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Dupilumab significantly improves sleep in adults with atopic dermatitis: results from the 12-week placebo-controlled period of the 24-week phase IV randomized double-blinded placebo-controlled DUPISTAD study

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Abstract

Background Sleep disturbance is a prominent symptom of atopic dermatitis (AD) and can result in insomnia, daytime fatigue, drowsiness, reduced productivity and impaired quality of life (QoL).

Objectives The Dupilumab Effect on Sleep in AD Patients (DUPISTAD) phase IV randomized double-blinded placebo-controlled study evaluated the impact of dupilumab treatment on sleep and other patient- and physician-reported outcomes.

Methods Adults with moderate-to-severe AD were randomized 2 : 1 to dupilumab 300 mg once every 2 weeks (q2w) or placebo for 12 weeks; concomitant topical corticosteroids were permitted. Patients subsequently entered an open-label phase and received dupilumab 300 mg q2w for a further 12 weeks. The primary endpoint was the percentage change in sleep quality from baseline to week 12, assessed using a novel numeric rating scale (NRS). Secondary and exploratory endpoints included percentage change in peak pruritus NRS (PP NRS), change in SCORing Atopic Dermatitis (SCORAD), SCORAD sleep visual analogue scale (VAS), Eczema Area and Severity Index, Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment T-score and the Epworth Sleepiness Scale. Sleep diary and wrist actigraphy measurements were recorded throughout the study.

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Results In total, 127 patients received dupilumab and 61 patients received placebo. Demographic and baseline disease characteristics were balanced between groups. Sleep quality NRS significantly improved in patients treated with dupilumab by week 12 vs. placebo [least squares mean of the difference (LSMD) −15.5%, $P<0.001$]. PP NRS (LSMD −27.9%, $P<0.001$), SCORAD (LSMD −15.1, $P<0.001$), SCORAD sleep VAS (LSMD −2.1, $P<0.001$) and PROMIS T-score (LSMD −3.6, $P<0.001$) were also significantly improved at week 12 with dupilumab vs. placebo. The overall percentage of patients reporting treatment-emergent adverse events was lower in the dupilumab group (56.7%) than in the placebo group (67.2%).

Conclusions Dupilumab significantly improved sleep quality and perception of sleep continuity, itch, metrics of AD severity and QoL in adults with moderate-to-severe AD, with an acceptable safety profile compared with placebo.

What is already known about this topic?

- Sleep disturbance is common in patients with atopic dermatitis (AD) and has a significant impact on quality of life (QoL).
- Sleep was previously shown to improve with dupilumab treatment in adult patients with AD.

What does this study add?

- The prospective double-blind Dupilumab Effect on Sleep in AD Patients (DUPISTAD) study provides further insight into the effect of dupilumab on sleep in patients with moderate-to-severe AD.
- Dupilumab significantly improved overall sleep, itch and other AD-related signs, symptoms and QoL in adults with moderate-to-severe AD, compared with placebo.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and pruritus (itch).[1,2] AD affects approximately 2–7% of adults worldwide.[3,4] In moderate-to-severe AD, lesions can be extensive with intense pruritus.[5] Sleep disturbance represents one of the prominent symptoms of AD, primarily related to night-time itching and scratching, affecting the ability to fall and stay asleep and leading to daytime drowsiness, a high burden of fatigue and reduced productivity and quality of life (QoL).[6–14] There is accumulating evidence to suggest that type 2 inflammation underlies the chronic itch in AD.[15]

Dupilumab is a fully human VelocImmune®-derived[16,17] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signalling of both IL-4 and IL-13, which are key and central drivers of type-2-mediated inflammation in AD.[18] Sleep disturbance was previously shown to improve with dupilumab treatment in adult patients with AD.[19] The prospective double-blind Dupilumab Effect on Sleep in AD Patients (DUPISTAD) study was designed to provide further insight into the effect of dupilumab on sleep in patients with moderate-to-severe AD using dedicated sleep outcome measures, while also assessing the clinical and patient-reported outcomes of AD.

The objective of this analysis was to assess the effect of dupilumab on sleep quality and duration in adult patients with moderate-to-severe AD following 12 weeks of treatment with the approved adult dose of dupilumab [300 mg once every 2 weeks (q2w)][20,21] compared with placebo.

Patients and methods

DUPISTAD (ClinicalTrials.gov: NCT04033367) was a phase IV randomized double-blinded placebo-controlled study that evaluated the impact of dupilumab treatment on sleep and other patient- and physician-reported outcomes in patients with AD. Patients were enrolled at 42 sites across 10 countries (Australia, France, Germany, Israel, Italy, Spain, Switzerland, the United Arab Emirates, the UK and the USA). Eligible patients were aged ≥ 18 years, had moderate-to-severe AD, as defined by an Eczema Area and Severity Index (EASI) score of ≥ 12, peak pruritus numeric rating scale (PP NRS) score of ≥ 3 and sleep disturbance numeric rating scale (NRS) score of ≥ 5, and had an inadequate response to topical AD treatments. Exclusion criteria included concomitant treatment with sedative anxiolytic or hypnotic treatments (other than melatonin) on a regular basis, systemic sedative antihistamines > 5 days per week, or treatment with antidepressants, beta blockers, clonidine, opioids, theophylline or other medications known to interfere with sleep. Full inclusion and exclusion criteria are provided in Appendix S1 (see Supporting Information). All patients were required to apply moisturizers (emollients) twice daily for at least seven consecutive days before randomization and throughout the study. Patients were randomized to receive dupilumab 300 mg administered as subcutaneous injection q2w (following a loading dose of 600 mg on day 1), or a matching placebo, for a period of 12 weeks. Patients were randomized using an interactive voice response/interactive web response system; patients and investigators were blinded to treatment. All patients subsequently entered a 12-week open-label treatment phase and received 300 mg q2w for a further 12 weeks. All patients were required to apply medium-potency topical corticosteroids (TCS) daily on active lesions. When the lesions were under control, TCS frequency was reduced to twice weekly.

