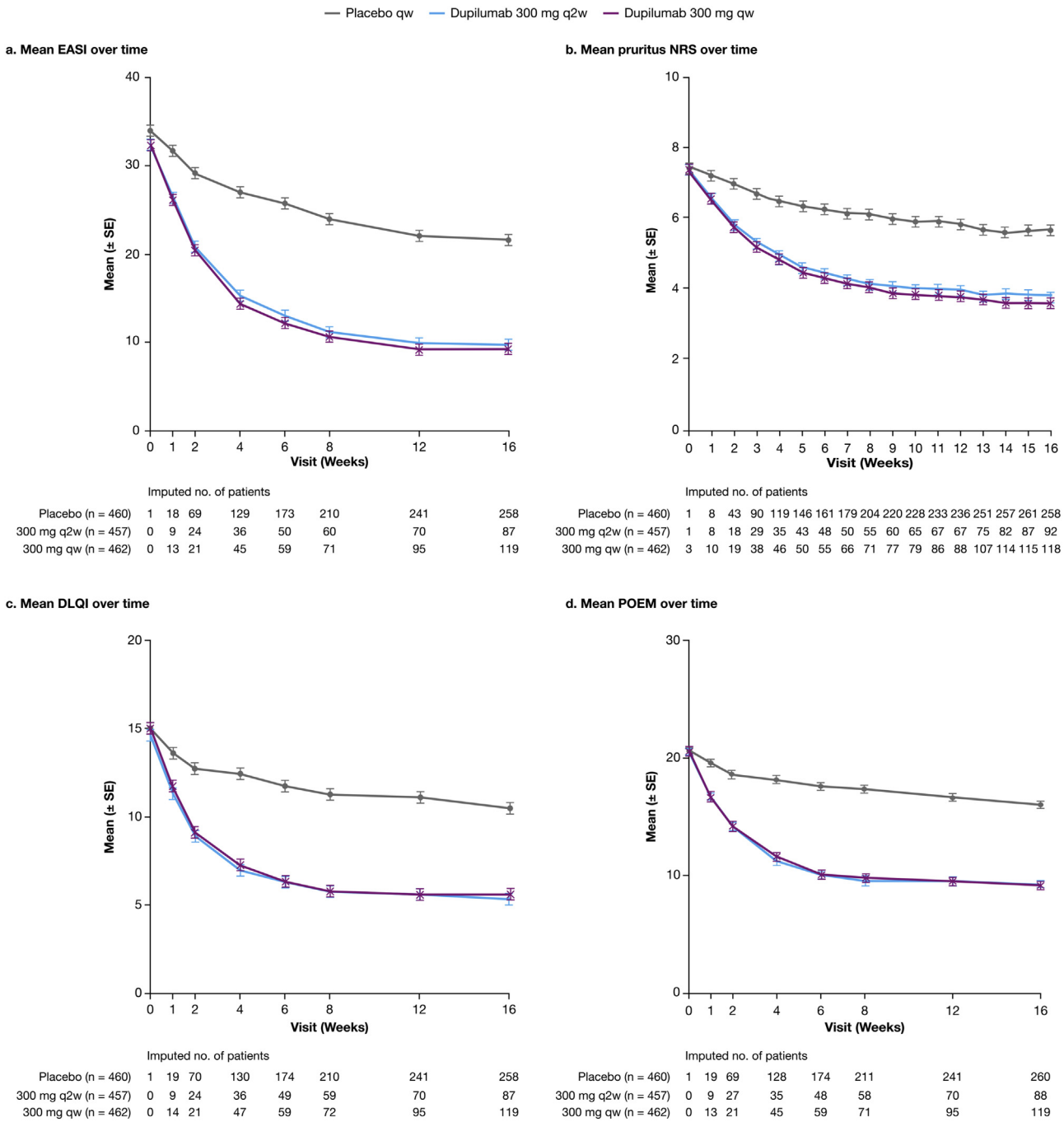

Fig. 1. Mean scores on the EASI (scale 0–72) (a), Peak Pruritus NRS (scale 0–10) (b), DLQI (scale 0–30) (c), and POEM (scale 0–28) (d) over time in dupilumab- and placebo-treated patients. Censored analysis of continuous endpoints: Categorized patients who received rescue treatment as missing data from the time of rescue; missing data were imputed by multiple imputation. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; qw, once weekly; q2w, every 2 weeks.

Serious adverse events were more common (approximately two-fold) with placebo than with dupilumab (Tables 3, S4). The only serious adverse events reported in >2 patients in any treatment group were exacerbation of AD (2 and 1 patients in the q2w and qw dose groups, respectively, versus 8 patients in the placebo group) and suicidal ideation (0 patients in the dupilumab groups versus 3 patients in the placebo group) (Table S4). Adverse events and serious adverse events leading to treatment discontinuation were uncommon in all treatment groups (Tables 3, S5).

The most common adverse events included exacerbation of AD (Medical Dictionary for Regulatory Activities preferred term "dermatitis atopic"), which was more common in the placebo group, nasaopharyngitis, which was balanced between treatment groups, and conjunctivitis and injection-site reactions, which were reported more often in dupilumab-treated patients (Table 3). Most injection-site reactions were of mild or moderate severity, self-limiting and required no treatment. Most cases of conjunctivitis were mild or moderate and resolved during the study treatment period. Only 1 patient (in the dupilumab 300 mg qw group) discontinued study treatment prematurely because of conjunctivitis.

Overall, the proportions of patients who had infections were similar in the dupilumab q2w, qw and placebo groups (31%, 31%

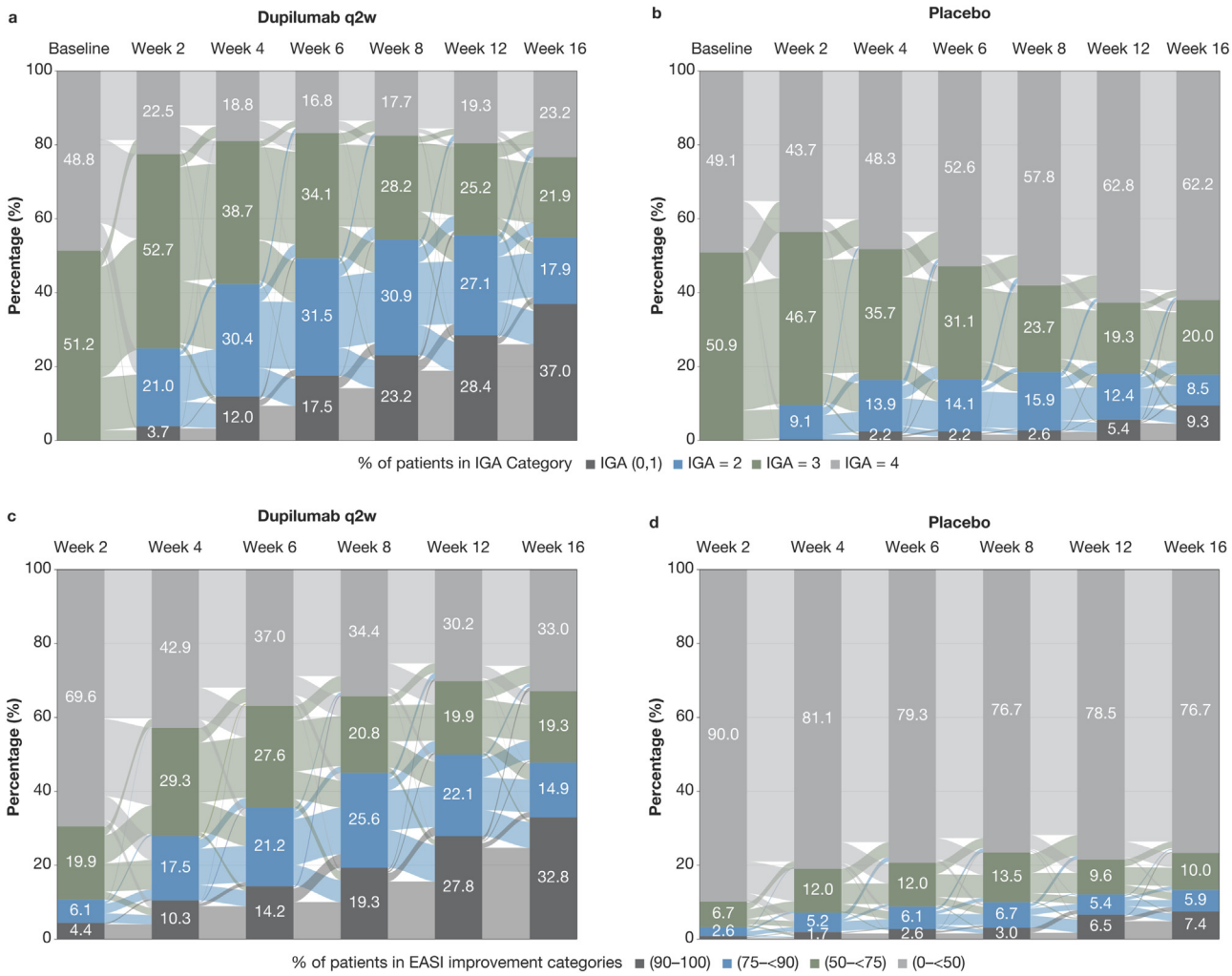

Fig. 2. The distribution of patients within the predefined IGA categories (0 or 1, 2, 3, and 4) in the dupilumab q2w (a) and placebo groups (b), and within the predefined EASI categories ≥90%; 75–<90%; 50–<75%; and <50% in the dupilumab q2w (c) and placebo groups (d). EASI, Eczema Area and Severity Index; EASI-50/75/90, improvement from baseline of ≥50%/≥75%/≥90% in EASI score; IGA, Investigator's Global Assessment; qw, once weekly; q2w, every 2 weeks.

and 30%, respectively) (Table 3). Non-herpetic skin infections were more common with placebo (Tables 3, S6); the difference in incidence was nominally significant in the combined dupilumab groups versus the placebo group (5.7% versus 9.4%, respectively; $P = 0.0093$). Herpes viral infections were reported in 5% of patients in both dupilumab groups and in 4% of patients in the placebo group (Table 3). Serious or severe infections occurred at numerically higher rates in the placebo than in the dupilumab groups (Table S7). Additional details of serious or severe infections are reported in Table S7.

There were 2 deaths in the SOLO studies; neither was considered related to the study drug. For further details see Simpson et al. [11]. Laboratory values, vital signs, and electrocardiographic assessments did not indicate clinically noteworthy differences between treatment groups. Small, transient increases from baseline in eosinophil counts were observed in the dupilumab groups at Weeks 4 and 8, with subsequent decreases toward or below baseline levels by Week 16 (Fig. S8, Table S8).

