



This is a repository copy of *The effect of dupilumab on caregiver- and patient-reported outcomes in young children with moderate-to-severe atopic dermatitis: results from a placebo-controlled, phase 3 study.*

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/217837/>

Version: Published Version

---

**Article:**

Paller, A.S., Silverberg, J.I., Simpson, E.L. et al. (7 more authors) (2025) The effect of dupilumab on caregiver- and patient-reported outcomes in young children with moderate-to-severe atopic dermatitis: results from a placebo-controlled, phase 3 study. *Journal of the American Academy of Dermatology*, 92 (1). pp. 116-126. ISSN 0190-9622

<https://doi.org/10.1016/j.jaad.2024.09.039>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>



# The effect of dupilumab on caregiver- and patient-reported outcomes in young children with moderate-to-severe atopic dermatitis: Results from a placebo-controlled, phase 3 study

Amy S. Paller, MD,<sup>a,b</sup> Jonathan I. Silverberg, MD, PhD,<sup>c</sup> Eric L. Simpson, MD,<sup>d</sup> Michael J. Cork, MB, PhD,<sup>e,f</sup> Peter D. Arkwright, MD, PhD,<sup>g</sup> Zhen Chen, PhD,<sup>h</sup> Ashish Bansal, MD, MBA,<sup>h</sup> Randy Prescilla, MD,<sup>i</sup> Zhixiao Wang, PhD,<sup>h</sup> and Ainara R. Marco, MD<sup>j</sup>

**Background:** Moderate-to-severe atopic dermatitis (AD) greatly impacts children/caregivers.

**Objective:** Evaluate the impact of treatment with dupilumab on caregiver- and patient-reported AD symptoms and quality of life (QoL) in young children.

**Methods:** In the LIBERTY AD PRESCHOOL (randomized, placebo-controlled) study, children aged 6 months to 5 years with moderate-to-severe AD received dupilumab or placebo plus low-potency topical corticosteroids for 16 weeks. This posthoc analysis assessed the change from baseline to week 16 in caregiver-reported outcome measures of AD symptoms (eg, itch and sleep) and QoL of patients and their caregivers/families.

**Results:** Dupilumab ( $n = 83$ ) vs placebo ( $n = 79$ ) provided significant improvements in caregiver-reported AD symptoms and QoL. Significant improvements were seen as early as week 4 and sustained through the end of the study. Additionally, dupilumab vs placebo provided rapid and significant improvement in QoL measures for the patients' caregivers/families.

**Limitations:** Few patients aged <2 years; significance only reported for prespecified endpoints; Infant's Dermatitis QoL Index severity strata adopted from Children's Dermatology Life Quality Index.

From the Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois<sup>a</sup>; Division of Dermatology, Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois<sup>b</sup>; Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, District of Columbia<sup>c</sup>; Department of Dermatology, Oregon Health & Science University, Portland, Oregon<sup>d</sup>; Sheffield Children's Hospital, Sheffield, UK<sup>e</sup>; Department of Infection, Immunity and Cardiovascular Disease, Sheffield Dermatology Research, University of Sheffield, Sheffield, UK<sup>f</sup>; Lydia Becker Institute of Immunology & Inflammation, University of Manchester, Manchester, UK<sup>g</sup>; Regeneron Pharmaceuticals Inc., Tarrytown, New York<sup>h</sup>; Sanofi, Cambridge, Massachusetts<sup>i</sup>; and Sanofi, Madrid, Spain.<sup>j</sup>

**Funding sources:** This research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. The journal's rapid service fees were funded by Sanofi and Regeneron Pharmaceuticals Inc.

**Patient consent:** Written informed consent was obtained from participants' parent(s) or legal guardian(s).

**IRB approval status:** Approved.

**Data sharing statement:** Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

Accepted for publication September 4, 2024.

**Correspondence to:** Amy S. Paller, MD, Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 N. St. Clair, Suite 1600, Chicago, IL 60611. E-mail: [apaller@northwestern.edu](mailto:apaller@northwestern.edu).

Published online September 28, 2024.

0190-9622

© 2024 by the American Academy of Dermatology, Inc. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaad.2024.09.039>

**Conclusion:** Dupilumab improved AD symptoms and QoL in patients and their caregivers/families. (J Am Acad Dermatol 2025;92:116-26.)

**Key words:** atopic dermatitis; burden of disease; caregivers; children; dupilumab; itch; quality of life; sleep.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory systemic disease characterized by red, inflamed skin lesions and itch (pruritus).<sup>1,2</sup> An international survey estimated AD prevalence at 12% among children aged 6 months to 5 years.<sup>3</sup> Moderate-to-severe AD can profoundly impact quality of life (QoL) in children due to intense pruritus, which can disturb sleep and cause school absence in children and work absences and decreased productivity in caregivers/families.<sup>4-10</sup>

Many symptoms (eg, pruritus, sleep disturbance) are difficult for clinicians to assess.<sup>11</sup> Patient-reported outcomes provide an important complement to clinician-reported outcomes. The US Food and Drug Administration and the International Society for Pharmacoeconomics and Outcomes Research Task Force support using observer-reported outcomes when young patients cannot provide reliable, valid, self-reported responses about their experiences.<sup>12,13</sup>

Dupilumab, a fully human VelocImmune-derived monoclonal antibody,<sup>14,15</sup> blocks the shared receptor component for interleukin-4 and -13, thus inhibiting their signaling. Phase 3 dupilumab trials in patients aged  $\geq 6$  months with moderate-to-severe AD demonstrated substantial improvements in AD signs, symptoms, and QoL with an acceptable safety profile.<sup>16-20</sup> We evaluated impact of dupilumab with concomitant low-potency topical corticosteroids (TCS) on patient- and caregiver-reported measures of AD symptoms and health-related QoL in children aged 6 months to 5 years with moderate-to-severe AD.

## METHODS

### Study design

LIBERTY AD PRESCHOOL (NCT03346434) was a phase 2/3, 2-part clinical study.<sup>20,21</sup> Part A and B results were previously reported.<sup>20,21</sup> We report patient-reported outcomes from part B, a 16-week, randomized, double-blind, placebo-controlled, phase 3 study in children aged 6 months to 5 years with moderate-to-severe AD.

## CAPSULE SUMMARY

- Moderate-to-severe atopic dermatitis is associated with intense itch and impaired sleep, which can have a significant negative impact on the quality of life of young children and their caregivers/families.
- Dupilumab improves atopic dermatitis symptoms and health-related quality of life measures in children aged 6 months to 5 years and their caregivers.

