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Dupilumab in children ages 6 months to 5 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial

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See Online for appendix.

A complete list of investigators is provided in the appendix, available at thelancet.com.

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Summary (Word count/word limit: 299/300; includes trial registration and funding statement)

Background Current systemic treatments for children <6 years with moderate-to-severe atopic dermatitis (AD) uncontrolled with topical therapies may have suboptimal efficacy and safety. Dupilumab is approved for older children and adults with AD and for other type 2 inflammatory conditions.

Methods This randomised, double-blind, placebo-controlled, phase 3 trial assessed dupilumab in patients ≥6 months to <6 years with moderate-to-severe AD inadequately controlled with topical therapies. Patients were enrolled from 31 hospitals, clinics, and academic institutions in Europe and North America. Patients were randomised 1:1 to subcutaneous placebo or dupilumab (≥5 kg to <15 kg: 200 mg; ≥15 kg to <30 kg: 300 mg) every 4 weeks plus low-potency topical corticosteroids (TCS) for 16 weeks. Randomisation was stratified by age, baseline weight, and region. Primary/key secondary endpoints at week 16 included proportions of patients with Investigator's Global Assessment (IGA) score 0/1 (clear/almost clear skin), and ≥75% improvement from baseline in Eczema Area and Severity Index (EASI-75).

Findings Participants were recruited from June 30, 2020, to February 12, 2021. A total of 162 patients were randomised to receive dupilumab (n=83) or placebo (n=79) plus TCS. Significantly more dupilumab- versus placebo-treated patients achieved IGA 0/1 (28% *vs* 4% [difference, 24%; 95% CI 13%, 34%]; p<0·0001) and EASI-75 (53% *vs* 11% [difference, 42%; 95% CI 29%, 55%]; p<0·0001) at week 16. Overall prevalence of adverse events was similar in the dupilumab (58/78 patients [74%]) and placebo arms (53/83 [64%]). Conjunctivitis incidence was higher with dupilumab than placebo (5% *vs* 0%). No dupilumab-related adverse events were serious or led to treatment discontinuation.

Interpretation Dupilumab significantly improved AD signs and symptoms versus placebo in children <6 years. Dupilumab was well tolerated, demonstrating an acceptable safety profile, similar to results in older children and adults.

Trial Registration ClinicalTrials.gov registration: NCT03346434.

Funding Sanofi and Regeneron Pharmaceuticals, Inc.

Research in context

Evidence before this study

Moderate-to-severe atopic dermatitis (AD) has a significant negative impact on quality of life among infants and young children as well as their family members and caregivers. Glucocorticoids are currently the only approved systemic treatment for AD in children younger than 6 years, although they are not recommended by multispecialty guidelines due to safety concerns. Currently available systemic therapies are used off-label without any data from rigorous clinical trials in this population to guide optimal use; furthermore, these agents have substantial safety concerns limiting use. Dupilumab is a fully human VelocImmune®-derived monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13. Dupilumab demonstrated efficacy and an acceptable safety profile in patients 6 years or older with moderate-to-severe AD and moderate-to-severe asthma, adults with chronic rhinosinusitis with nasal polyposis, and patients 12 years or older with eosinophilic esophagitis. These findings demonstrate that IL-4 and IL-13 are key and central drivers of type 2 inflammation in multiple type 2 inflammatory diseases. To identify clinical trials of systemic biologic treatment for AD in infants and young children, we searched PubMed using the search terms “atopic dermatitis” or “eczema” and “systemic”, “clinical trial”, “antibody”, “infant”, “children”, and “human”, published from January 1, 1995, to April 15, 2022. We identified two relevant clinical studies: one open-label study of single-dose dupilumab treatment in children with severely uncontrolled AD 6 months to younger than 6 years, and one randomised controlled study of symbiotic treatment in infants with AD. No other randomised controlled studies of systemic treatment for AD in this age group were identified; therefore, neither a meta-analysis nor a systemic review was performed.

Added value of this study

To our knowledge, this is the first large-scale, randomised, placebo-controlled trial of a monoclonal antibody in any skin disease, including AD, in children as young as 6 months. Because immunomodulating treatment may impact immune development in children and the immune mechanisms underlying AD in paediatric patients may differ from those in adults, safety and efficacy of immunomodulatory agents needs to be assessed in dedicated,

age-specific clinical trials. Patients were randomly assigned (1:1) to subcutaneous placebo or a weight-tiered, fixed-dose regimen of dupilumab (≥5 kg to <15 kg: 200 mg; ≥15 kg to <30 kg: 300 mg) every 4 weeks plus low-potency topical corticosteroids (TCS) for 16 weeks. Our results show clinically meaningful and statistically significant improvements with dupilumab treatment versus placebo in multiple physician-assessed and patient/caregiver-reported outcomes, including AD extent and severity, pruritus, and skin pain. Dupilumab also significantly improved patients' sleep quality and quality of life of patients and family members and caregivers. Rapid improvements in multiple domains were observed as early as week 1, including improvements in skin lesions and pruritus. Dupilumab had an acceptable safety profile, with safety findings similar to those observed in older children and adults.

Implications of all the available evidence

Infants and young children with moderate-to-severe AD that is inadequately controlled with topical therapies have a high unmet medical need. This study provides critical evidence supporting the efficacy and safety of dupilumab with concomitant TCS in this young patient population with a potentially immature immune system. These results constitute pivotal trial data supporting planned global approvals of dupilumab in infants and children with AD and will inform and potentially change clinical practice worldwide.

Introduction

Atopic dermatitis (AD) is a chronic type 2 inflammatory skin disease with prevalence of 19% or higher in children younger than 6 years.[1] Age of onset is younger than 5 years in 85–90% of patients.[2] AD is characterised by widespread eczematous lesions associated with severe pruritus and increased risk of skin infections.[3]

Moderate-to-severe AD substantially reduces quality of life of infants and young children and their family members.[4] Type 2 inflammation–mediated comorbidities, such as asthma and food allergies, often occur at an earlier age in children with AD than those without AD.[5,6]

Although not recommended by multispecialty guidelines, glucocorticoids are the only approved systemic treatment for AD in children younger than 6 years.[7] Glucocorticoids and other immunosuppressants (such as cyclosporine B, azathioprine, mycophenolate mofetil, and methotrexate) have safety concerns, limiting chronic use.[7]

Dupilumab is a fully human monoclonal antibody that inhibits the signaling of the interleukin-4 (IL-4) and IL-13 pathways. Dupilumab was invented using Regeneron's proprietary *VelocImmune®* technology, which produces fully human therapeutic antibodies using genetically modified mice.[8,9] IL-4 and IL-13 are key drivers of type 2 inflammation, which evolved to protect the body from helminths.[10,11] IL-4 and IL-13 recruit innate effector cells, including mast cells, eosinophils, and innate lymphoid type 2 cells, induce class switching in B cells, stimulate sensory neurons, and promote the itch/scratch cycle. Aberrant type 2 inflammation results in damage to the barrier integrity of the epidermis and other epithelia, thereby playing a major role in multiple related and often comorbid diseases. In phase 3 clinical trials, dupilumab has demonstrated significant clinical benefit together with a decrease in type 2 inflammation in multiple type 2 disorders, including AD, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis,[12–19] and is approved for treatment of patients ages 6 months and older with moderate-to-severe AD, as well as for moderate-to-severe asthma (6 years and older), chronic rhinosinusitis with nasal polyposis (adults), and eosinophilic esophagitis (12 years and older, weighing at least 40 kg).[20,21] Dupilumab has demonstrated a consistently acceptable safety profile, and unlike

most other immunomodulators, is not an immunosuppressant; in particular, dupilumab treatment in AD does not increase infection risk overall and is associated with lower rates of skin infections compared with placebo.[22,23]

Here we present results from a randomised, placebo-controlled trial evaluating efficacy and safety of dupilumab with concomitant low-potency topical corticosteroids (TCS) in children 6 months to younger than 6 years with moderate-to-severe AD.

Methods

Study design

Herein we report the phase 3 results from a phase 2/3 study (ClinicalTrials.gov Identifier: NCT03346434). Phase 3 (LIBERTY AD PRESCHOOL Part B) was a randomised, double-blind, placebo-controlled, parallel-group clinical trial in patients 6 months to younger than 6 years with moderate-to-severe AD inadequately controlled with standard-of-care TCS. Phase 2 results, which characterised pharmacokinetics and safety from this patient population, were previously reported.[12]

Patients were enrolled in North America and Europe from June 30, 2020, to February 12, 2021. Patients were enrolled from 31 hospitals, clinics, and academic institutions in Europe and North America. The trial included a screening period of up to 56 days (including 2 weeks of TCS standardisation), a 16-week treatment period, and a 12-week follow-up period for patients who did not enroll in a subsequent open-label extension trial (NCT02612454) (appendix p 29).

The protocol (available at thelancet.com) was developed by the study sponsors (Sanofi and Regeneron Pharmaceuticals, Inc.). The trial was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An Independent Data and Safety Monitoring Committee conducted blinded monitoring of patient safety data (appendix pp 8–9). Local institutional review boards or ethics committees at each trial center oversaw

trial conduct and documentation and reviewed and approved the study protocol. For each patient, written informed consent was obtained from a parent or legal guardian.

Patients

Patients were 6 months to younger than 6 years at screening, with moderate-to-severe AD (Investigator's Global Assessment [IGA] score 3 or 4), diagnosed according to consensus criteria of the American Academy of Dermatology (appendix pp 4–8), and inadequate response to TCS (defined as a course of TCS for 28 days within the last 6 months) prior to screening, thus ensuring that patients with chronic recalcitrant disease were enrolled.[24] The number of patients with moderate AD (IGA 3) was limited to approximately 40.

Randomisation and masking

Randomisation was performed by a central interactive web response system, stratified by baseline disease severity (IGA 3 *vs* 4), baseline bodyweight (≥5 kg to <15 kg *vs* ≥15 kg to <30 kg), and region (North America *vs* Europe). This sequence was generated by a biostatistician who did not play any further role in the trial. Blinded study drug kits coded with a medication numbering system were used to mask treatment allocation. Lists linking the codes with product lot numbers were not accessible to individuals involved in study conduct. Participants, people giving the interventions, those assessing outcomes, and those analysing the data were masked to group assignment.

Procedures

Patients were randomised 1:1 to receive subcutaneous dupilumab (200 mg or 300 mg: baseline body weight ≥5 kg to <15 kg or ≥15 kg to <30 kg, respectively) or matched placebo every 4 weeks (q4w) during a 16-week treatment period. From day −14 to the end of the treatment period, patients received a standardised once-daily regimen of low-potency TCS (hydrocortisone acetate 1% cream); TCS use was tapered to 3 times per week once IGA at least 2 was achieved and stopped at IGA=0. Moisturiser use was required twice daily for at least 7 consecutive days before randomisation and throughout the trial. Systemic immunomodulating treatments (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine), medium- or higher-potency TCS, crisaborole, and topical

calcineurin inhibitors were prohibited but could be used as rescue for worsening disease at investigator's discretion after day 14 (appendix pp 9–10). If rescue medication was topical, patients could continue their assigned study treatment; if systemic, study treatment was permanently discontinued. Live vaccines were prohibited within 4 weeks prior to the baseline visit or during the study (appendix pp 9–10), consistent with recent consensus recommendations.[25]

Outcomes

The primary efficacy endpoint was the proportion of patients achieving IGA score of 0 or 1 (clear/almost clear skin) at week 16. The proportion of patients who achieved at least a 75% improvement from baseline in Eczema Area and Severity Index (EASI-75) at week 16 was a key secondary endpoint (co-primary for European Union [EU] and EU reference market countries). Other key secondary endpoints were percent change from baseline to week 16 in EASI and weekly mean of daily worst scratch/itch Numerical Rating Scale (NRS) score (itch assessed by parents or caregivers; appendix pp 11–13). For subgroup analyses, see the appendix (appendix pp 13–14).

Additional endpoints at week 16 included the proportion of patients with EASI improvement from baseline of at least 50% (EASI-50) or at least 90% (EASI-90), the proportion with 4-point or higher improvement in worst scratch/itch NRS score, change from baseline in percent body surface area affected, change from baseline in Patient-Oriented Eczema Measure, change from baseline in patient's skin pain NRS (pain assessed by parents or caregivers; appendix pp 12–13), and percent change from baseline in Scoring AD score (appendix pp 11–12). Safety outcomes included treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events (AEs) leading to treatment discontinuation.

Statistical analysis

A sample size of 160 patients (80 per treatment group), at the 2-sided 5% significance level, was estimated to provide 88% power to detect a difference of 21% between treatment groups in the proportion of patients with IGA 0 or 1 at week 16, assuming response rates of 33% and 11% for the dupilumab and placebo groups, respectively; and 99% power to detect a 43% difference of percentage of patients with EASI-75 at week 16,

assuming response rates of 70% and 27%, respectively. Assumptions for power calculations were based on the LIBERTY AD PEDS phase 3 trial in children 6–11 years (NCT03345914).[17]

Categorical endpoints were analysed using a Cochran-Mantel-Haenszel test, after adjustment for randomisation strata. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs, or lack of efficacy were considered non-responders. Missing data due to any other reason, including COVID-19, were imputed using multiple imputation (appendix, pp 16–17).