4. Discussion

In this pooled analysis of the phase 3 SOLO 1 and SOLO 2 studies, 16-week dupilumab treatment (versus placebo) significantly improved clinical parameters and symptoms of AD, including itch as early as Day 2, and aspects of mental health and QoL, including pain/discomfort, and had an acceptable safety profile in adults with moderate-to-severe AD. Outcomes were similar for both dupilumab dose regimens. These results are consistent with the data reported from the individual SOLO studies [11].

The post-hoc pooled analysis of response distribution over time by score category on the IGA (0 or 1, 2, 3, or 4) and EASI (≥90%, ≥75 to <90%, ≥50 to <75%, and <50%) showed steady improvement in response distributions through Week 16 in patients receiving dupilumab; occasional fluctuations in the distribution patterns probably reflected fluctuations in the disease course over time and, to some degree, the inherent variability of the outcome measures. This variability was also noted in the placebo group; however, clinically meaningful levels of response were achieved in substantially fewer placebo-treated than dupilumab-treated patients. This observation highlights the complex dynamics of clinical responses in AD and indicates that an analysis of single time points may not adequately characterize the treatment effect.

In addition to DLQI, the generic EQ-5D was also used to assess HRQoL in patients with moderate-to-severe AD in the SOLO trials; results of these analyses have been reported [27]. Pain/discomfort was one of the most affected dimensions of EQ-5D in the SOLO pooled population at baseline [27], consistent with the baseline burden reported in the phase 2b dupilumab study [8]. Dupilumab

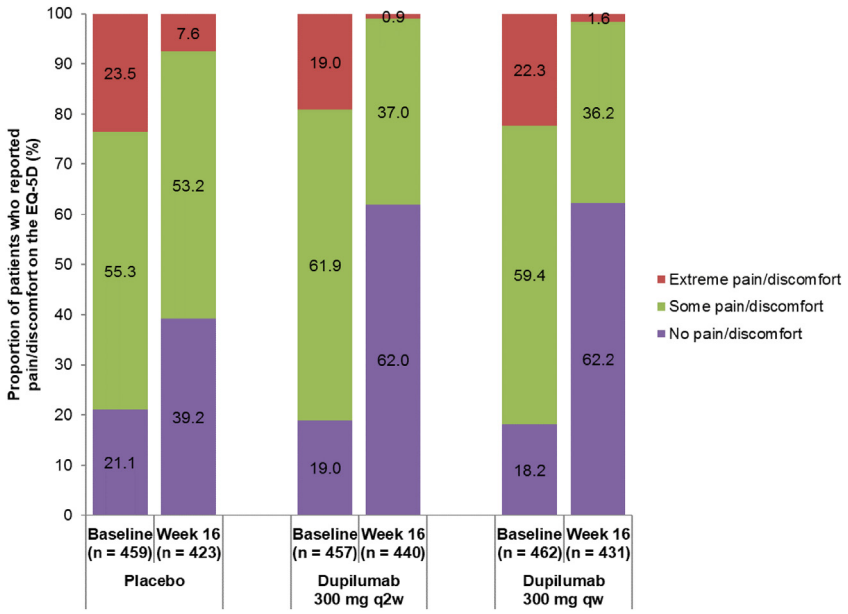

Fig. 3. Proportion of patients who reported pain/discomfort on the EQ-5D. Censored analysis for binary outcomes: Patients were categorized as nonresponders from the time rescue medication was used; missing data considered as nonresponder. EQ-5D, 5-dimension 3-level EuroQol; qw, once weekly; q2w, every 2 weeks.

Table 3
Adverse events.

Adverse event	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Patients, n (%)			
With ≥1 adverse event	313 (68.6)	321 (69.0)	307 (67.5)
With ≥1 serious adverse event	24 (5.3)	11 (2.4)	10 (2.2)
Died	0	0	1 (0.2)
With ≥1 adverse event leading to treatment discontinuation	7 (1.5)	6 (1.3)	7 (1.5)
Most common adverse events[a]			
Infections and infestations[b]	139 (30.5)	145 (31.2)	142 (31.2)
Nasopharyngitis	39 (8.6)	42 (9.0)	45 (9.9)
Upper respiratory tract infection	10 (2.2)	13 (2.8)	20 (4.4)
Serious or severe infections[b]	10 (2.2)	4 (0.9)	3 (0.7)
Non-herpetic skin infections[c]	43 (9.4)	23 (4.9)	29 (6.4)
Skin structures and soft tissue infections[d]	20 (4.4)	9 (1.9)	7 (1.5)
Any herpes viral infection[d]	17 (3.7)	25 (5.4)	21 (4.6)
Oral herpes	8 (1.8)	17 (3.7)	13 (2.9)
Herpes simplex	4 (0.9)	7 (1.5)	3 (0.7)
Eczema herpeticum	3 (0.7)	3 (0.6)	1 (0.2)
Herpes zoster	2 (0.4)	1 (0.2)	0
Genital herpes	1 (0.2)	0	1 (0.2)
Herpes ophthalmic	1 (0.2)	0	1 (0.2)
Herpes virus infection	1 (0.2)	0	1 (0.2)
Herpes simplex otitis externa	0	1 (0.2)	0
Ophthalmic herpes simplex	0	0	1 (0.2)
Dermatitis atopic[e]	148 (32.5)	62 (13.3)	59 (13.0)
Injection-site reactions[d]	33 (7.2)	57 (12.3)	76 (16.7)
Conjunctivitis[f]	10 (2.2)	45 (9.7)	33 (7.3)
Headache	24 (5.3)	40 (8.6)	33 (7.3)
Diarrhea	7 (1.6)	16 (3.4)	10 (2.2)
Back pain	9 (2.0)	9 (2.0)	10 (2.2)
Arthralgia	9 (2.0)	12 (2.6)	3 (0.7)
Nausea	4 (0.9)	10 (2.2)	9 (2.0)
Fatigue	4 (0.9)	11 (2.4)	7 (1.5)
Dizziness	9 (2.0)	6 (1.3)	4 (0.9)
Blood creatine phosphokinase increased	7 (1.5)	9 (1.9)	3 (0.7)

MedDRA, Medical Dictionary for Regulatory Activities; qw, once weekly; q2w, every 2 weeks.
[a] Adverse events reported at the level of MedDRA preferred term occurring in ≥2% of patients in any treatment group, except for preferred terms of herpes viral infections (MedDRA high level term).
[b] Reported as MedDRA system organ class.
[c] Adjudicated.
[d] Reported as MedDRA high level term.
[e] Preferred term denotes exacerbation of atopic dermatitis.
[f] Cluster of preferred terms includes conjunctivitis of unspecified cause, allergic, bacterial and viral conjunctivitis, and atopic keratoconjunctivitis.

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versus placebo significantly reduced symptoms of pain/discomfort in patients who reported at least some pain/discomfort at baseline. Pain is an important symptom of AD [9,10]. In the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative), the results of a global patient survey (N = 1111) identified pain/soreness, together with itch, as the items most important to patients when judging treatment response [28]. Despite its importance, pain/soreness is generally not recorded in AD clinical trials [12].

Sensitivity analyses demonstrated that the primary efficacy outcome was not biased by the statistical convention used in the primary analysis, in which patients who received rescue treatment for AD were counted as nonresponders (nonresponder imputation [NRI]), although this conservative method did result in lower response rates overall. Outcomes remained statistically significant for all key endpoints even when data after rescue treatment were included (all-observed analysis); however, a much greater proportion of placebo-treated than dupilumab-treated patients received rescue treatment. Furthermore, response rates calculated using all observed data are more consistent with real-life scenarios. Although these data are confounded by the effect of rescue treatment, which favors the placebo group, they more accurately reflect results (versus those of the very conservative NRI analysis) that may be expected from using dupilumab in clinical practice.

Consistent with data from the individual SOLO studies, this pooled analysis allowed us to confirm the acceptable safety profile of dupilumab: no new safety signals were observed in the pooled population. The lower incidence of non-herpetic skin infections in the dupilumab versus the placebo groups is consistent with findings from the individual SOLO studies [11] as well as the subsequent phase 3 studies of dupilumab with concomitant TCS [24,25], in which the incidence of non-herpetic skin infections was lower in patients treated with dupilumab plus TCS than in patients treated with placebo plus TCS. These results are also consistent with the notion that reducing type 2 skin inflammation promotes normalization of the skin barrier and antimicrobial responses [29–37].

The incidence of conjunctivitis was higher with dupilumab than placebo, consistent with findings from the individual SOLO studies [11] and other dupilumab studies in AD [23–25]. The cause of this apparent imbalance is not clear. Similar to the data from the two SOLO studies reported here, more than 90% of cases of conjunctivitis in clinical trials of dupilumab in AD were mild or moderate, and more than 75% resolved or were resolving during study treatment [38]. Notably, dupilumab-associated increases in rates of conjunctivitis have not been seen in studies of other type 2 diseases e.g. asthma [39–42] and CRSwNP [43].

In conclusion, similar to the early-phase dupilumab studies and SOLO 1 and SOLO 2 trials, this pooled analysis of SOLO 1 and SOLO 2 demonstrates that dupilumab monotherapy (versus placebo) leads to rapid, robust, and significant improvement in AD signs, patient-reported outcomes including itch, pain, and sleep disturbance, symptoms of anxiety/depression, and HRQoL. The pooled data show that dupilumab has an acceptable safety profile (no new safety signals were observed) and an overall favorable benefit-risk ratio in a population of AD patients with a high burden of disease and limited therapeutic options. These results support the importance of inhibiting the activity of the type 2 cytokines IL-4 and IL-13 in the treatment of AD. In addition, efficacy and safety findings for dupilumab in phase 3 trials of asthma and early-phase trials of CRSwNP and eosinophilic esophagitis indicate that IL-4 and IL-13 play an important role not only in AD but also in other type 2 atopic/allergic diseases that are common comorbidities in AD patients.

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Conflict of interest statement

D. Thaçi has acted as consultant, member of scientific advisory boards or lecturer for Abbvie, Almiral, Amgen, Biogen-Idec, BMS, Boehringer-Ingelheim, Celgene, Dignity, Dr. Reddy, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Mitsubishi, Morphosis, MSD, Mundipharma, Novartis, Pfizer, La Roche-Posay, Roche, Regeneron/Sanofi, Sandoz-Hexal, and Xenoport, and has received grants or research support from Celgene and Novartis.