The study design was previously reported.<sup>20</sup> Briefly, it included patients aged 6 months to 5 years at screening, diagnosed with AD,<sup>22</sup> and a documented recent history ( $\leq 6$  months before screening) of inadequate response to topical AD medication. Inclusion criteria were moderate-to-severe AD (Investigator's Global Assessment [IGA] score 3/4), Eczema Area and Severity Index score  $\geq 16$ , body surface area affected by AD  $\geq 10\%$ , and Worst Scratch/Itch Numeric Rating Scale (WSI-NRS) score  $\geq 4$ .

Patients received subcutaneous dupilumab (200 mg for baseline bodyweight of  $\geq 5$  to  $<15$  kg, 300 mg for  $\geq 15$  to  $<30$  kg) or matched placebo every 4 weeks for 16 weeks, with standardized regimen of concomitant once-daily low-potency TCS, tapered to 3 times per week for patients with IGA score  $\leq 2$ , and stopped for patients with IGA score of 0. Patient-reported outcomes were evaluated during in-clinic visits, at baseline and weeks 1, 2, and 4, then monthly through week 16, and at weekly telephone calls between visits. There was a 12-week follow-up period for patients who did not enroll in a subsequent open-label extension trial.

LIBERTY AD PRESCHOOL was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent committee conducted blinded monitoring of patient safety data. Local institutional review boards or ethics committees reviewed and approved the study protocol and oversaw trial conduct and documentation. Written informed consent was obtained from participants' parent(s) or legal guardian(s). Consolidated Standards of Reporting Trials guidelines were followed for reporting results.

### Caregiver- and patient-reported outcomes

Several patient-/caregiver-reported outcome measures are used to evaluate AD symptoms and QoL (Supplementary Table I, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>). Caregiver-reported WSI-NRS measures worst

*Abbreviations used:*

AD:	atopic dermatitis
CDLQI:	Children's Dermatology Life Quality Index
CI:	confidence interval
DFI:	Dermatitis Family Impact
EASI:	Eczema Area and Severity Index
IDQoL:	Infant's Dermatitis Quality of Life Index
IGA:	Investigator's Global Assessment
LS:	least squares
NRS:	Numeric Rating Scale
POEM:	Patient-Oriented Eczema Measure
q4w:	every 4 weeks
QoL:	quality of life
SD:	standard deviation
TCS:	topical corticosteroid(s)
WOCF:	worst-observation-carried-forward
WSI-NRS:	Worst Scratch/Itch Numeric Rating Scale

scratch/itch on an 11-point scale (range: 0 [no itching] to 10 [worst itching possible] over the past 24 hours; clinically meaningful change: 3–4 points) and has been validated in children aged 6 months to 5 years with moderate-to-severe AD.<sup>23</sup> Patient's and caregiver's Sleep Quality NRS is an 11-point caregiver-reported measure (range: 0 [worst possible sleep] to 10 [best possible sleep] over the past 24 hours) validated in children aged 6 months to 5 years with moderate-to-severe AD.<sup>24</sup> Patient-Oriented Eczema Measure (POEM) measures frequency of AD signs and symptoms and sleep disturbance during the past week using 7 items rated on a 5-point scale (range: 0 [no days] to 4 [every day]) validated for use with children, adolescents, and adults with AD (total score range: 0–28; clinically meaningful change in children/adolescents: 6 points; in adults: 4 points).<sup>25–30</sup> Howells et al<sup>31</sup> recommended that changes of 4 or more points in POEM are likely clinically important in young children with AD. Internal analysis using data from the current study suggests that a 6-point change in POEM is a reasonable threshold for defining meaningful within-patient change in patients aged 6 months to 5 years, consistent with previous publications.<sup>31</sup> Although individual sleep-related items from POEM were validated in adult AD patients,<sup>32</sup> individual items were not validated in children aged 6 months to 5 years. Children's Dermatology Life Quality Index (CDLQI) comprises 10 questions evaluated on a 4-point scale (range: 0 [not at all] to 3 [very much]), measures skin disease impact on health-related QoL in children, and is validated in patients aged 4 to 17 years (total score range: 0–30 points; clinically meaningful change: 6 points).<sup>25,26,33,34</sup> Infants' Dermatitis Quality of Life Index (IDQoL) comprises 10

questions to assess QoL with questions evaluated on a 4-point scale, and is validated in children aged <4 years (total score range: 0–30; clinically meaningful change in patients 6 months to 5 years: 6 points) with AD.<sup>34,35</sup> Dermatitis Family Impact (DFI), comprising 10 questions evaluated on a 4-point scale (range: 0 [not at all] to 3 [very much]; total score range: 0–30; clinically meaningful change in patients aged 6 months to 5 years: 7 points), evaluates how children (<16 years) with AD affect adult family members' QoL.<sup>34,36</sup>

Endpoints reported here include prespecified secondary endpoints<sup>20</sup> and posthoc analyses, including caregiver-reported WSI-NRS (least squares [LS] mean change from baseline to week 16 and proportion of patients with  $\geq 4$ -point improvement); patient's and caregiver's Sleep Quality NRS (LS mean change from baseline to week 16); CDLQI (patients  $\geq 4$  years) or IDQoL (patients <4 years; LS mean absolute score from baseline to week 16); DFI (LS mean absolute score from baseline to week 16); proportion of family members reporting “not at all” or “a little” for individual DFI items (baseline and week 16); POEM total score (baseline to week 16) and proportion of patients with  $\geq 6$ -point improvement in POEM total score (baseline to week 16); POEM items: difference between week 16 and baseline in proportion of patients reporting numbers of days with itchy skin over the previous 7 days and proportion of patients reporting numbers of days with disturbed sleep over the previous 7 days. Analyses of the proportion of patients reporting individual POEM items, proportion of patients with  $\geq 6$ -point improvement in POEM total score, and proportion of family members reporting individual DFI items were all posthoc, as were correlation analyses for outcomes at baseline.

WSI-NRS was assessed daily and averaged weekly; patient's Sleep Quality NRS was assessed daily, averaged weekly, and reported at weeks 1, 2, 4, and 16; CDLQI, IDQoL, DFI, and POEM were assessed at weeks 2, 4, 8, 12, and 16; and weekly mean caregiver Sleep Quality NRS was assessed at weeks 1, 2, 4, and 16.