DUPISTAD was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each participating site oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Amendments to the study protocol are summarized in Table S1 (see Supporting Information).

Study outcomes

The primary endpoint of the study was percentage change from baseline to week 12 in sleep quality, assessed on a NRS ranging from 0 to 10,[22] where 0 was 'worst possible sleep' (i.e. lowest quality) and 10 was 'best possible sleep' (i.e. highest quality). However, this scale was reversed for the analysis (Table S2; see Supporting Information) to ensure accurate, in-proportion representation of the primary endpoint results. As the primary endpoint was percentage change from baseline, using the unmodified scale would have led to disproportionately large changes in patients with very low sleep quality scores at baseline, compared with those with higher scores, or even resulted in no data (i.e. not possible to calculate percentage change) for patients with a sleep NRS score = 0 at baseline. Furthermore, as other AD outcome measures [e.g. PP NRS, Patient-Oriented SCORing Atopic Dermatitis (SCORAD) sleep visual analogue scale (VAS), etc.][23,24] use scales with opposite directionality (0 or 'left end' = best, 10 or 'right end' = worst), reversing the sleep NRS made it compatible with other outcome measures, better suited for correlation analyses, and confirmed that it would not affect the magnitude of change or interpretation of the results.

Secondary and exploratory study endpoints included percentage change from baseline to week 12 in PP NRS; change from baseline to week 12 in SCORAD, SCORAD sleep VAS, Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment T-score and the Epworth Sleepiness Scale (ESS); percentage change from baseline to week 12 in sleep efficiency, total sleep time, wake after sleep onset and sleep onset latency based on actigraphy data; and proportion of patients achieving EASI 50, EASI 75 and EASI 90 (i.e. a 50%, 75% or 90% reduction in EASI score) at week 12 vs. baseline EASI score.

Assessments

The treating clinician assessed the AD disease status severity utilizing the EASI (range 0–72)[25] and SCORAD (range 0–103).[24] Patient-reported data included the sleep disturbance NRS score (range 0–10), PP NRS (range 0–10),[23] DLQI (range 0–30),[26] POEM (range 0–28),[27] SCORAD sleep VAS [0–100 mm (0 to < 40 mm indicating none or mild impairment, 40 to < 70 mm moderate impairment, 70 to < 90 mm severe impairment and ≥ 90 mm very severe impairment)],[27,28] PROMIS T-score (a standardized score with a mean of 50 and an SD of 10 that is measured on a scale of 30–80, with 30 being the worst and 80 being the best sleep)[29] and ESS (range 0–24).[30] For each of these metrics, higher scores represent greater severity. Wrist actigraphy using the Actiwatch Spectrum® (Philips Respironics, Inc., Murrysville, PA, USA) was used to provide estimates of the duration, timing and patterns of sleep. A sleep diary was also used for patient-reported measures of sleep metrics. With regard to safety, all adverse events were recorded and were coded using the Medical Dictionary for Regulatory Activities, version 24.0.

Statistical analysis

Efficacy analyses were conducted using the modified intention-to-treat population, which included all randomized patients who had a baseline assessment and at least one postbaseline assessment. The percentage change from baseline to week 12 in sleep quality NRS was analysed using a mixed effect model with repeated measures with treatment, baseline value, randomization stratum, visit, treatment by visit interaction and baseline value by visit interaction terms (all as fixed effects) in the model. A similar approach was used for analysis of secondary continuous endpoints. Endpoints comparing proportion of patients meeting certain criteria at a specific visit were analysed via the Cochran–Mantel–Haenszel test adjusted by the randomization stratum. Least squares means of the difference (LSMD) between the dupilumab group and the placebo group were calculated, and the corresponding 95% confidence intervals (CIs) of the differences and *P*-values were also provided. Safety analyses were performed on the safety set (all patients who received at least one dose of the study drug); analyses were descriptive. All statistical analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

Results

Patient disposition

In total, 127 patients received dupilumab 300 mg q2w and 61 patients received placebo between 22 August 2019 and 6 October 2021 (Table S3; see Supporting Information). Mean baseline demographics and disease characteristics were

Table 1 Baseline demographics and disease characteristics

Parameter[a]	Dupilumab 300 mg q2w (*N* = 127)	Placebo (*N* = 61)
Age, years	36.2 (14.7)	34.5 (15.4)
Male, *n* (%)	61 (48.0)	30 (49.2)
Race, *n* (%)		
White	103 (81.1)	46 (75.4)
Black or African American	6 (4.7)	1 (2.6)
Asian	13 (10.2)	11 (18.0)
Multiple	2 (1.6)	0
Not reported/unknown	3 (2.4)	3 (4.9)
Sleep quality NRS	6.7 (1.1)	7.0 (1.1)
SCORAD total score	64.7 (12.5)	62.8 (12.5)
SCORAD sleep VAS	7.1 (1.8)	7.0 (2.0)
PROMIS sleep-related impairment T-score	60.9 (5.7)	61.5 (5.8)
IGA, *n* (%)		
3	79 (62.2)	44 (72.1)
4	48 (37.8)	17 (27.9)
EASI	26.2 (11.9)	26.0 (9.9)
PP NRS	7.5 (1.4)	7.6 (1.5)
POEM	23.2 (3.9)	22.6 (4.6)
DLQI	16.2 (6.4)	16.8 (6.3)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; PP, peak pruritus; PROMIS, Patient-Reported Outcomes Measurement Information System; q2w, once every 2 weeks; SCORAD, SCORing Atopic Dermatitis; VAS, visual analogue scale. [a]Values are presented as mean (SD) unless otherwise stated.

well balanced between groups (Table 1). Mean SCORAD total score was 64.7 in the dupilumab group and 62.8 in the placebo group. Mean EASI score was 26.2 vs. 26.0 in the dupilumab and placebo groups, respectively. The QoL burden, as measured by DLQI and POEM, was relatively high in both groups.