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M. Deleuran has acted as consultant, investigator, member of scientific advisory boards and/or lecturer for Abbvie, Galapagos, LEO Pharma, MSD, Novartis, Pfizer, Pierre Fabre, La Roche-Posay, Roche, Regeneron Pharmaceuticals, Inc., and Sanofi-Genzyme.

Y. Kataoka has received lecture honoraria from Sysmex.

Z. Chen, A. Gadkari, B. Akinlade, N.M.H. Graham and M. Ardeleanu are employees and shareholders of Regeneron Pharmaceuticals, Inc.

L. Eckert and G. Pirozzi are employees of Sanofi; may hold stock or stock options in the company.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.02.002.

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SUPPLEMENTARY MATERIALS

Thaçi D, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2)

Supplementary text

Pre-specified study endpoints

- Proportion of patients achieving IGA 0 or 1 (i.e. clear or almost clear) and a reduction from baseline of ≥2 points at Week 16
- Proportion of patients achieving EASI-75 at Week 16 (EASI scores range from 0–72, with higher scores indicating greater severity)
- Percentage change from baseline to Week 16 in pruritus NRS (scale ranges from 0–10, with higher scores indicating more severe pruritus)
- Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus NRS from baseline to Week 2, Week 4 and Week 16
- Proportion of patients with ≥3-point improvement (reduction) of weekly average of peak daily pruritus NRS from baseline to Week 16
- Absolute change from baseline to Week 16 in pruritus NRS
- Percentage change from baseline to Week 16 in EASI score
- Proportion of patients with an improvement on the EASI score of ≥50% (EASI-50) at Week 16

23 – Proportion of patients with an improvement on the EASI score of ≥90% (EASI-90) at Week
24 16
25 – Absolute change from baseline to Week 16 in BSA
26 – Percentage change from baseline to Week 16 in SCORAD score (scale ranges from 0–103;
27 higher score indicates greater severity)
28 – Percentage change from baseline to Week 16 in Global Individual Signs Score (GISS) (scale
29 ranges from 0–12, with higher scores meaning greater severity)
30 – Absolute change from baseline to Week 16 in Dermatology Life Quality Index (DLQI) score
31 (scale ranges from 0–30, with higher scores indicating greater effect on quality of life)
32 – Absolute change from baseline to Week 16 in Patient Oriented Eczema Measure (POEM)
33 (scale ranges from 0–28, with higher scores indicating a greater symptom burden)
34 – Absolute change from baseline to Week 16 and total Hospital Anxiety Depression Scale
35 (HADS) scores (scale ranges from 0–28, with higher scores indicating a greater burden of
36 anxiety or depression symptoms)
37 – Percentage change from baseline to Week 2 in pruritus NRS
38 – Proportion of patients with an improvement of ≥4 points (the minimal clinically important
39 difference [MCID]) from baseline to Week 16 in DLQI (in the subset of patients with DLQI
40 ≥4 at baseline)
41 – Proportion of patients with an improvement of ≥4 points (the MCID) from baseline to
42 Week 16 in POEM (in the subset of patients with POEM ≥4 at baseline)
43 – Proportion of patients with HADS anxiety (HADS-A) and depression (HADS-D) subscores of
44 <8 at Week 16 among patients who had a baseline HADS-A or HADS-D subscore of ≥8,
45 which is the cut-off for identifying patients with anxiety or depression (Bjelland 2002).

SUPPLEMENTARY MATERIAL

Supplementary tables

Table S1. Prior use of systemic medication for AD[a] (safety analysis set).

Prior systemic therapy, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
All systemic medications	233 (51.1)	232 (49.9)	215 (47.3)
Systemic corticosteroids	160 (35.1)	156 (33.5)	137 (30.1)
Systemic non-steroidal immunosuppressants	121 (26.5)	135 (29.0)	135 (29.7)
Cyclosporine	93 (20.4)	107 (23.0)	101 (22.2)
Methotrexate	32 (7.0)	37 (8.0)	40 (8.8)
Mycophenolate sodium	1 (0.2)	1 (0.2)	1 (0.2)
Mycophenolate mofetil	9 (2.0)	21 (4.5)	15 (3.3)
Azathioprine	19 (4.2)	24 (5.2)	19 (4.2)

[a] Systemic medication for AD ended prior to baseline.

Table S2. Sensitivity analyses.

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Primary analysis			
IGA score of 0 or 1 and ≥2-point improvement from baseline at Week 16, n (%)	43 (9.3)	169 (37.0)***	170 (36.8)***
Difference versus placebo (95% CI)		27.6 (22.5, 32.8)***	27.4 (22.3, 32.6)***
EASI-75 at Week 16, n (%)	61 (13.3)	218 (47.7)***	232 (50.2)***
Difference versus placebo (95% CI)		34.4 (28.9, 40.0)***	37.0 (31.4, 42.5)***
EASI-50 at Week 16, n (%)	107 (23.3)	306 (67.0)***	282 (61.0)***
Difference versus placebo (95% CI)		43.7 (37.9, 49.5)***	37.8 (31.9, 43.7)***
Pruritus NRS ≥3-point improvement from baseline, n (%)	67/447 (15.0)	220/451 (48.8)***	224/445 (50.3)***
Difference versus placebo (95% CI)		33.8 (28.1, 39.5)***	35.3 (29.6, 41.1)***
Pruritus NRS ≥4-point improvement from baseline, n (%)	47/433 (10.9)	168/438 (38.4)***	170/429 (39.6)***
Difference versus placebo (95% CI)		27.5 (22.1, 32.9)***	28.8 (23.3, 34.3)***
Sensitivity analysis 1: Last observation carried forward; patient considered as nonresponder after rescue treatment			
IGA score of 0 or 1 and ≥2-point improvement from baseline at Week 16, n (%)	47 (10.2)	171 (37.4)***	179 (38.7)***

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Difference versus placebo (95% CI)		27.2 (22.0, 32.4)***	28.5 (23.3, 33.8)***
EASI-75 at Week 16, n (%)	70 (15.2)	230 (50.3)***	258 (55.8)***
Difference versus placebo (95% CI)		35.1 (29.5, 40.8)***	40.6 (35.0, 46.2)***
EASI-50 at Week 16, n (%)	134 (29.1)	339 (74.2)***	332 (71.9)***
Difference versus placebo (95% CI)		45.0 (39.3, 50.8)***	42.7 (36.9, 48.6)***
Pruritus NRS ≥3-point improvement from baseline, n (%)	92/447 (20.6)	241/451 (53.4)***	254/445 (57.1)***
Difference versus placebo (95% CI)		32.9 (26.9, 38.8)***	36.5 (30.6, 42.4)***
Pruritus NRS ≥4-point improvement from baseline, n (%)	58/433 (13.4)	179/438 (40.9)***	191/429 (44.5)***
Difference versus placebo (95% CI)		27.5 (21.9, 33.1)***	31.1 (25.4, 36.8)***
Sensitivity analysis 2: All observed values regardless of rescue treatment; missing considered as nonresponder			
IGA score of 0 or 1 and ≥2-point improvement from baseline at Week 16, n (%)	54 (11.7)	178 (38.9)***	176 (38.1)***
Difference versus placebo (95% CI)		27.2 (21.9, 32.6)***	26.4 (21.0, 31.7)***
EASI-75 at Week 16, n (%)	87 (18.9)	249 (54.5)***	274 (59.3)***
Difference versus placebo (95% CI)		35.6 (29.8, 41.4)***	40.4 (34.7, 46.1)***

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
EASI-50 at Week 16, n (%)	174 (37.8)	357 (78.1)***	354 (76.6)***
Difference versus placebo (95% CI)		40.3 (34.5, 46.1)***	38.8 (32.9, 44.7)***
Pruritus NRS ≥3-point improvement from baseline, n (%)	125/447 (28.0)	262/451 (58.1)***	271/445 (60.9)***
Difference versus placebo (95% CI)		30.1 (24.0, 36.3)***	32.9 (26.8, 39.1)***
Pruritus NRS ≥4-point improvement from baseline, n (%)	83/433 (19.2)	196/438 (44.7)***	207/429 (48.3)***
Difference versus placebo (95% CI)		25.6 (19.6, 31.5)***	29.1 (23.1, 35.1)***
Sensitivity analysis 3: All observed values regardless of rescue treatment; missing data not imputed			
IGA score of 0 or 1 and ≥2-point improvement from baseline at Week 16, n/N1 (%)	54/424 (12.7)	178/440 (40.5)***	176/431 (40.8)***
Difference versus placebo (95% CI)		27.7 (22.1, 33.3)***	28.1 (22.5, 33.7)***
EASI-75 at Week 16 —n/N1 (%)	87/424 (20.5)	249/440 (56.6)***	274/431 (63.6)***
Difference versus placebo (95% CI)		36.1 (30.1, 42.1)***	43.1 (37.1, 49.0)***
EASI-50 at Week 16, n (%)	174/424 (41.0)	357/440 (81.1)***	354/431 (82.1)***
Difference versus placebo (95% CI)		40.1 (34.2, 46.0)***	41.1 (35.2, 47.0)***
Pruritus NRS ≥3-point improvement from baseline, n (%)	125/406 (30.8)	262/426 (61.5)***	271/421 (64.4)***

Endpoint	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
Difference versus placebo (95% CI)		30.7 (24.3, 37.2)***	33.6 (27.2, 40.0)***
Pruritus NRS ≥4-point improvement from baseline, n (%)	83/393 (21.1)	196/414 (47.3)***	207/405 (51.1)***
Difference versus placebo (95% CI)		26.2 (20.0, 33.0)***	30.0 (23.7, 36.3)***

EASI, Eczema Area and Severity Index; EASI-50/EASI-75, ≥50%/≥75% improvement from baseline in EASI score; IGA, Investigator's Global Assessment; n, number of patients; N1, number of patients without missing data at Week 16.

*** $P < 0.0001$ versus placebo.

Table S3. Proportion of patients receiving rescue therapy during the study treatment period (full analysis set).

Rescue therapy, n (%)	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)
All rescue medications (topical and/or systemic)	237 (52)	78 (17)	100 (22)
Topical rescue	220 (48)	74 (16)	93 (20)
Topical corticosteroids	214 (47)	70 (15)	84 (18)
Topical calcineurin inhibitors	41 (9)	11 (2)	28 (6)
Systemic rescue	56 (12)	7 (2)	15 (3)
Systemic corticosteroids	47 (10)	5 (1)	12 (3)
Systemic non-steroidal immunosuppressants	22 (5)	4 (1)	4 (1)
Cyclosporin	18 (4)	3 (1)	3 (1)
Methotrexate	3 (1)	0	0
Mycophenolate sodium	0	1 (< 1)	0
Mycophenolate mofetil	0	0	1 (< 1)
Azathioprine	2 (< 1)	0	0

Table S4. Serious adverse events during the study treatment period (MedDRA PTs) (safety analysis set).