Continuous endpoints were analysed using analysis of covariance, with treatment group, stratification factors, and relevant baseline measurements included in the model. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs, or lack of efficacy were imputed by worst observation carried forward. Missing values due to other reasons were handled by multiple imputation (appendix, pp 16–17).

A hierarchical procedure was used to control the overall type 1 error rate at 0.05 for the primary and secondary endpoints for dupilumab versus placebo (appendix pp 18–19). Each hypothesis was formally tested only if the preceding one was significant at the 2-sided 0.05 significance level. The primary efficacy analyses were conducted using the full analysis set, which included all randomised patients based on the treatment allocated (as randomised). Sensitivity analyses were performed for primary and key secondary endpoints using all observed values regardless of rescue treatment use (appendix p 13). P values for comparisons not in the hierarchy are nominal. All statistics for safety, biomarkers, and pharmacokinetics were descriptive. Safety analyses were conducted using the safety analysis set, which included all randomised patients who received any study drug, as treated. If a patient was randomised and did not receive any study treatment, they were not included in the safety analysis set. Biomarker analyses were conducted using the full analysis set. The pharmacokinetics analysis population included all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. Statistical analyses were performed using SAS version 9·4 (Cary, NC, USA) or higher.

Role of the funding source

Data were collected by the investigators and analysed by the funders of the study. The funders contributed to study design, data analysis, and data interpretation, and funded the writing of the report.

Results

Patients were recruited from June 30, 2020, to February 12, 2021. In total, 197 participants were screened; 35 failed screening and were excluded, and 162 patients were randomised (83 dupilumab, 79 placebo; figure 1), with 51 and 111 patients in the 5-kg to less than 15-kg and 15-kg to less than 30-kg weight categories, respectively. One patient in the placebo group was randomised but not treated due to a randomisation error; this patient was included in the efficacy analyses and was imputed using multiple imputation. A total of 82 of 83 patients (98·9%) in the dupilumab group and 75 of 79 (94·9%) in the placebo group completed the study treatment. Baseline demographics were balanced between treatment arms (table 1). Overall, 125/162 patients (77%) had severe disease (IGA 4) at baseline. Almost 30% (46/161) of patients had previously used systemic medications for AD, including 25/161 (16%) with prior systemic non-steroidal immunosuppressants (including cyclosporine A [17/161 patients; 11%], methotrexate [11/161; 7%], mycophenolate [2/161; 1%], and azathioprine [1/161; 1%]). Most patients (131/161; 81%) had at least 1 concurrent type 2 inflammatory disease, most commonly food allergy (110/162; 68%) and allergic rhinitis (71/162; 44%).

Dupilumab significantly improved efficacy versus placebo for the primary, key secondary, and other secondary endpoints (table 2, figure 2; appendix pp 20, 30). At week 16, significantly more dupilumab-treated patients achieved IGA 0 or 1 (primary endpoint) than placebo (28% [23/83 patients] *vs* 4% [3/79], respectively; p<0·0001; difference *vs* placebo 24%, 95% confidence interval [CI] 13–34%; table 2, figure 2A). A significantly greater proportion of dupilumab-treated patients achieved EASI-75 at week 16 than placebo (53% [44/83 patients] *vs* 11% [8/79], respectively; p<0·0001; difference *vs* placebo 42%, 95% CI 29–55%) (table 2, figure 2B). Improvements in AD signs with dupilumab as assessed by IGA 0 or 1 (figure 2A) and EASI-75 (figure 2B) were observed from week 4 and week 2, respectively.

At week 16, least squares (LS) mean percent change (± standard error [SE]) from baseline in EASI was significantly greater with dupilumab than placebo (−70·0% ± 4·9% *vs* −19·6% ± 5·1%, respectively; p<0·0001; difference *vs* placebo −50·4%, 95% CI −62·4% to −38·4%; table 2, figure 2C), as was LS mean percent change in worst scratch/itch NRS score (−49·4% ± 5·0% *vs* −2·2% ± 5·2%, respectively; p<0·0001; difference *vs* placebo −47·1%, 95% CI −59·5% to −34·8%; table 2, figure 2D). Improvement with dupilumab in EASI (figure 2C) and worst scratch/itch NRS scores (figure 2D) was observed from week 1. At week 16, sleep quality in both patients and caregivers was significantly improved with dupilumab *vs* placebo (patients: 2·0 ± 0·3 *vs* 0·3 ± 0·3, respectively; p<0·0001; difference 1·7, 95% CI 1·1–2·3; caregivers: 1·8 ± 0·3 *vs* 0·3 ± 0·3, respectively; p<0·0002; difference 1·5, 95% CI 0·9–2·1; table 2; appendix p 20). Dupilumab also significantly improved *vs* placebo LS mean change from baseline in patients' skin pain NRS (−3·9 ± 0·3 *vs* −0·6 ± 0·3, respectively; p<0·0001; difference −3·3, 95% CI −4·0 to −2·6), Children's Dermatology Life Quality Index (−10·0 ± 1·6 *vs* −2·5 ± 1·7, respectively; p<0·0001; difference −7·5, 95% CI −10·3 to −4·8), Infants' Dermatitis Quality of Life Index (−10·9 ± 1·2 *vs* −2·0 ± 1·1, respectively; p<0·0001; difference −9·0, 95% CI −11·7 to −6·2), and Dermatitis Family Impact Questionnaire (−10·5 ± 0·8 *vs* −2·7 ± 0·8, respectively; p<0·0001; difference −7·8, 95% CI −9·8 to −5·8) scores (table 2). For all other endpoints prespecified in the hierarchy, improvements were significantly greater with dupilumab than placebo at week 16 (table 2).

Consistent beneficial effects favouring dupilumab versus placebo were observed in all subgroups analysed for achievement of IGA 0 or 1 and EASI-75 at week 16 (appendix pp 21–23, 31–32). There was a similar trend for a numerically higher effect with dupilumab versus placebo in patients younger than 2 years (N=11) (appendix p 21). Additionally, subgroup analysis by patient weight strata (≥5 kg to <15 kg, ≥15 kg to <30 kg) showed a consistent trend of dupilumab benefit versus placebo in both weight groups for all endpoints evaluated (appendix pp 22–23).

A substantially lower proportion of dupilumab- versus placebo-treated patients used 1 or more rescue medications (19% [16/83 patients] *vs* 63% [49/78], respectively) (appendix p 33). The LS mean weekly doses of medium- to high-potency TCS were significantly different in the dupilumab and placebo groups (3·0 *vs* 6·1 g, respectively; p=0·046; LS mean difference [95% CI] −3·1 [−6·22 to −0·07]) (appendix p 20). Rescue was

predominantly topical therapies; the only systemic medications used as rescue for AD exacerbation were systemic corticosteroids: one and two patients in the dupilumab and placebo groups, respectively.

Sensitivity analyses using all observed values regardless of rescue treatment use showed minimal impact of rescue treatment on primary and key secondary endpoints at week 16 (appendix pp 34–36). For other key secondary endpoints, the placebo response was numerically higher in the sensitivity analyses than the primary analysis; however, superiority of dupilumab over placebo was maintained.

Overall TEAE incidence during the 16-week treatment period was similar between treatment arms, with a trend toward fewer TEAEs in the dupilumab arm, driven mainly by lower incidence of skin infections and AD exacerbations (table 3; appendix p 24–28). The three most commonly reported TEAEs were AD exacerbation (13% [11/83 patients] and 32% [25/78], dupilumab and placebo, respectively), nasopharyngitis (8% [7/83] and 9% [7/78]), and upper respiratory tract infection (6% [5/83] and 8% [6/78]) (table 3). TEAEs that occurred in at least 3% of dupilumab-treated patients and at a higher rate than in placebo-treated patients were molluscum contagiosum (MC; 5% [4/83] *vs* 3% [2/78]), viral gastroenteritis (4% [3/83] *vs* 0), rhinorrhea (5% [4/83] *vs* 1% [1/78]), and dental caries (5% [4/83] *vs* 0). Serious TEAEs occurred only in the placebo arm (4/78 patients [5%]) (table 3). One patient in each arm discontinued treatment due to non-serious TEAEs: nightmares due to blood draws (placebo) and AD exacerbation (dupilumab).

Skin infection incidence with placebo (24% [19/78]) was double that with dupilumab (12% [10/83]). Serious skin infections were reported only in the placebo arm (2 patients). Herpes viral infection (HLT) incidence was comparable between groups (6% [5/83] *vs* 5% [4/78], dupilumab and placebo, respectively). There was one case (1% [1/78]) of eczema herpeticum in the placebo arm (appendix pp 25–26). Conjunctivitis (narrow group) incidence was higher with dupilumab than placebo (5% [4/83] *vs* 0, respectively) (table 3); all cases were mild and resolved. The median time to onset was 79 days (range [quartile 1 to quartile 3], 66·0 to 93·0 days), and the median duration of these events was 24·5 days (range [quartile 1 to quartile 3], 7 to 47·5 days). There were 2/83 cases of blepharitis (2·4%) in the dupilumab group and none in the placebo group. The proportion of patients with

1 or more injection-site reactions was low: two patients each (2% [2/83] *vs* 3% [2/78], respectively) (table 3). Safety outcomes in patients younger than 2 years were similar to the overall safety population (appendix p 27). A transient increase in mean, but not median, blood eosinophil count in the dupilumab arm was seen at week 4, with a trend toward reverting to baseline values at week 16 (appendix p 37) and no associated clinical adverse events.

Median baseline levels of serum thymus and activation-regulated chemokine (TARC/CCL17) were similar between treatment groups (table 1); greater reduction in TARC from baseline with dupilumab versus placebo was observed as early as week 4 and maintained through week 16 (−83% *vs* −13%, respectively). At week 16, serum total IgE decreased from baseline with dupilumab but increased with placebo (−71% *vs* 28%, respectively) (appendix p 38).

Mean trough concentrations of functional dupilumab in serum were similar between patients with body weight 5 kg to less than 15 kg (200 mg dupilumab q4w) and 15 kg to less than 30 kg (300 mg dupilumab q4w) throughout the treatment period and at week 16 (109 mg/L and 110 mg/L, respectively) (appendix p 39).

In general, the safety profile for dupilumab was comparable across the two baseline weight subgroups (appendix, p 28). For severe and serious TEAEs, incidence rates were slightly higher in the placebo arm as compared with dupilumab in both weight subgroups. Severe TEAEs occurred at slightly higher rates in the higher baseline weight group than the lower baseline weight group and at higher rates in placebo-treated patients in both weight subgroups (≥5 kg to <15 kg, 0/26 vs 2/24 patients [8%], dupilumab *vs* placebo, respectively; ≥15 kg to <30 kg, 2/57 [4%] *vs* 8/54 [15%], respectively). Rates of serious TEAEs were low and comparable in both weight groups (≥5 kg to <15 kg, 0/26 *vs* 1/24 patients [4%], dupilumab *vs* placebo, respectively; ≥15 kg to <30 kg, 0/57 *vs* 3/54 [6%], respectively). TEAEs deemed related to the study drug occurred at a slightly higher rate in the higher baseline weight group than the lower weight group; rates for dupilumab-treated patients were comparable with rates in the placebo group in both weight groups (≥5 kg to <15 kg, 1/26 [3%] *vs* 0/24 patients, dupilumab *vs* placebo,

respectively; ≥15 kg to <30 kg, 8/57 [14%] *vs* 5/54 [9%], respectively). These numbers should be interpreted with caution, given the small numbers of patients with these categories of TEAEs in each subgroup.

Discussion

To our knowledge, this is the first large-scale, randomised, placebo-controlled trial of a monoclonal antibody in any skin disease in children as young as 6 months. Patients had high baseline disease and symptom burden with impaired quality of life. Nearly 30% required prior use of systemic immunosuppressants, and approximately 80% had 1 or more comorbid type 2 conditions, demonstrating a substantial unmet medical need for efficacious and safe treatment options for this population.

Dupilumab provided clinically meaningful and statistically significant improvements versus placebo in multiple physician-assessed and patient- or caregiver-reported outcomes, including AD extent and severity, pruritus, and skin pain. Importantly, dupilumab also significantly improved patients' sleep quality and quality of life of patients and caregivers. Improvements in multiple domains occurred as early as week 1, including in skin lesions and pruritus.