Primary efficacy endpoint

Overall, the improvement in sleep NRS was significantly greater with dupilumab than with placebo, with a LSMD of −15.5% (95% CI −24.1 to −6.9) by week 12, representing a 47.7% improvement in sleep with dupilumab vs. 33.0% in the placebo group ($P<0.001$) (Figure 1). Dupilumab treatment was associated with significant improvement in sleep compared with placebo across most subgroups, including patients with PP NRS ≥ 7 at baseline [mean percentage change from baseline in the dupilumab and placebo groups of −51.1 (SD 27.5) and −31.8 (SD 29.3), respectively; LSMD −19.6 (95% CI −30.2 to −8.9), $P<0.001$] (Table 2).

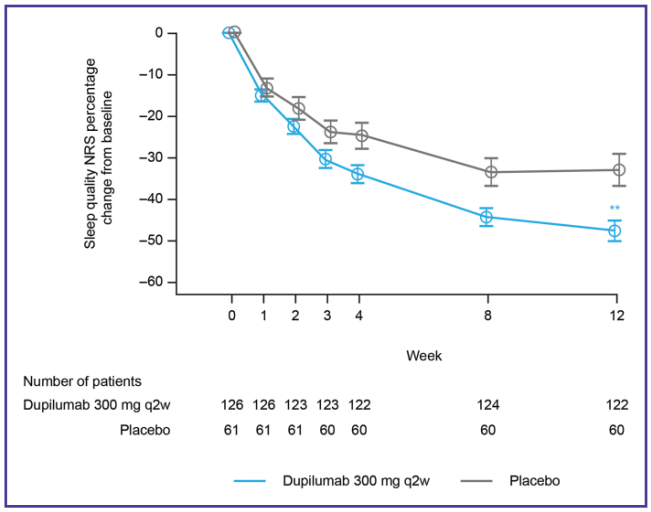

Figure 1 Sleep quality numeric rating scale (NRS) percentage change from baseline over time. q2w, once every 2 weeks. Modified intention-to-treat population, mean (SE). $^{**}P<0.001$.

Table 2 Overview of mean and change from baseline to week 12 in sleep quality numeric rating scale (NRS)

	Dupilumab 300 mg q2w (*N* = 127)			Placebo (*N* = 61)			LSMD (95% CI) between the dupilumab and placebo groups	*P*-values[a]
	Baseline	Week 12	Percentage change from baseline	Baseline	Week 12	Percentage change from baseline		
Sleep quality NRS[b]	*n* = 126 6.7 (1.1)	*n* = 122 3.4 (1.8)	−47.7 (27.2)	*n* = 61 7.0 (1.1)	*n* = 60 4.6 (2.0)	−33.0 (29.5)	−15.5 (−24.1 to −6.9)	< 0.001
Age, years								
≥ 18 to < 40	*n* = 78 6.7 (1.2)	*n* = 75 3.4 (1.7)	−48.2 (24.9)	*n* = 41 7.0 (1.2)	*n* = 41 4.6 (2.1)	−33.3 (31.7)	−15.9 (−26.1 to −5.7)	0.002
≥ 40 to < 65	*n* = 39 6.6 (1.0)	*n* = 39 3.7 (2.2)	−44.8 (31.2)	*n* = 15 6.8 (0.7)	*n* = 14 4.5 (1.9)	−34.6 (26.7)	−10.7 (−29.8–8.4)	0.267
≥ 65	*n* = 9 6.6 (1.2)	*n* = 8 2.6 (1.6)	−57.6 (28.9)	*n* = 5 7.3 (0.9)	*n* = 5 5.4 (1.7)	−25.5 (21.1)	−27.9 (−68.7–12.9)	0.157
Sex								
Male	*n* = 60 6.7 (1.0)	*n* = 59 3.2 (1.8)	−51.3 (27.5)	*n* = 30 7.0 (1.1)	*n* = 29 4.6 (2.3)	−34.3 (30.8)	−17.8 (−30.7 to −5.0)	0.007
Female	*n* = 66 6.7 (1.3)	*n* = 63 3.7 (1.8)	−44.4 (26.8)	*n* = 31 7.0 (1.1)	*n* = 31 4.7 (1.7)	−31.7 (28.8)	−13.5 (−25.2 to −1.7)	0.025
Bodyweight, kg								
< 70	*n* = 58 6.7 (1.2)	*n* = 55 3.4 (1.8)	−48.2 (26.4)	*n* = 31 6.9 (0.9)	*n* = 30 4.5 (2.0)	−34.0 (31.2)	−13.7 (−26.2 to −1.2)	0.033
≥ 70 to < 100	*n* = 53 6.6 (1.0)	*n* = 52 3.5 (1.8)	−45.4 (28.5)	*n* = 24 7.1 (1.3)	*n* = 24 4.6 (2.1)	−34.2 (27.6)	−14.5 (−28.3 to −0.6)	0.041
≥ 100	*n* = 14 6.9 (1.5)	*n* = 14 3.3 (2.1)	−52.4 (26.9)	*n* = 6 6.9 (1.1)	*n* = 6 5.3 (2.4)	−23.5 (32.0)	−26.6 (−56.0–2.7)	0.073
Baseline PP NRS								
< 7	*n* = 38 6.0 (0.8)	*n* = 36 3.5 (1.6)	−40.6 (26.6)	*n* = 18 6.6 (0.6)	*n* = 18 4.0 (2.2)	−39.3 (30.9)	−2.1 (−20.2–16.0)	0.816
≥ 7	*n* = 86 7.0 (1.1)	*n* = 82 3.4 (2.0)	−51.1 (27.5)	*n* = 39 7.2 (1.1)	*n* = 38 4.8 (1.9)	−31.8 (29.3)	−19.6 (−30.2 to −8.9)	< 0.001