## Analysis

Analyses were performed using the full analysis set (all randomized patients). Continuous endpoints were analyzed using an analysis of covariance model with baseline measurement as covariate and treatment and randomization strata (region [North America vs Europe], baseline disease severity [IGA 3 vs 4], and baseline bodyweight group [<30 kg vs  $\geq 30$  kg]) as fixed factors. For categorical endpoints, *P* values were derived by Cochran-Mantel-Haenszel test stratified by region (North America vs

**Table 1.** Baseline demographics and disease characteristics

Characteristic	Placebo + TCS (n = 79)	Dupilumab + TCS (n = 83)	Overall (N = 162)
Age (y), mean (SD)	3.8 (1.3)	3.9 (1.2)	3.8 (1.2)
≥6 mo to <2 y, n (%)	5 (6)	6 (7)	11 (7)
≥2 to 5 y, n (%)	74 (94)	77 (93)	151 (93)
Sex (male), n (%)	55 (70)	44 (53)	99 (61)
Race, n (%)			
White	53 (67)	58 (70)	111 (68)
Black or African American	16 (20)	14 (17)	30 (18)
Asian	4 (5)	6 (7)	10 (6)
Other	4 (5)	3 (4)	7 (4)
Weight (kg), mean (SD)	16.7 (3.6)	17.1 (4.4)	16.9 (4.0)
5 to <15 kg, n (%)	25 (32)	26 (31)	51 (31)
15 to <30 kg, n (%)	54 (68)	57 (69)	111 (68)
Age at AD disease onset, n (%)			
<6 mo	57 (72)	50 (60)	107 (66)
≥6 mo	22 (28)	33 (40)	55 (34)
Duration of AD (y), mean (SD)	3.4 (1.3)	3.4 (1.3)	3.4 (1.3)
Disease characteristics, mean (SD)*			
IGA score 3, n (%) (range 0-4)	17 (21)	20 (24)	37 (23)
IGA score 4, n (%) (range 0-4)	62 (78)	63 (76)	125 (77)
EASI total score (range 0-72)	33.1 (12.2)	35.1 (13.9)	34.1 (13.1)
Sleep Quality NRS score (range 0-10)	4.6 (2.1)	4.9 (1.9)	4.8 (2.0)
Skin pain NRS score (range 0-10)	7.2 (1.8)	6.8 (1.8)	7.0 (1.8)
WSI-NRS score (range 0-10)	7.6 (1.5)	7.5 (1.3)	7.6 (1.4)
POEM total score (range 0-28)	23.3 (4.0)	23.1 (4.5)	23.2 (4.3)
CDLQI total score (range 0-30)	17.7 (6.3) (n = 38)	17.5 (5.4) (n = 48)	17.6 (5.8) (n = 86)
IDQoL total score (range 0-30)	17.1 (5.4) (n = 41)	17.4 (5.4) (n = 35)	17.2 (5.4) (n = 76)
DFI (range 0-30)	17.6 (7.2)	17.2 (6.0)	17.4 (6.6)
Caregiver Sleep Quality NRS (range 0-10)	4.7 (2.1)	5.1 (1.9)	4.9 (2.0)

AD, Atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index (≥4 to <18 years); DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; IDQoL, Infant's Dermatitis Quality of Life Index (<4 years); IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCS, (low-potency) topical corticosteroid(s); WSI-NRS, Worst Scratch/Itch Numeric Rating Scale.

\*Unless otherwise noted.

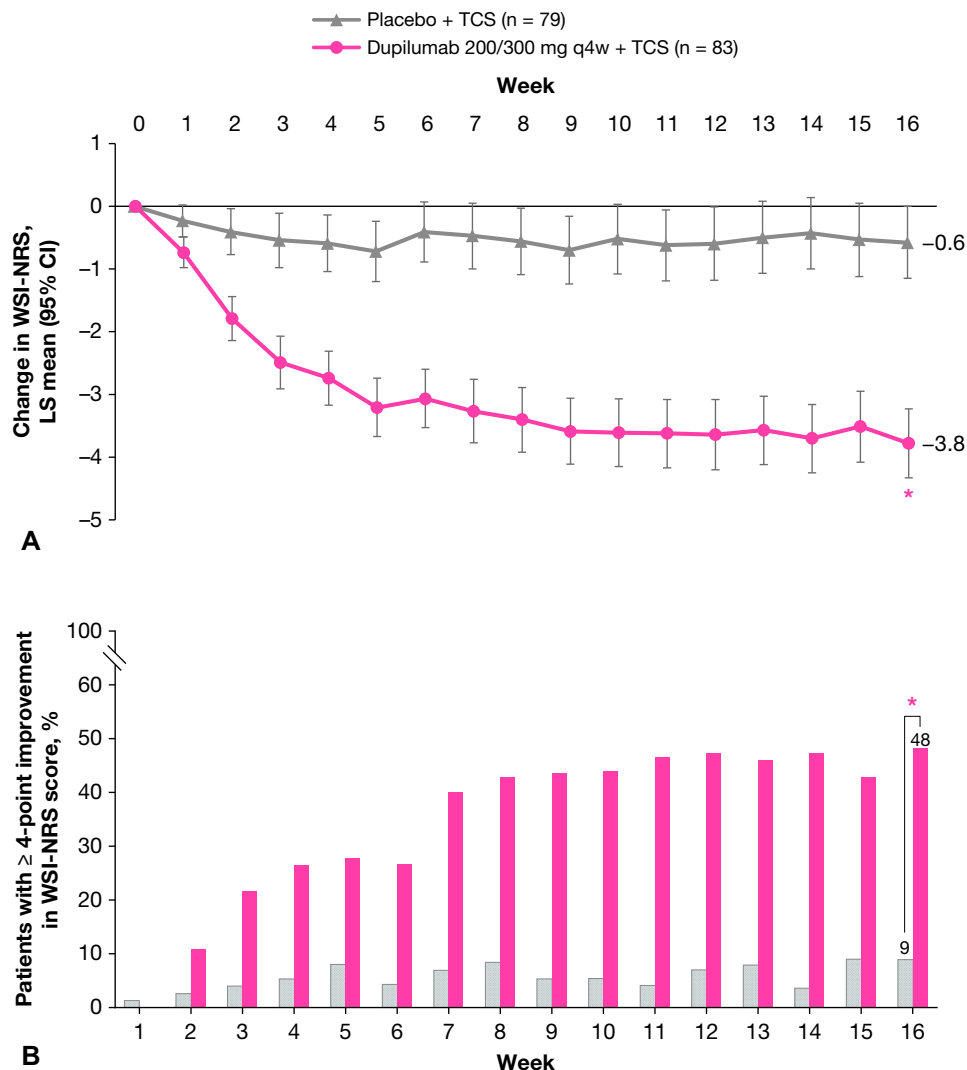
Europe), baseline disease severity (IGA 3 vs 4), and baseline bodyweight group (5 to <15 kg vs 15 to <30 kg). The stratum for region = EU, baseline bodyweight <15 kg, IGA = 3 included only 2 patients, so was combined with the stratum for region = EU, baseline bodyweight ≥15 kg, IGA = 3. Statistical significance was calculated for prespecified endpoints for dupilumab vs placebo at week 16, as described previously.<sup>20</sup> P values generated for posthoc analyses were regarded as nominal and have not been included.