Patients with serious adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
≥1 Serious adverse event	24 (5.3)	11 (2.4)	10 (2.2)
Acute myocardial infarction	0	1 (0.2)	1 (0.2)
Myocardial infarction	0	0	1 (0.2)
Coronary artery disease	1 (0.2)	0	0
Cardiac failure, congestive	0	0	1 (0.2)
Abdominal pain	0	0	1 (0.2)
Colonic pseudo-obstruction	0	0	1 (0.2)
Abscess sweat gland	0	1 (0.2)	0
Kidney infection	0	0	1 (0.2)
Mastitis	1 (0.2)	0	0
Urinary tract infection bacterial	1 (0.2)	0	0
Cellulitis	0	0	1 (0.2)

Patients with serious adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Erysipelas	0	0	1 (0.2)
Endocarditis bacterial	1 (0.2)	0	0
Sepsis	2 (0.4)	0	0
Septic embolus	1 (0.2)	0	0
Skin infection	1 (0.2)	0	0
Dermatitis atopic	8 (1.8)	2 (0.4)	1 (0.2)
Dermatitis exfoliative	0	1 (0.2)	0
Clavicle fracture	0	1 (0.2)	0
Laceration	0	1 (0.2)	0
Concussion	1 (0.2)	0	0
Fall	0	1 (0.2)	0
Ligament sprain	1 (0.2)	0	0
Radius fracture	0	1 (0.2)	

Patients with serious adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Cerebrovascular accident	1 (0.2)	0	0
Headache	0	1 (0.2)	0
Subarachnoid hemorrhage	0	1 (0.2)	0
Completed suicide	0	0	1 (0.2)
Delirium	0	0	1 (0.2)
Confusional state	1 (0.2)	0	0
Psychotic disorder	1 (0.2)	0	0
Depression	1 (0.2)	0	0
Suicidal ideation	3 (0.7)	0	0
Lipoma	0	1 (0.2)	0
Hodgkin's disease	0	0	1 (0.2)
Nephrolithiasis	0	0	1 (0.2)
Limb operation	0	1 (0.2)	0

Patients with serious adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Anemia	1 (0.2)	0	0
Thrombocytopenia	1 (0.2)	0	0
Hyperglycemia	1 (0.2)	0	0
Failure to thrive	1 (0.2)	0	0
Intervertebral disc protrusion	1 (0.2)	0	0
Bursitis	1 (0.2)	0	0
Aortic stenosis	1 (0.2)	0	0
Abortion spontaneous	0	0	1 (0.2)
Angle closure glaucoma	1 (0.2)	0	0
Acute kidney injury	2 (0.4)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital

anomaly/birth defect; or is an important medical event. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Table S5. Adverse events (MedDRA PTs) leading to permanent treatment discontinuation (safety analysis set).

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
≥1 Adverse event	7 (1.5)	6 (1.3)	7 (1.5)
Dermatitis atopic	3 (0.7)	3 (0.7)	1 (0.2)
Dermatitis allergic	0	0	1 (0.2)
Lymphocytosis	0	0	1 (0.2)
Neutropenia	0	1 (0.2)	0
Diarrhea	0	0	1 (0.2)
Acute myocardial infarction	0	1 (0.2)	0
Conjunctivitis allergic	0	0	1 (0.2)
Angle closure glaucoma	1 (0.2)	0	0
Folliculitis	0	0	1 (0.2)
Eczema impetiginous	0	1 (0.2)	0
Endocarditis bacterial	1 (0.2)	0	0

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Sepsis	1 (0.2)	0	0
Septic embolus	1 (0.2)	0	0
Hodgkin's disease	0	0	1 (0.2)
Lethargy	0	0	1 (0.2)
Cerebrovascular accident	1 (0.2)	0	0
Clavicle fracture	0	1 (0.2)	0
Laceration	0	1 (0.2)	0
Suicidal ideation	2 (0.4)	0	0
Psychotic disorder	1 (0.2)	0	0
Abortion spontaneous	0	0	1 (0.2)
Acute kidney injury	1 (0.2)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Table S6. Non-herpetic skin infections during the study treatment period (MedDRA PTs) (safety analysis set).

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Adjudicated non-herpetic skin infections[a]	43 (9.4)	23 (4.9)	29 (6.4)
Folliculitis	8 (1.8)	4 (0.9)	6 (1.3)
Impetigo	7 (1.5)	3 (0.6)	2 (0.4)
Skin infection	7 (1.5)	3 (0.6)	2 (0.4)
Cellulitis	4 (0.9)	1 (0.2)	3 (0.7)
Eczema impetiginous	1 (0.2)	3 (0.6)	2 (0.4)
Molluscum contagiosum	2 (0.4)	1 (0.2)	3 (0.7)
Furuncle	1 (0.2)	2 (0.4)	1 (0.2)
Staphylococcal skin infection	2 (0.4)	1 (0.2)	1 (0.2)
Subcutaneous abscess	3 (0.7)	1 (0.2)	0
Otitis externa	0	2 (0.4)	1 (0.2)
Tinea versicolour	1 (0.2)	1 (0.2)	1 (0.2)

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Erysipelas	1 (0.2)	0	1 (0.2)
Infected dermal cyst	0	1 (0.2)	1 (0.2)
Paronychia	2 (0.4)	0	0
Rash pustular	1 (0.2)	0	1 (0.2)
Skin bacterial infection	2 (0.4)	0	0
Tinea pedis	2 (0.4)	0	0
Abscess limb	0	0	1 (0.2)
Abscess sweat gland	0	1 (0.2)	0
Acne pustular	0	0	1 (0.2)
Body tinea	0	0	1 (0.2)
Eyelid infection	0	0	1 (0.2)
Intertrigo	1 (0.2)	0	0
Onychomycosis	1 (0.2)	0	0

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Otitis externa fungal	0	0	1 (0.2)
Soft tissue infection	1 (0.2)	0	0
Staphylococcal impetigo	0	1 (0.2)	0
Tinea manuum	1 (0.2)	0	0
Wound infection	0	0	1 (0.2)

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

[a] Skin infections were adjudicated by the medical director for each study. Infections are listed as MedDRA PTs.

Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Table S7. Serious or severe infections during the study treatment period (MedDRA PTs) (safety analysis set).

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Serious or severe infections	10 (2.2)	4 (0.9)	3 (0.7)
Folliculitis	2 (0.4)	0	0
Sepsis	2 (0.4)	0	0
Abscess sweat gland	0	1 (0.2)	0
Cellulitis	0	0	1 (0.2)
Conjunctivitis	0	1 (0.2)	0
Conjunctivitis bacterial	0	1 (0.2)	0
Endocarditis bacterial	1 (0.2)	0	0
Erysipelas	0	0	1 (0.2)
Herpes simplex	0	1 (0.2)	0
Kidney infection	0	0	1 (0.2)
Mastitis	1 (0.2)	0	0

Patients with adverse event, n (%)	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Nasopharyngitis	1 (0.2)	0	0
Pharyngitis	1 (0.2)	0	0
Septic embolus	1 (0.2)	0	0
Skin infection	1 (0.2)	0	0
Soft tissue infection	1 (0.2)	0	0
Urinary tract infection bacterial	1 (0.2)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event. Severe adverse events were defined as those that produce significant impairment of functioning or incapacitation and are a definite hazard to the patient's health. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Table S8. Mean and median changes from baseline in eosinophils.

Event	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)
Change from baseline (10^9 per liter)			
Week 4			
N	426	437	429
Mean (SD)	−0.01 (0.522)	0.09 (0.576)	0.10 (0.593)
Median	0.00	0.00	0.00
Q1, Q3	−0.20, 0.10	−0.10, 0.20	−0.10, 0.20
Week 8			
N	402	431	416
Mean (SD)	−0.11 (0.558)	0.07 (0.636)	0.08 (0.720)
Median	−0.10	0.00	0.00
Q1, Q3	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 12			
N	398	431	413

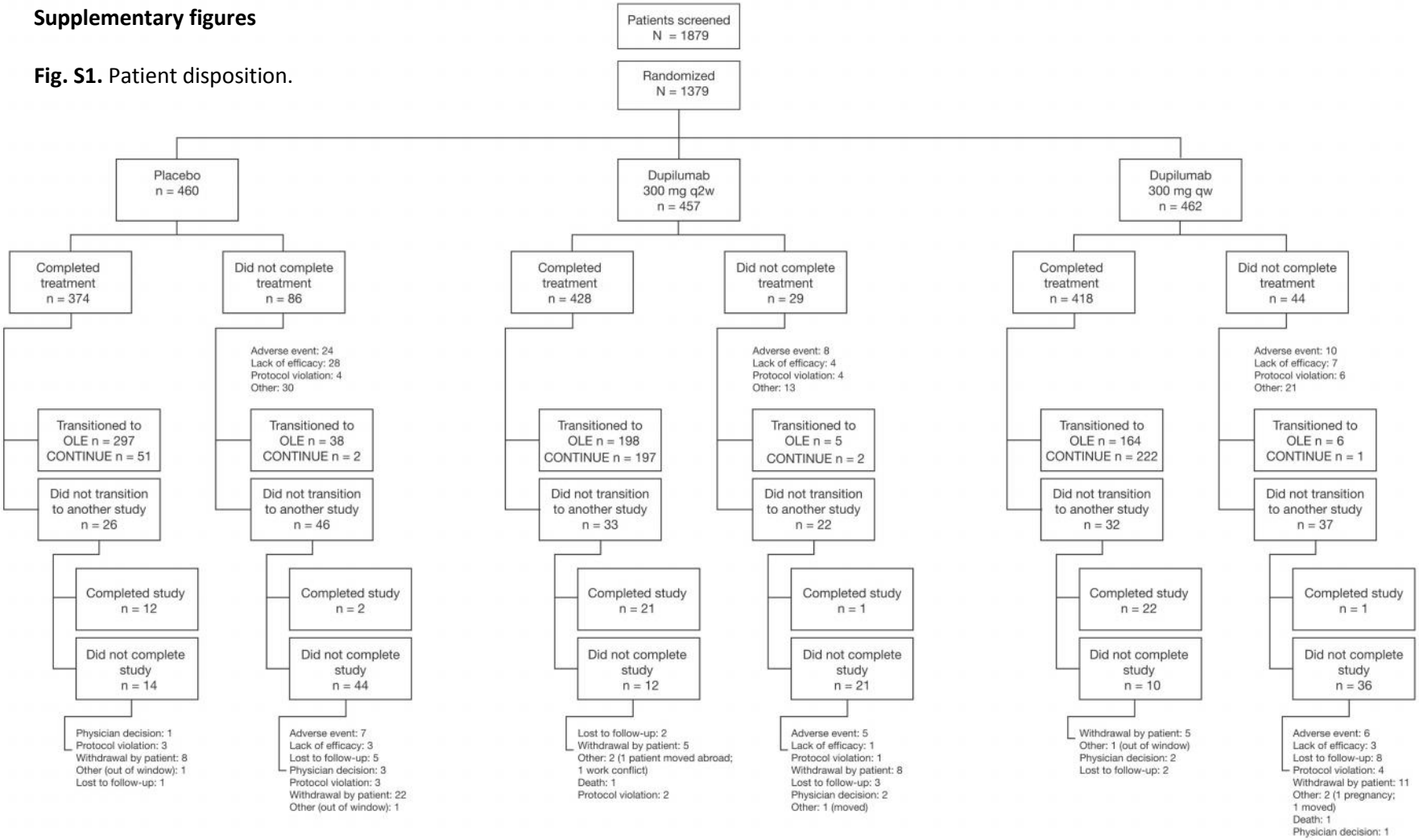
Mean (SD)	−0.13 (0.575)	0.01 (0.576)	0.03 (0.586)
Median	−0.10	0.00	0.00
Q1, Q3	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 16			
N	411	434	413
Mean (SD)	−0.15 (0.525)	−0.02 (0.606)	0.01 (0.592)
Median	−0.10	0.00	0.00
Q1, Q3	−0.30, 0.10	−0.20, 0.10	−0.20, 0.20