CI, confidence interval; LSMD, least squares mean of the difference; PP, peak pruritus; q2w, once every 2 weeks. [a]The overall familywise type I error rate was controlled at the 0.05 level (two-sided) using a sequential testing procedure (in the order shown in the table). To proceed to the secondary endpoints, the primary endpoint must be significant at the 0.05 significance level. Each endpoint was tested at the 0.05 (two-sided) level of significance. If at any step the null statistical hypothesis of no treatment difference is not rejected (i.e. $P>0.05$), the endpoints listed after that step were reported at the nominal level. [b]Primary endpoint. Values are presented as mean (SD).

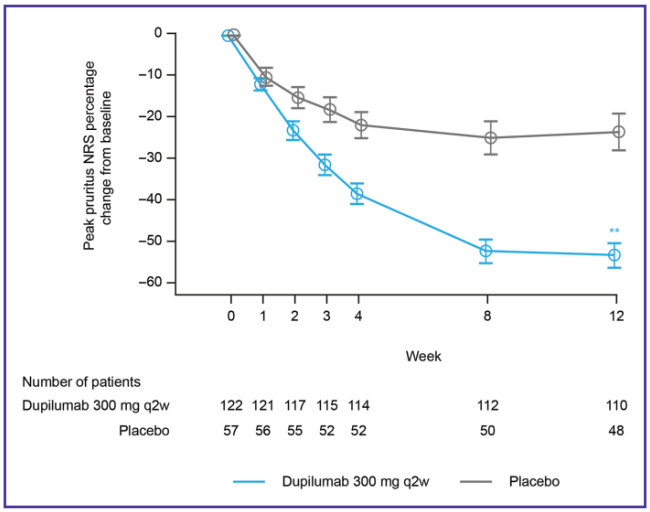

Figure 2 Percentage change in peak pruritus numeric rating scale (NRS) over time. q2w, once every 2 weeks. Modified intention-to-treat population, mean (SE). $^{**}P<0.001$.

Secondary endpoints measuring disease severity and quality of life

Itch, as measured by weekly patient-reported PP NRS, was significantly reduced with dupilumab vs. placebo [LSMD 27.9% (95% CI −38.0 to −17.8), $P<0.001$] (Figure 2). Mean PP NRS scores reported at baseline were 7.5 and 7.6 in the dupilumab and placebo groups, respectively. At week 12, this decreased to 3.5 in the dupilumab group and 5.9 in the placebo group, representing a mean percentage change from baseline of −52.5 (SD 30.6) and −23.3 (SD 30.1), respectively. A ≥4-point improvement in PP NRS was achieved by 74.0% of patients in the dupilumab group compared with 49.2% of patients in the placebo group.

Clinical signs and symptoms, as measured by total SCORAD score, also significantly improved with dupilumab. Mean change from baseline in the dupilumab group was −37.8 (SD 17.7) compared with −20.6 (SD 17.9) in the placebo group [LSMD −15.1 (95% CI −20.6 to −9.6), $P<0.001$] (Figure 3a), with patients treatd with dupilumab moving from a mean SCORAD score considered to be severe at baseline [64.7 (SD 12.5)] to one considered mild [26.8 (SD 16.8)] at week 12. QoL metrics of POEM and DLQI both demonstrated a significantly greater improvement with dupilumab than with placebo. Mean change from baseline in POEM was −13.6 (SD 7.5) and −4.4 (SD 6.8) in the dupilumab and placebo groups, respectively [LSMD −8.3 (95% CI −10.9 to −5.8), $P<0.001$]. Mean change in DLQI from baseline was −11.8 (SD 6.5) and −7.5 (SD 6.8) in the dupilumab and placebo groups, respectively [LSMD −4.5 (95% CI −6.4 to −2.6), $P<0.001$] (Table 3). Lastly, significantly more patients treated with dupilumab achieved the clinically meaningful endpoints of EASI 50, EASI 75 (both $P<0.001$) and EASI 90 ($P=0.002$) than those receiving placebo (Figure 4).