Dupilumab consistently showed numerically higher treatment benefit in prespecified subgroups. Sensitivity analyses were consistent with the primary analyses, confirming robustness of the treatment effect. Fewer dupilumab- versus placebo-treated patients required rescue therapy and the mean weekly usage of medium-to-high potency TCS was lower with dupilumab, suggesting a steroid-sparing effect of dupilumab, relevant given safety concerns surrounding TCS use in young children.[7]

Dupilumab had an acceptable AE profile, with safety findings similar to those observed in older children and adults,[13–17] and was well tolerated across subgroups, including in patients younger than 2 years. A transient increase in mean eosinophil count was observed with dupilumab, without clinical relevance, consistent with previous trials.[26–28] Viral gastroenteritis and dental caries occurred at a higher rate in the dupilumab group than the placebo group; however, the numbers of cases were too few to draw any conclusions, and these differences have not been seen in other trials. Conjunctivitis incidence was higher in the dupilumab group than the placebo

group; all cases were mild and resolved, consistent with previous dupilumab trials in AD.[13–17,29,30] Ocular surface disorders such as conjunctivitis are common in patients with AD. Multiple hypotheses have been proposed for mechanisms underlying the increased incidence of conjunctivitis with dupilumab treatment in patients with AD, including the effects of IL-4 and IL-13 inhibition on reduced expression of mucins in goblet cells, a dupilumab–AD interaction, epithelial barrier dysfunction, increased *Demodex* mites, and other proposed mechanisms.[29–31] Further research into this phenomenon is ongoing.

No serious infections were noted with dupilumab, similar to previous dupilumab clinical trials in children and adults.[22,23] Data showing the lack of serious infections, the limited duration of treatment notwithstanding, are reassuring, given the potentially immature immune system in this paediatric population. Skin infection incidence was lower with dupilumab than placebo. These results are consistent with prior clinical findings that, unlike most other immunomodulators, dupilumab is not an immunosuppressant. In a comprehensive pooled analysis of seven randomised, placebo-controlled dupilumab trials in adults with moderate-to-severe AD, as well as in a separate pooled analysis of AD trials in children and adolescents, dupilumab did not increase overall infection risk, and was instead associated with lower rates of skin infections compared with placebo.[22,23] As in those previous pooled analyses, skin infection incidence was substantially lower with dupilumab than placebo in this current trial in children younger than 6 years. One likely mechanism of decreased skin infections is improved skin barrier integrity and increased antimicrobial peptides.[32] Additionally, IL-4 and IL-13 inhibition is not thought to affect antibacterial immune response.[33] MC incidence was numerically higher with dupilumab than placebo; however, numbers were small (dupilumab, 4; placebo, 2), and cases were mild, consistent with previous studies in children 6–11 years.[17,23] The primary defense mechanism against this viral infection is mediated by Th1 cytokines; case reports suggest resolution of MC after dupilumab treatment.[34–36]

The weight-tiered, fixed-dose regimen of dupilumab normalised exposure between weight subgroups and mean trough concentrations at week 16 were similar to or greater than approved regimens in older children and adults with AD.[37] Biomarker results were consistent with previous trials in older children and adults.[15,38]

This study has several strengths, including the randomised, double-blind, placebo-controlled design. The background use of topical therapy allowed assessment of efficacy and safety of dupilumab treatment in infants and very young children in a manner consistent with how a biologic medication may be used in real-life conditions. Limitations include the relatively low number of patients younger than 2 years (although the lower weight category was well represented) and the relatively short 16-week treatment duration. An open-label study to evaluate long-term safety and efficacy [NCT02612454] is ongoing. Another limitation is the limited geographic footprint of this trial, with no sites outside North America or Europe.

In conclusion, dupilumab with concomitant low-potency TCS significantly improved AD signs, symptoms, and quality of life (of both patients and caregivers) versus placebo in children 6 months to younger than 6 years with moderate-to-severe AD. Improvements occurred as early as week 1 and continued throughout the 16-week treatment period. Dupilumab was well tolerated and demonstrated an acceptable safety profile—including substantially decreased incidence of skin infections—in this young patient population with a high unmet medical need.

Contributors

ASP, ELS, ECS, MJC, ZW, BA, MPK, MAK, NP, DMW, GDY, JTO, and AB contributed to study concept and design. ASP, ELS, ECS, MJC, AW, PDA, WS, MEG, LCS, RS, BL, and SM acquired data. YS conducted the statistical analyses on the data. YS and AB verified the data. ASP, ELS, ECS, MJC, ZW, LPM, NA, YS, EL, BA, MD, MPK, MAK, ADB, NP, DMW, GDY, JTO, and AB interpreted the data. All authors provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript. All authors had full access to all the data in the study, had the ability to review the data, and had final responsibility for the decision to submit for publication.

Declaration of interests

ASP has been an investigator for AbbVie, AnaptysBio, Dermavant, Eli Lilly, Incyte, Janssen, Krystal Biotech, LEO Pharma, Regeneron Pharmaceuticals, Inc., and UCB; a consultant with honorarium for AbbVie, Acrotech, Almirall, Amgen, Amryt Pharma, Arcutis Antiobix, Arena Pharmaceuticals, Azitra, BioCryst, BiomX, Boehringer Ingelheim, Botanix, BridgeBio, Bristol Myers Squibb, Castle Creek Biosciences, Catawba Research, Eli Lilly, Exicure, Gilead, Incyte, Janssen, Johnson & Johnson, Kamari Pharma, LEO Pharma, Novartis, OM Pharma, Pfizer, Pierre Fabre Dermo-Cosmetics, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi, Seanergy, UCB, and Union; and on the Data and Safety Monitoring Board for AbbVie, Abeona, Bausch, Galderma, and Novan. ELS has been an investigator for AbbVie, Eli Lilly, Incyte, Kyowa Hakko Kirin, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, and Trevi Therapeutics; received consultant fees from AbbVie, Amgen, Arena Pharmaceuticals, Aslan Pharma, Benevolent AI Bio Limited “BAI”, BiomX Ltd, Bluefin Biomedicine Inc., Boehringer Ingelheim, Boston Consulting Group, Collective Acumen LLC (CA), Coronado, Corevita, Dermavant, Eli Lilly, Evidera, ExcerptaMedica, Forté Bio RX, Galderma, GSK, Incyte, Janssen, Kyowa Hakko Kirin, LEO Pharma, Menlo Therapeutics, Merck, Novartis, Pfizer, Pierre Fabre Dermo-Cosmetics, Regeneron Pharmaceuticals, Inc., Roivant, Sanofi, SPARC India, Trevi Therapeutics, and Valeant; received study grants from AbbVie, Amgen, Arcutis, Aslan Pharma, Corevita, Eli

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Data Sharing

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymised participant data will be considered for sharing once the

product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA), 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/.

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Tables and figures

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

	Placebo + TCS (n=79)*	**Dupilumab + TCS (n=83)***	**Overall (N=162)***
Age, years	3·8 (2·9:4·8)	4·2 (3·1:4·8)	4·0 (3·1:4·8)
Minimum	0·6	0·8	0·6
Maximum	5·9	5·8	5·9
Age at disease onset, months			
<6	57 (72%)	50 (60%)	107 (66%)
≥6	22 (28%)	33 (40%)	55 (34%)
Age group			
≥6 months to <2 years†	5 (6%)	6 (7%)	11 (7%)
≥2 years to <6 years	74 (94%)	77 (93%)	151 (93%)
Gender (male)	55 (70%)	44 (53%)	99 (61%)
Race			
White	53 (67%)	58 (70%)	111 (68%)
Black or African American	16 (20%)	14 (17%)	30 (18%)
Asian	4 (5%)	6 (7%)	10 (6%)
Native Hawaiian/other Pacific Islander	1 (1%)	0	1 (1%)
Not reported	1 (1%)	2 (2%)	3 (2%)
Other	4 (5%)	3 (4%)	7 (4%)
Ethnicity			
Not Hispanic or Latino	70 (89%)	72 (87%)	142 (88%)
Hispanic or Latino	9 (11%)	11 (13%)	20 (12%)
Weight, kg	16·7 (3·6)	17·1 (4·4)	16·9 (4·0)
Weight group, kg			

	Placebo + TCS (n=79)*	**Dupilumab + TCS (n=83)***	**Overall (N=162)***
≥5 to <15	25 (32%)	26 (31%)	51 (32%)
≥15 to <30	54 (68%)	57 (69%)	111 (68%)
BMI, kg/m^2	16·2 (1·9)	17·0 (5·6)	16·6 (4·2)
Region			
North America	51 (65%)	53 (64%)	104 (64%)
Europe	28 (35%)	30 (36%)	58 (36%)
Duration of AD‡, years	3·4 (1·3)	3·4 (1·3)	3·4 (1·3)
Patients with IGA score (range 0–4)			
3	17 (22%)	20 (24%)	37 (23%)
4	62 (79%)	63 (76%)	125 (77%)
EASI (range 0–72)	33·1 (12·2)	35·1 (13·9)	34·1 (13·1)
Worst scratch/itch NRS score§ (range 0–10)	7·6 (1·5)	7·5 (1·3)	7·6 (1·4)
Percent BSA involvement	57·4% (20·9)	59·3% (22·5)	58·4% (21·7)
POEM (range 0–28)	23·3 (4·0)	23·1 (4·5)	23·2 (4·3)
SCORAD (range 0–103)	72·2 (11·4)	72·7 (13·0)	72·4 (12·2)
Patient sleep quality NRS§ (range 0–10)	4·6 (2·1)	4·9 (1·9)	4·8 (2·0)
Caregiver sleep quality NRS§ (range 0–10)	4·7 (2·1)	5·1 (1·9)	4·9 (2·0)
Patient skin pain NRS (range 0–10)	7·2 (1·8)	6·8 (1·8)	7·0 (1·8)
DFI¶ (range 0–30)	17·6 (7·2)	17·2 (6·0)	17·4 (6·6)
CDLQI¶ (range 0–30)	17·7 (6·3) (n=38)	17·5 (5·4) (n=48)	17·6 (5·8) (n=86)
IDQoL¶ (range 0–30)	17·1 (5·4) (n=41)	17·4 (5·4) (n=35)	17·2 (5·4) (n=76)
Biomarkers			
Serum TARC, pg/mL	3190·0 (1625·0:10300·0) (n=72)	3295·0 (1430·0:11100·0) (n=74)	3230·0 (1580·0:10500·0) (n=146)

	Placebo + TCS (n=79)*	**Dupilumab + TCS (n=83)***	**Overall (N=162)***
Serum total IgE, kU/L	3240·0 (414·0:9420·0) (n=69)	2190·0 (570·0:10 400·0) (n=71)	2665·0 (465·0:9665·0) (n=140)
Eosinophils × 10^9/L	0·9 (0·5:1·6) (n=78)	1·0 (0·5:1·4) (n=82)	0·9 (0·5:1·5) (n=161)
Patients with ≥1 concurrent atopic/allergic condition‖	65 (83%)	66 (80%)	131 (81%)
Food allergy‖	55 (71%)	55 (66%)	110 (68%)
Allergic rhinitis‖	36 (46%)	35 (42%)	71 (44%)
Asthma‖	21 (27%)	20 (24%)	41 (26%)
Urticaria‖	15 (19%)	14 (17%)	29 (18%)
Allergic conjunctivitis‖	3 (4%)	4 (5%)	7 (4%)
Other allergies‖**	42 (54%)	43 (52%)	85 (53%)
Prior systemic medications for AD‖	22 (28%)	24 (29%)	46 (29%)
Prior systemic glucocorticoids‖	14 (18%)	16 (19%)	30 (19%)
Prior systemic non-steroidal immunosuppressants‖	12 (15%)	13 (16%)	25 (16%)
Cyclosporine A‖	7 (9%)	10 (12%)	17 (11%)
Methotrexate‖	7 (9%)	4 (5%)	11 (7%)
Mycophenolate‖	1 (1%)	1 (1%)	2 (1%)
Azathioprine‖	1 (1%)	0	1 (1%)

Data are n (%), median (IQR), or mean (SD). Higher score indicates worse disease/larger impact, except for Patient Sleep Quality NRS, where higher score indicates better sleep quality.

AD=atopic dermatitis. BMI=body mass index. BSA=body surface area. CDLQI=Children's Dermatology Life Quality Index. DFI=Dermatitis Family Impact. EASI=Eczema Area and Severity Index. IDQoL=Infants' Dermatitis Quality of Life. IGA=Investigator's Global Assessment. IQR=interquartile range.

NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. Q=quartile. SCORAD=SCORing Atopic Dermatitis. SD=standard deviation. TARC=thymus and activation-regulated chemokine. TCS=topical corticosteroids.

*Full analysis set. †The youngest patient in the dupilumab arm was 10 months; the two youngest patients in the placebo arm were both 7 months, with baseline body weights of 7·5 kg and 9·4 kg; 7·5 kg was the lowest baseline body weight in the study. ‡Duration of AD (mean [SD], years) for patients ages 6 months to younger than 2 years (n=11) was 0·8 (0·4). §Weekly mean of daily measure. ¶CDLQI assesses quality of life in paediatric patients ages 4 years to younger than 18 years; IDQoL, in patients younger than 4 years; and DFI, in caregivers. ‖Assessed in safety analysis set. **Refers to allergies to plants, animals, dust, mites, medication, etc.

