Ann Allergy Asthma Immunol 000 (2026) 1–7

Contents lists available at ScienceDirect

Dupilumab treatment restores epithelial barrier in nonlesional and lesional skin in children with atopic dermatitis

Michael J. Cork, MB, PhD, FRCP[*,†]; Peck Y. Ong, MD[‡]; Simon G. Danby, PhD[†,§]; Robert A. Byers, PhD[†,§]; Stephen J. Matcher, PhD[†,§]; Oludolapo S. Katibi, MBBS, FMCPaed, MMedSC Dermatology, MRCPCH, PhD[‖,¶]; Kirsty Brown, BSc[†,§]; Paul V. Andrew, BSc[†,§]; Abigail Pinnock, PhD[†,§]; Anna Poyner, BSc[†,§]; Laura Johnson, MSc[¶]; Stuart Gormley, MRes[¶]; Alison Hyde, BSc[#]; Marco Ramirez-Gama, BSc[**]; Shannon Garcia, BSc[**]; Patricia A. Taylor, NP[**]; Gabriel Bologna, MSc[††]; Amy H. Praestgaard, MSc[‡‡]; Joseph Zahn, MD[§§]; Annie Zhang, MD[‡‡]; Donald Y.M. Leung, MD, PhD[**]

[*] *Sheffield Children's National Institute for Health and Care Research Commercial Research Delivery Centre, Sheffield, United Kingdom*
[†] *Sheffield Dermatology Research, Division of Clinical Medicine, University of Sheffield Medical School, Sheffield, United Kingdom*
[‡] *Division of Allergy and Clinical Immunology, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California*
[§] *National Institute for Health and Care Research Sheffield Biomedical Research Centre, Sheffield, United Kingdom*
[‖] *Department of Paediatrics & Child Health, University of Ilorin, Ilorin, Nigeria*
[¶] *Sheffield Children's National Health Service Foundation Trust, Sheffield, United Kingdom*
[#] *Department of Infection, Immunity and Cardiovascular Disease, Sheffield Dermatology Research, University of Sheffield, Sheffield, United Kingdom*
[**] *Department of Pediatrics, National Jewish Health, Denver, Colorado*
[††] *Ividata Life Sciences, contractor for Sanofi, Chilly-Mazarin, France*
[‡‡] *Sanofi, Cambridge, Massachusetts*
[§§] *Regeneron Pharmaceuticals Inc., Tarrytown, New York*

ARTICLE INFO

Article history:
Received for publication October 18, 2025.
Received in revised form January 14, 2026.
Accepted for publication January 15, 2026.

ABSTRACT

Background: Skin barrier dysfunction and inflammation characterize both lesional and nonlesional skin in moderate-to-severe atopic dermatitis (AD) and are associated with relapses and atopic march progression.
Objective: To assess the effects of dupilumab treatment on skin barrier function and integrity using noninvasive methods in children aged 6 to 11 years with moderate-to-severe AD compared with matched healthy volunteers.
Methods: Patients received dupilumab for 16 weeks. Transepidermal water loss (TEWL) before (basal) and after skin tape stripping and epidermal thickness (T_E), measured by optical coherence tomography, were assessed to week 28.
Results: The PEdiatric skin barrier function and LIpidomics STudy in patients with Atopic Dermatitis (PELISTAD) enrolled 23 patients and 18 healthy volunteers. Mean ± SD basal TEWL was significantly higher in AD lesional/nonlesional skin at baseline (55.1 ± 5.5/28.0 ± 3.1 g × m^{-2} × h^{-1}) than in healthy skin (14.0 ± 1.6) and decreased to 30.3 ± 3.1/22.0 ± 2.6 at week 16 and to 29.7 ± 4.3/18.3 ± 2.1 at week 28; TEWL after 5 of 20 skin tape stripping improved similarly. Baseline mean ± SD T_E in lesional/nonlesional skin (251.1 ± 25.8/166.1 ± 15.2 μm) was significantly higher than in healthy skin (118.2 ± 5.1) and decreased to 196.8 ± 18.4/141.9 ± 11.9 at week 16 and to 160.4 ± 12.9/142.7 ± 15.6 at week 28. At weeks 16 and 28, there was no significant difference between TEWL and epidermal thickness in AD lesional and nonlesional skin vs healthy skin.
Conclusion: Using noninvasive techniques to monitor epithelial function, dupilumab treatment restored skin barrier function in children with AD. Improvements achieved at week 16 were sustained to week 28.
Trial Registration: ClinicalTrials.gov Identifier: PELISTAD (NCT04718870).

Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory systemic disease with varied phenotypes/endotypes, all of which have in common inherited and/or acquired defects of the skin barrier. These defects facilitate penetration of allergens and microbes with

Address correspondence to: Donald Y. M. Leung, MD, PhD, Department of Pediatrics, National Jewish Health, Room K801, 1400 Jackson Street, Denver, CO 80206. E-mail: LeungD@NJHealth.org.

https://doi.org/10.1016/j.anai.2026.01.008

activation of skin's innate immunity and a type 2–skewed immune response.[1-3] Overexpression of type 2 cytokines promotes sensitization to environmental allergens and amplifies barrier defects by multiple mechanisms, including physical damage through itch-scratch, increased turnover of keratinocytes, and dysregulation of structural stratum corneum (SC) proteins, lipid components, and microbiome, to ultimately reinforce the inflammatory response, leading to a self-sustained pathologic cycle.[1-3]

Repair of the skin barrier is thought to break the pathologic cycle by preventing further entry of inflammation-eliciting agents, thus sustainably preventing relapses.[3] In children with moderate-to-severe AD, transepidermal water loss (TEWL), reflecting barrier function,[4] was found increased even in nonlesional areas,[3,5,6] indicating persistent subclinical effects of inflammation despite clinical relief and highlighting the need for assessing therapeutic effects in nonlesional skin in addition to lesional AD skin. Apart from its role in facilitating AD flares, skin barrier dysfunction in children was associated with development of food allergies, allergic rhinosinusitis, and childhood asthma.[1,7,8] The serial acquisition of new allergen sensitizations with development of atopic comorbidities, known as "the atopic march," is driven by particular skin barrier endotypes that may lead to severe, chronic skin inflammation with systemic spillover of inflammatory cytokines,[3,7-10] suggesting that prevention must address skin barrier integrity and chronic inflammation. Furthermore, the circulating immune phenotype in AD changes with age and disease course,[11] implying that the timing of therapeutic intervention is relevant.[9] Childhood is believed to represent a window of opportunity for preventing further allergies due to increased plasticity of the immune system.[9,12] Previous studies have revealed that controlled AD in younger patients associates with higher rates of off-treatment remission and with lower risk of onset of new allergies or other AD comorbidities than in older patients.[13-16] These findings led to the current train of thought supporting the importance of early intervention to control AD for achieving sustained remission and/or prevention of other allergic diseases.[9,12]

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation. Several studies in adults with AD treated with dupilumab reported improved SC hydration and reduced TEWL.[17-21] Recently, normalization of the SC lipid composition after 16 weeks of dupilumab treatment was demonstrated using minimally invasive skin tape stripping (STS).[21]

Monitoring the effects of treatment on epidermal inflammation is currently complicated by the need to perform biopsies. Optical coherence tomography (OCT) is a novel, noninvasive approach to assess skin inflammation in situ and provides structural images comparable with histology sections, from which epidermal thickness (T_E) and other inflammatory markers can be extrapolated.[22]

In this study, we used TEWL and OCT to noninvasively evaluate changes in lesional and nonlesional skin barrier function and inflammatory status, respectively, in school-aged children with moderate or severe AD treated with dupilumab, compared with matched healthy volunteers, for 28 weeks, including 12 weeks post-treatment. In parallel, we assessed changes in clinician- and patient-reported outcomes.