Patients missing values at week 16 due to rescue treatment use, withdrawn consent, or study withdrawal due to adverse events or lack of efficacy were imputed by the worst-observation-carried-forward (WOCF) method. If no postbaseline values were available, the baseline value was used. Data for patients with missing values due to other reasons, including COVID-19, were imputed by multiple imputation based on all observed data before imputation by

WOCF. Missing data were imputed 40 times to generate 40 complete datasets, and week 16 data were analyzed using an analysis of covariance model and results combined using Rubin's formula. The imputation model included treatment group, baseline value, and randomization strata (baseline weight group, baseline IGA, region), and values at every clinic visit. Patients with missing DFI scores at week 16 were considered nonresponders. For POEM, data are reported as all observed values regardless of rescue treatment use.

Correlation analyses were performed for itch (WSI-NRS) vs sleep (Sleep Quality NRS), itch (WSI-NRS) vs QoL (CDLQI/IDQoL), and QoL (CDLQI/IDQoL) vs sleep (Sleep Quality NRS) (Supplementary Methods, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzfz598/1>).

All analyses were performed using SAS version 9.4 (SAS Institute) or higher.



**Fig 1. A,** LS mean (95% CI) change in WSI-NRS score over time. **B,** Proportion of patients with at least a 4-point improvement in WSI-NRS score over time. *CI*, Confidence interval; *LS*, least squares; *NRS*, Numeric Rating Scale; *q4w*, every 4 weeks; *TCS*, (low-potency) topical corticosteroid(s); *WSI-NRS*, Worst Scratch/Itch Numeric Rating Scale. \* $P < .0001$  vs placebo.

## RESULTS

Analysis included 162 patients (83 dupilumab, 79 placebo). Baseline demographics and disease characteristics were previously reported<sup>20</sup> and balanced between dupilumab and placebo groups (Table I).

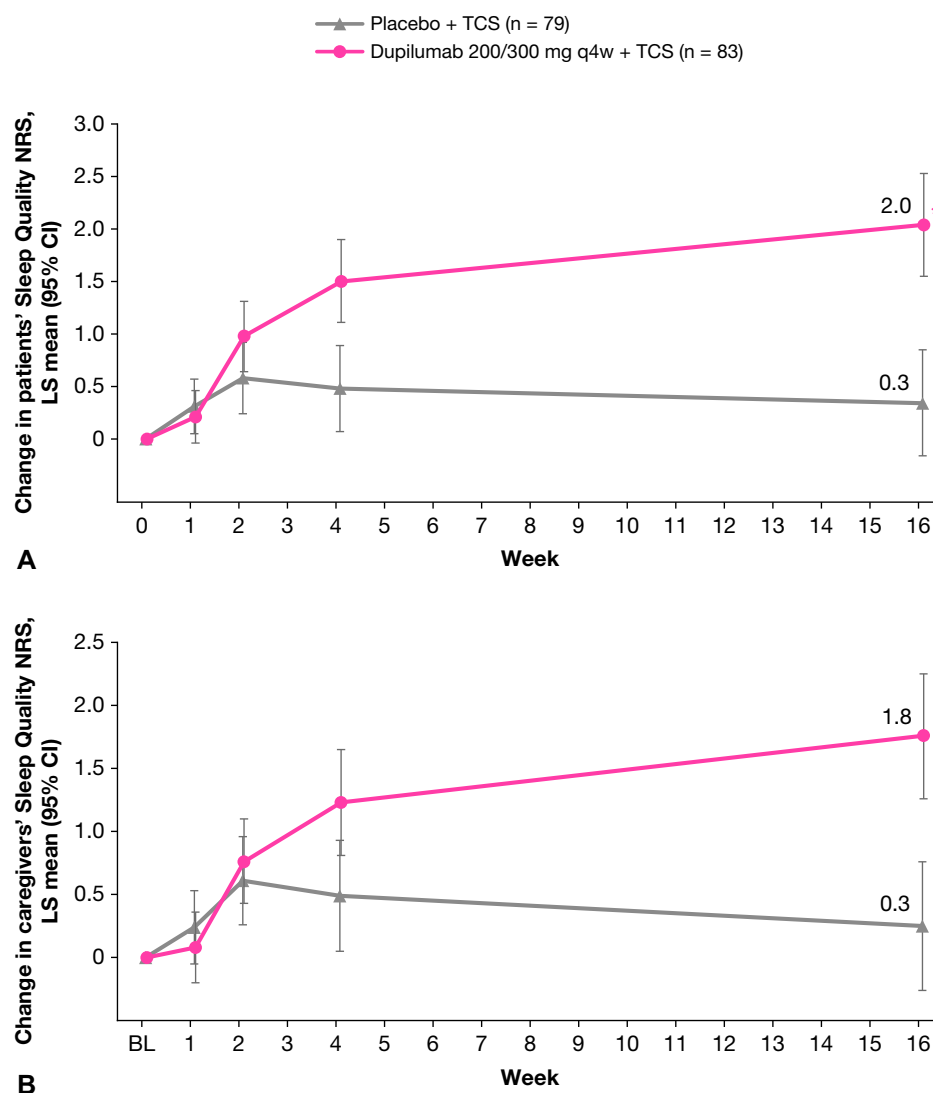
LS mean (95% CI) change from baseline in weekly average of daily WSI-NRS was greater with dupilumab vs placebo as early as week 1 and sustained through week 16 ( $-3.8$  [ $-4.33$  to  $-3.23$ ] vs  $-0.6$  [ $-1.16$  to  $-0.01$ ];  $P < .0001$ ; Fig 1, A; Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>). The proportion of patients achieving a clinically meaningful response ( $\geq 4$ -point improvement from baseline) for WSI-NRS was greater for dupilumab vs placebo from week 4 and sustained through week 16 (48% vs 9%;

$P < .0001$ ; Fig 1, B; Supplementary Table III, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>).

Improvements in sleep quality in patients and caregivers were greater with dupilumab vs placebo as early as week 4, with a difference in LS mean (95% CI) change from baseline in Sleep Quality NRS at week 16 for patients ( $2.0$  [ $1.55$ - $2.53$ ] vs  $0.3$  [ $-0.17$  to  $0.84$ ];  $P < .0001$ ) (Fig 2, A; Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>) and caregivers ( $1.8$  [ $1.26$ - $2.25$ ] vs  $0.3$  [ $-0.26$  to  $0.76$ ]) (Fig 2, B; Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>).