Table 2: **Efficacy outcomes at week 16**

	Endpoints	Placebo + TCS (n=79)	Dupilumab + TCS (n=83)	Difference *vs* placebo (95% CI)	p value *vs* placebo
Primary	Proportion of patients with IGA 0 to 1	3 (4%)	23 (28%)	24% (13% to 34%)	<0·0001
Key secondary	Proportion of patients with EASI-75	8 (11%)	44 (53%)	42% (29% to 55%)	<0·0001
	Percent change from baseline in EASI	−19·6% (5·1)	−70·0% (4·9)	−50·4% (−62·4% to −38·4%)	<0·0001
	Percent change from baseline in worst scratch/itch NRS score	−2·2% (5·2)	−49·4% (5·0)	−47·1% (−59·5% to −34·8%)	<0·0001
Other secondary	Proportion of patients with ≥4-point improvement of pruritus NRS score*	7/78 (9%)	40/83 (48%)	39% (26% to 52%)	<0·0001
	Proportion of patients with ≥3-point improvement of pruritus NRS score†	8/78 (10%)	44/83 (53%)	43% (30% to 57%)	<0·0001
	Proportion of patients with EASI-50	16 (20%)	57 (69%)	49% (35% to 62%)	<0·0001
	Proportion of patients with EASI-90	2 (3%)	21 (25%)	23% (12% to 33%)	<0·0001

	Change from baseline in percent BSA affected by AD	−10·7 (2·9)	−35·0 (2·8)	−24·3 (−31·2 to −17·3)	<0·0001
	Change from baseline in POEM	−3·8 (0·9)	−12·9 (0·9)	−9·1 (−11· to, −6·9)	<0·0001
	Percent change from baseline in SCORAD	−16·2% (3·5)	−54·7% (3·4)	−38·4% (−46·7% to −30·2%)	<0·0001
	Change from baseline in patient's sleep quality NRS‡	0·3 (0·3)	2·0 (0·3)	1·7 (1·1 to 2·3)	<0·0001
	Change from baseline in patient's skin pain NRS score	−0·6 (0·3)	−3·9 (0·3)	−3·3 (−4·0 to −2·6)	<0·0001
	Change from baseline in DFI	−2·7 (0·8)	−10·5 (0·8)	−7·8 (−9·8 to −5·8)	<0·0001
	Change from baseline in CDLQI (n=47 in dupilumab, n=38 in placebo arm)	−2·5 (1·7)	−10·0 (1·6)	−7·5 (−10·3 to −4·8)	<0·0001
	Change from baseline in IDQOL (n=36 in dupilumab, n=41 in placebo arm)	−2·0 (1·1)	−10·9 (1·2)	−9·0 (−11·7 to −6·2)	<0·0001

Data are n (%) or LS mean (SE). Proportions of patients achieving a categorical endpoint are presented as model-derived estimates. CDLQI assesses QoL in paediatric patients 4 years to younger than 18 years; IDQoL, in patients younger than 4 years; DFI, in caregivers.

AD=atopic dermatitis. BSA=body surface area. CDLQI=Children's Dermatology Life Quality Index. CI=confidence interval. DFI=Dermatitis Family Impact. EASI=Eczema Area and Severity Index. EASI-50/-75/-90=at least 50%/≥75%/≥90% improvement from baseline in EASI. IDQoL=Infants' Dermatitis Quality of Life. IGA=Investigator's Global Assessment. LS=least squares. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. QoL=quality of life. SCORAD=Scorning Atopic Dermatitis. SE=standard error. TCS=topical corticosteroids.

*Among patients with baseline NRS score 4 or higher. †Among patients with baseline NRS score 3 or higher. ‡Increase in score means improvement.

Table 3: **Safety assessment**

TEAEs	**Placebo + TCS (n=78)***	**Dupilumab + TCS (n=83)**
Overview		
Patients with ≥1 TEAE	58 (74%)	53 (64%)
Patients with TEAE leading to treatment discontinuation	1 (1%)†	1 (1%)‡
Patients with ≥1 serious TEAE	4 (5%)§	0
Deaths	0	0
Patients with ≥1 severe TEAE	10 (13%)	2 (2%)
Patients with ≥1 TEAE deemed related to study drug	5 (6%)	9 (11%)
Patients with TEAE of special interest	0	1 (1%)¶
Conjunctivitis (narrow group)‖	0	4 (5%)
Conjunctivitis allergic	0	1 (1%)
Conjunctivitis	0	3 (4%)
Skin infections (SOC) (excluding herpes viral infections)	19 (24%)	10 (12%)
Herpes viral infections (HLT)	4 (5%)	5 (6%)
Injection-site reactions (HLT)	2 (3%)	2 (2%)
TEAEs reported in ≥3% of patients **Primary SOC**** **Preferred Term**		
Infections and infestations	40 (51%)	35 (42%)
Nasopharyngitis	7 (9%)	7 (8%)
Upper respiratory tract infection	6 (8%)	5 (6%)
Molluscum contagiosum	2 (3%)	4 (5%)
Conjunctivitis	0	3 (4%)
Viral gastroenteritis	0	3 (4%)

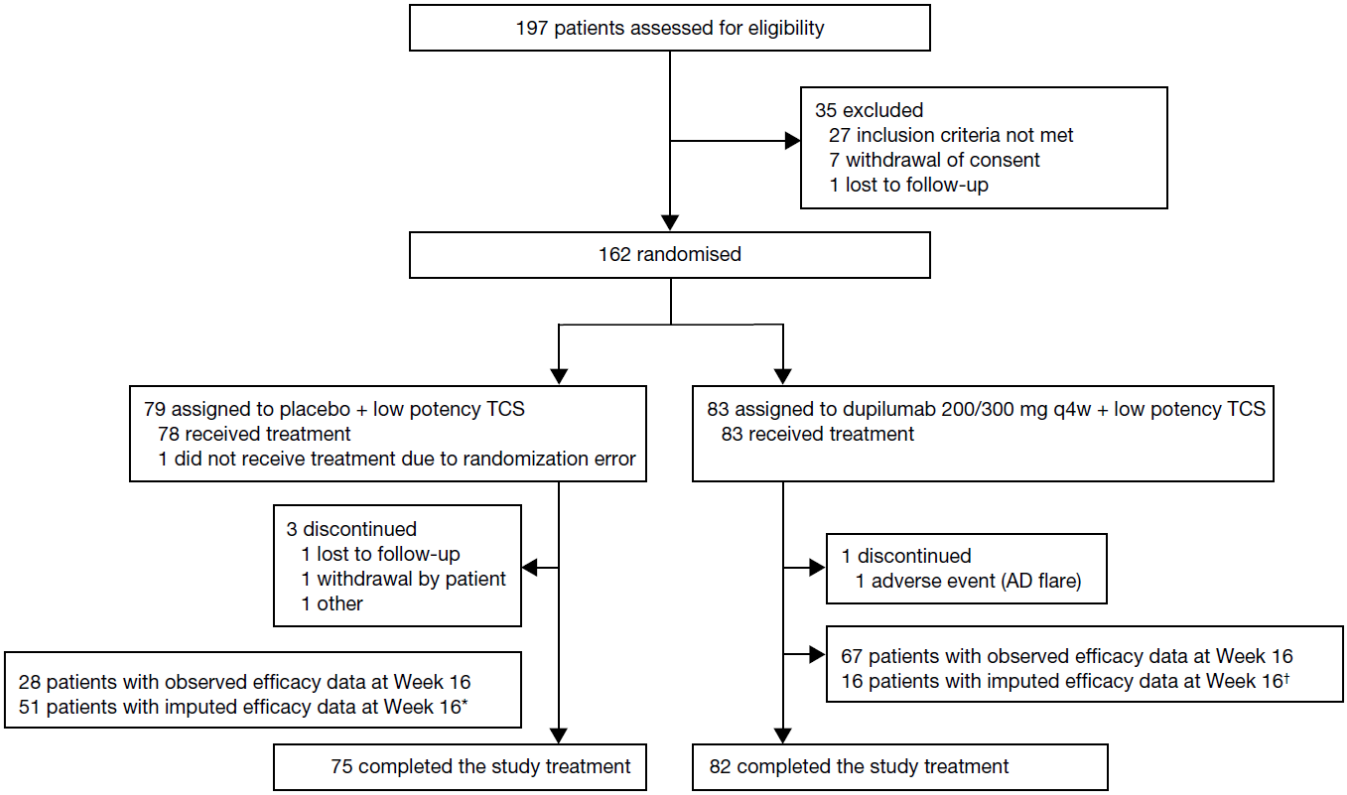
Impetigo	6 (8%)	3 (4%)
Respiratory tract infection viral	3 (4%)	0
Staphylococcal skin infection	3 (4%)	0
Skin and subcutaneous tissue disorders	28 (36%)	17 (20%)
Dermatitis atopic††	25 (32%)	11 (13%)
Urticaria	4 (5%)	1 (1%)
Respiratory, thoracic, and mediastinal disorders	15 (19%)	9 (11%)
Rhinorrhea	1 (1%)	4 (5%)
Asthma	5 (6%)	3 (4%)
Cough	5 (6%)	0
Gastrointestinal disorders	6 (8%)	8 (10%)
Dental caries	0	4 (5%)
Blood and lymphatic system disorders	7 (9%)	6 (7%)
Lymphadenopathy	6 (8%)	3 (4%)
General disorders and administration site conditions	9 (12%)	5 (6%)
Pyrexia	7 (9%)	1 (1%)

Data are n (%).

AD=atopic dermatitis. AE=adverse event. HLT=MedDRA High Level Term. MedDRA=Medical Dictionary for Regulatory Activities. PT=MedDRA Preferred Term. SAE=serious adverse event. SOC=MedDRA System Organ Class. TCS=topical corticosteroid. TEAE=treatment-emergent adverse event.

*One patient in the placebo + TCS treatment group was excluded from the safety analysis set, as this patient was randomised in error and did not receive study treatment. †Patient discontinued due to TEAE of nightmares due to blood draws. ‡Patient discontinued due to TEAE of AD flare. §One patient had 1 SAE of dermatitis atopic and 1 SAE of dermatitis infected; 1 patient had an SAE of hypersensitivity; 1 patient had an SAE of staphylococcal bacteremia; and 1 patient had an SAE of cellulitis staphylococcal. ¶Blepharitis. ‖Narrow conjunctivitis group is a customised MedDRA query (similar to standardised MedDRA queries), which enables searching of the safety database in a consistent fashion across different dupilumab studies to detect events of conjunctivitis. Narrow conjunctivitis group includes the following MedDRA PTs: atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral. **MedDRA Version 23·1. ††Exacerbation of AD.

Figure 1: **CONSORT diagram**



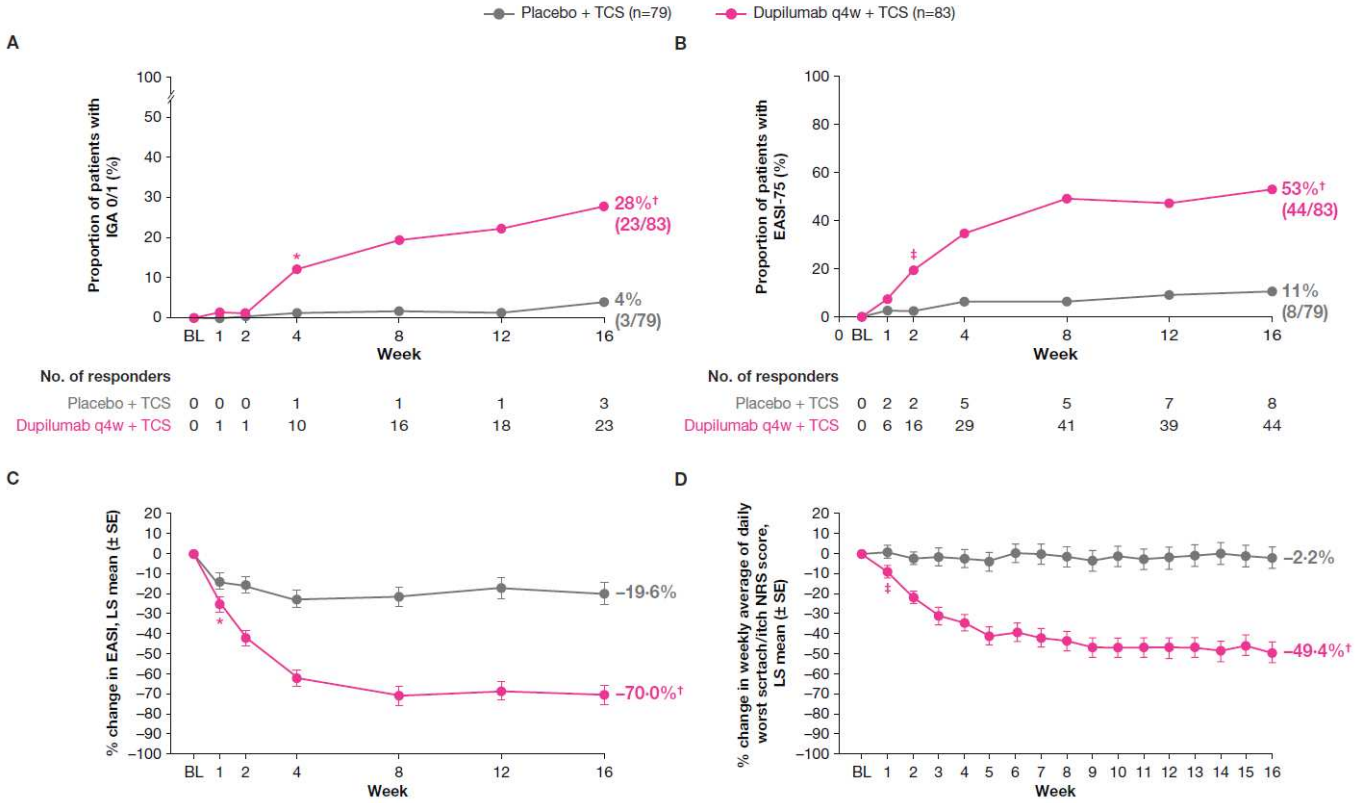
One patient in the placebo + TCS group was randomised but not treated due to a randomisation error. The patient was randomised by the interactive voice response system/interactive web response system at the site but did not come to the randomisation visit.