Methods

Study Design

The PEdiatric skin barrier function and LIpidomics STudy in patients with Atopic Dermatitis (PELISTAD; NCT04718870) was an open-label, phase 4 study of dupilumab in young children with moderate-to-severe or severe AD, with a matched healthy volunteer cohort as reference. Participants were enrolled at 3 sites in the United States and United Kingdom from February 2021 to November 2022. PELISTAD comprised a 4-week screening period, a 16-week treatment period for patients with AD or observation for healthy volunteers, and a 12-week follow-up period.

PELISTAD was conducted following protocols and consensus of ethical principles derived from international guidelines, including the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and the Council for International Organizations of Medical Sciences International Ethical Guidelines, and all applicable laws, rules, and regulations. Participants' legally authorized representatives provided signed informed consent, and participants provided informed assent.

Participants

Eligible patients were male or female children aged 6 to 11 years with AD diagnosed for at least 1 year; with Investigator's Global Assessment (IGA; range 0-4) score more than or equal to 3 (United States) or IGA equals to 4 (United Kingdom) at screening (as per approved dupilumab label indication in each country); with active lesions on the upper, lower limb, or trunk; with Individual Sign Score (ISS; range 0-3) for severity of erythema or edema/papulation more than or equal to 2; and a nonlesional skin area approximately 4 cm away from the lesional area. Healthy volunteers, with no current dermatologic or systemic conditions that could interfere with assessments, were age matched (±2 years) and sex matched to a selected patient by study site.

Exclusion criteria comprised treatment with dupilumab within 6 months of screening, or with other systemics within 4 weeks from baseline; topical treatment for AD within 1 week of screening; skin conditions other than AD that could confound assessments; cracked, crusted, oozing, or bleeding AD lesions in the target area; ocular disorders that could affect participation in the study; severe concomitant illness; and hypersensitivity to dupilumab/excipients or adhesive tape components.

Treatment

Patients with AD received subcutaneous dupilumab (600 mg loading dose, followed by 300 mg every 4 weeks if baseline weight was 15 to <30 kg, or 400 mg on day 1, then 200 mg every 2 weeks if weight was 30 to <60 kg) for 16 weeks. Use of concomitant topical medications was prohibited until week 16. In case of intolerable AD facial or genital symptoms, rescue medication, including topical corticosteroids, could be provided at the discretion of the investigator and was recorded accordingly. Dupilumab could be used as a rescue medication during the 12-week follow-up in patients with IGA score 4 or experiencing intolerable symptoms. Healthy volunteers did not receive any study treatment. Topical corticosteroids use in the predefined assessment areas was completely prohibited throughout the study.

Patients were required not to apply emollients on or within 5 cm from predefined assessment areas from day −7 to the study period, but using standardized emollients on other body areas was recommended.

Procedures

TEWL before STS (basal TEWL) and after STS ($g \times m^{-2} \times h^{-1}$) was measured using the AquaFlux AF200 (Biox, London, United Kingdom) in predefined areas (lesional/nonlesional) in patients with AD and in anatomically matched areas in healthy volunteers. Given the high variability of TEWL measurements in healthy skin, there is currently no defined range of normal values, nor a defined threshold for clinically meaningful improvement.[4] To minimize variability due to external factors, measurements were generally conducted in the same room throughout the study, with temperature set between 19°C and 23°C and humidity set below 60%, after acclimatization of participants to the room for a minimum of 20 minutes.

STS was performed up to 20 consecutive tape strips, using commercially available adhesive discs, with TEWL measurements being conducted before STS and after every 5 STS. TEWL area under the curve (AUC) was calculated as an integral of TEWL values before and after 5, 10, 15, and 20 STS (TEWL5/10/15/20) longitudinally assessed over time.[3,4] In each lesional and nonlesional predefined area, 3 closely adjacent but not overlapping spots were marked for alternate visit use (1 spot per visit) to allow time for skin recovery.

OCT assessments were performed using a VivoSight Dx OCT machine (Michelson Diagnostics Ltd, Orpington, Kent, United Kingdom) before TEWL/STS assessments. Two volumetric images of 4 × 4 × 2 mm (x-y-z), with a lateral scan spacing of 10 μm, were taken for each target area (separate, adjacent sites for each scan) using bespoke software developed by the University of Sheffield. Mean T_E across the full scan volume was measured as previously reported.[23]

Additional methodology information can be found in eMethods.

Outcome Measures

End points in lesional, nonlesional, and healthy skin groups included basal TEWL, TEWL5, TEWL AUC up to 20 STS (TEWL AUC20), and T_E over time from baseline to week 28. Clinical efficacy end points in patients with AD included changes from baseline to week 28 in Eczema Area and Severity Index (EASI), ISS, Worst Itch Numeric Rating Scale (NRS), Worst Pain NRS, Patient-Oriented Eczema Measure (POEM), and Children's Dermatology Life Quality Index (CDLQI). Given the age group, Worst Itch NRS and Worst Pain NRS were collected twice per 24 hours, corresponding to "today" and "last night."

Statistical Analyses

No formal sample size calculation was performed. TEWL mean changes vs baseline were analyzed using a paired sample *t* test if data were normally distributed or Wilcoxon signed rank test if data were not normally distributed. For comparison with healthy skin, the adjusted least squares (LS) mean was derived from a mixed-effect model with repeated measures, with absolute values and mean change from baseline values separately as the response variables, and baseline values of TEWL, age, sex, visit, and visit-by-skin type interaction as covariates for lesional or nonlesional skin vs healthy skin. All reported *P* values are nominal, and no adjustment for multiple testing was performed.

Results

Baseline Demographic and Disease Characteristics

PELISTAD enrolled 23 children with AD and 18 healthy volunteers, with mean ages (±SD) of 7.8 ± 1.6 and 8.2 ± 1.8, respectively. Furthermore, 15 patients (65.2%) had been diagnosed with AD before age 2 years and 56.5% had food allergy, 39.1% had asthma, and 21.7% had allergic rhinitis. At baseline, mean (±SD) EASI score was 34.8 ± 11.9, ISS score was 8.6 ± 1.7, Worst Itch NRS today score was 7.6 ± 2.1, POEM mean (±SD) score was 22.3 ± 5.7, and CDLQI was 18.0 ± 7.7 (Table 1).

Table 1
Baseline Demographic and Disease Characteristics

	Patients with AD (n = 23)	Healthy volunteers (n = 18)
Age (y), mean (SD)	7.8 (1.6)	8.2 (1.8)
Sex, n (%)		
Male	15 (65.2)	10 (55.6)
Female	8 (34.8)	8 (44.4)
Race, n (%)		
White	16 (69.6)	9 (50.0)
Black/African American	2 (8.7)	2 (11.1)
Asian	3 (13.0)	6 (33.3)
Multiple—Black or African American/White	1 (4.3)	0 (0.0)
Not reported	1 (4.3)	1 (5.6)
Baseline weight (kg), n (%)		
15 to <30	12 (52.2)	8 (44.4)
30 to <60	11 (47.8)	9 (50.0)
≥60	0 (0.0)	1 (5.6)
Years since AD diagnosis, mean (SD)	7.1 (2.0)	N/A
Onset before 2 y of age, n (%)	15 (65.2)	N/A
Onset ≥ 2 y of age, n (%)	8 (34.8)	N/A
Patients with history of atopic (co)morbidities, n (%)		
Food allergy	13 (56.5)	0
Asthma	9 (39.1)	0
Allergic rhinitis	5 (21.7)	0
Allergic conjunctivitis	0	0
Eosinophilic esophagitis	0	0
EASI, mean (SD)	34.8 (11.9)	N/A
ISS, mean (SD)	8.6 (1.7)	N/A
Worst itch NRS today, mean (SD)	7.6 (2.1)	N/A
Worst itch NRS last night, mean (SD)	7.1 (2.5)	N/A
Skin pain NRS, worst pain today, mean (SD)	6.8 (2.5)	N/A
Skin pain NRS, worst pain last night, mean (SD)	6.5 (3.1)	N/A
POEM, mean (SD)	22.3 (5.7)	N/A
CDLQI, mean (SD)	18.0 (7.7)	N/A
Sleep disturbance, mean (SD)	6.9 (2.5)	N/A

Abbreviations: AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index (range 0-30); EASI, Eczema Area and Severity Index (range 0-72); ISS, Individual Signs Score (range 0-12); N/A, not applicable; NRS, Numeric Rating Scale (range 0-10); POEM, Patient-Oriented Eczema Measure (range 0-28); SD, standard deviation.

