# Dupilumab significantly improves sleep outcomes in adult patients with atopic dermatitis: results from five randomized clinical trials

*Editor*

Sleep disturbances are part of a symptom triad, along with itch and pain, that patients with atopic dermatitis (AD) report as being frequent and burdensome.[1] The effects of dupilumab on sleep were evaluated in adults with chronic AD in five randomized, double-blind, placebo-controlled clinical trials ($N$ = 2632). The Phase 2b (NCT01859988)[2] and the two Phase 3 SOLO trials (SOLO 1, NCT02277743; SOLO 2, NCT02277769)[3] were 16-week studies of dupilumab monotherapy, the 16-week CAFÉ (NCT02755649)[4] and the 52-week CHRONOS trials (NCT02260986)[5] evaluated dupilumab with concomitant topical corticosteroids (TCS). Sleep disturbances were assessed using the Scoring Atopic Dermatitis Visual Analogue Scale (VAS) for average sleep loss over the previous 3 days (0 = no sleep loss to 10 = maximum sleep loss) and the Patient-Oriented Eczema Measure (POEM) question on frequency of sleep disruption over the past week due to AD; both have been recently validated for use as single-item measures.[6]

Mean (SD) baseline VAS scores ranged from 4.3 (3.3) to 5.6 (3.0) across studies, with no differences among treatment groups within each study. Significant reductions from baseline observed at both dupilumab doses vs. placebo at Week 1 in the pooled SOLO 1 and 2 trials were maintained over 16 weeks (Fig. 1a). Similarly, significant reductions with dupilumab vs. placebo at Week 1 in Phase 2b and Week 2 in CAFÉ (both $P < 0.05$) were maintained through Week 16 (data not shown). In CHRONOS (Fig. 1b), reduction in VAS score at Week 1 with dupilumab 300 mg q2W + TCS was significant vs. placebo + TCS, and both dosing schedules showed significant reductions at Week 2 that were maintained at Weeks 16 and 52.

The magnitude of the differences vs. placebo at Week 16 was similar across all studies; least squares mean differences ranged from −1.5 (95% CI, −2.0, −1.0) to −2.2 (95% CI, −3.2, −1.3) for the q2w dose, and from −1.6 (95% CI, −2.0, −1.3) to −2.8 (−3.7, −1.8) for the qw dose (all $P < 0.0001$).

Using the POEM sleep item, the majority of patients (56.1–72.1%) across treatment groups in all studies reported sleep disturbances ≥3 nights in the past week. At Week 16 in the pooled SOLO 1 and 2 trials (Fig. 2a), sleep disturbances were reported to be less frequent among dupilumab-treated patients vs. placebo-treated patients; in particular, 58.6–63.4% of dupilumab-treated patients vs. 40.5% of placebo-treated patients reported no days of sleep disturbances. In CHRONOS, significant differences at Week 16 in sleep disturbance frequency between dupilumab + TCS and placebo + TCS were maintained at Week 52 (Fig. 2b), including 79.4–83.3% of dupilumab + TCS-treated patients with no days of sleep disturbances vs. 57.4% with placebo + TCS-treated patients. Results at Week 16 in the Phase 2b and CAFÉ trials were consistent with the other trials (data not shown).

The mechanism by which dupilumab improves sleep in AD is not clear, but is likely multifactorial stemming from its effects on reducing itch as well as inhibition of IL-4 and IL-13 signalling pathways; the expression of IL-4Rα on sensory neurons[7] suggests that by acting on these pathways, dupilumab may reduce neuronal responsiveness to pruritogens. Since there is a reciprocal mechanistic relationship between sleep and inflammatory pathways,[8] it is possible that the effects of dupilumab on transcription of inflammatory markers[9] may modulate downstream signalling pathways that overlap with sleep regulation. Nocturnal itching may also contribute to sleep disturbance in AD. Circadian rhythm is thought to modulate skin barrier permeability, which is higher at night and is associated with increased itch severity and endogenous cortisol release[10]; endogenous cortisol has an anti-inflammatory effect and is at its lowest levels in the evening and at night. Consequently, it may be hypothesized that dupilumab may additionally have collateral effects on sleep through cytokine signalling and by modulating circadian mechanisms.

Strengths of this analysis are that consistent results were observed across studies, and both intensity and frequency of sleep disturbances were assessed. A limitation is that objective sleep measures were not included in the trials. It should also be noted that the minimum clinically relevant changes have not been determined for either of the measures used. Additionally, these items may not represent all the dimensions of sleep that may be affected by AD.

These results demonstrate that dupilumab treatment, regardless of TCS use, significantly improves sleep relative to placebo by reducing the frequency of sleep disturbances and nightly sleep loss as early as 1 week after treatment, and maintenance of the effect during treatment duration. These results also emphasize the need for assessing sleep impairment in patients with AD.