AD=atopic dermatitis. q4w=every 4 weeks. TCS=topical corticosteroid.

*Of the 51 placebo-treated patients for whom data were imputed, 49 received rescue treatment and 2 had missing data. †All 16 dupilumab-treated patients for whom data were imputed received rescue treatment.

Figure 2: **Primary and key secondary endpoints**

(A) Proportion of patients with an IGA score of 0 to 1 through week 16 (primary endpoint); (B) proportion of patients with EASI-75 through week 16 (key secondary endpoint, identified as a co-primary endpoint for EU or EU Reference Market Countries); (C) least squares mean percent change (± SE) in EASI from baseline through week 16 (key secondary endpoint); (D) least squares mean percent change (± SE) in worst scratch/itch score from baseline through week 16 (key secondary endpoint).



For panels A and B, values after first rescue treatment use were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy were considered as non-responders. Patients with missing values due to other reasons including COVID-19 were imputed by MI. For panels C and D, values after first rescue treatment use were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy were imputed by WOCF method. Patients with missing values due to other reasons including COVID-19 were imputed by MI. All non-missing data before imputation of WOCF were used for MI. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates.

AE=adverse event. BL=baseline. EASI=Eczema Area and Severity Index. EASI-75at least 75% improvement from baseline in EASI. EU=European Union. IGA=Investigator's Global Assessment. LS=least squares. MI=multiple imputation. NRS=Numerical Rating Scale. q4w=every 4 weeks. SE=standard error. TCS=topical corticosteroid. WOCF=worst-observation carried forward.

*Nominal p<0·05. †p<0·0001. ‡Nominal p<0·01.

Appendix

Dupilumab in children ages 6 months to 5 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial

Amy S Paller, Eric L Simpson, Elaine C Siegfried, Michael J Cork, Andreas Wollenberg, Peter D Arkwright, Weily Soong, Mercedes E Gonzalez, Lynda C Schneider, Robert Sidbury, Benjamin Lockshin, Steven Meltzer, Zhixiao Wang, Leda P Mannent, Nikhil Amin, Yiping Sun, Elizabeth Laws, Bolanle Akinlade, Myles Dillon, Matthew P Kosloski, Mohamed A Kamal, Ariane Dubost-Brama, Naimish Patel, David M Weinreich, George D Yancopoulos, John T O'Malley, Ashish Bansal

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1. Participating Investigators

Country	Investigators
United States	Amber Pepper, Amy S Paller, Benjamin Lockshin, David Cohen, David Pariser, Elaine C Siegfried, Eric L Simpson, Jeffrey Leflein, Jeffrey Weinberg, John Browning, Joyce Teng, Lara Wine Lee, Lawrence Sher, Lucia Diaz, Lynda Schneider, Mercedes E Gonzalez, Ned Rupp, Peck Ong, Robert Cartwright, Robert Sidbury, Weily Soong
Germany	Andreas Pinter, Andreas Wollenberg, Christina Schnopp
United Kingdom	Michael J Cork, Peter D Arkwright
Poland	Anna Korkosz, Dorota Bystrzanowska, Ewa Sygula, Jacek Zdybski, Kamila Padlewska

2. Methods

2.1. Patient Eligibility Criteria

Detailed inclusion criteria

- Male or female 6 months to younger than 6 years at screening visit
- Diagnosis of atopic dermatitis (AD) according to the American Academy of Dermatology consensus criteria at screening visit[1]
- Investigator's Global Assessment (IGA) score 3 or higher at screening and baseline visits
- Eczema Area and Severity Index (EASI) 16 or higher at the screening and baseline visits

- Baseline worst scratch/itch Numeric Rating Scale (NRS) score weekly mean score for maximum scratch/itch intensity 4 or higher
- 10% or higher body surface area (BSA) of AD involvement at the screening and baseline visits
- Patients with documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s)
- At least 11 (of a total of 14) daily applications of medium-potency topical corticosteroids (TCS) during the 2-week TCS standardisation period (beginning on day −14) leading up to the baseline visit (not including the day of randomisation)
- At least 11 (of a total of 14) applications of a topical emollient (moisturiser) during the 7 consecutive days immediately before the baseline visit (not including the day of randomisation)
- Parent(s) or legal guardian–provided signed informed consent. Assent collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based on age and level of maturity of the patient
- Parents, caregivers, or legal guardians, as appropriate, are able to understand and complete the study requirements and study-related questionnaires

Detailed exclusion criteria

- Prior treatment with dupilumab
- History of important side effects to low-potency TCS (e.g., intolerance to treatment, hypersensitivity reactions to hydrocortisone 1%/hydrocortisone acetate 1% cream, significant skin atrophy, systemic effects), as assessed by the investigator or patient's treating physician
- Treatment with a topical investigational drug within 2 weeks or within 5 half-lives (if known), whichever is longer, or treatment with a systemic investigational drug prior to the baseline visit
- Treatment with a topical calcineurin inhibitor within 2 weeks prior to the baseline visit

- Use of any of the following treatments within 4 weeks before baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during first 4 weeks of study treatment:
  - Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine A, mycophenolate mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate)
  - Phototherapy for AD
  - Treatment with biologics, as follows:
    - Any cell-depleting agents including, but not limited to, rituximab: within 6 months before the baseline visit, or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer
    - Other biologics: within 5 half-lives (if known) or 16 weeks before the baseline visit, whichever is longer
- Treatment with crisaborole within 2 weeks prior to the baseline visit
- Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment
- Initiation of treatment with prescription moisturisers or moisturisers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin-degradation products during the screening period
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoal, or antifungals within 2 weeks before the baseline visit
- Established diagnosis of a primary immunodeficiency disorder (e.g., Severe Combined Immunodeficiency, Wiskott-Aldrich syndrome, DiGeorge syndrome, X-linked agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency. Patients suspected to have immunodeficiency based on their clinical presentation (history of invasive opportunistic infections, eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, chronic mucocutaneous candidiasis, etc. or otherwise

recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the investigator)

- Eczema as part of a genodermatosis syndrome, such as Netherton syndrome, hyper IgE syndrome, Wiskott-Aldrich syndrome, etc.
- Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit
- Established diagnosis of hepatitis B viral infection at the time of screening or positive for hepatitis B surface antigen or hepatitis B core antibody at the time of screening
- Established diagnosis of hepatitis C viral infection at the time of screening or positive for hepatitis C antibody at the screening visit
- History of past or current tuberculosis or other mycobacterial infection
- Known hepatic disease or on current treatment for hepatic disease, including, but not limited to, acute or chronic hepatitis, cirrhosis or hepatic failure, or evidence of liver disease as indicated by persistent (confirmed by repeated tests 2 or more weeks apart) elevated transaminases (alanine aminotransferase and/or aspartate aminotransferase) more than 3 times the upper limit of normal (ULN) during the screening period
- Presence of any one or more of the following abnormalities in laboratory tests at screening:
  - Platelets ≤100 × 10^3/µL
  - Neutrophils ≤1.0 × 10^3/µL for patients younger than 1 year; neutrophils ≤1.5 × 10^3/µL for patients 1 year to younger than 6 years
  - Creatine phosphokinase >2.5 × ULN
  - Serum creatinine >1.5 × ULN
  - Eosinophils >5000/µL
- Presence of skin comorbidities that may interfere with study assessments

- History of malignancy before the baseline visit
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomisation
- Severe concomitant illness(es) that, in the investigator's judgement, would adversely affect the patient's participation in the study
- Any other medical or psychological conditions, including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments
- Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
- Planned major surgical procedure during the patient's participation in this study
- Patient or immediate family is a member of the dupilumab investigational team
- Body weight <5 kg or ≥30 kg

2.2 Data and Safety Monitoring Committee

An Independent Data Monitoring Committee (IDMC), composed of members who are independent from the sponsor and the study investigators, monitored patient safety by conducting formal reviews of accumulated safety data. If requested, the IDMC could be given access to any other requested data for the purposes of a risk–benefit assessment.

The IDMC provided the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC was provided with a summary of the data analysed during these meetings. Advice of IDMC could be sought by the internal safety monitoring team regarding decisions to suspend dosing. The IDMC instituted any measures that

could be required for ensuring the integrity of the study results during the study execution. This committee was in place for the duration of the study to monitor the safety of the patients and to provide the sponsor with appropriate recommendations in due time to ensure patient safety. All activities and responsibilities of the IDMC are described in the IDMC charter.

2.3 Rescue Treatment

As rescue treatment, medium- or high-potency TCS, systemic corticosteroids, non-steroidal immunosuppressants (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine), crisaborole, or topical calcineurin inhibitors could be provided to study patients at the discretion of the investigator. The use of rescue treatment was only allowed after day 14 of the study. Investigators were required to perform an IGA prior to starting rescue treatment and could initiate rescue treatment only in patients who either had an IGA score 3 or higher or had intolerable symptoms.

2.4 Prohibited Medications

Treatment with the following concomitant medications was prohibited during the study. Study drug was immediately discontinued if any of the following were used during the study:

- Treatment with a live (attenuated) vaccine; below is a list of examples of such vaccines
  - Chickenpox (Varicella)
  - Influenza
  - Measles (Rubeola)
  - Measles–mumps–rubella combination
  - Measles–mumps–rubella–varicella combination
  - Mumps

  - Oral polio (Sabin)
  - Oral typhoid
  - Rubella
  - Smallpox (Vaccinia)
  - Yellow fever
  - Bacillus Calmette-Guerin
  - Rotavirus

NOTE: Treatment with an inactivated vaccine (e.g., diphtheria–pertussis–tetanus, hepatitis A, hepatitis B, inactivated polio vaccine, *Haemophilus influenzae* type b, meningococcal, pneumococcal, and flu shot) was permitted during the study as well as during the screening period, without any requirement for washout prior to baseline visit. Live vaccines were prohibited within 4 weeks prior to the baseline visit or during the study, consistent with recent consensus recommendations.[2]

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic non-steroidal immunosuppressant (could be used as rescue)
- Treatment with medium-potency, high-potency, or very high-potency TCS (medium- or high-potency steroids could be used as rescue; a course of treatment with medium-potency TCS could also be given during the screening period to demonstrate inadequate response to TCS and confirm eligibility for the study)
- Treatment with topical calcineurin inhibitors (could be used as rescue); use was not permitted during the 2-week screening period leading up to the baseline visit, the treatment, and follow-up periods

2.5 Endpoints

Primary endpoint

- The primary endpoint was defined for the United States (US) and US Reference Market Countries: proportion of patients with an IGA score of 0 to 1 (on a 5-point scale) at week 16

Key secondary endpoints

- Proportion of patients with 75% or more improvement from baseline in EASI (EASI-75) at week 16 (identified as a co-primary endpoint for European Union [EU] or EU Reference Market Countries)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly mean of daily worst scratch/itch NRS score (itch was assessed by a parent/caregiver [see below])

Other secondary endpoints

- Proportion of patients with 50% or more improvement from baseline in EASI (EASI-50) at week 16
- Proportion of patients with 90% or more improvement from baseline in EASI (EASI-90) at week 16
- Change from baseline to week 16 in percent BSA affected by AD
- Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD) (subjective assessment of itch and sleeplessness was recorded for each symptom by the parent/caregiver or relative)
- Change from baseline to week 16 in weekly mean of daily worst scratch/itch NRS score (itch was assessed by a parent/caregiver)
- Proportion of patients with 4-point improvement or higher (reduction) of weekly mean of daily worst scratch/itch NRS score from baseline at week 16 (itch was assessed by a parent/caregiver)
- Proportion of patients with 3-point improvement or higher (reduction) of weekly mean of daily worst scratch/itch NRS score from baseline at week 16 (itch was assessed by a parent/caregiver)