Efficacy on Skin Barrier Repair

Mean basal TEWL (±SE) in AD lesional/nonlesional skin decreased from 55.1 ± 5.5/28.0 ± 3.1 g × m^{-2} × h^{-1} at baseline compared with 14.0 ± 1.6 in healthy skin, to 30.3 ± 3.1/22.0 ± 2.6 at week 16 (*P* vs baseline <.0001/.0788) compared with 21.4 ± 6.8 in healthy skin, and 29.7 ± 4.3/18.3 ± 2.1 at week 28 (*P* vs baseline .0017/.0013) compared with 15.0 ± 1.5 in healthy skin (Fig. 1a; eTable 1). Mean TEWL5 decreased in lesional/nonlesional skin from 67.1 ± 6.0/39.7 ± 4.2 at baseline compared with 18.0 ± 2.2 in healthy skin, to 37.3 ± 3.7/30.7 ± 2.8 at week 16 (*P* vs baseline <.0001/.0680) compared with 19.9 ± 2.1 in healthy skin, and 34.0 ± 4.3/24.9 ± 3.3 at week 28 (*P* vs baseline .0008/.0002) compared with 18.5 ± 2.0 in healthy skin (Fig. 1b; eTable 1). Mean TEWL AUC20 decreased in lesional/nonlesional skin from 1440.0 ± 119.0/1103.3 ± 87.3 at baseline compared with 431.3 ± 58.7 in healthy skin, to 903.5 ± 72.3/888.9 ± 71.6 at week 16 (*P* vs baseline .0006/.0334) compared with 518.5 ± 72.6 in healthy skin, and 797.5 ± 71.9/717.2 ± 60.8 at week 28 (*P* vs baseline .0002/<.0001) compared with 416.9 ± 42.4 in healthy skin (Fig 1c; eTable 1).

At baseline, adjusted LS mean basal TEWL, TEWL5, and TEWL AUC20 in each lesional/nonlesional skin area were significantly higher compared with healthy skin; with dupilumab treatment, these decreased to values no longer significantly different to healthy skin starting from week 4 in both lesional and nonlesional skin and maintained to week 28 (Fig 1).

Efficacy on Epidermal Thickness and Erythema Reduction

OCT-measured T_E mean (±SE) in lesional/nonlesional skin decreased from 251.1 ± 25.8/166.1 ± 15.2 μm at baseline compared with 118.2 ± 5.1 in healthy skin, to 196.8 ± 18.4/141.9 ± 11.9 at week 16 (*P* vs baseline .0077/.0102) compared with 121.8 ± 5.9 in healthy skin, and was 160.4 ± 12.9/142.7 ± 15.6 at week 28 (*P* vs baseline .0008/.0096) compared with 102.5 ± 3.8 in healthy skin. The adjusted LS mean T_E in lesional/nonlesional skin was no longer significantly different than that in healthy skin from week 1 to week 28 (Fig 2a and b; eFig 1).

Standardized photographs revealed improvements in skin lesions and reduced erythema at week 16 compared with baseline (eFig 2, representative patient lesional skin photograph before and after treatment).

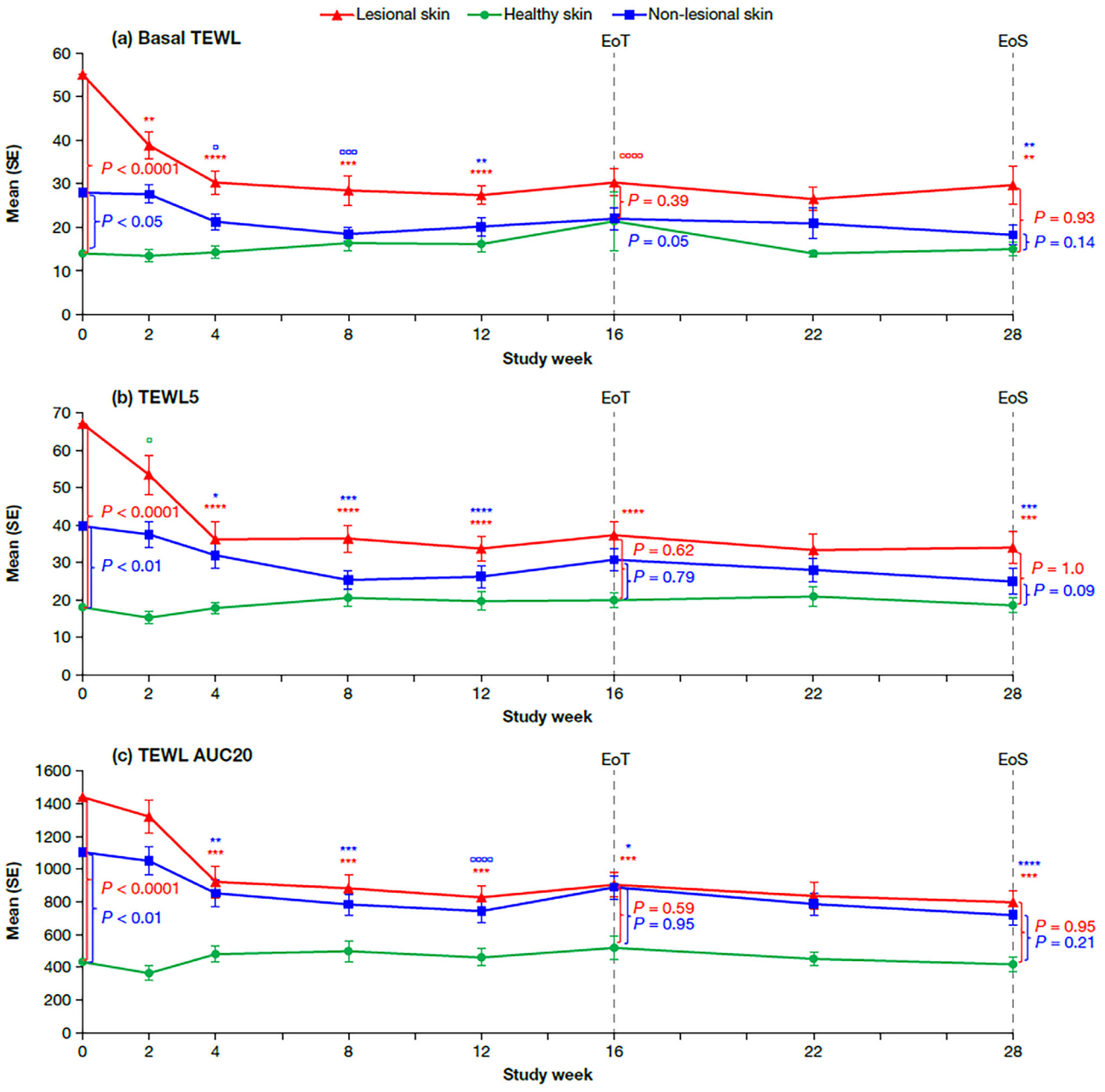


Figure 1. TEWL to week 28. (a) Basal TEWL. (b) TEWL5. (c) TEWL AUC20. */ˆ, *P* less than .05; **/¨, *P* less than .01; ***/‴, *P* less than .001; ****/⁗, *P* less than .0001; *, paired sample *t* test; ˆ,Wilcoxon signed rank test; AUC, area under the curve; EoS/T, end of study/treatment; SE, standard error; TEWL/5, transepidermal water loss/after 5 skin tape strips.