## Conflict of interest

L. Beck is a consultant for AbbVie, Allakos, Arena Pharma, AstraZeneca, Connect Biopharma, Leo Pharma, Lilly, Novan, Novartis, Pfizer, Regeneron, Sanofi, UCB and Vimalan and an investigator for AbbVie, Leo Pharma, Pfizer and Regeneron and owns stock in Pfizer and Medtronics. G. Yosipovitch has received research funding from Leo, Sun Pharma, Kiniksa, Pfizer, Sanofi Regeneron and Vanda, and is a consultant for and advisory board member of Sanofi Regeneron, Pfizer, Eli Lilly, Novartis, Menlo Therapeutics, Trevi, Sienna, AbbVie, Bayer, Ortho and Kiniksa. E.L. Simpson has received grant/research

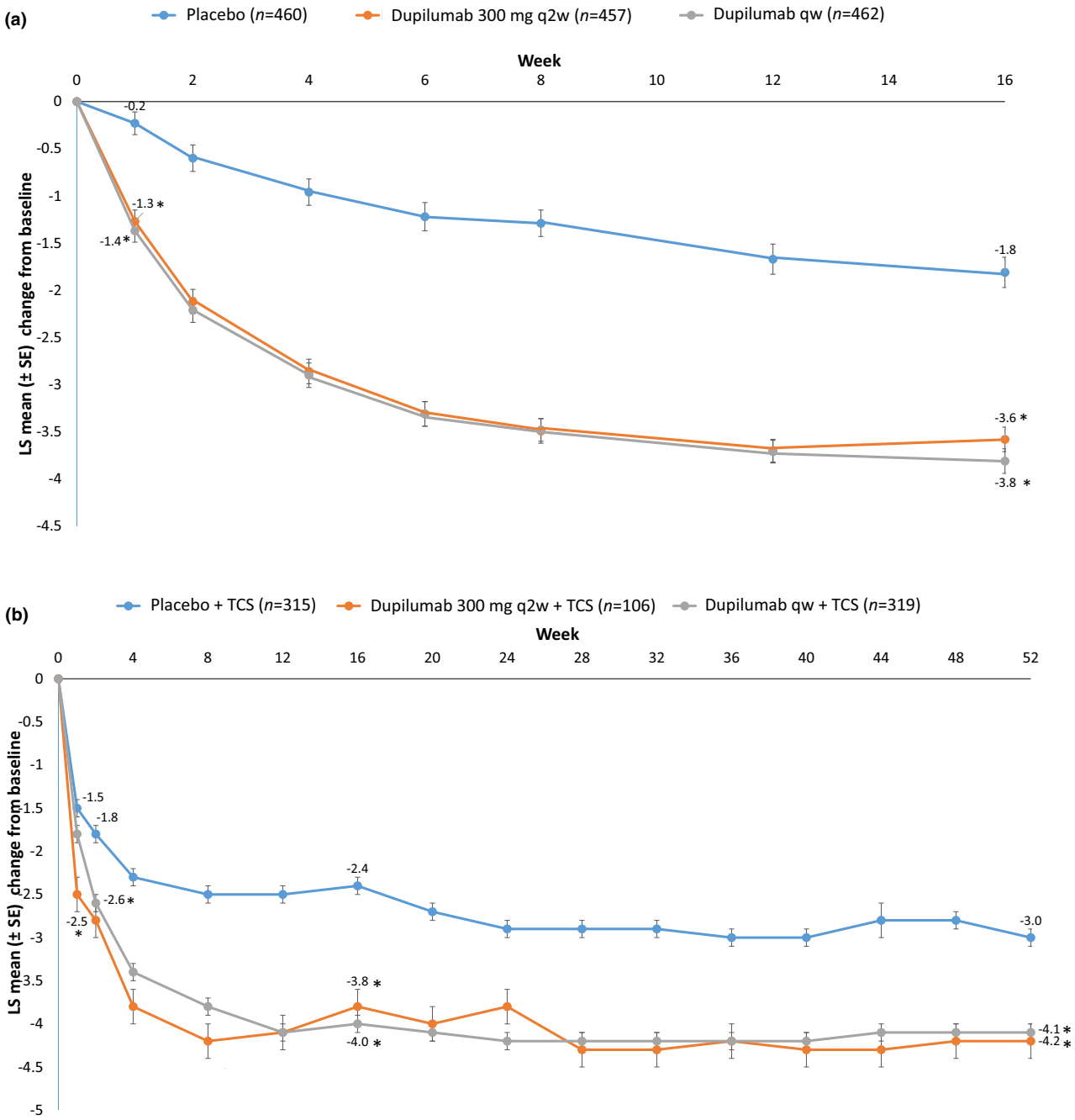


**Figure 1** Dupilumab reduced sleep loss as indicated by significant reductions from baseline in scores on the Scoring Atopic Dermatitis Sleep Loss Visual Analogue Scale (0–10). (a) Pooled SOLO 1 and 2 trials. (b) CHRONOS trial. Numbers and significance are shown only for baseline, first significant divergence vs. placebo, Week 16 and Week 52 (CHRONOS). Lower scores indicate less sleep loss on average over the last 3 days. *$P \leq 0.0001$ vs. placebo using analysis of covariance (ANCOVA) with baseline measurement as covariate and the treatment, region, baseline Investigator Global Assessment strata and study identifier as fixed factors [all evaluated time points between first significant divergence and end point were also significant for dupilumab vs. placebo ($P \leq 0.0001$)]. *LS*, least squares; SE, standard error; qw, once weekly; q2w, every two weeks; TCS, topical corticosteroids.