- Change from baseline to week 16 in skin pain NRS score (skin pain was assessed by a parent/caregiver [see below])
- Change from baseline to week 16 in sleep quality NRS score (assessment of sleep quality and other sleep-related concepts using sleep diary was completed by parent/caregiver)
- Change from baseline to week 16 in health-related quality of life, as measured by Children's Dermatology Life Quality Index (patients 4 or older; administered to patients with assistance of a parent or adult "as necessary") or Infants' Dermatology Quality of Life Index (patients aged <4 years; completed by the child's parent or caregiver)
- Change from baseline to week 16 in Dermatitis Family Impact questionnaire (completed by an adult family member of a child affected by AD)
- Change from baseline to week 16 in Patient-Oriented Eczema Measure (administered to parents/caregivers)
- Topical treatment for AD: proportion of TCS medication-free days from baseline to week 16
- Mean weekly dose of low-potency TCS through week 16
- Mean of caregiver-missed workdays from baseline to week 16
- Mean weekly dose of medium- or high-potency TCS through week 16

Tertiary/exploratory endpoints

- Pharmacokinetic (PK) variables were functional dupilumab concentrations collected at sampling timepoints as specified in the protocol
- Biomarkers: thymus and activation-regulated chemokine, total serum IgE

Safety endpoints

- Incidence of serious adverse events (AEs) through week 16
- Incidence of skin infection treatment-emergent adverse events (excluding herpetic infections) through week 16

Details of caregiver assessment of daily worst scratch/itch NRS and skin pain NRS

- During the development of the two instruments (scratch/itch NRS and skin pain NRS), concept elicitation/cognitive debriefing interviews provided evidence that caregivers can differentiate the two concepts (data on file).[3,] Caregivers reported that their assessment of itch was based on observing their child "scratch" or "itch" the AD-affected area. In addition, their assessment was based on their child providing further confirmation of itching (e.g., complaining about itchy or 'scratchy' skin, asking the parent to assist in scratching or rubbing the itchy skin, or to apply a product to the affected area). For the caregivers with non-verbal children, confirmation of itching was largely based on observing their child scratching as well as their child's demeanour (e.g., irritability, crying, whining) and other non-verbal cues (e.g., pointing to the area with AD). For skin pain, caregivers generally reported that they could recognise pain or discomfort in their children after observing excessive scratching that sometimes led to bleeding, by their child's reaction (e.g., crying) when applying lotion to the AD-affected area, or by recognising their children's known pain behaviours. For those caregivers whose children were verbal, pain was indicated from the child's own reporting or otherwise indicating that their skin hurt.

2.6 Sensitivity Analyses

A sensitivity analysis on primary and co-primary efficacy endpoints using the tipping-point analysis method was planned in the statistical analysis to investigate the impact of the missing values for the primary efficacy analysis. This sensitivity analysis was not conducted because the number of patients with missing values was too small to allow a meaningful tipping-point analysis; multiple imputation (MI) was only implemented for 1 patient in the IGA 0 or 1 and EASI-75 responder analyses. Instead, post hoc sensitivity analyses using all observed values regardless of rescue treatment used were added for the primary and key secondary endpoints.

2.7 Subgroup Analyses

The analysis method for the subgroups will be the same as the primary analysis as appropriate. If for any reason, such as a small number of patients in a subgroup, the model-based inferential statistics cannot be computed, or deemed inappropriate, only descriptive statistics will be provided. Subgroups analysed here are:

- Patients aged <2 years
- Sex (male/female)
- Race (White, Black/African American, Other)
- Baseline weight group (5 kg to <15 kg and 15 kg to <30 kg)
- Region (North America, Europe)
- Age of disease onset (younger than 6 months or 6 months or older)
- Baseline IGA score (IGA 4 or 3)
- Baseline EASI (<25 and ≥25)
- Baseline BSA affected (<50% and ≥50%)
- Baseline Peak NRS score (<7 and ≥7)
- Previous use of systemic immunosuppressants (systemic corticosteroids and systemic non-steroidal immunosuppressant) (yes/no)

2.8 Statistical Analysis

Efficacy, safety, and PK analyses were performed in the full analysis set (all randomised patients as allocated), safety analysis set (all randomised patients who received any study drug, per actual treatment received) and PK set (all randomised patients who received any study drug with at least one non-missing drug concentration result), respectively.

- For continuous variables, descriptive statistics included the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum
- For categorical or ordinal data, frequencies and percentages were displayed for each category
- All data were summarised by 2 treatment groups (ie, dupilumab 200/300 mg every 4 weeks [q4w] and placebo)

Primary endpoint/co-primary endpoints (EU)

- Intercurrent events were handled as follows:
  - Discontinuation of study intervention: data collected after the patient discontinued treatment were included in the analyses
  - Initiation of rescue treatment: patients were considered as non-responders after such events
- Missing data imputation rules
  - Missing data due to withdrawn consent and lack of efficacy were imputed as non-responders
  - Missing data due to any other reason, including COVID-19, were imputed using MI as follows:
    - The underlying continuous (e.g., EASI) or categorical variable (e.g., IGA) will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI using the following steps:
      - Step 1: The monotone missing pattern is induced by the Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. The monotone missing pattern means that if a patient has a missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

- Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates, including treatment groups, randomisation strata (baseline weight group, baseline IGA, and region), and relevant baseline variables. For the categorical variable, such as IGA, a logistic regression under the monotone option will be used.
- Based on each imputed data, the response status (responder or non-responder) will be determined for each patient
- Once imputations are made, the week 16 data (binary response) of each of the 40 complete datasets will be analysed using the CMH test. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.[4] An appropriate transformation (such as Wilson-Hilferty transformation) of CMH test statistics can be used in Rubin's formula.[5]

Key secondary endpoints (continuous)

- Intercurrent events were handled as follows:
  - Discontinuation of study intervention: data collected after the patient discontinued treatment were included in the analyses
  - Initiation of rescue treatment: data after rescue treatment were assigned by post-baseline worst observation carried forward (WOCF). If there was no post-baseline assessment, the baseline value was used
- Missing data imputation rules

- Missing data due to withdrawn consent, AE, or lack of efficacy were imputed by post-baseline WOCF. If there was no post-baseline assessment, the baseline value was used
- Missing values due to other reasons, including COVID-19, were imputed by the MI approach, as follows:
    - For continuous variables, the MI will be performed based on all observed data before the imputation by the WOCF approach. To account for the uncertainty in the imputation, missing data from the FAS will be imputed 40 times to generate 40 complete data sets by using the SAS procedure MI following the two steps as follows:
        - Step 1: The monotone missing pattern is induced by the MCMC method in the MI procedure using seed number 12345. The monotone missing pattern means that if a patient has a missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.
        - Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomisation strata (baseline weight group, baseline IGA, and region), and relevant baseline variables.
        - Once imputations are made, the week 16 data (binary response) of each of the 40 complete datasets will be analysed using the ANCOVA model, with treatment, randomisation strata (baseline weight group, baseline IGA, and region), and relevant baseline included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.[5]
        - The imputation model will include:

- The covariates included in the ANCOVA model, including the treatment group, the baseline value, and the randomisation strata (baseline weight group, baseline IGA, and region).
- Measured endpoint values at every clinic visit (e.g., weeks 1, 2, 4, 8, 12, and 16 for EASI)

3. Tables and Figures

Table S1: **Primary analysis hierarchical testing order**

Level	Endpoints	Testing order
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	1
Co-primary/key secondary endpoint*	Proportion of patients with EASI-75 at week 16	2
Secondary endpoints	Percent change in EASI score from baseline to week 16†	3
	Percent change from baseline to week 16 in weekly mean of daily worst scratch/itch score†	4
	Proportion of patients with improvement (reduction) of weekly mean of daily worst itch NRS score ≥4 from baseline at week 16	5
	Proportion of patients with improvement (reduction) of weekly mean of daily worst itch NRS score ≥3 from baseline at week 16	6
	Proportion of patients with EASI-50 at week 16	7
	Proportion of patients with EASI-90 at week 16	8
	Change from baseline to week 16 in percent BSA affected by AD	9
	Change from baseline to week 16 in POEM score	10

	Percent change from baseline in SCORAD score at week 16	11
	Change from baseline in patient's sleep quality NRS score at week 16	12
	Change from baseline in patient's skin pain NRS score at week 16	13
	Change from baseline in DFI score at week 16	14
	Change from baseline in CDLQI at week 16	15
	Change from baseline in IDQOL at week 16	16

AD=atopic dermatitis. BSA=body surface area. CDLQI=Children's Dermatology Life Quality Index. DFI=Dermatitis Family Impact. EASI=Eczema Area and Severity Index. EASI-50/-75/-90=at least 50%/≥75%/≥90% improvement from baseline in EASI. IDQOL=Infants' Dermatitis Quality of Life. IGA=Investigator's Global Assessment. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. SCORAD, SCORing Atopic Dermatitis.

*Co-primary endpoint for EU and EU Reference Market Countries only, key secondary for USA. †Key secondary endpoint.

Table S2: **Efficacy outcomes at week 16**

	Endpoints	**Placebo + TCS (n=79)**	**Dupilumab 200/300mg q4w + TCS (n=83)**	**Difference *vs* placebo (95% CI)**	**p value *vs* placebo,**
Other secondary endpoints	Weekly mean caregiver sleep quality NRS score, LS mean change from baseline (SE)*	0·3 (0·3)	1·8 (0·3)	1·5 (0·9 to 2·1)	0·0002
	Caregiver workdays missed, mean (SD)	5·1 (9·0) (n=57)†	2·5 (5·5) (n=57)†	NA	NA
	Weekly dose of low potency TCS, mean (SD), g	13·4 (1·4)	10·5 (1·4)	−2·9 (−6·4 to 0·6)	0·10
	Weekly dose of medium-to-high potency TCS, mean (SD), g	6·1 (1·7)	3·0 (1·5)	−3·1 (−6·2 to −0·1)	0·046

CI=confidence interval. LS=least squares. NA=not applicable. NRS=Numerical Rating Scale. q4w=every 4 weeks. SD=standard deviation.

SE=standard error. TCS=topical corticosteroid.

*Increase in score means improvement. †Patients with data available; statistical testing was not planned for this endpoint.

Table S3: **Efficacy outcomes in patients younger than 2 years**

Efficacy outcomes	**Placebo + TCS (n=5)***	**Dupilumab 200/300mg q4w + TCS (n=6)**
IGA 0/1 at week 16	1 (20%)	2 (33%)
EASI-75 at week 16	1 (25%)†	4 (67%)
% Change in EASI from baseline to week 16	–30·0% (35·6)	–64·6% (42·1)
% Change in worst scratch/itch NRS from baseline to week 16	–5·5% (11·8)	–52·4% (39·8)

Data are n (%) or LS mean (SE). IGA score range: 0–4; EASI range: 0–72; worst scratch/itch NRS score range: 0–10. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates.

EASI=Eczema Area and Severity Index. EASI-75=at least 75% improvement from baseline in EASI. IGA=Investigator's Global Assessment. LS=least squares. MI=multiple imputation. NRS=Numerical Rating Scale. q4w=every 4 weeks. SE, standard error. TCS=topical corticosteroid.

*One patient in the placebo plus TCS treatment group was randomised in error and did not receive study treatment. †Patients with missing values of EASI score due to other reasons, including COVID-19, are imputed by MI, and the response status is then derived. All non-missing data are used for MI.