Clinician- and Patient-Reported Outcomes

Mean (±SE) EASI score decreased from 34.8 ± 2.6 at baseline to 11.3 ± 2.5 at week 16, ISS from 8.3 ± 0.4 to 4.5 ± 0.6, Worst Itch NRS today from 7.6 ± 0.5 to 3.0 ± 0.6, Worst Skin Pain NRS today from 6.8 ± 0.6 to 2.3 ± 0.6, POEM from 22.3 ± 1.3 to 9.8 ± 1.6, and CDLQI from 18.0 ± 1.6 to 6.8 ± 1.6; improvements were sustained to week 28 (Fig 3a-f;eFig 3).

Safety

In the AD cohort, 21 patients (91.3%) experienced treatment-emergent adverse events. None were serious, severe, or led to treatment discontinuation (eTable 2). Treatment-emergent adverse events present in at least 5% of patients up to week 28 were dermatitis atopic (78.3%), medical device site hemorrhage (26.1%), upper respiratory tract infection (17.4%), urticaria (13.0%), gastroenteritis (13.0%), headache (13.0%), eye pain (8.7%), and eye pruritus (8.7%).

Discussion

In this study, consistent with previous reports,[5,6,24] we found that TEWL was significantly higher at baseline in lesional and nonlesional skin of patients with AD compared with healthy volunteers. By week 2, treatment with dupilumab resulted in rapid, statistically significant reduction vs baseline in TEWL across AD skin. Adjusted mean TEWL values in lesional and nonlesional skin were no longer significantly different from those in healthy skin starting from week 4. Clinician- and patient-reported outcomes revealed a similar improvement pattern. Normalization of post-STS TEWL across AD skin suggests that the integrity of the skin barrier was recovered with dupilumab treatment, enabling it to withstand the physical disruption by tape stripping. These findings confirm previous reports revealing improved epidermal proteomic and lipidomic profile in patients with AD treated with dupilumab.[21,25,26]

The OCT images revealed marked epidermal hyperplasia in clinically unaffected skin, highlighting the advantages of using this technique

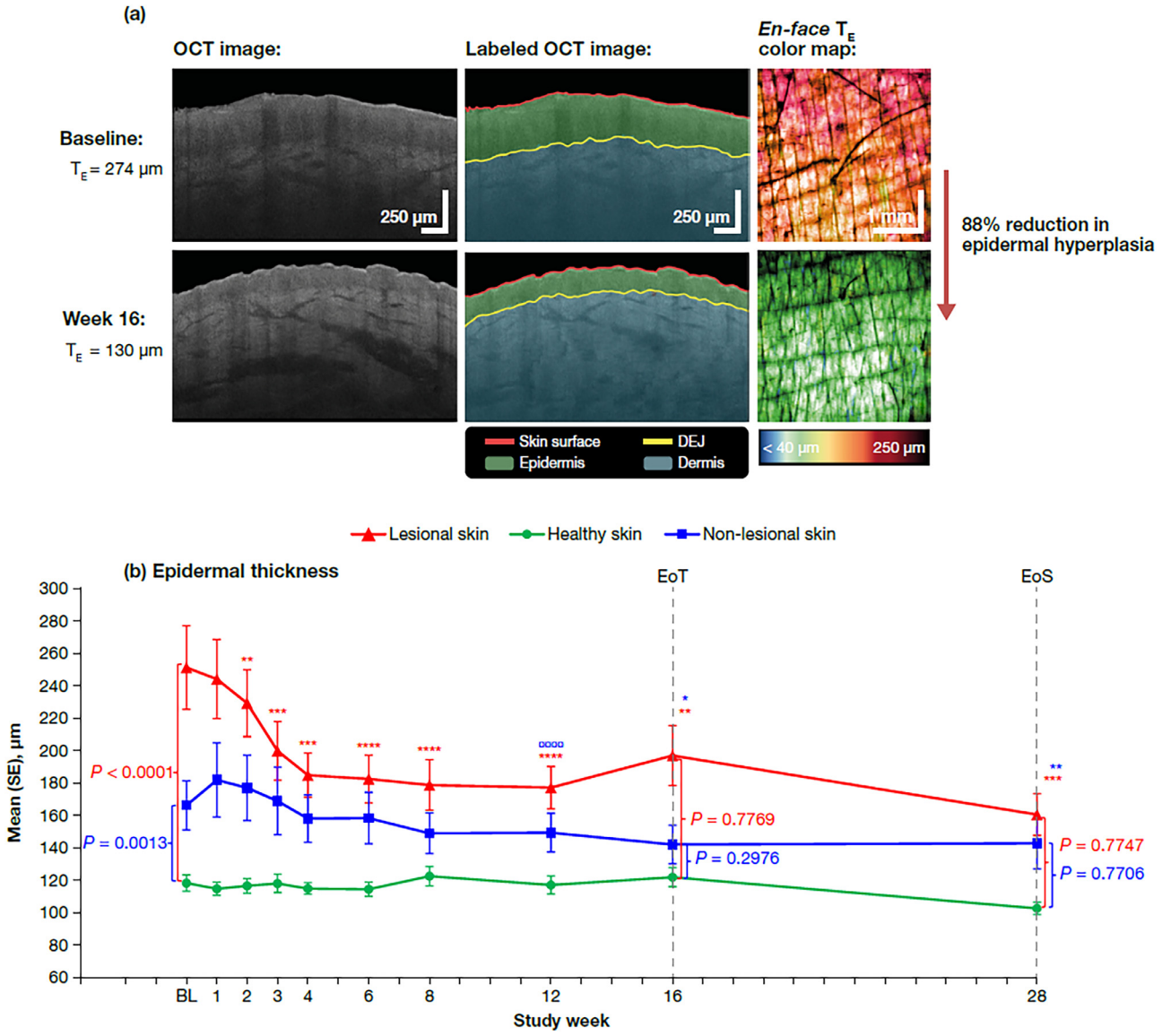


Figure 2. T_E by OCT. (a) Representative lesional skin OCT. (b) Mean change to week 28. */¯, *P* less than .05; **/¯, *P* less than .01; ***/¯, *P* less than .001; ****/¯, *P* less than .0001; *, paired sample *t* test; ¯, Wilcoxon signed rank; EoS/T, end of study/treatment; OCT, optical coherence tomography; SE, standard error; T_E, epidermal thickness.

over and above clinical observations alone. Previously, dupilumab treatment was found to significantly reduce T_E in skin biopsies compared with placebo[26] and to downregulate the expression of the *K16* and *Mki67* genes, suggesting normalization of the physiological keratinocyte turnover and terminal differentiation, essential for a normal SC architecture and for commensal colonization.[26] Novel findings in this study are that a reduction in T_E with dupilumab treatment takes place in the nonlesional skin in addition to lesional AD skin and that improvements are maintained to week 28.

This study adds support for the use of OCT for noninvasive monitoring of treatment effects. Other inflammatory markers accessible through OCT are superficial plexus depth and blood vessel diameter and density (data not shown). An OCT variant, polarization-sensitive OCT, was also recently used to measure dermal collagen variation with treatment,[27] indicating further applicability for upcoming studies.