Q1, first quartile; Q3, third quartile; SD, standard deviation.

SUPPLEMENTARY MATERIAL

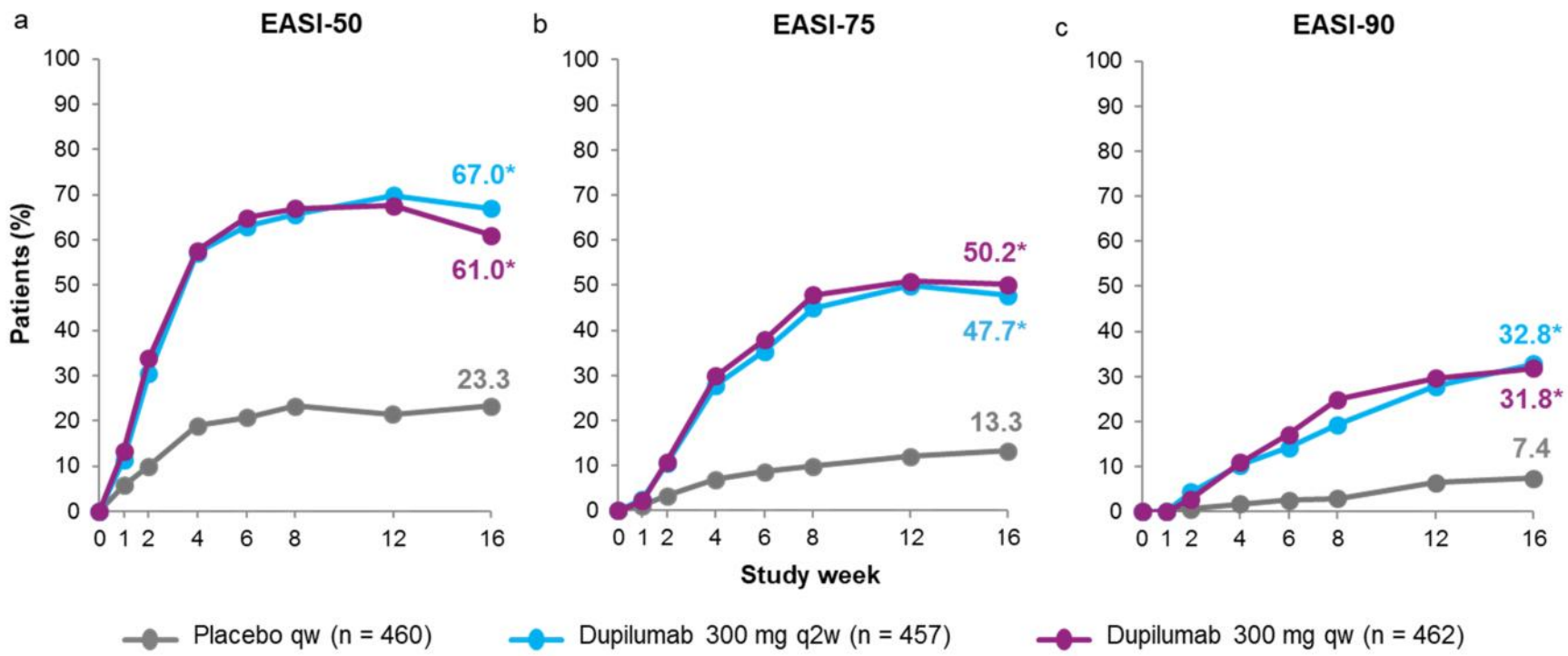
Supplementary figures

Fig. S1. Patient disposition.



OLE, open-label extension study; q2w, every 2 weeks; qw, once weekly.

Fig. S2. Proportion of patients achieving EASI-50 (a), EASI-75 (b), and EASI-90 (c) from baseline through Week 16.

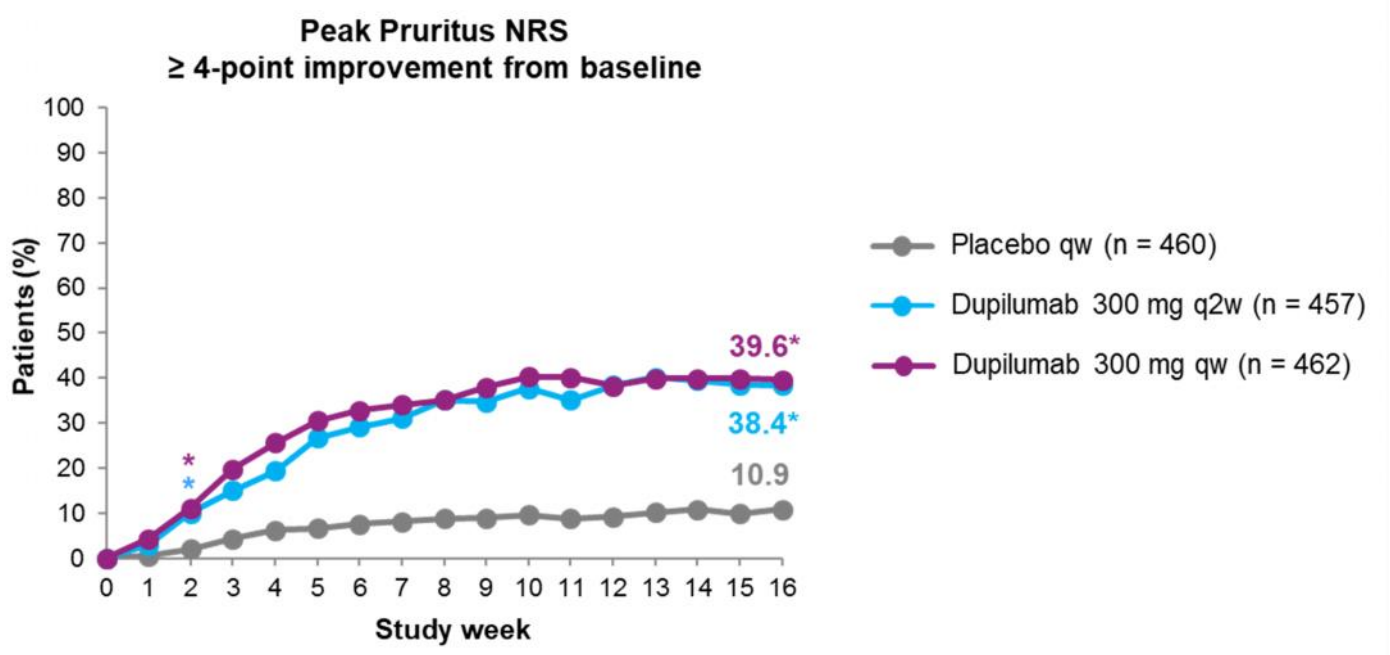


EASI, Eczema Area and Severity Index; EASI-50/75/90, improvement from baseline of ≥50%/≥75%/≥90% in EASI score; qw, once weekly; q2w, every 2 weeks.

* $P < 0.0001$ versus placebo.

Fig. S3. Proportion of patients achieving ≥4-point improvement (reduction) from baseline through Week 16 in peak pruritus NRS (a); LS mean change from baseline in total HADS scores (b); proportion of patients achieving ≥4-point improvement (reduction) from baseline through Week 16 in DLQI (c) and POEM (d).