Table S4: **Efficacy outcomes at week 16 according to baseline body weight**

Endpoint	Baseline body weight ≥5 kg to <15 kg			Baseline body weight ≥15 kg to <30 kg		
	Placebo + TCS (n=25)	Dupilumab 200 mg q4w + TCS (n=26)	Difference *vs* placebo (95% CI)	Placebo + TCS (n=54)	Dupilumab 300 mg q4w + TCS (n=57)	Difference *vs* placebo (%) (95% CI)
IGA 0/1 at week 16	1 (4%)	10 (39%)	34% (14 to 55)	2 (4%)	13 (23%)	19% (7 to 31)
EASI-75 at week 16	2 (9%)	15 (58%)	49% (26 to 71)	6 (12%)	29 (51%)	39% (24 to 55)
% Change in EASI score from baseline to week 16	–14·6 %(8·8)	–57·3% (8·2)	–42·7% (–66·2 to –19·2)	–10·1% (5·3)	–65·5% (5·1)	–55·4% (–69·9 to –40·9)
% Change worst scratch/itch NRS score from baseline to week 16	11·5% (10·6)	–44·0% (10·3)	–55·5% (–84·4 to –26·5)	–5·6% (4·0)	–47·3% (3·9)	–41·7% (–52·6 to –30·8)
≥4-point reduction in worst scratch/itch NRS score from baseline to week 16	1/24 (6%)	13/26 (52%)	46% (24 to 68)	6/54 (10%)	27/57 (47%)	36% (20 to 52)
≥3-point reduction in worst scratch/itch NRS score from baseline to week 16	2/24 (7%)	15/26 (56%)	49% (27 to 72)	6/54 (11%)	30/57 (52%)	41% (25 to 57)
Proportion of patients with EASI-50 at week 16	4 (18%)	16 (62%)	44% (20 to 68)	12 (21%)	41 (72%)	51% (34 to 67)
Proportion of patients with EASI-90 at week 16	0	9 (35%)	34% (15 to 53)	2 (4%)	12 (21%)	17% (6 to 29)
Change in percent BSA affected by AD from baseline to week 16	–8·1 (5·2)	–29·5 (5·0)	–21·4 (–35·6 to –7·2)	–7·3 (3·0)	–33·2 (2·9)	–25·9 (–34·1 to –17·8)
Change in POEM score from baseline to week 16	–1·9 (1·6)	–11·3 (1·5)	–9·4 (–13·7 to –5·1)	–2·8 (1·0)	–11·8 (1·0)	–9·1 (–11·7 to –6·4)
% Change in SCORAD score from baseline to week 16	–13·9% (5·6)	–46·4% (5·3)	–32·5% (–47·7 to –17·4)	–10·3% (3·6)	–51·5% (3·5)	–41·2% (–51·0 to –31·4)
Change in patient's sleep quality NRS score from baseline to week 16	0·1 (0·4)	1·5 (0·4)	1·4 (0·4 to 2·4)	0·3 (0·3)	2·1 (0·3)	1·8 (1·1 to 2·6)
Change in patient's skin pain NRS score from baseline to week 16	0 (0·5)	–3·5 (0·5)	–3·5 (–4·9 to –2·2)	–0·6 (0·3)	–3·8 (0·3)	–3·3 (–4·1 to –2·4)

Data are n (%) or LS mean (SE). IGA score range: 0–4; EASI score range: 0–72; worst scratch/itch, sleep quality, and patient's skin pain NRS score ranges: 0–10; POEM score range: 0–28; SCORAD score range: 0–103. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates.

AD=atopic dermatitis. BSA=body surface area. EASI=Eczema Area and Severity Index. EASI-50/-75/-90=at least 50%/≥75%/≥90% improvement from baseline in EASI. IGA=Investigator's Global Assessment. LS=least squares. NRS=Numerical Rating Scale. POEM=Patient-Oriented Eczema Measure. q4w=every 4 weeks. SCORAD=SCORing Atopic Dermatitis. SE=standard error. TCS=topical corticosteroids.

Table S5: **Overview of treatment-emergent SAEs**

Primary System Organ Class **Preferred Term***	**Placebo + TCS** **(n=78)†**	**Dupilumab 200/300 mg q4w + TCS** **(n=83)**
Number of such events	5	0
Patients with at least 1 such event	4 (5%)	0
Infections and infestations	3 (4%)	0
Cellulitis staphylococcal	1 (1%)	0
Dermatitis infected	1 (1%)	0
Staphylococcal bacteremia	1 (1%)	0
Skin and subcutaneous tissue disorders	1 (1%)	0
Dermatitis atopic‡	1 (1%)	0
Immune system disorders	1 (1%)	0
Hypersensitivity§	1 (1%)	0

Data are n or n (%). Patients may have had more than one event.

AD=atopic dermatitis. MedDRA=Medical Dictionary for Regulatory Activities. q4w=every 4 weeks. SAE, serious adverse event. TCS=topical corticosteroid.

*MedDRA Version 23·1. †One patient in the placebo plus TCS treatment group was randomised in error and did not receive study treatment. ‡Exacerbation of AD. §Patient presented with swelling and skin erosions on the left side of the face, especially around the periorbital area.

Table S6: **Overview of skin infections**

High Level Term **Preferred Term***	**Placebo + TCS** **(n=78)**	**Dupilumab 200/300 mg q4w + TCS** **(n=83)**
Patients with at least 1 such event	19 (24%)	10 (12%)
Skin structures and soft tissue infections	9 (12%)	6 (7%)
Impetigo	6 (8%)	3 (4%)
Dermatitis infected	1 (1%)	1 (1%)
Paronychia	1 (1%)	1 (1%)
Skin infection	1 (1%)	1 (1%)
Molluscum contagiosum viral infections	2 (3%)	4 (5%)
Molluscum contagiosum	2 (3%)	4 (5%)
Bacterial infections NEC	3 (4%)	1 (1%)
Cellulitis	1 (1%)	1 (1%)
Skin bacterial infection	2 (3%)	0
Candida infections	1 (1%)	0
Genital candidiasis	1 (1%)	0
Infections NEC	2 (3%)	0
Abscess limb	1 (1%)	0
Superinfection	1 (1%)	0
Staphylococcal infections	7 (9%)	0
Cellulitis staphylococcal	1 (1%)	0
Furuncle	1 (1%)	0
Staphylococcal abscess	1 (1%)	0
Staphylococcal infection	1 (1%)	0
Staphylococcal skin infection	3 (4%)	0
Herpes viral infections	4 (5%)	5 (6%)
Herpes virus infection	0	2 (2%)
Varicella	0	2 (2%)

Eczema herpeticum	1 (1%)	0
Oral herpes	2 (3%)	1 (1%)
Herpes simplex	1 (1%)	0

Data are n (%). A total of 21 (13%) patients (7 [9%] and 14 [17%] in the dupilumab and placebo arm, respectively) had a prior history of herpes viral infections, including eczema herpeticum, genital herpes, herpes ophthalmic, *Herpes simplex*, and oral herpes.

MedDRA=Medical Dictionary for Regulatory Activities. NEC=not elsewhere classified. q4w, every 4 weeks. TCS=topical corticosteroid.

*MedDRA Version 23·1.

Table S7: **Safety outcomes in patients younger than 2 years**

Safety outcomes	**Placebo + TCS (n=4)***	**Dupilumab 200/300 mg q4w + TCS (n=6)**
Deaths	0	0
TEAEs	3 (75%)	4 (67%)
SAEs	0	0
Aes leading to treatment discontinuation	0	1 (17%)†
TEAEs of special interest	0	0
Conjunctivitis (narrow group)	0	0
Injection-site reaction (HLT)	0	1 (17%)
Skin infections	0	1 (17%)

Data are n (%).

AD=atopic dermatitis. AE=adverse event. HLT=MedDRA High Level Term. MedDRA=Medical Dictionary for Regulatory Activities. q4w=every 4 weeks. SAE=serious AE. TEAE=treatment-emergent adverse event. TCS=topical corticosteroids.

*One patient included in the placebo group was randomised in error and did not receive study treatment and was therefore not included in the safety analysis set. †Patient discontinued due to AE of AD flare.

Table S8: **Safety outcomes according to baseline body weight**

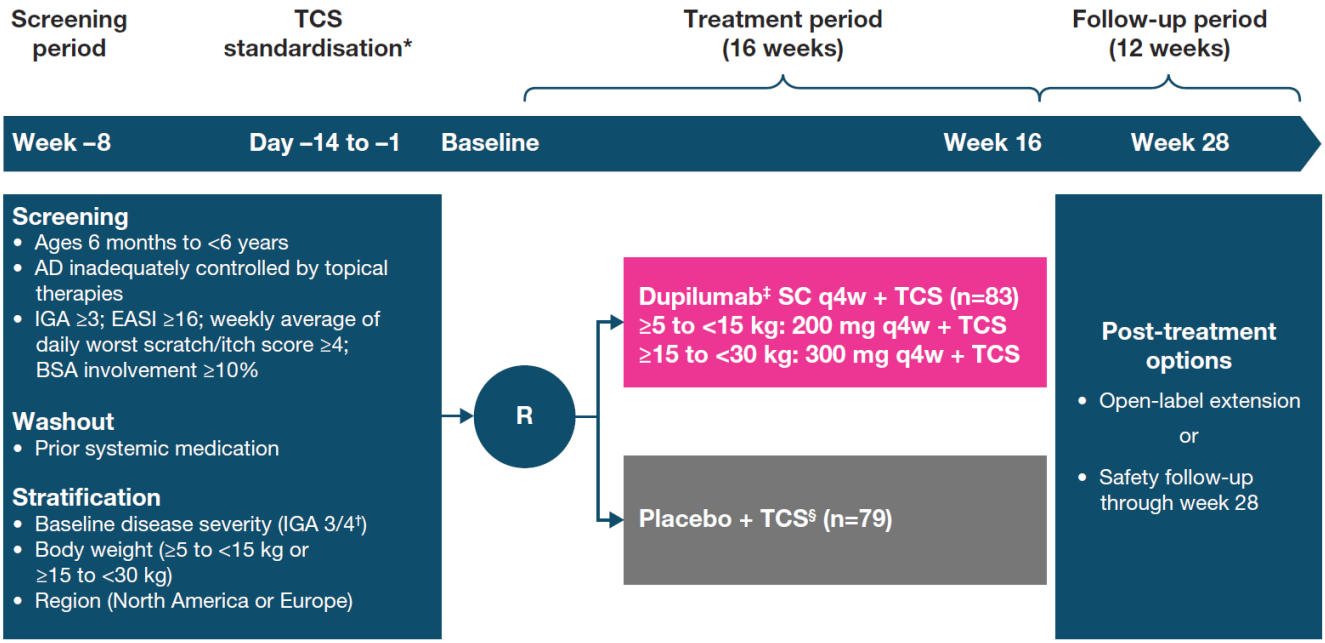
Overview	Baseline body weight ≥5 kg to <15 kg		Baseline body weight ≥15 kg to <30 kg	
	Placebo + TCS (n=24)*	Dupilumab 200 mg q4w + TCS (n=26)	Placebo + TCS (n=54)	Dupilumab 300 mg q4w + TCS (n=57)
Patients with ≥1 TEAE	20 (83%)	15 (58%)	38 (70%)	38 (67%)
Patients with TEAE leading to permanent treatment discontinuation	0	1 (4%)†	1 (2%)‡	0
Patients with ≥1 TEAE deemed related to study drug	0	1 (3%)	5 (9%)	8 (14%)
Patients with ≥1 severe TEAE	2 (8%)	0	8 (15%)	2 (4%)
Patients with ≥1 serious TEAE	1 (4%)	0	3 (6%)	0
Deaths	0	0	0	0
Patients with ≥1 serious TEAE deemed related to study drug	0	0	0	0
Patients with serious TEAE leading to permanent treatment discontinuation	0	0	0	0

Data are n (%).

AD=atopic dermatitis. q4w=every 4 weeks. TCS=topical corticosteroids. TEAE=treatment-emergent adverse event.

*One patient included in the placebo group was randomised in error and did not receive study treatment and was therefore not included in the safety analysis set. †Patient discontinued due to AE of AD flare. ‡Patient discontinued due to TEAE of nightmares due to blood draws.

Figure S1: **Study design of LIBERTY AD PRESCHOOL study (NCT03346434)**

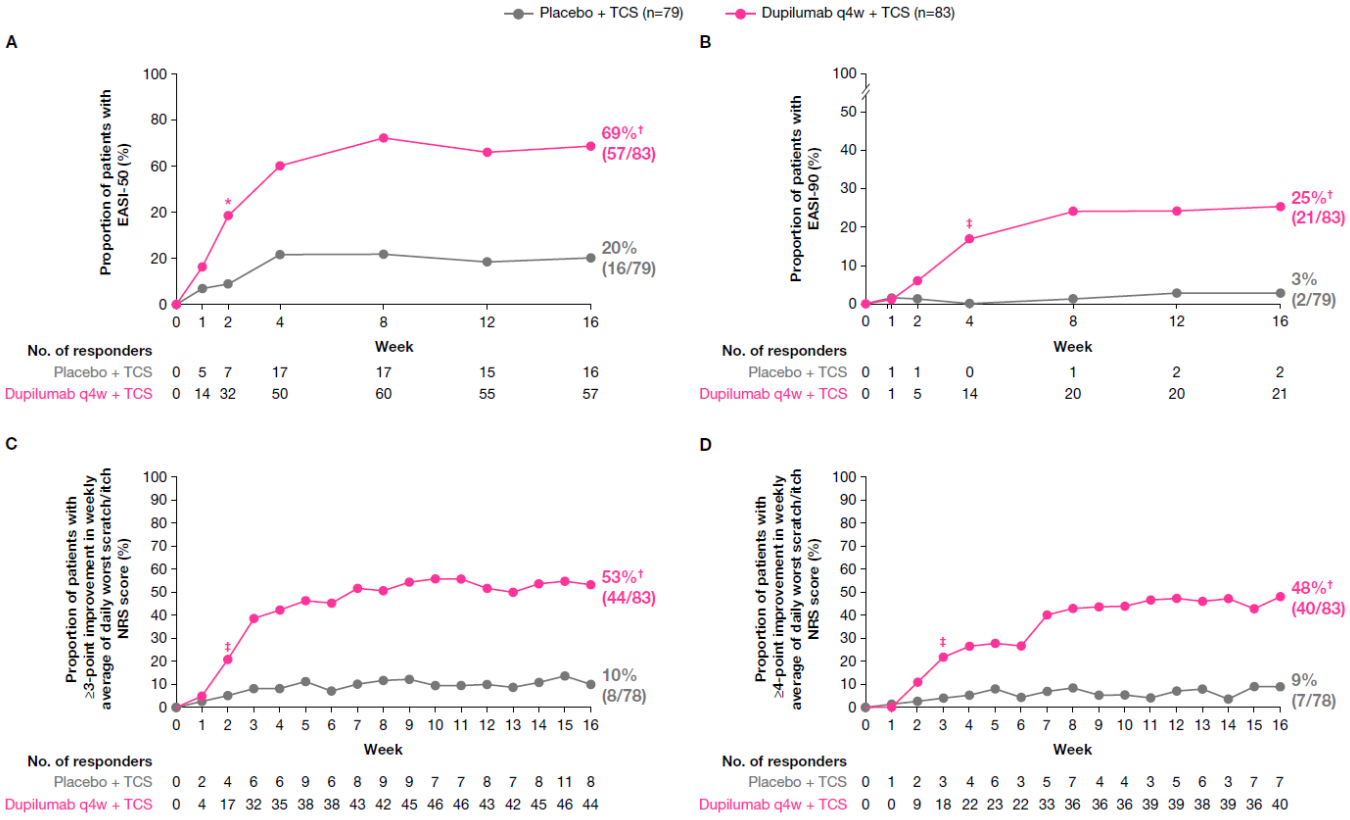


AD=atopic dermatitis. BSA=body surface area. EASI=Eczema Area and Severity Index. IGA=Investigator's Global Assessment. NRS=Numerical Rating Scale. q4w=every 4 weeks. R=randomisation. SC=subcutaneous. TCS=topical corticosteroid.