Sleep secondary and exploratory endpoints

SCORAD sleep VAS was significantly decreased at week 12 with dupilumab vs. placebo. Mean change from baseline in the dupilumab group was −4.9 (SD 3.0) compared with −2.3 (SD 3.0) in the placebo group [LSMD −2.1 (95% CI −3.0 to −1.2), $P<0.001$] (Figure 3b). The PROMIS sleep-related impairment T-score was also reduced significantly more with dupilumab than with placebo at week 12 [mean change from baseline −11.4 (SD 6.7) with dupilumab vs. −7.8 (SD 7.2) with placebo; LSMD −3.6 (95% CI −5.7 to −1.5), $P<0.001$] (Table 3). Sleep diary data at week 12 showed a significantly larger reduction in awakenings [mean change from baseline −1.5 (SD 1.7) vs. −0.9 (SD 1.3) for dupilumab vs. placebo; LSMD −0.5 (95% CI −0.8 to −0.1), $P=0.010$] and improved sleep efficiency [mean change from baseline 12.2 (SD 16.4) vs. 7.7 (SD 13.9) for dupilumab vs placebo; LSMD 4.3 (95% CI 0.4–8.3), $P=0.033$] with dupilumab vs. placebo. Sleepiness, as measured by the ESS, was significantly reduced at week 12 with dupilumab vs. placebo [mean change from baseline −4.1 (SD 4.9) vs. −1.3 (SD 4.8) for dupilumab vs. placebo; LSMD −2.6 points (95% CI −4.1

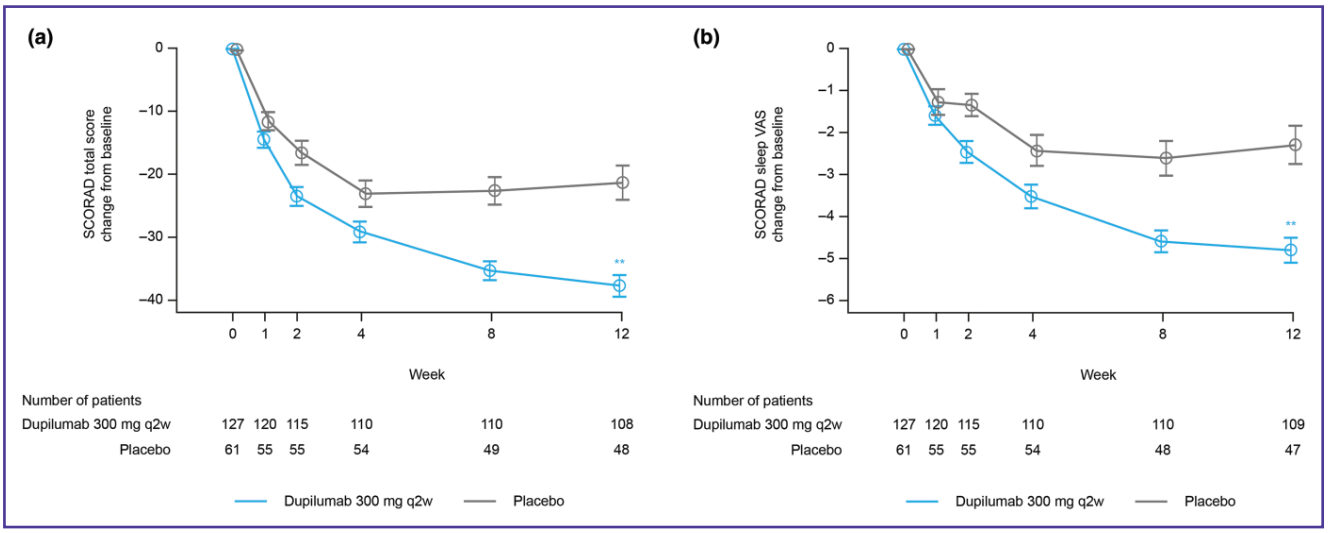

Figure 3 Change in (a) SCORing Atopic Dermatitis (SCORAD) total score and (b) SCORAD sleep visual analogue scale (VAS) over time. q2w, once every 2 weeks. Modified intention-to-treat population, mean (SE). $^{**}P<0.001$.

Table 3 Overview of mean and change from baseline to week 12 in secondary and selected exploratory endpoints