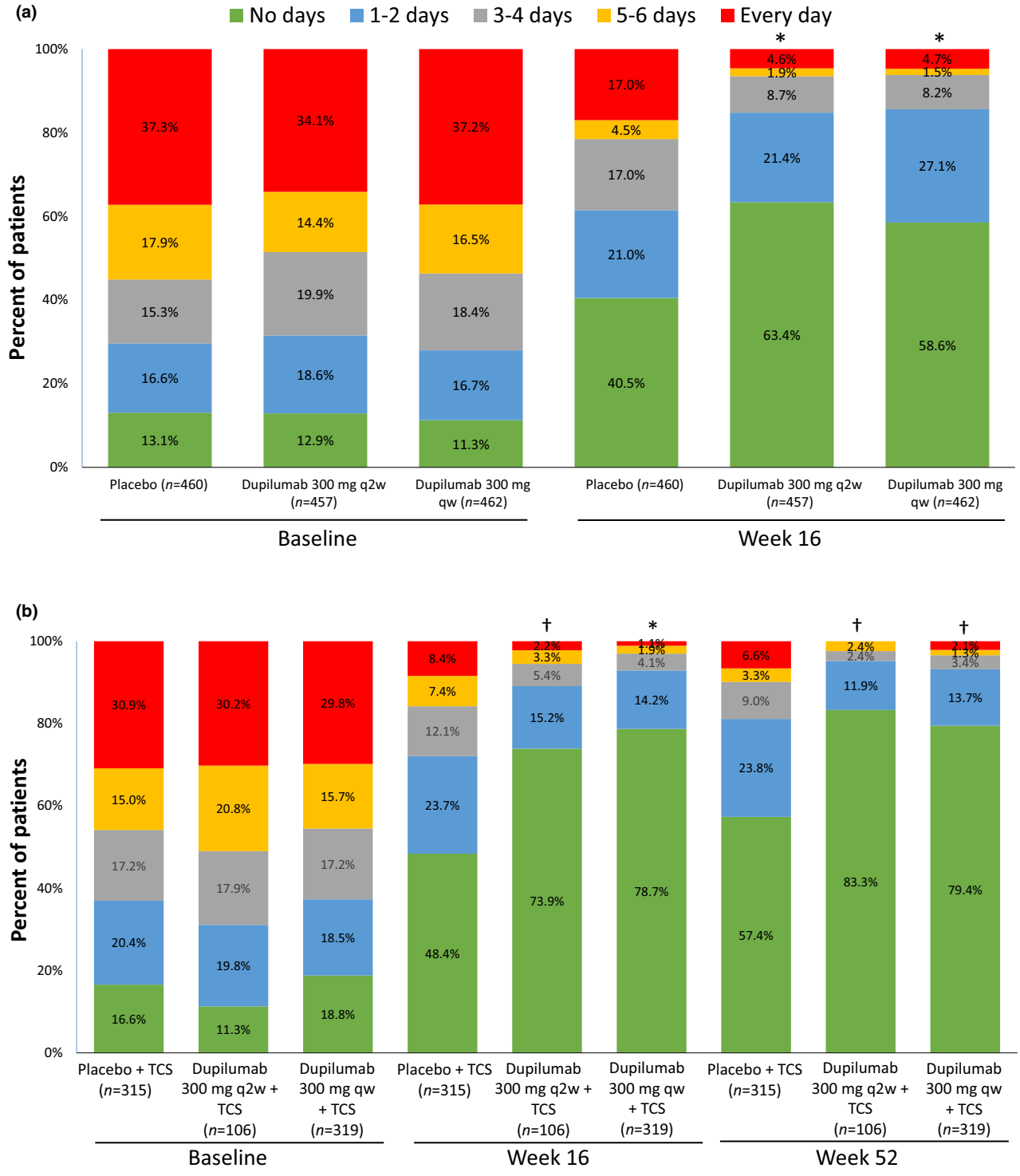


**Figure 2** Dupilumab reduced the number of days with sleep disturbance in the past week assessed using item 2 on the Patient-Oriented Eczema Measure (POEM). (a) Pooled SOLO 1 and 2 trials. (b) CHRONOS trial. *$P < 0.0001$ and †$P < 0.05$ vs. placebo using chi-square tests. qw, once weekly; q2w, every two weeks; TCS, topical corticosteroids.

support from AbbVie, Eli Lilly Co., Galderma, Kyowa Hakko Kirin, Leo Pharmaceutical Co., Merck, Pfizer and Regeneron Pharmaceuticals, Inc., and consulting fees from AbbVie Inc., Boehringer Ingelheim, Dermavant, Eli Lilly Co., Forte Bio, Incyte, Leo Pharmaceutical Co., Menlo Therapeutics, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme and Valeant. J.I. Silverberg has acted as a consultant for, and/or received grants/honoraria from, AbbVie, AnaptysBio, Asana Biosciences, LLC, Eli Lilly and Company, Galderma Research & Development, LLC, GlaxoSmithKline, Glenmark Generics Inc., Kiniksa Pharmaceuticals, Ltd., Leo Pharma Inc., Medimmune, Menlo Therapeutics, Pfizer Inc., PuriCore, Inc., Regeneron Pharmaceuticals, Inc., and Sanofi. Eckert L, Plaum S and Guillemin I are employees of and stockholders in Sanofi. Pirozzi G was an employee of Sanofi at the time of the study and is currently a full-time employee of Alexion Pharmaceuticals, Inc. Chen Z, Ardeleanu M and Graham N employees of and stockholders in Regeneron Pharmaceuticals, Inc. Gadkari A was an employee of Regeneron Pharmaceuticals, Inc., at the time of the study, and is currently a full-time employee of Boehringer Ingelheim.

## Funding source

This study was financially supported by Regeneron Pharmaceuticals, Inc., and Sanofi.

L.A. Beck,[1,*] J.I. Silverberg,[2,3,4,5] E.L. Simpson,[6] G. Yosipovitch,[7] L. Eckert,[8] I. Guillemin,[9] Z. Chen,[10] M. Ardeleanu,[10] S. Plaum,[11] N. Graham,[10] M. Ruddy,[10] G. Pirozzi,[11] A. Gadkari[10]