From week 2, LS mean (95% CI) change from baseline in POEM total score was greater for



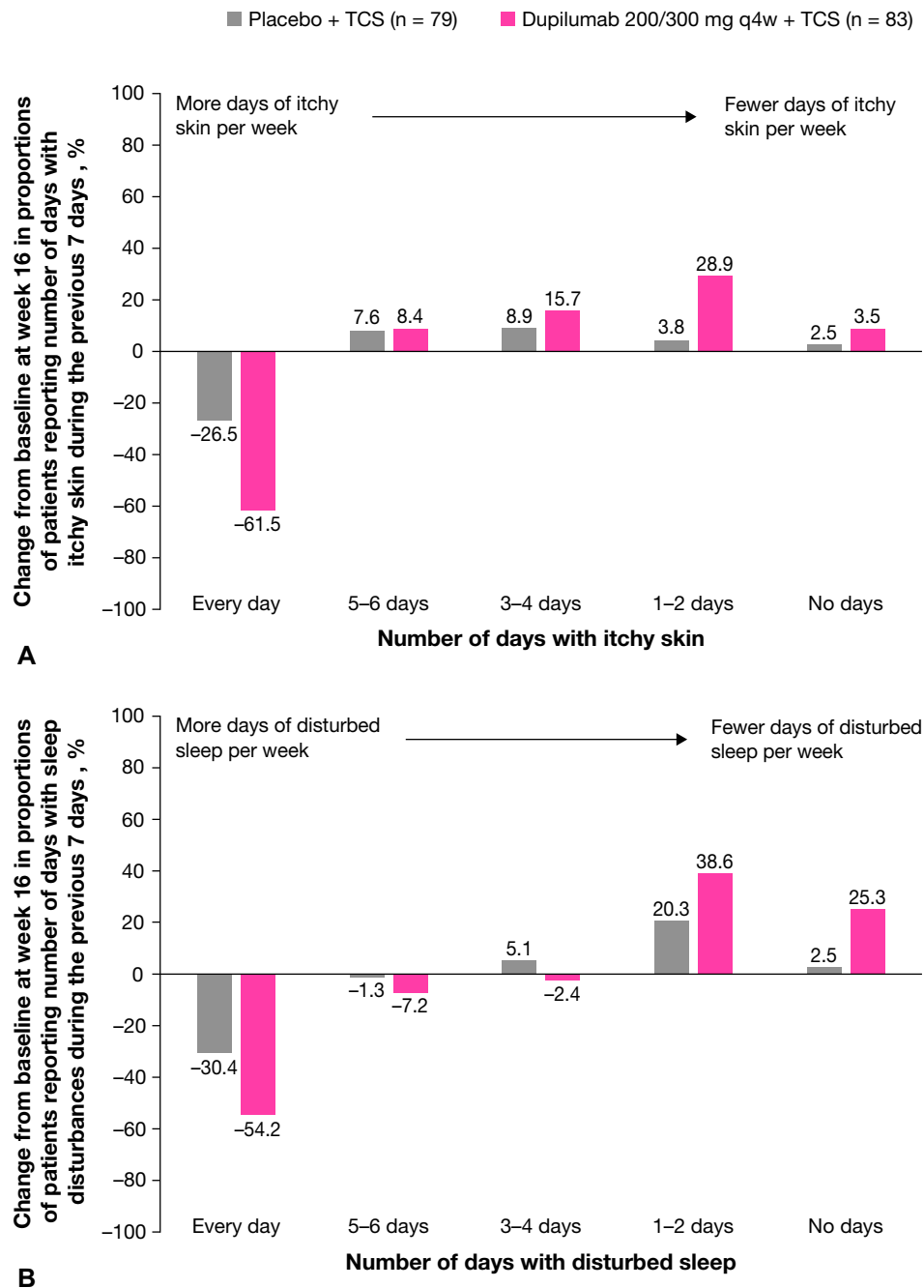


**Fig 2.** LS mean (95% CI) change in Sleep Quality NRS over time. **A**, Patients and **B**, caregivers. BL, Baseline; CI, confidence interval; LS, least squares; NRS, Numeric Rating Scale; q4w, every 4 weeks; TCS, (low-potency) topical corticosteroid(s). \* $P < .0001$  vs placebo.

dupilumab vs placebo, sustained through week 16 ( $-12.9$  [ $-14.6$  to  $-11.1$ ] vs  $-3.8$  [ $-5.6$  to  $-2.0$ ];  $P < .0001$ ; Supplementary Fig 1, A, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>). A greater proportion of patients achieved  $\geq 6$ -point improvement in POEM total score, evident from week 2 and maintained through week 16 (61% vs 19%; Supplementary Fig 1, B, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>). The difference between week 16 and baseline in the proportion of patients reporting no days and 1-2 days of the previous 7 days with itchy skin was greater for patients treated with dupilumab vs placebo ( $+3.5\%$  vs  $+2.5\%$  and  $+28.9\%$  vs  $+3.8\%$ , respectively; Fig 3, A), as was the difference between week 16 and

baseline in proportion of patients reporting no days and 1-2 days of the previous 7 days with sleep disturbances ( $+25.3\%$  vs  $+2.5\%$  and  $+38.6\%$  vs  $+20.3\%$ , respectively; Fig 3, B).

A greater benefit in patient and caregiver QoL was seen for dupilumab vs placebo at week 16 in LS mean (95% CI) IDQoL ( $6.3$  [ $4.04$ - $8.58$ ] vs  $15.3$  [ $13.16$ - $17.38$ ];  $P < .0001$ ; Supplementary Fig 2, A and Table II, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>, CDLQI ( $7.5$  [ $4.46$ - $10.57$ ] vs  $15.0$  [ $11.77$ - $18.29$ ];  $P < .0001$ ) (Supplementary Fig 2, B and Table II, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzf598/1>, and total DFI score ( $6.9$  [ $5.33$ - $8.49$ ] vs  $14.7$  [ $13.09$ - $16.35$ ];  $P < .0001$ ; Supplementary Fig 2, C and Table II, available via Mendeley at