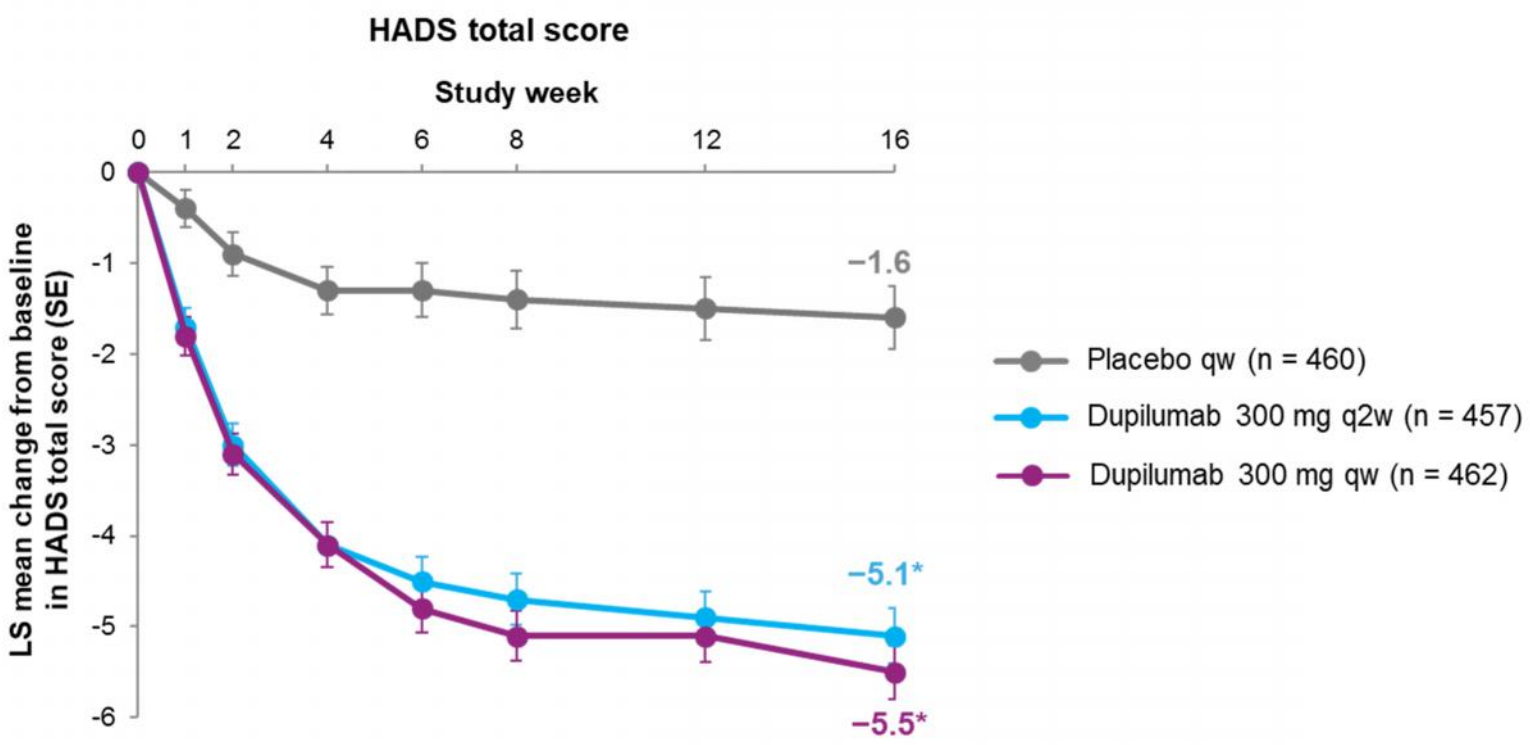
(a)



* $P < 0.0001$ versus placebo.

Censored analysis for binary outcomes: Patients were categorized as nonresponders from the time rescue medication was used; missing considered as nonresponder.

(b)

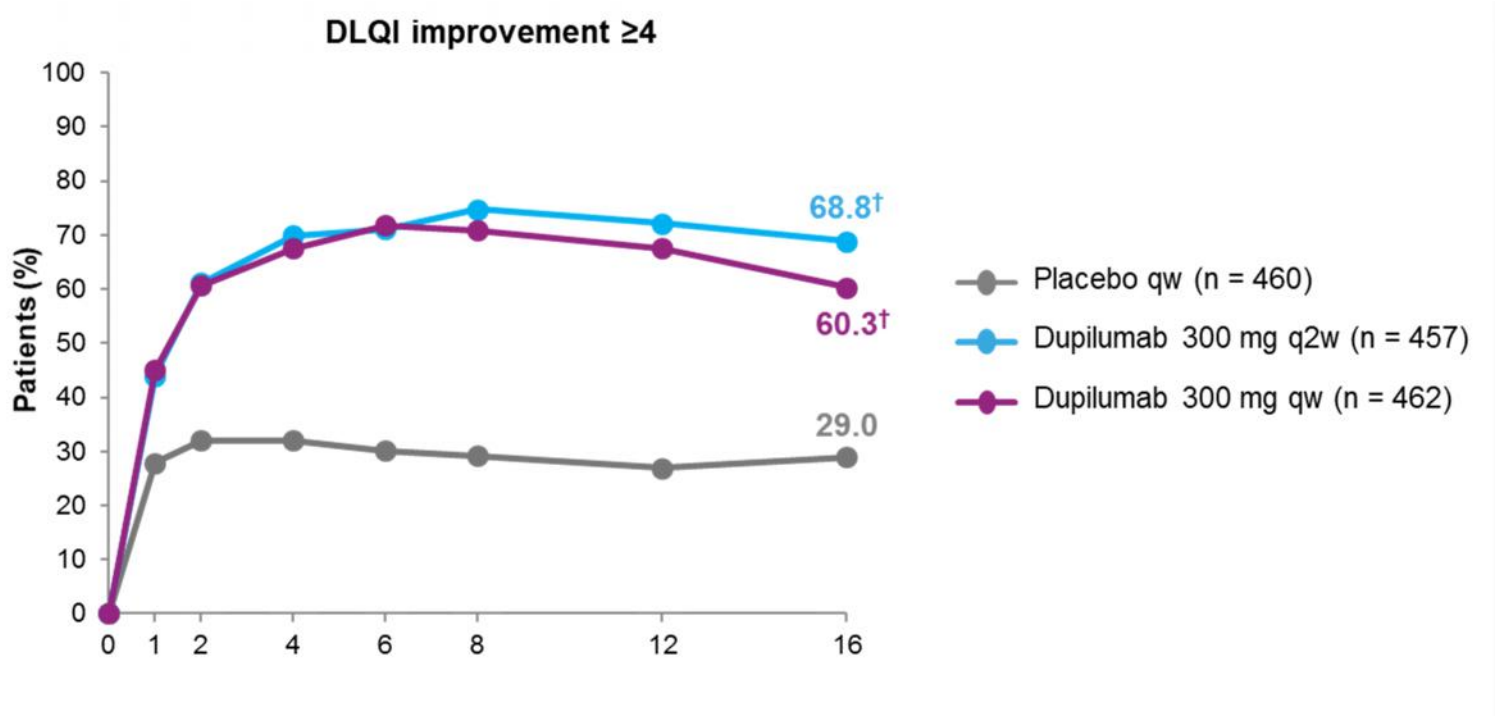


LS, least squares.

* *P* < 0.0001 versus placebo.

Censored analysis of continuous endpoints: Categorized patients who received rescue treatment as missing data from the time of rescue; missing data were imputed by multiple imputation.

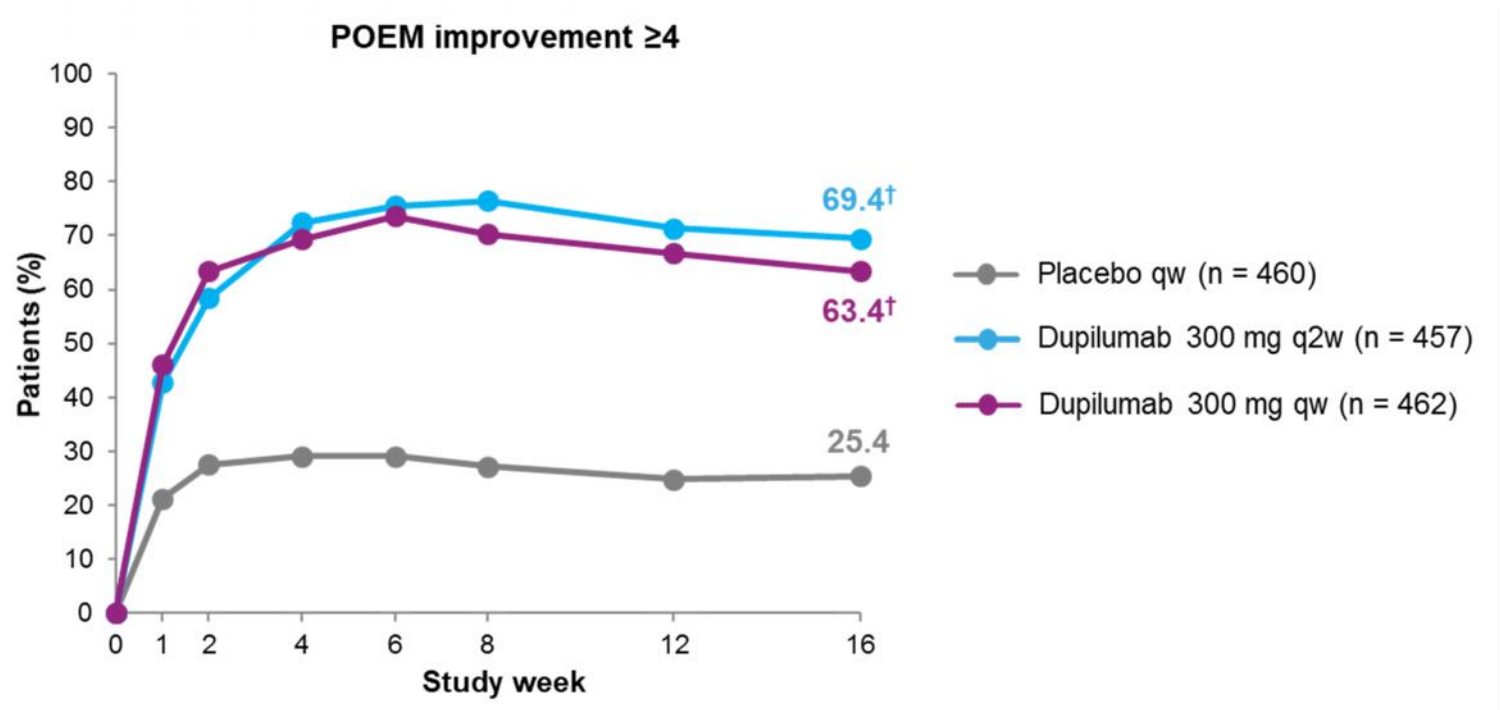
(c)



† Nominal $P < 0.0001$ versus placebo.

Censored analysis for binary outcomes: Patients were categorized as nonresponders from the time rescue medication was used; missing considered as nonresponder.