[1]Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA, [2]Department of Dermatology, The George Washington School of Medicine and Health Sciences, Washington, DC, USA, [3]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, [4]Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, [5]Northwestern Medicine Multidisciplinary Eczema Center, Chicago, IL, USA, [6]Department of Dermatology, Oregon Health and Science University, Portland, OR, USA, [7]Miami Itch Center, Dr Phillip Frost Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA, [8]Sanofi, Chilly-Mazarin, France, [9]Sanofi, Lyon, France, [10]Regeneron Pharmaceuticals, Tarrytown, NY, USA, [11]Sanofi, Bridgewater, NJ, USA

*Correspondence: L.A. Beck. E-mail: lisa_beck@urmc.rochester.edu

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DOI: 10.1111/jdv.16865

# Demographic and clinical characteristics of extramammary Paget's disease patients in Japan from 2000 to 2019

*Editor*

Extramammary Paget's disease (EMPD) is a rare adenocarcinoma that arises in apocrine gland-bearing skin and is associated with increased risk of underlying or distant malignancies. The demographic and clinical characteristics of biopsy-confirmed, newly diagnosed EMPD patients from 2000 to 2019 were analysed across seven institutions in Japan. Indeed, 544 patients were identified, of which 327 (60.1%) of patients were males and 217 (39.9%) patients were females; the male-to-female incidence ratio was 1.5: 1.0. The mean age at diagnosis was 72.1 ± 11.3 years for males and 72.2 ± 10.6 years for females. Invasive EMPD was more diagnosed in males (55.4% vs. 39.2% in females). The scrotum (56.9%) and penis (14.1%) in males and the vulva (88.9%) in females were the predominant primary sites of EMPD development in this cohort (Fig. 1).

Notably, 87 (16%) of the 544 EMPD patients had at least one additional invasive malignancy (a total of 102 malignancies). Of these 87 patients, 61 (70.1%) were males (Table 1). The average time between EMPD and malignancies that preceded EMPD diagnosis was 5.5 ± 6.7 years, and an average of 3.3 ± 3.9 years

 