	Dupilumab 300 mg q2w (*N*=127)			Placebo (*N*=61)			LSMD (95% CI) between the dupilumab and placebo groups	*P*-values[a]
	Baseline	Week 12	Percentage change/ change	Baseline	Week 12	Percentage change/ change		
EASI score	*n*=127	*n*=109		*n*=61	*n*=48			
	26.2 (11.9)	6.1 (7.4)	−74.1 (38.0)	26.0 (9.9)	12.8 (10.3)	−50.3 (38.3)	−25.1 (−37.7 to −12.5)	< 0.001
DLQI score	*n*=115	*n*=90		*n*=52	*n*=39			
	16.2 (6.4)	4.5 (5.2)	−11.8 (6.5)	16.8 (6.3)	9.3 (5.4)	−7.5 (6.8)	−4.5 (−6.4 to −2.6)	< 0.001
POEM score	*n*=115	*n*=90		*n*=52	*n*=39			
	23.2 (3.9)	9.5 (7.1)	−13.6 (7.5)	22.6 (4.6)	17.9 (7.4)	−4.4 (6.8)	−8.3 (−10.9 to −5.8)	< 0.001
PROMIS sleep-related impairment T-score	*n*=117	*n*=103		*n*=56	*n*=54			
	60.9 (5.7)	49.8 (6.8)	−11.4 (6.7)	61.6 (5.7)	54.0 (7.0)	−7.8 (7.2)	−3.6 (−5.7 to −1.5)	< 0.001
Weekly average awakenings (sleep diary)	*n*=122	*n*=117		*n*=61	*n*=57			
	2.8 (1.8)	1.3 (1.1)	−1.5 (1.7)	2.6 (1.2)	1.6 (1.4)	−0.9 (1.3)	−0.5 (−0.8 to −0.1)	0.010
Rested NRS at awakening (sleep diary)	*n*=122	*n*=117		*n*=61	*n*=57			
	3.5 (1.3)	6.3 (1.8)	2.8 (1.9)	3.4 (1.4)	5.1 (1.9)	1.9 (1.9)	1.0 (0.5–1.5)	< 0.001
Weekly average sleep efficiency (sleep diary)	*n*=122	*n*=117		*n*=61	*n*=57			
	75.4 (17.1)	87.8 (15.1)	12.2 (16.3)	76.4 (13.7)	83.8 (12.0)	7.7 (13.9)	4.3 (0.4–8.3)	0.033
Weekly average sleep onset latency (sleep diary), min	*n*=122	*n*=117		*n*=61	*n*=57			
	75.0 (68.8)	44.3 (76.0)	−28.7 (97.7)	72.9 (63.6)	56.1 (55.0)	−19.6 (79.2)	−11.3 (−33.5–11.0)	0.320
Weekly average total sleep time (sleep diary), min	*n*=122	*n*=117		*n*=61	*n*=57			
	408.7 (143.6)	453.4 (121.0)	47.0 (151.8)	411.7 (103.5)	437.4 (82.2)	33.5 (87.1)	18.9 (−13.8–51.7)	0.255
Weekly average wake after sleep onset (sleep diary), min	*n*=122	*n*=117		*n*=61	*n*=57			
	61.9 (68.9)	24.7 (56.3)	−36.0 (48.4)	57.8 (45.8)	32.3 (43.4)	−24.4 (35.9)	−9.8 (−21.7 to −2.0)	0.104
ESS score	*n*=114	*n*=99		*n*=52	*n*=50			
	10.9 (4.5)	6.8 (4.9)	−4.1 (4.9)	10.5 (4.9)	9.3 (5.0)	−1.3 (4.8)	−2.6 (−4.0 to −1.2)	< 0.001
Sleep efficiency (actigraphy), %	*n*=118	*n*=108		*n*=56	*n*=47			
	75.7 (9.0)	77.3 (7.6)	1.8 (6.6)	76.5 (6.6)	78.0 (7.0)	1.5 (6.0)	0.2 (−1.6–2.0)	0.824
Total sleep time (actigraphy), min	*n*=118	*n*=108		*n*=56	*n*=47			
	369.1 (85.0)	375.5 (70.6)	9.0 (71.0)	370.8 (60.4)	372.4 (66.4)	−6.4 (55.6)	10.6 (−8.2–29.5)	0.268
Wake after sleep onset (actigraphy), min	*n*=118	*n*=108		*n*=56	*n*=47			
	72.3 (26.5)	65.8 (28.3)	−6.8 (22.8)	74.3 (29.9)	66.7 (27.4)	−9.2 (24.7)	0.7 (−6.5–7.9)	0.842
Sleep onset latency (actigraphy), min	*n*=118	*n*=108		*n*=56	*n*=47			
	24.7 (17.6)	23.4 (15.4)	−1.4 (20.0)	24.0 (18.0)	21.6 (17.2)	−3.4 (21.5)	2.1 (−3.1–7.3)	0.427

CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ESS, Epworth Sleepiness Scale; LSMD, least squares mean of the difference; POEM, Patient-Oriented Eczema Measure; PROMIS, Patient-Reported Outcomes Measurement Information System; NRS, numeric rating scale; q2w, once every 2 weeks. [a]The overall familywise type I error rate was controlled at the 0.05 level (two-sided) using a sequential testing procedure (in the order shown in the table). To proceed to the secondary endpoints, the primary endpoint must be significant at the 0.05 significance level. Each endpoint was tested at the 0.05 (two-sided) level of significance. If at any step the null statistical hypothesis of no treatment difference is not rejected (i.e. $P > 0.05$), the endpoints listed after that step were reported at the nominal level. Values are presented as mean (SD) unless otherwise stated.

to −1.2), $P < 0.001$]. Mean sleepiness reduction on ESS was 4.1 points, which exceeds the 3-point threshold of clinical significance. Actigraphy did not discern any significant differences between dupilumab and placebo with respect to sleep onset latency, wake after sleep onset, total sleep time or sleep efficiency (Table 3).

Safety

The overall percentage of patients reporting treatment-emergent adverse events (TEAEs) was lower in the dupilumab group (56.7%) than in the placebo group (67.2%) (Table 4). The most frequently reported TEAEs (preferred term with an incidence ≥ 5% in any treatment group) were in 'Infections and infestations', 'Nervous system disorders' and 'Skin and subcutaneous tissue disorders' (Table S4; see Supporting Information). Most infections were mild or moderate in severity. Conjunctivitis was reported in a higher proportion of patients receiving dupilumab than in those receiving placebo (9.4% vs. 4.9%), while headache and AD were reported in a higher proportion of patients receiving placebo than in