In addition to local consequences, skin barrier defects in patients with AD increase susceptibility to aeroallergen triggers. In younger children and infants, inherent skin barrier defects lead to an increase in C-C motif chemokine ligand 17, thymic stromal lymphopoietin, and type 2 inflammation and subsequent allergic sensitization.[3,28-30] Similarly, mechanical injury of the skin, including abnormalities of the skin lipidome, were found to be associated with food sensitization and the development of food allergies, highlighting the importance of skin barrier permeability dysregulation in the development of atopic diseases.[31]

Subclinical skin inflammation that persists between acute inflammatory episodes, evidenced by increased TEWL and T_E in nonlesional AD skin, is considered a link between skin and systemic inflammation and a checkpoint for progression to the atopic march.[9,12] Further studies are needed to explore the complete and sustained reversal of chronic inflammation. Our results reveal that improvements in TEWL and T_E were still progressing at week 16, suggesting that a longer treatment period may provide further benefits. A series of recent clinical findings support the potential role of dupilumab treatment for AD in sustained disease remission[32] and in prevention of further allergic diseases[14,16,33] and indicate that early treatment is beneficial. Two studies comparing the incidence of atopic diseases in pediatric patients treated with dupilumab to equal numbers of children receiving other systemic therapies found that dupilumab-treated children had fewer atopic diseases and that the benefit increased with an earlier treatment age.[14,16] In a post hoc analysis of 12 clinical trials of dupilumab in adolescents and adults with AD, dupilumab-treated patients were

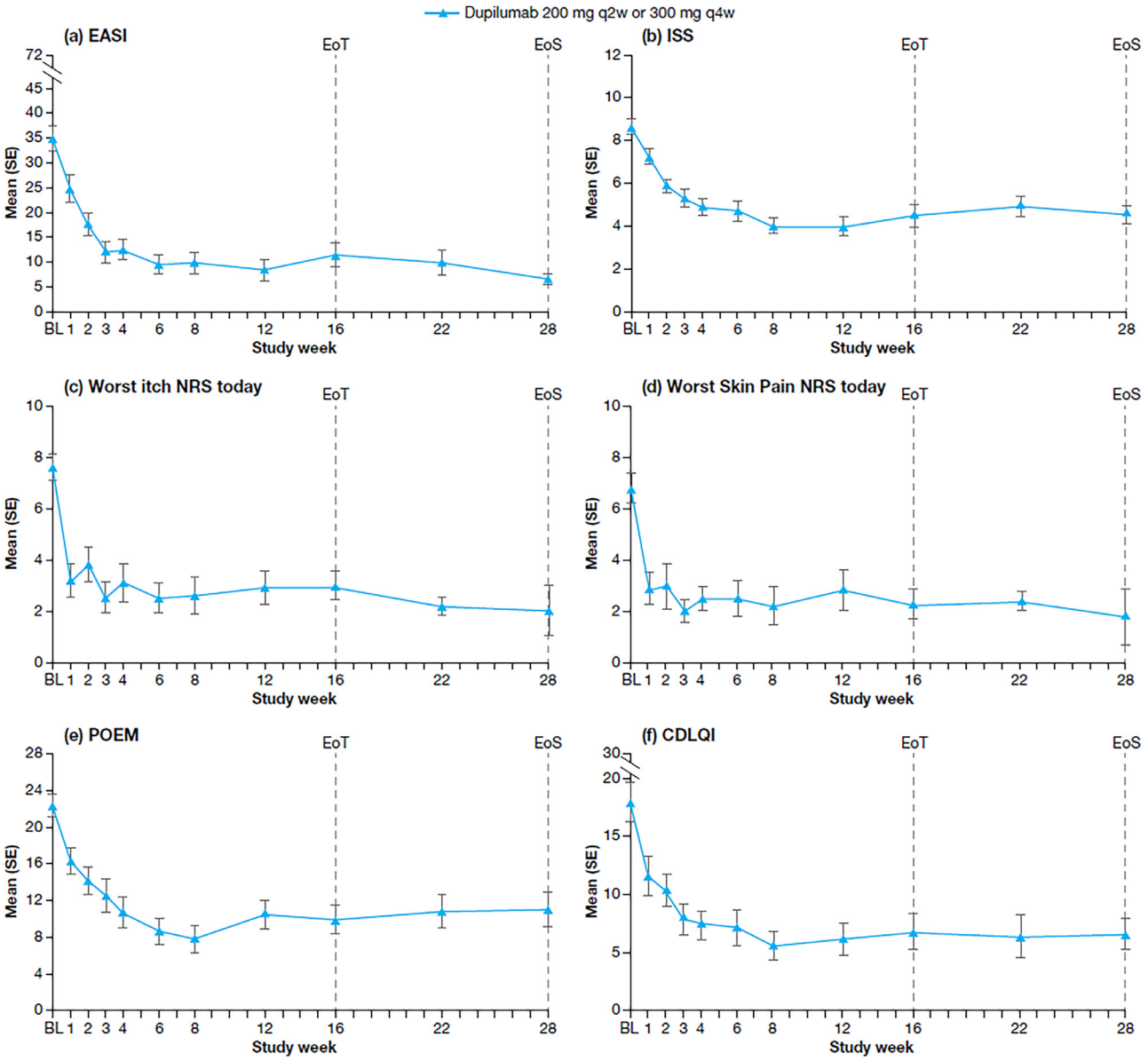


Figure 3. Clinician- and patient-reported outcomes to week 28. (a) EASI. (b) ISS. (c) Worst itch NRS today. (d) Worst Skin Pain NRS today. (e) POEM. (f) CDLQI. BL, baseline; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EoS/T, end of study/treatment; ISS, Individual Sign Score; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; q2/4w, every 2/4 weeks; SE, standard error.

found less likely to develop new allergic diseases or to undergo worsening of already existent ones compared with placebo recipients.[33] Although a formal definition of disease modification in AD is pending, our results connect dupilumab's anti–IL-4/IL-13 action to skin barrier repair and reduction in skin inflammation, including in nonlesional skin, pointing toward a possible modifying effect on the natural course of AD, especially pertinent for this immune-malleable age group.[9,12]

Strengths of this study include comparison with healthy volunteers, multiple longitudinal TEWL assessments, parallel OCT and photo skin imaging to complement TEWL measurements, and assessments up to week 28. Limitations were the small study size and low representation of racial backgrounds other than White, the open-label design, permitted use of dupilumab as a rescue medication during follow-up, and lack of a non-treated AD cohort.

In conclusion, dupilumab treatment restored skin barrier function and reduced T_E in lesional and nonlesional skin, in parallel with improvements of disease signs and symptoms, in children aged 6 to 11 years with moderate-to-severe or severe AD. These improvements were maintained to week 28..

Acknowledgments

The authors thank the patients and their families for their participation in these studies, and thank Adriana Mello, PharmD, PGCB, of Sanofi, and Purvi Kobawala Smith, MS, MPH, of Regeneron Pharmaceuticals Inc., for their coordination and critical review of the manuscript. Medical writing support, under the direction of the authors, was provided by Iulia Oprea, MD, PhD, of the Publications and Medical Affairs Division of Omnicom Health Medical Communications, funded by Sanofi and Regeneron Pharmaceuticals Inc. in accordance with the Good Publication Practice (GPP2022) guidelines. .

Data Availability

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 reidentification. Submit requests to https://vivli.org/.