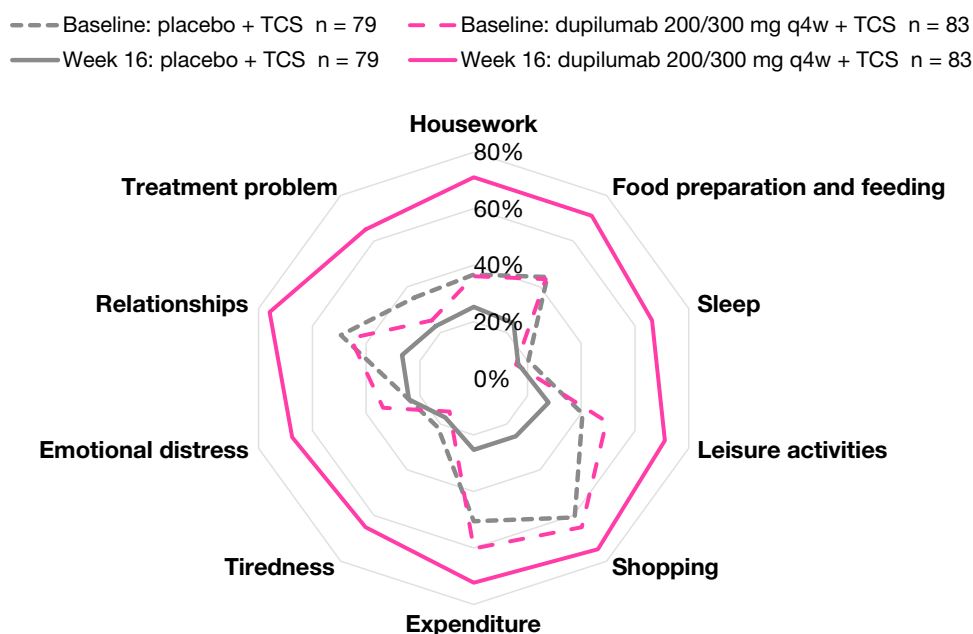


**Fig 3.** Days with **A**, itchy skin and **B**, disturbed sleep in the last 7 days (POEM). POEM evaluates symptoms during the previous 7 days on a 5-point scale: 0 = no days, 1 = 1-2 days, 2 = 3-4 days, 3 = 5-6 days, 4 = every day.<sup>27</sup> POEM, Patient-Oriented Eczema Measure; *q4w*, every 4 weeks; TCS, (low-potency) topical corticosteroid(s).

<https://data.mendeley.com/datasets/9xvwbzfz598/1>. For all QoL measures, differences between dupilumab and placebo groups were evident from week 2 (Supplementary Fig 2, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzfz598/1>). At week 16, a greater proportion of patients treated with dupilumab vs placebo achieved a  $\geq 6$ -point improvement from baseline in CDLQI total score

(66% vs 16%) and IDQoL total score (65% vs 6%) and a  $\geq 7$ -point improvement in DFI total score (59% vs 16%). In each case, a difference between dupilumab and placebo was evident from weeks 2 or 4. Furthermore, a greater proportion of patients treated with dupilumab vs placebo reported “not at all” or “a little” for each of 10 individual items of the DFI questionnaire at week 16 (Fig 4).





**Fig 4.** Baseline and week 16: proportion of family members reporting “not at all” or “a little” effect of treatment on aspects of everyday life. *DFI*, Dermatitis Family Impact; *q4w*, every 4 weeks; *TCS*, (low-potency) topical corticosteroid(s).

Correlation analyses at baseline showed small-to-moderate correlations (range:  $-0.51$  to  $0.33$ ) between measures of QoL (IDQoL, CDLQI), and measures of pruritus (WSI-NRS) and sleep quality (Sleep Quality NRS), as well as between Sleep Quality NRS and WSI-NRS (Supplementary Table IV, available via Mendeley at <https://data.mendeley.com/datasets/9xvwbzfz598/1>).

## Safety

Safety results were previously reported.<sup>20</sup> Dupilumab was well tolerated with an acceptable safety profile, consistent with the known dupilumab safety profile and similar to that in older children and adults.<sup>16-19,37</sup>

## DISCUSSION

Patient-/caregiver-reported outcome measures can provide important information on treatment value from the patient's perspective.<sup>1,12,13</sup> Caregiver-reported measures are particularly helpful for young children, who cannot provide reliable, valid, self-reported responses. This study showed that dupilumab plus low-potency TCS for 16 weeks provided rapid and significant improvements in pruritus, sleep, and health-related QoL in patients aged 6 months to 5 years with moderate-to-severe AD, and QoL of their caregivers. More patients treated with dupilumab plus TCS vs placebo plus TCS achieved clinically meaningful

improvements in WSI-NRS within 4 weeks, and improvements in sleep quality within 4 weeks in children and caregivers. Additionally, dupilumab treatment provided rapid, significant improvement of health-related QoL measures, including CDLQI, IDQoL, and DFI, in patients and caregivers. These results are consistent with studies of dupilumab in adults ( $>18$  years),<sup>38-41</sup> adolescents (12-18 years),<sup>18,42</sup> and children (6-11 years).<sup>19</sup>

Short-term consequences of sleep disruption include increased stress responsivity, reduced QoL, and emotional distress in otherwise healthy individuals, and may diminish health-related QoL of children/adolescents with underlying medical conditions.<sup>43</sup> Sleep disturbances in children are associated with decreased neurobehavioral functioning, higher rates of behavioral problems, and reduced cognitive performance.<sup>44,45</sup> Therefore, it is important for healthcare professionals to treat symptoms of underlying medical conditions effectively to optimize sleep continuity.<sup>43</sup> Improvements in sleep quality during dupilumab treatment benefit children with AD and their families. QoL improvements were seen in overall DFI at week 16 and all items related to AD impact on family life, representing a reduced burden on family QoL. Because pruritus negatively affects sleep and health-related QoL,<sup>1,46,47</sup> the rapid improvements in sleep quality and QoL may be consequences of rapid improvements in pruritus. Baseline correlation

analyses revealed only small-to-moderate correlations between measures in this study, underscoring the importance of evaluating multiple domains to fully capture AD severity and burden.

Strengths of this study are as follows: randomized and placebo-controlled, with most data concerning prespecified secondary endpoints. Limitations are as follows: few patients in the youngest age group ( $\geq 6$  months to  $< 2$  years); significance only reported for prespecified endpoints at week 16; *P* values for all other analyses were nominal and not reported; relatively short, 16-week duration; and severity strata for IDQoL were adopted from CDLQI. Future studies should explore long-term follow-up to confirm sustained improvement in QoL scores and sleep beyond 16 weeks of treatment.

## CONCLUSIONS

Dupilumab treatment with concomitant low-potency TCS for 16 weeks improved AD symptoms within 4 weeks in patients with AD aged 6 months to 5 years, and rapidly improved health-related QoL in patients and their caregivers.

Medical writing and editorial assistance were provided by Liselotte van Delden of Excerpta Medica, funded by Sanofi and Regeneron Pharmaceuticals Inc, according to the Good Publication Practice guidelines. The National Institute for Health and Care Research provided support to the Manchester Clinical Research Facility at Royal Manchester Children's Hospital.