(d)

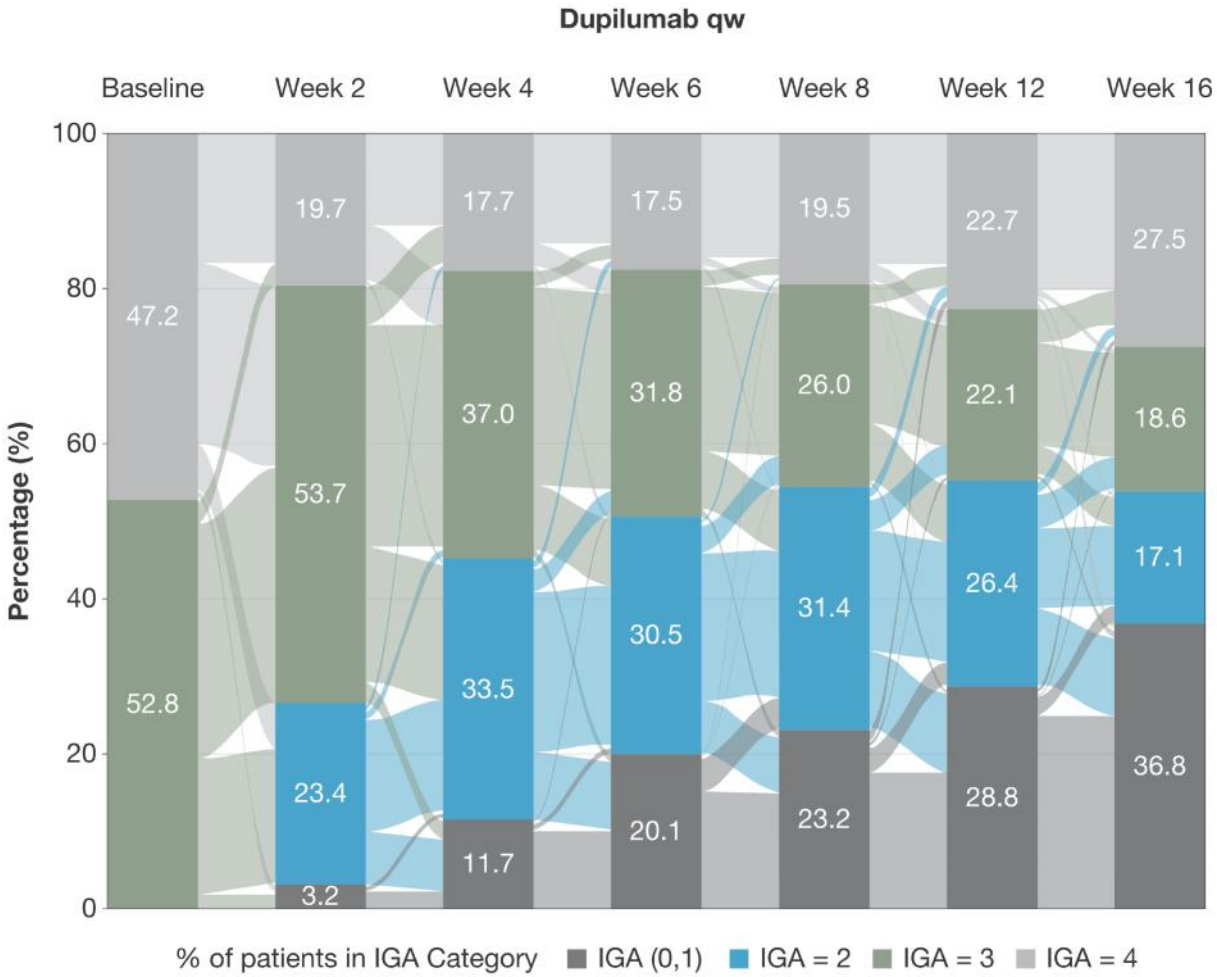


† Nominal $P < 0.0001$ versus placebo.

Censored analysis for binary outcomes: Patients were categorized as nonresponders from the time rescue medication was used; missing considered as nonresponder.

Fig. S4. The distribution of patients in the dupilumab qw group within the predefined IGA categories (0 or 1; 2; 3; and 4) (a) and EASI categories ≥90%; ≥75 to <90%; ≥50 to <75%; and <50% (b).

(a)



(b)

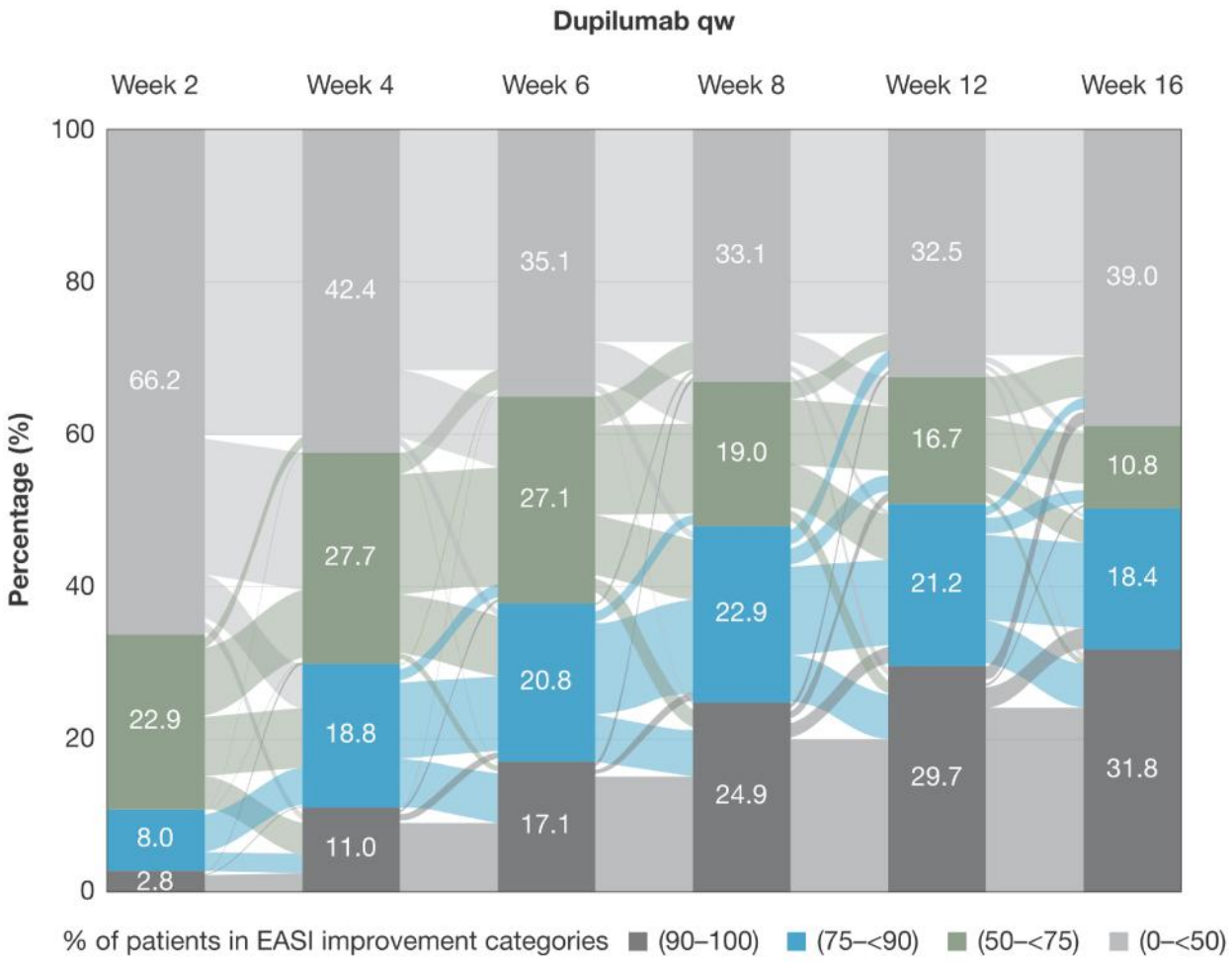

Dupilumab qw
Week 2
Week 4
Week 6
Week 8
Week 12
Week 16
Percentage (%)
100
80
60
40
20
0
66.2
22.9
8.0
2.8
42.4
27.7
18.8
11.0
35.1
27.1
20.8
17.1
33.1
19.0
22.9
24.9
32.5
16.7
21.2
29.7
39.0
10.8
18.4
31.8
% of patients in EASI improvement categories
(90–100)
(75–<90)
(50–<75)
(0–<50)

Fig. S5. Cumulative proportion of patients receiving rescue therapy during the treatment period.