Disclosures

Prof. Cork reported receiving research grants (to institution) from Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Perrigo (ACO Nordic), Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi (&Kymab); personal consulting fees from Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Perrigo (ACO Nordic), Pfizer, Procter & Gamble, Regeneron Pharmaceuticals Inc., and Sanofi; personal payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Johnson & Johnson, L'Oréal, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi; support for personal travel and accommodation expenses and fees for participation on a data and safety monitoring board or advisory board from L'Oréal, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi; and a voluntary medical advisor for National Eczema Society, United Kingdom. Dr Ong has consulted for Amgen, Astria, and Dermavant; and received research grants from Regeneron Pharmaceuticals Inc. and Sanofi. Dr Danby is an investigator and/or consultant for Almirall, Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Perrigo, Pfizer, Rohto Pharmaceutical, and Sanofi. Dr Matcher is an investigator and/or consultant for LEO Pharma, Pfizer, and Sanofi; and has previously received funding from Michelson Diagnostics Ltd. Mr Bologna is an employee of Ividata Life Sciences, contracted by Sanofi. Ms Praestgaard and Dr Zhang are Sanofi employees and may hold stock and/or stock options in the company. Dr Zahn is an employee and shareholder of Regeneron Pharmaceuticals Inc. Prof. Leung is a consultant with Apollo Therapeutics, Astria Therapeutics, Jasper Therapeutics, LEO Pharma, Regeneron Pharmaceuticals Inc., Sanofi, and Takeda; and has received research grants from Sanofi. The remaining authors have no conflicts of interest to report.

Funding

This work was funded by Sanofi and Regeneron Pharmaceuticals Inc.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.anai.2026.01.008.

References

1. Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases. *J Allergy Clin Immunol*. 2020;145(6):1485–1497.
2. Beck LA, Cork MJ, Amagai M, De Benedetto A, Kabashima K, Hamilton JD, et al. Type 2 inflammation contributes to skin barrier dysfunction in atopic dermatitis. *JID Innov*. 2022;2(5):100131.
3. Van den Bogaard EH, Elias PM, Goleva E, Berdyshev E, Smits JPH, Danby SG, et al. Targeting skin barrier function in atopic dermatitis. *J Allergy Clin Immunol Pract*. 2023;11(5):1335–1346.
4. Alexander H, Brown S, Danby S, Flohr C. Research techniques made simple: transepidermal water loss measurement as a research tool. *J Invest Dermatol*. 2018;138(11):2295–2300.e1.
5. Kim J, Kim BE, Goleva E, Berdyshev E, Bae J, Kim S, et al. Alterations of epidermal lipid profiles and skin microbiome in in children with atopic dermatitis. *Allergy Asthma Immunol Res*. 2023;15(2):186–200.
6. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol*. 1995;75(6):429–433.
7. Berdyshev E, Goleva E, Bronova I, Bronoff AS, Hoffman BC, Ramirez-Gama MA, et al. Unique skin abnormality in patients with peanut allergy but no atopic dermatitis. *J Allergy Clin Immunol*. 2021;147(1):361–367.e1.
8. Goleva E, Calatroni A, LeBeau P, Berdyshev E, Taylor P, Kreimer S, et al. Skin tape proteomics identifies pathways associated with transepidermal water loss and allergen polysensitization in atopic dermatitis. *J Allergy Clin Immunol*. 2020;146(6):1367–1378.
9. Bieber T. The paradigm shift in drug development for atopic dermatitis: addressing the variables of the equation leading to disease modification. *Ann Allergy Asthma Immunol*. 2025;134(2):144–150.
10. Tang X, Li M. The role of the skin in the atopic march. *Int Immunol*. 2024;36(11):567–577.
11. Czarnowicki T, He H, Canter T, Han J, Lefferdink R, Erickson T, et al. Evolution of pathologic T-cell subsets in patients with atopic dermatitis from infancy to adulthood. *J Allergy Clin Immunol*. 2020;145(1):215–228.
12. Jacobson ME, Seshadri RS, Morimoto R, Grinich E, Haag C, Nguyen K, et al. Early intervention and disease modification in atopic dermatitis – the current state of the field and barriers to progress. *J Eur Acad Dermatol Venereol*. 2024;38(4):665–672.
13. Kamata M, Sun DI, Paller AS. Deciding which patients with atopic dermatitis to prioritize for biologics and Janus kinase inhibitors. *J Allergy Clin Immunol Pract*. 2025;13(8):1901–1910.e1.
14. Tsai SYC, Gaffin JM, Hawryluk EB, Ruran HB, Bartnikas LM, Oyoshi MK, et al. Evaluation of dupilumab on the disease burden in children and adolescents with atopic dermatitis: a population-based cohort study. *Allergy*. 2024;79(10):2748–2758.
15. Choi UE, Deng J, Parthasarathi V, Liao V, D'Amiano A, Taylor M, et al. Risk factors and temporal associations of progression of the atopic march in children with early-onset atopic dermatitis. *J Am Acad Dermatol*. 2025;92(4):732–740.
16. Lin TL, Fan YH, Fan KS, Juan CK, Wu CY. Reduced atopic march risk in pediatric atopic dermatitis patients prescribed dupilumab versus conventional immunomodulatory therapy: a population-based cohort study. *J Am Acad Dermatol*. 2024;91(3):466–473.
17. Montero-Vilchez T, Rodriguez-Pozo JA, Diaz-Calvillo P, Salazar-Nievas M, Tercedor-Sanchez J, Molina-Leyva A, et al. Dupilumab improves skin barrier function in adults with atopic dermatitis: a prospective observational study. *J Clin Med*. 2022;11(12):3341.
18. Ferucci S, Romagnuolo M, Maronese CA, Germiniasi F, Tavecchio S, Angileri L, et al. Skin barrier status during dupilumab treatment in patients with severe atopic dermatitis. *Ther Adv Chronic Dis*. 2021;12:20406223211058332.
19. Cristaudo A, Pigliacelli F, Sperati F, Orsini D, Cameli N, Morrone A, et al. Instrumental evaluation of skin barrier function and clinical outcomes during dupilumab treatment for atopic dermatitis: an observational study. *Skin Res Technol*. 2021;27(5):810–813.
20. Lee SJ, Kim SE, Shin KO, Park K, Lee SE. Dupilumab therapy improves stratum corneum hydration and skin dysbiosis in patients with atopic dermatitis. *Allergy Asthma Immunol Res*. 2021;13(5):762–775.
21. Berdyshev E, Goleva E, Bissonnette R, Bronova I, Bronoff AS, Richers BN, et al. Dupilumab significantly improves skin barrier function in patients with moderate-to-severe atopic dermatitis. *Allergy*. 2022;77(11):3388–3397.
22. Revin DG, Byers RA, Duan MQ, Li W, Matcher SJ. Visible-light optical coherence tomography platform for the characterization of the skin barrier. *Biomed Opt Express*. 2023;14(8):3914–3923.
23. Byers RA, Maiti R, Danby SG, Pang EJ, Mitchell B, Carré MJ, et al. Sub-clinical assessment of atopic dermatitis severity using angiographic optical coherence tomography. *Biomed Opt Express*. 2018;9(4):2001–2017.
24. Montero-Vilchez T, Cuenca-Barrales C, Rodriguez-Pozo JA, Diaz-Calvillo P, Tercedor-Sanchez J, Martinez-Lopez A, et al. Epidermal barrier function and skin homeostasis in atopic dermatitis: the impact of age. *Life (Basel)*. 2022;12(1):132.
25. Mikhaylov D, Del Duca E, Meyer Olesen C, He H, Wu J, Ungar B, et al. Transcriptomic profiling of tape-strips from moderate to severe atopic dermatitis patients treated with dupilumab. *Dermatitis*. 2021;32(1S):S71–S80.
26. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143(1):155–172.
27. Duan MQ, Byers RA, Danby SG, Sahib S, Cha A, Zang C, et al. Potential application of PS-OCT in the safety assessment of non-steroidal topical creams for atopic dermatitis treatment. *Biomed Opt Express*. 2023;14(8):4126–4136.
28. Rinnov MR, Halling AS, Gerner T, Ravn NH, Knudgaard MH, Trautner S, et al. Skin biomarkers predict development of atopic dermatitis in infancy. *Allergy*. 2023;78(3):791–802.
29. Wärnberg Gerdin S, Lie A, Asarnoj A, Borres MP, Lødrup Carlsen KC, Färdig M, et al. Impaired skin barrier and allergic sensitization in early infancy. *Allergy*. 2022;77(5):1464–1476.
30. Berdyshev E, Kim J, Kim BE, Goleva E, Lyubchenko T, Bronova I, et al. Stratum corneum lipid and cytokine biomarkers at age 2 months predict the future onset of atopic dermatitis. *J Allergy Clin Immunol*. 2023;151(5):1307–1316.
31. Hui-Beckman JW, Goleva E, Berdyshev E, Leung DYM. Endotypes of atopic dermatitis and food allergy. *J Allergy Clin Immunol*. 2023;151(1):26–28.
32. Siegfried EC, Bieber T, Paller A, Simpson EL, Cork MJ, Weidinger S, et al. *Clinical Remission and Therapy-Free Remission in Pediatric Patients With Moderate-to-Severe Atopic Dermatitis Treated With Dupilumab: Open-Label Extension Study Preliminary Data*. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://onlinelibrary.wiley.com/doi/am-pdf/10.1111/pde.15584, Accessed on February 6, 2026.
33. Geba GP, Li D, Xu M, Mohammadi K, Attre R, Ardeleanu M, et al. Attenuating the atopic march: meta-analysis of the dupilumab atopic dermatitis database for incident allergic events. *J Allergy Clin Immunol*. 2023;151(3):756–766.