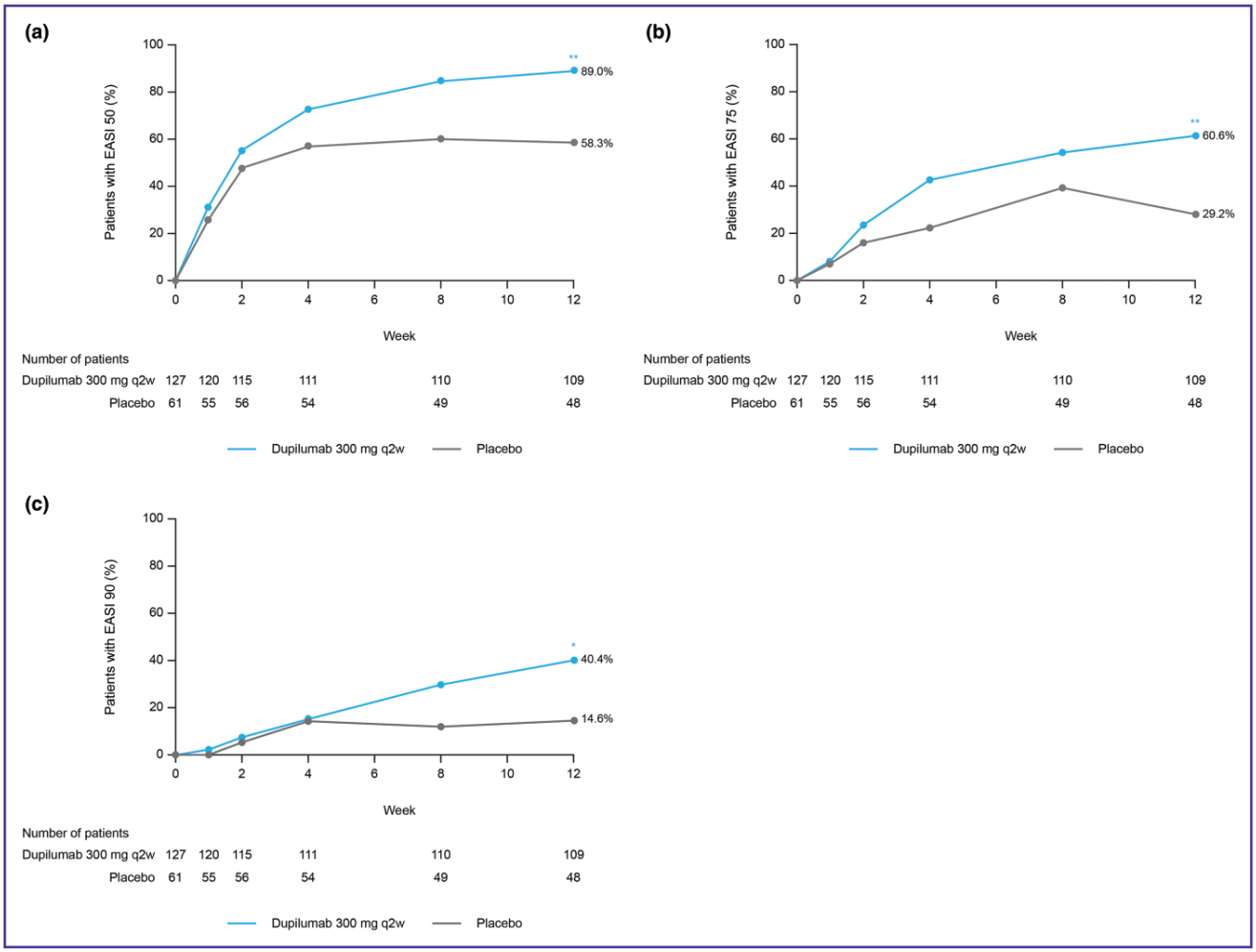

Figure 4 Percentage of patients with (a) EASI 50, (b) EASI 75 and (c) EASI 90 over time. EASI, Eczema Area and Severity Index; EASI 50, 50% decrease in EASI score; EASI 75, 75% decrease in EASI score; EASI 90, 90% decrease in EASI score; q2w, once every 2 weeks. Modified intention-to-treat population, mean. *$P<0.05$. **$P<0.001$.

Table 4 Summary of treatment-emergent adverse events (TEAEs) during the double-blind treatment period

	Dupilumab 300 mg q2w (*N*=127)	Placebo (*N*=61)
TEAE	72 (56.7)	41 (67.2)
Serious TEAE	2 (1.6)	1 (1.6)
TEAE leading to permanent treatment discontinuation	3 (2.4)	1 (1.6)
TEAE of special interest	4 (3.1)	1 (1.6)
Serious TEAE of special interest[a]	1 (0.8)	1 (1.6)
TEAE leading to death	0	0

q2w, once every 2 weeks. [a]Prespecified TEAEs of special interest included anaphylaxis, systemic or severe hypersensitivity reactions, malignancy (except *in situ* carcinoma of the cervix and nonbasal cell carcinoma of the skin), helminth infections, suicide-related events, any type of conjunctivitis or blepharitis (severe or serious), keratitis, pregnancy occurring in a female patient or female partner of a male patient administered investigational medicinal product (IMP)/noninvestigational medicinal product (NIMP) or symptomatic overdose of IMP/NIMP. Data are presented as *n* (%).

those receiving dupilumab (8.2% and 13.1% in the placebo group and 7.1% and 3.1% in the dupilumab group, respectively).

Discussion

The primary endpoint of improvement in sleep NRS was significantly improved in patients treated with dupilumab at week 12 compared with those receiving placebo. The results from DUPISTAD support previous reports of improved sleep quality in adult patients with AD who received dupilumab.[19] Furthermore, while a high placebo response was observed, the threshold for meaningful change (i.e. a 2- to 5-point reduction)[22] was met, with sleep NRS scores in patients treated with dupilumab improving by a mean of 3.2 points. Secondary endpoints, including PP NRS, EASI 50, EASI 75, DLQI, POEM, SCORAD, sleep efficiency, SCORAD sleep VAS and PROMIS sleep-related impairment T-score, were also significantly improved with dupilumab vs. placebo, with improvements reaching significance as early as week 2 and continuing through week 12. It is important to note that all patients in this study were provided with TCS to be used as needed, and patients were required to moisturize all eczematous lesions, which may have contributed to the improvements in all AD metrics and sleep achieved in the placebo arm.