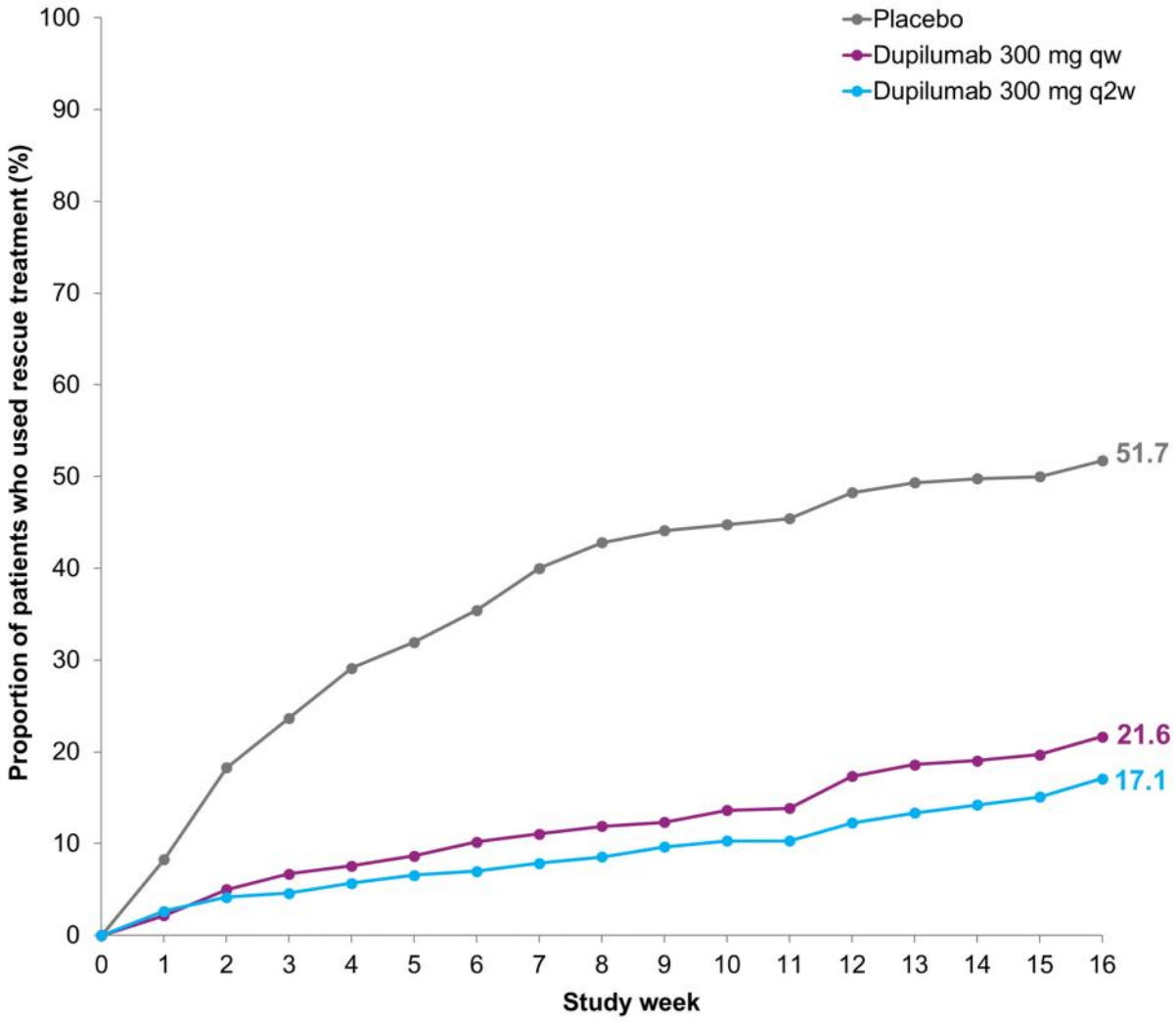
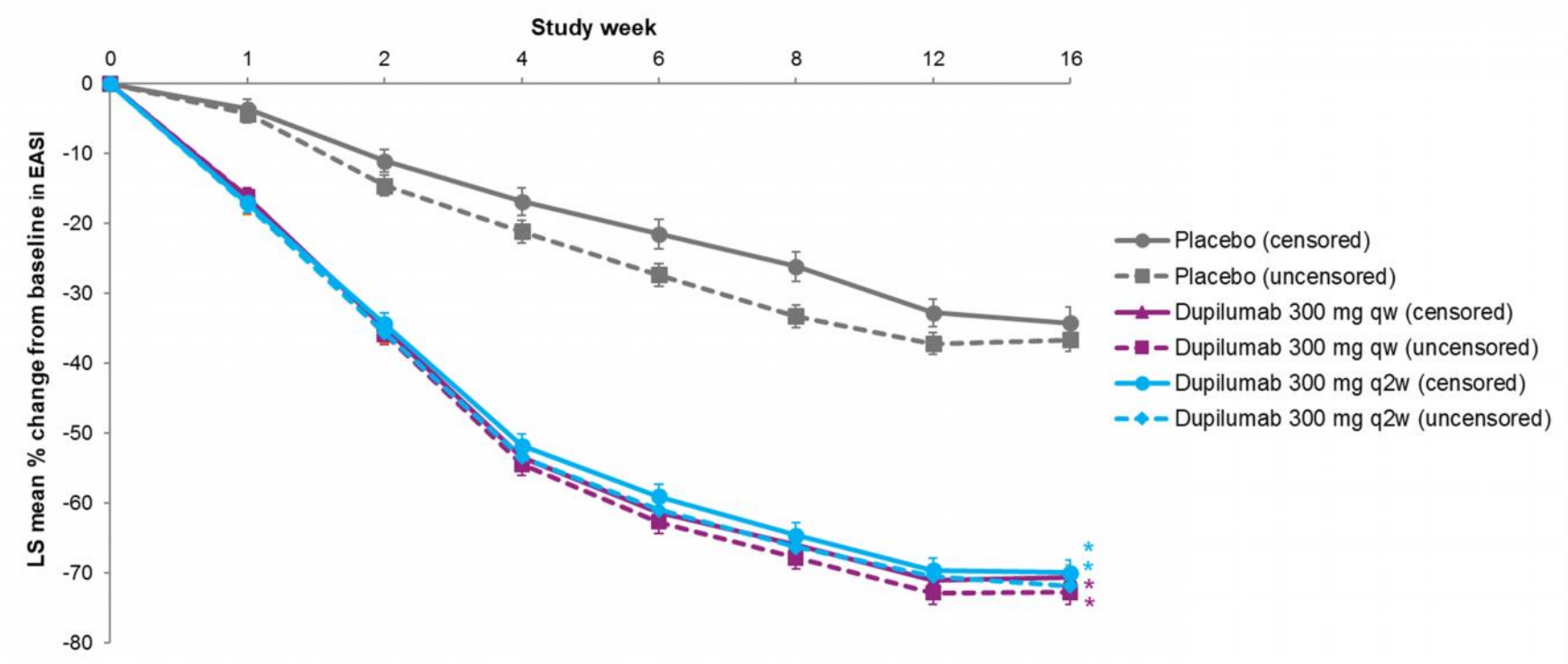


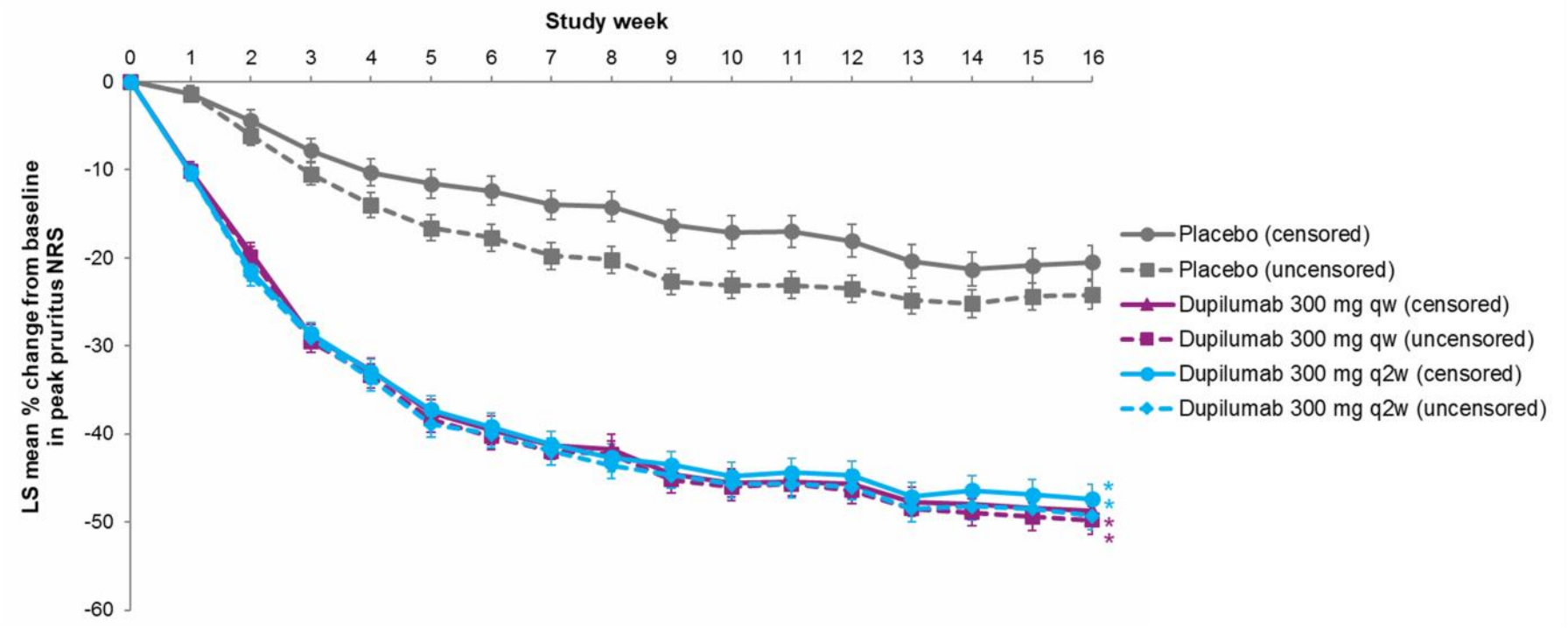
Fig. S6. EASI: least squares mean percentage change over time, primary analysis, and sensitivity analysis.



LS, least squares.

* $P < 0.0001$ versus placebo.

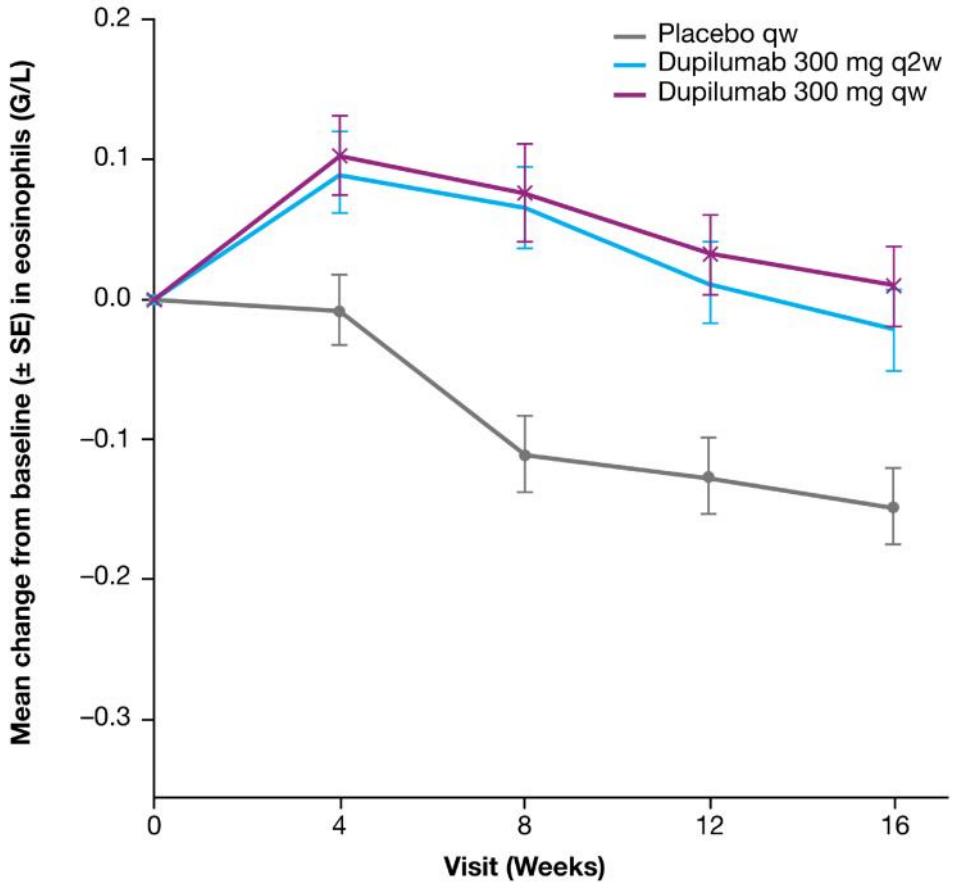
Fig. S7. Pruritus NRS: least squares mean percentage change over time, primary analysis, and sensitivity analysis.



LS, least squares.

* $P < 0.0001$ versus placebo.

Fig. S8. Change in average eosinophils (10^9 per liter) from baseline through Week 16.



No. of patients in each visit

Placebo qw (n = 456)	454	426	402	398	411
Dupilumab 300 mg q2w (n = 465)	465	437	431	431	434
Dupilumab 300 mg qw (n = 455)	453	429	416	413	413