Supplementary Data

eMethods

Stereo images captured using the 3-dimensional LifeVizMicro camera system (QantifiCare S.A., Biot, France) were used to calculate the TIssue Viability Imaging (TiVi) index, computed as a ratio between red and green channel values for every pixel.[1,2] Higher TiVi corresponds to higher red channel values, indicating a higher concentration of red blood cells (vasodilatation). The overall TiVi index of the target area was calculated as the mean value of individual pixel TiVis.

eReferences

1. McNamara PM, O'Doherty J, O'Connell M-L, Fitzgerald BW, Anderson CD, Nilsson GE, et al. Tissue viability (TiVi) imaging: utility in assessment of rapid changes in the cutaneous microvasculature. Progress in Biomedical Optics and Imaging – Proceedings of SPIE. Volume 7563. Dynamics and Fluctuations in Biomedical Photonics VII; 7563OW (2010). https://doi.org/10.1117/12.852383
2. Zhai H, Chan HP, Farahmand S, Nilsson GE, Maibach HI. Tissue viability imaging: mapping skin erythema. *Skin Res Technol*. 2009;15(1):14–19.

eTable 1
TEWL Measurement Results

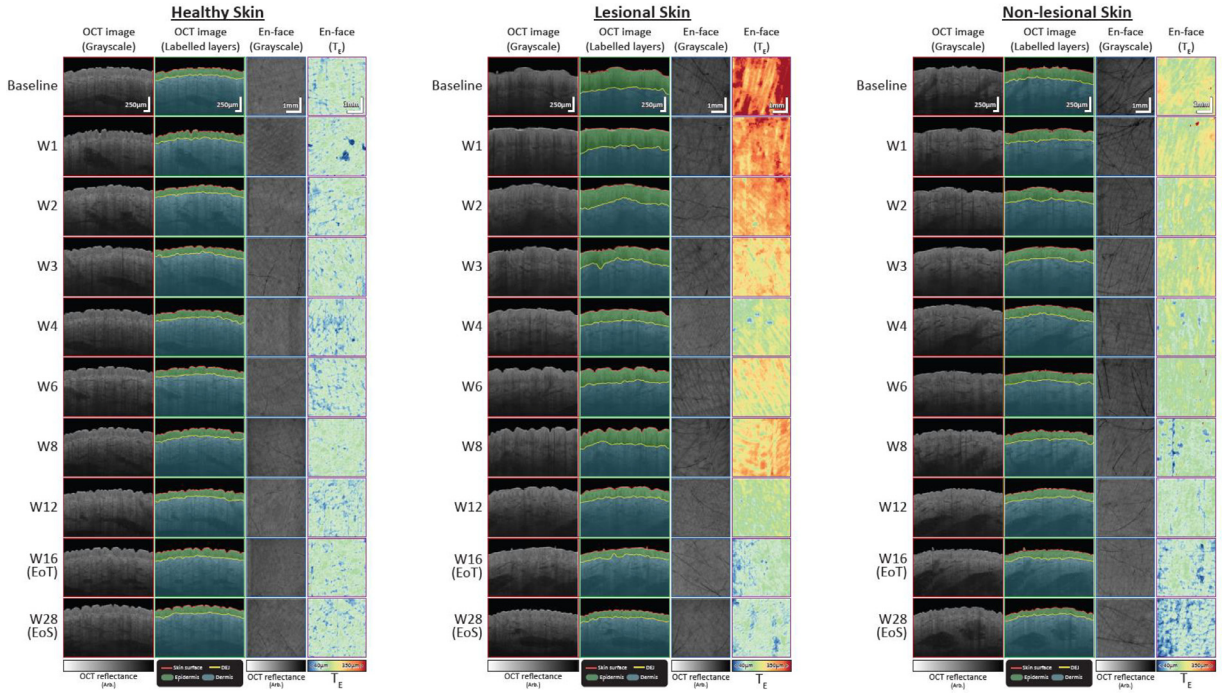
TEWL over time	AD lesional skin			AD nonlesional skin			Healthy skin
	TEWL mean (SE)	*P* vs baseline	*P* vs healthy	TEWL mean (SE)	*P* vs baseline	*P* vs healthy	TEWL mean (SE)
Basal TEWL							
Baseline	55.1 (5.5)	N/A	<.0001	28.0 (3.1)	N/A	.0334	14.0 (1.6)
Week 2	38.8 (3.1)	.0048	.0262	27.6 (2.1)	.8661	.0429	13.5 (1.4)
Week 4	30.3 (2.7)	<.0001	.7361	21.3 (1.9)	.0249	.7228	14.3 (1.4)
Week 8	28.5 (3.4)	.0001	.7487	18.5 (1.6)	.0002	.0940	16.4 (1.7)
Week 12	27.4 (2.1)	<.0001	.5896	20.2 (2.1)	.0029	.2164	16.2 (1.9)
Week 16	30.3 (3.1)	<.0001	.3921	22.0 (2.6)	.0788	.0512	21.4 (6.8)
Week 22	26.5 (2.6)	N/A	N/A	20.9 (3.4)	N/A	N/A	14.0 (0.8)
Week 28	29.7 (4.3)	.0017	.9320	18.3 (2.1)	.0013	.1411	15.0 (1.5)
TEWL5							
Baseline	67.1 (6.0)	N/A	<.0001	39.7 (4.2)	N/A	.0040	18.0 (2.2)
Week 2	53.5 (5.3)	.0515	.0005	37.5 (3.4)	.5439	.0072	15.2 (1.7)
Week 4	36.2 (4.7)	<.0001	.7353	31.9 (3.4)	.0386	.5701	17.8 (1.5)
Week 8	36.4 (3.6)	<.0001	.9457	25.3 (2.3)	.0002	.0720	20.5 (2.3)
Week 12	33.7 (3.2)	<.0001	.8173	26.2 (2.9)	<.0001	.1338	19.6 (2.5)
Week 16	37.3 (3.7)	<.0001	.6248	30.7 (2.9)	.0680	.7899	19.9 (2.1)
Week 22	33.3 (4.4)	N/A	N/A	28.0 (3.2)	N/A	N/A	20.9 (2.6)
Week 28	34.0 (4.3)	.0008	.9986	24.9 (3.3)	.0002	.0903	18.5 (2.0)
TEWL AUC20							
Baseline	1440.0 (119.0)	N/A	<.0001	1103.3 (87.3)	N/A	<.01	431.3 (58.7)
Week 2	1320.8 (98.2)	.1764	<.0001	1049.8 (84.4)	.4560	.0022	363.0 (43.1)
Week 4	921.6 (96.5)	.0003	.4766	852.9 (80.1)	.0092	.7187	479.2 (48.0)
Week 8	882.5 (80.5)	.0002	.6965	783.3 (63.7)	.0001	.2739	497.8 (62.1)
Week 12	827.5 (71.2)	.0003	.8411	742.6 (69.7)	<.0001	.1473	459.2 (53.0)
Week 16	903.5 (72.3)	.0006	.5929	888.9 (71.6)	.0334	.9521	518.5 (72.6)
Week 22	835.2 (84.3)	N/A	N/A	786.0 (66.4)	N/A	N/A	450.5 (40.9)
Week 28	797.5 (71.9)	.0002	.95	717.2 (60.8)	<.0001	.2090	416.9 (42.4)3