## Conflicts of interest

Dr Paller is a consultant for and has received honoraria from Aegerion Pharma, Azitra, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Castle Creek Biosciences, Eli Lilly, Janssen, Krystal Biotech, LEO Pharma, Novartis, Regeneron Pharmaceuticals Inc, Sanofi, Seanergy, TWI Biotechnology, and UCB, is an investigator for AbbVie, Dermavant, Eli Lilly, Incyte, Janssen, Krystal Biotech, LEO Pharma, and UCB, and is on the data and safety monitoring boards of AbbVie, Abeona Therapeutics, Catawba Research, Galderma, and InMed Pharmaceuticals. Dr Silverberg has received honoraria as a consultant and/or advisory board member from AbbVie, Alamar Biosciences, Aldena Therapeutics, Amgen, AOBiome, Arcutis Biotherapeutics, Arena Pharmaceuticals, Asana BioSciences, Aslan Pharmaceuticals, BiomX, Biosion, Bodewell, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celgene, Connect Biopharma, CorEvitas, Dermavant, Dermira, DermTech, Eli Lilly, Galderma, GSK, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Menlo Therapeutics, Novartis, Optum, Pfizer, RAPT Therapeutics, Recludix Pharma, Regeneron Pharmaceuticals Inc, Sanofi, Shaperon, Target-RWE, UNION therapeutics, and UpToDate, has received speaker fees from AbbVie, Eli Lilly, LEO Pharma, Pfizer, Regeneron Pharmaceuticals Inc,

and Sanofi, and institution grants from Galderma, Incyte, and Pfizer. Dr Simpson has received personal fees from AbbVie, Advances in Cosmetic and Medical Dermatology Hawaii, Amgen, AOBiome, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharmaceuticals, Boehringer Ingelheim, BMS, Boston Consulting Group, Collective Acumen, CorEvitas, Dermira, Eli Lilly, Evelo Biosciences, Evidera, Excerpta Medica, Forté Biosciences, Fraunhofer, Galderma, GSK, Incyte, Janssen, Johnson & Johnson, Kyowa Kirin, LEO Pharma, Medscape, Merck, Maui Derm, MJH Life Sciences, MLG Operating, Pfizer, Physicians World, PRImE, Regeneron Pharmaceuticals Inc, Revolutionizing Atopic Dermatitis, Roivant Sciences, Sanofi, Trevi Therapeutics, Valeant, Vindico Medical Education, and WebMD, and has received grants as a principal investigator from AbbVie, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Castle Creek Biosciences, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Kirin, National Jewish Health, LEO Pharma, Pfizer, Regeneron Pharmaceuticals Inc, Sanofi, and Target RWE. Dr Cork is an investigator and/or consultant for AbbVie, Astellas Pharma, Boots, Dermavant, Galapagos, Galderma, Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron Pharmaceuticals Inc, and Sanofi. Dr Arkwright is an investigator at Regeneron Pharmaceuticals Inc and LEO Pharma, and is a research grant advisor and lecturer with Sanofi. Dr Chen, Dr Bansal, and Dr Wang are employees/ shareholders of Regeneron Pharmaceuticals Inc. Dr Prescilla and Dr Marco are employees of Sanofi and may hold stock and/or stock options in the company. Dr Cork has no conflict of interest to declare.

## REFERENCES

1. Na CH, Chung J, Simpson EL. Quality of life and disease impact of atopic dermatitis and psoriasis on children and their families. *Children (Basel)*. 2019;6(12):133. <https://doi.org/10.3390/children6120133>
2. Brenninkmeijer EE, Legierse CM, Sillevs Smitt JH, Last BF, Grootenhuys MA, Bos JD. The course of life of patients with childhood atopic dermatitis. *Pediatr Dermatol*. 2009;26(1):14-22. <https://doi.org/10.1111/j.1525-1470.2008.00745.x>
3. Silverberg JI, Barbarot S, Gadkari A, et al. Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. *Ann Allergy Asthma Immunol*. 2021;126(4):417-428.e2. <https://doi.org/10.1016/j.anai.2020.12.020>
4. Misery L, Belloni Fortina A, El Hachem M, et al. A position paper on the management of itch and pain in atopic dermatitis from the International Society of Atopic Dermatitis (ISAD)/Oriented Patient-Education Network in Dermatology (OPENED) task force. *J Eur Acad Dermatol Venereol*. 2021;35(4):787-796. <https://doi.org/10.1111/jdv.16916>
5. Ramirez FD, Chen S, Langan SM, et al. Association of atopic dermatitis with sleep quality in children. *JAMA Pediatr*. 2019;173(5):e190025. <https://doi.org/10.1001/jamapediatrics.2019.0025>
6. Meltzer LJ, Flewelling KD, Jump S, Gyorkos E, White M, Hauk PJ. Impact of atopic dermatitis treatment on child and parent sleep, daytime functioning, and quality of life. *Ann Allergy Asthma Immunol*. 2020;124(4):385-392. <https://doi.org/10.1016/j.anai.2019.12.024>