The reductions in itch observed with 12 weeks of dupilumab treatment were clinically meaningful, with

an approximate 4-point mean improvement in PP NRS being achieved in the dupilumab-treated group.[23] This is an important result that may be reflected in the reported improvements in sleep, as it has been reported extensively that night-time itching and scratching affects sleep in patients with AD.[6–14] However, reduction in inflammation has also been linked to better sleep, and as dupilumab inhibits signalling of both IL-4 and IL-13, which are key drivers of type-2-mediated inflammation, the improvements in sleep observed in this study may also stem from reduced inflammation.[18,31–33]

Furthermore, the minimally clinically important difference threshold of 8.7 points[27] was met for SCORAD total score, with the dupilumab group improving by an average of 37.8 points. Likewise, the clinically significant EASI 50[34] was also achieved in the vast majority of patients treated with dupilumab. With regard to the impact of AD on QoL, DLQI scores improved from a severe impact to a mild impact with dupilumab and optional TCS, whereas in the placebo and optional TCS group, DLQI scores improved only from a severe impact to a moderate impact, according to established severity strata for DLQI.[35]

Patient-reported awakening and sleep efficiency (captured by sleep diary) were also significantly improved with dupilumab vs. placebo. However, dupilumab showed no statistically significant benefit over placebo on sleep onset latency and total sleep time, based on sleep diary data. Conceivably, as sleep becomes more restorative, sleep duration may not increase. Improvement of sleep efficiency and wake after sleep onset time was not noted with actigraphy. This may be related to differences between the population of patients with AD and the populations of usually healthy individuals that are studied to validate actigraphy estimates of sleep parameters.[36,37] In addition, wrist-worn actigraphy may have caused discomfort in patients with local lesions, resulting in additional pruritus and scratching. The assessment of patient-reported sleep quality is important in this population, and a possible limitation of wrist actigraphy could be that it is not as sensitive to sleep disturbance in patients with AD. More specific wearables may be required to measure night-time scratch activity.

The primary endpoint of this study was a novel NRS (sleep NRS) developed to assess sleep quality. As such, it was directionally different (higher score = better) from all other numeric scales such as itch, SCORAD sleep VAS, etc., which are designed to measure discomfort and inconvenience (i.e. higher score = worse). A limitation of these findings is that no validation data or psychometric properties are currently available for this novel NRS. While various actigraphy devices have been used for collecting objective wrist-movement data that might correlate with sleep, data assessed by actigraphy remain open to issues of validity and reliability, particularly in patients with poor sleep quality.[36,37] Dupilumab significantly improved overall sleep continuity and quality, and also reduced daytime sleepiness, itch and other AD-related signs, symptoms and QoL in adults with moderate-to-severe AD vs. placebo. These improvements with dupilumab started as early as week 2 and continued throughout the study. Dupilumab demonstrated a similar safety profile to that observed in earlier trials, with no new safety concerns identified. Future analyses will assess the persistence of dupilumab's effect on sleep disturbance through 24 weeks.

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Conflicts of interest

J.F.M. has been a principal investigator, advisory board member and consultant for Regeneron Pharmaceuticals Inc. and Sanofi. A.S.C. has been a principal investigator for Regeneron Pharmaceuticals Inc., Sanofi and AbbVie, in addition to working as an advisory board member for Pfizer. E.D. has been a principal investigator for Regeneron Pharmaceuticals Inc. and Sanofi. A.C. has been a principal investigator for Regeneron Pharmaceuticals Inc. and Sanofi. P.F. has received grant support from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sanofi and Sun Pharma. P.F. has also been an investigator for AbbVie, Akaal Pharma, Amgen, Arcutis, Argenx, Aslan Pharmaceuticals, AstraZeneca, BMS, Boehringer Ingelheim, Botanix, Celgene, Celtaxsys, CSL, Cutanea, Dermira, Eli Lilly, Galderma, Genentech, Geneseq Biosciences, GSK, Hexima, Janssen, Kymab, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Reistone Biopharma, Roche, Sanofi, Sun Pharma, Teva, UCB Pharma and Valeant. P.F. has also been an advisory board member for AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, Mayne Pharma, Merck, Novartis, Pfizer, Sanofi, Sun Pharma, UCB Pharma and Valeant, and has been a consultant for Aslan Pharmaceuticals, BMS, Eli Lilly, Galderma, GenesisCare, Janssen, LEO Pharma, Mayne Pharma, MedImmune, Novartis, Pfizer, Roche and UCB Pharma. P.F. has received travel grants from AbbVie, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Roche, Sanofi and Sun Pharma, and has been a speaker for AbbVie, Amgen, BMS, Celgene, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Roche, Sanofi, Sun Pharma and Valeant. A.A. has been a principal investigator for Regeneron Pharmaceuticals Inc. and Sanofi. S.G. has been a principal investigator for Regeneron Pharmaceuticals Inc. and Sanofi. A.P. has been a principal investigator for Regeneron Pharmaceuticals Inc. and Sanofi and has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall-Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, Celltrion, GSK, Eli Lilly, Galderma, Hexal, Janssen, Klinge Pharma, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron Pharmaceuticals Inc., Roche, Sandoz Biopharmaceuticals, Sanofi, Schering-Plough and UCB Pharma. R.D-G. has been a principal investigator for

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Data availability

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol, blank case report form, statistical analysis plan and dataset specifications. Amendments to the study protocol are summarized in Table S1 (see Supporting Information). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies and process for requesting access can be found at https://www.vivli.org/.

Ethics statement

The Dupilumab Effect on Sleep in AD Patients (DUPISTAD) study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each participating site oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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