Abbreviations: AD, atopic dermatitis; AUC, area under the curve; AUC20, area under the curve before and up to 20 skin tape strips; LS, least squares; MMRM, mixed-effect model with repeated measures; N/A, not available; SE, standard error; TEWL, transepidermal water loss; TEWL5, transepidermal water loss after 5 skin tape strips.
NOTE. *P* values vs baseline were derived using a paired sample *t* test if data followed a normal distribution and a Wilcoxon signed rank test if data were not normally distributed. For comparison with healthy skin, an adjusted LS mean (SE) was derived from an MMRM with absolute values and mean change from baseline values separately as the response variables, and baseline values of TEWL, age, sex, visit, visit-by-skin type interaction as covariates, for lesional or nonlesional vs healthy skin. The AUC was calculated using a trapezoidal method with up to 20 skin tape strips.

eTable 2
Safety to week 28

n (%)	Dupilumab (n = 23)
Patients with any TEAE	21 (91.3)
Patients with any severe TEAE	0
Patients with any treatment-emergent SAE	0
Patients with any TEAE leading to permanent study intervention discontinuation	0
Patients with any treatment-emergent AESI	0
TEAEs occurring in ≥5% of patients, patients with at least 1 event, n (%) (MedDRA PT)	
Dermatitis atopic	18 (78.3)
Eye pain	2 (8.7)
Eye pruritus	2 (8.7)
Gastroenteritis	3 (13.0)
Headache	3 (13.0)
Medical device site hemorrhage	6 (26.1)
Upper respiratory tract infection	4 (17.4)
Urticaria	3 (13.0)

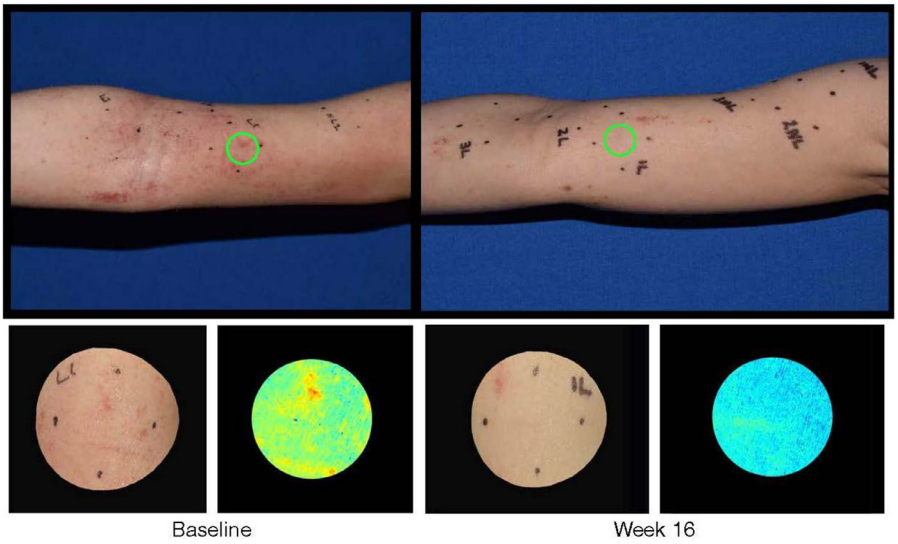
Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.



eFigure 1. Representative OCT images. Example of over-time OCT images from a healthy volunteer and a patient with AD representative for the trial patient population. AD, atopic dermatitis; EoS, end of study; EoT, end of treatment; OCT, optical coherence tomography; T_E, epidermal thickness.

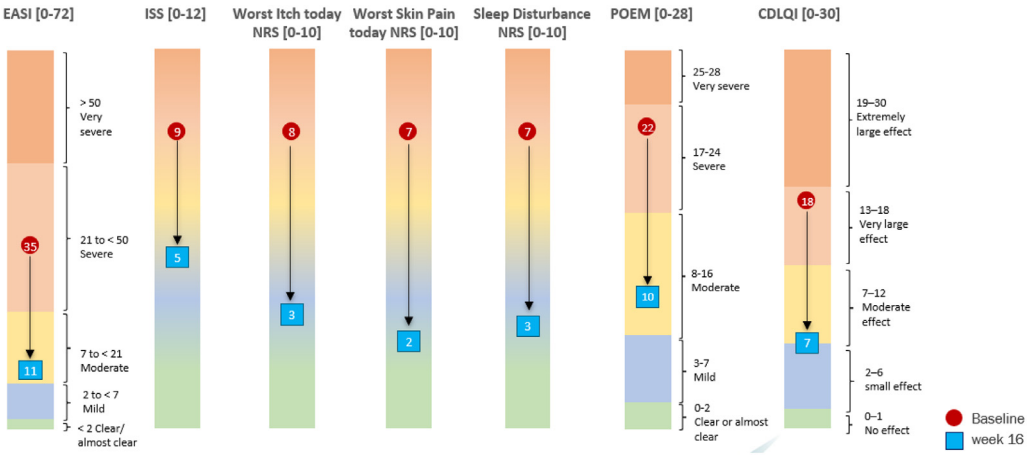
The first column shows cross-sectional OCT B-scans for each of the study visits. The second column shows these same B-scans with the skin layers labeled for clarity, with the epidermis shown as *green* and the dermis as *blue*. The third column shows each OCT volume from a top-down (*en-face*) perspective, showing the grayscale reflectance across the full 4 × 4-mm scan region. The final column shows a parametric map of the T_E across the *en-face* plane, where *red* corresponds to areas of thickened skin, while *blue* corresponds to thinner regions of skin. T_E (μm) values over time were as follows:

T_E	Healthy	Lesional	Nonlesional
Baseline	123.50	343.03	200.99
Week1	124.59	306.59	199.78
Week2	121.24	291.33	179.92
Week3	125.33	243.64	188.67
Week4	116.62	190.56	166.34
Week6	118.24	224.00	162.57
Week8	129.00	257.85	144.79
Week12	118.08	172.82	134.99
Week16	131.03	130.12	120.39
Week28	121.68	121.48	105.85



eFigure 2. Clinical photographs of representative patient at baseline and week 16. TiVi, Tissue Viability Imaging.

Standardized photographs taken at baseline (upper left) and week 16 (upper right) and colorimetric images of the target lesion at baseline (lower left) and week 16 (lower right). The *red/yellow* hues in the colorimetric images represent a high concentration of RBC, associated with increased erythema, and the *blue/green* hues represent a low concentration of RBC, associated with decreased erythema. The patient's computed TiVi index was 0.161 at baseline and decreased to 0.141 at week 16.



eFigure 3. Mean change from baseline at week 16 in clinical and patient-reported outcomes. CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ISS, Individual Sign Score; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure.

Rainbow graph developed by Ana B. Rossi and Marthe Vuillet of Sanofi.