7. Meltzer LJ, Booster GD. Sleep disturbance in caregivers of children with respiratory and atopic disease. *Pediatr Psychol*. 2016;41(6):643-650. <https://doi.org/10.1093/jpepsy/jsw016>
8. Ramirez FD, Chen S, Langan SM, et al. Assessment of sleep disturbances and exhaustion in mothers of children with atopic dermatitis. *JAMA Dermatol*. 2019;155(5):556-563. <https://doi.org/10.1001/jamadermatol.2018.5641>
9. Yang EJ, Beck KM, Sekhon S, Bhutani T, Koo J. The impact of pediatric atopic dermatitis on families: a review. *Pediatr Dermatol*. 2019;36(1):66-71. <https://doi.org/10.1111/pde.13727>
10. Cheng BT, Silverberg JL. Association of pediatric atopic dermatitis and psoriasis with school absenteeism and parental work absenteeism: a cross-sectional United States population-based study. *J Am Acad Dermatol*. 2021;85(4):885-892. <https://doi.org/10.1016/j.jaad.2021.02.069>
11. Townshend AP, Chen CM, Williams HC. How prominent are patient-reported outcomes in clinical trials of dermatological treatments? *Br J Dermatol*. 2008;159(5):1152-1159. <https://doi.org/10.1111/j.1365-2133.2008.08799.x>
12. Food and Drug Administration (FDA). Patient-focused drug development: selecting, developing, or modifying fit-for-purpose clinical outcome assessments. June 2022. Accessed January 26, 2024. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome>
13. Matza LS, Patrick DL, Riley AW, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. *Value Health*. 2013;16(4):461-479. <https://doi.org/10.1016/j.jval.2013.04.004>
14. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A*. 2014;111(14):5147-5152. <https://doi.org/10.1073/pnas.1323896111>
15. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A*. 2014;111(14):5153-5158. <https://doi.org/10.1073/pnas.1324022111>
16. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. <https://doi.org/10.1056/NEJMoa1610020>
17. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303. [https://doi.org/10.1016/S0140-6736\(17\)31191-1](https://doi.org/10.1016/S0140-6736(17)31191-1)
18. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44-56. <https://doi.org/10.1001/jamadermatol.2019.3336>
19. Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol*. 2020;83(5):1282-1293. <https://doi.org/10.1016/j.jaad.2020.06.054>
20. Paller AS, Simpson EL, Siegfried EC, et al. Dupilumab in children ages 6 months to 5 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2022;400(10356):908-919. [https://doi.org/10.1016/S0140-6736\(22\)01539-2](https://doi.org/10.1016/S0140-6736(22)01539-2)
21. Paller AS, Siegfried EC, Simpson EL, et al. A phase 2, open-label study of single-dose dupilumab in children aged 6 months to <6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. *J Eur Acad Dermatol Venereol*. 2021;35(2):464-475. <https://doi.org/10.1111/jdv.16928>
22. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-351. <https://doi.org/10.1016/j.jaad.2013.10.010>
23. Paller AS, Siegfried E, Marron SE, et al. Development and validation of a caregiver-reported Numeric Rating Scale for measuring worst scratch/itch in patients aged 6 months to younger than 6 years with atopic dermatitis. *J Am Acad Dermatol*. 2024;90(2):382-385. <https://doi.org/10.1016/j.jaad.2023.08.104>
24. Paller AS, Siegfried E, Marron SE, et al. Skin pain and sleep quality numeric rating scales for children aged 6 months to 5 years with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2024;00:1-4. <https://doi.org/10.1111/jdv.20199>
25. Simpson EL, de Bruin-Weller M, Eckert L, et al. Responder threshold for patient-oriented eczema measure (POEM) and Children's Dermatology life quality Index (CDLQI) in adolescents with atopic dermatitis. *Dermatol Ther (Heidelb)*. 2019;9(4):799-805. <https://doi.org/10.1007/s13555-019-00333-2>
26. Simpson EL, de Bruin-Weller M, Bansal A, et al. Definition of clinically meaningful within-patient changes in POEM and CDLQI in children 6 to 11 years of age with severe atopic dermatitis. *Dermatol Ther (Heidelb)*. 2021;11(4):1415-1422. <https://doi.org/10.1007/s13555-021-00543-7>
27. Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol*. 2004;140(12):1513-1519. <https://doi.org/10.1001/archderm.140.12.1513>
28. Coutanceau C, Stalder JF. Analysis of correlations between patient-oriented SCORAD (PO-SCORAD) and other assessment scores of atopic dermatitis severity and quality of life. *Dermatology*. 2014;229(3):248-255. <https://doi.org/10.1001/10.1159/000365075>
29. Silverberg JL, Margolis DJ, Boguniewicz M, et al. Validation of five patient-reported outcomes for atopic dermatitis severity in adults. *Br J Dermatol*. 2020;182(1):104-111. <https://doi.org/10.1111/bjd.18002>
30. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy*. 2012;67(1):99-106. <https://doi.org/10.1111/j.1398-9995.2011.02719.x>
31. Howells L, Ratib S, Chalmers JR, Bradshaw L, Thomas KS, CLOTHES Trial Team. How should minimally important change scores for the Patient-Oriented Eczema Measure be interpreted? A validation using varied methods. *Br J Dermatol*. 2018;178(5):1135-1142. <https://doi.org/10.1111/bjd.16367>
32. Lei D, Yousaf M, Janmohamed SR, et al. Validation of four single-item patient-reported assessments of sleep in adult atopic dermatitis patients. *Ann Allergy Asthma Immunol*. 2020;124(3):261-266. <https://doi.org/10.1016/j.anai.2019.12.002>
33. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol*. 1995;132(6):942-949. <https://doi.org/10.1111/j.1365-2133.1995.tb16953.x>

34. Paller AS, Marron SE, Whalley D, et al. Clinically meaningful change threshold in health-related quality of life among patients aged 6 months to 5 years with atopic dermatitis and their caregiver(s)/family. *JEADV Clin Pract*. 2024;3(1):253-257. <https://doi.org/10.1002/jvc2.290>
35. Lewis-Jones MS, Finlay AY, Dykes PJ. The infants' dermatitis quality of life index. *Br J Dermatol*. 2001;144(1):104-110. <https://doi.org/10.1046/j.1365-2133.2001.03960.x>
36. Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol*. 1998;138(1):107-113. <https://doi.org/10.1046/j.1365-2133.1998.02034.x>
37. Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol*. 2020;182(1):85-96. <https://doi.org/10.1111/bjd.18476>
38. Cork MJ, Eckert L, Simpson EL, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *J Dermatolog Treat*. 2020;31(6):606-614. <https://doi.org/10.1080/09546634.2019.1612836>
39. Silverberg JI, Simpson EL, Boguniewicz M, et al. Dupilumab provides rapid and sustained clinically meaningful responses in adults with moderate-to-severe atopic dermatitis. *Acta Derm Venereol*. 2021;101(11):adv00585. <https://doi.org/10.2340/actadv.v101.307>
40. Milanesi N, Gola M, Cartocci A, et al. Effect of dupilumab on sleep disturbances in adult patients with severe atopic dermatitis. *Ital J Dermatol Venereol*. 2022;157(2):142-145. <https://doi.org/10.23736/S2784-8671.21.07072-9>
41. Beck LA, Silverberg JI, Simpson EL, et al. Dupilumab significantly improves sleep outcomes in adult patients with atopic dermatitis: results from five randomized clinical trials. *J Eur Acad Dermatol Venereol*. 2021;35(2):e130-e133. <https://doi.org/10.1111/jdv.16865>
42. Paller AS, Bansal A, Simpson EL, et al. Clinically meaningful responses to dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: post-hoc analyses from a randomized clinical trial. *Am J Clin Dermatol*. 2020;21(1):119-131. <https://doi.org/10.1007/s40257-019-00478-y>
43. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep*. 2017;9:151-161. <https://doi.org/10.2147/NSS.S134864>
44. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Dev*. 2002;73(2):405-417. <https://doi.org/10.1111/1467-8624.00414>
45. Touchette E, Petit D, Séguin JR, Boivin M, Tremblay RE, Montplaisir JY. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep*. 2007;30(9):1213-1219. <https://doi.org/10.1093/sleep/30.9.1213>
46. Ständer S, Yosipovitch G, Bushmakina AG, et al. Examining the association between pruritus and quality of life in patients with atopic dermatitis treated with crisaborole. *J Eur Acad Dermatol Venereol*. 2019;33(9):1742-1746. <https://doi.org/10.1111/jdv.15712>
47. Barbarot S, Silverberg JI, Gadkari A, et al. The family impact of atopic dermatitis in the pediatric population: results from an international cross-sectional study. *J Pediatr*. 2022;246:220-226.e5. <https://doi.org/10.1016/j.jpeds.2022.04.027>