*Starting on day –14, all patients were to initiate a standardised low-potency TCS treatment regimen (hydrocortisone acetate 1% cream).

†Number of patients with IGA 3 was capped to 40. ‡No loading dose; weight-tiered doses assigned by baseline body weight for the duration of the study. §Placebo was matched based on baseline weight category.

Figure S2: **Secondary endpoints.** (A) Proportion of patients with EASI-50 through week 16; (B) proportion of patients with EASI-90 through week 16; (C) proportion of patients with ≥3-point improvement in weekly mean of daily worst scratch/itch NRS score from baseline through week 16; (D) proportion of patients with ≥4-point improvement in weekly mean of daily worst scratch/itch NRS score from baseline through week 16.

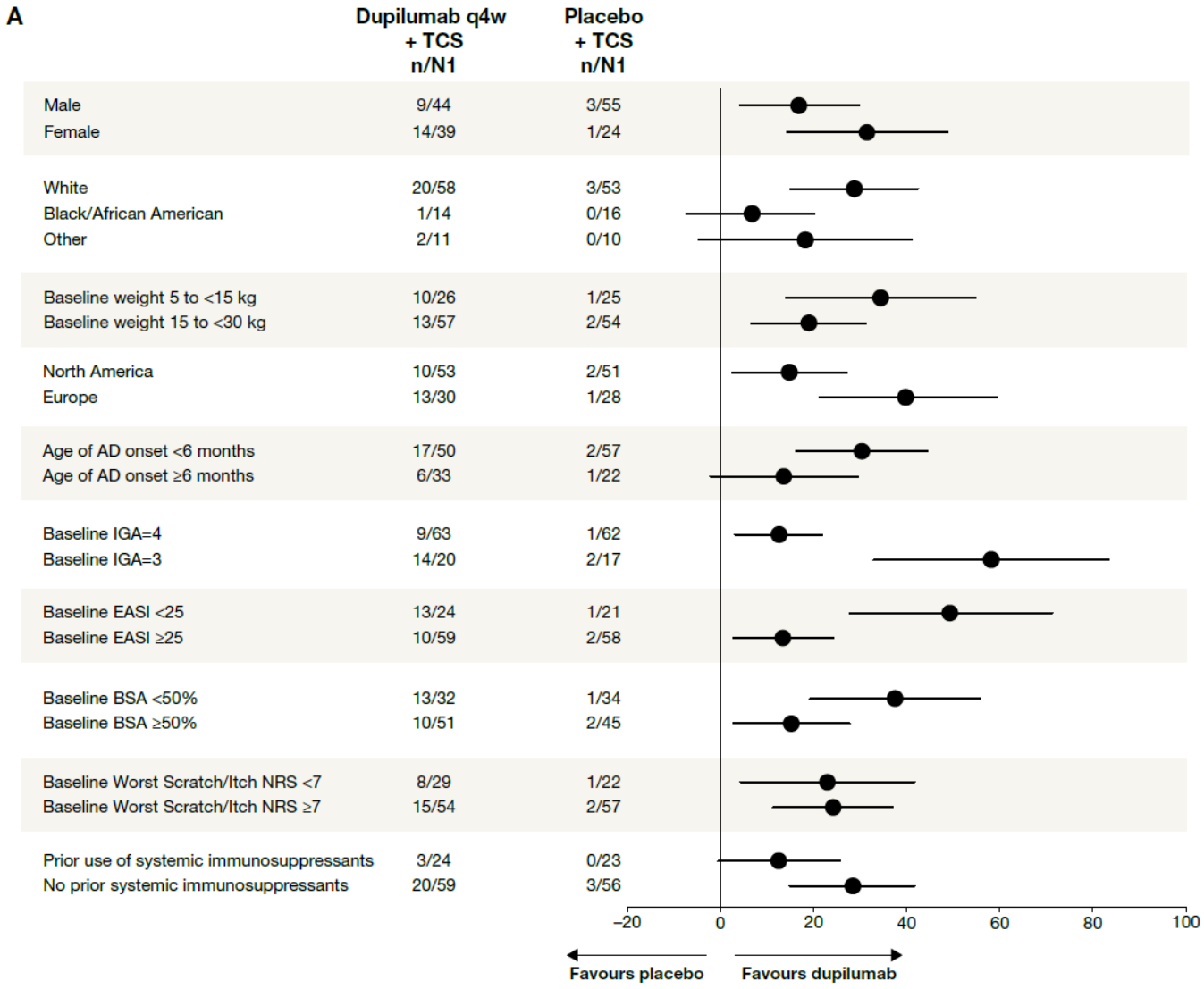


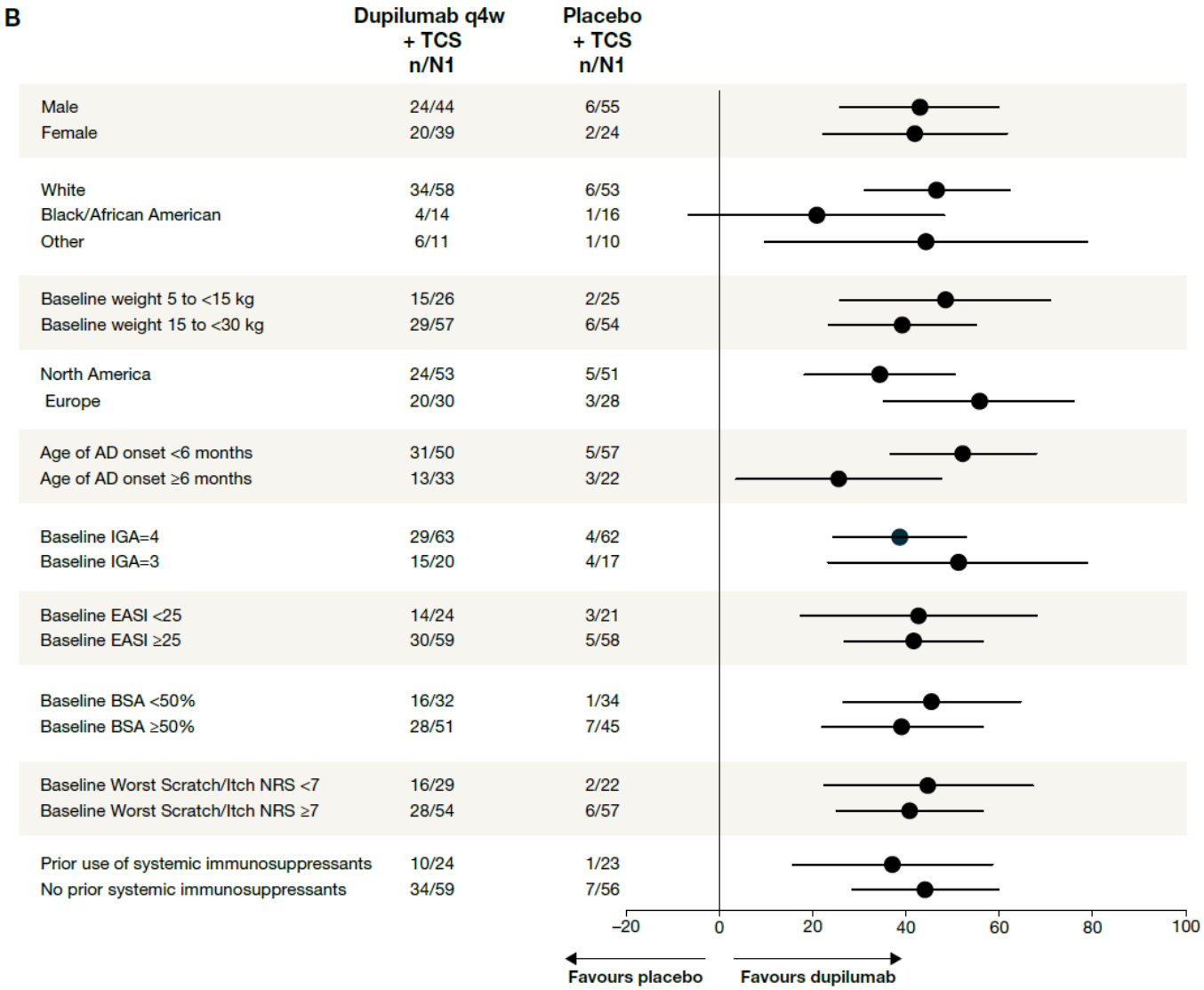
IGA score range: 0–4; EASI score range: 0–72; worst scratch/itch NRS score range: 0–10. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates.

EASI=Eczema Area and Severity Index. EASI-50/-90=at least 50%/≥90% improvement from baseline in EASI. NRS=Numerical Rating Scale. q4w=every 4 weeks. TCS, topical corticosteroid.

*nominal p<0·0001. †p<0·0001. ‡nominal p<0·01.

Figure S3: **Forest plots for achievement of (A) IGA 0/1 and (B) EASI-75, at week 16 by subgroup**

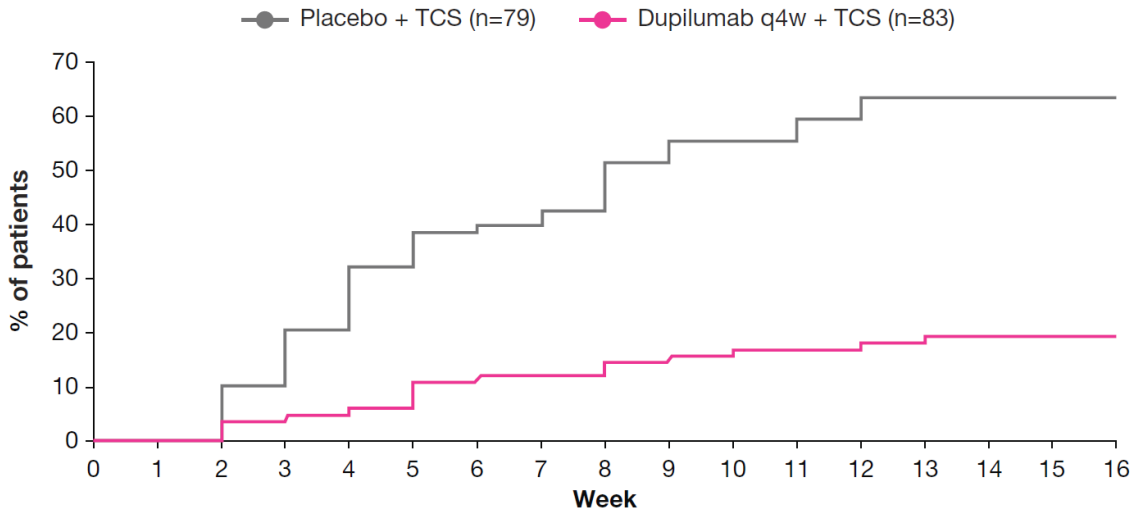




IGA score range: 0–4; EASI range: 0–72; worst scratch/itch NRS score range: 0–10. Proportions of patients achieving a categorical endpoint are presented as model-derived estimates.

AD=atopic dermatitis. BSA=body surface area. EASI=Eczema Area and Severity Index. EASI-75=at least 75% improvement from baseline in EASI. IGA=Investigator's Global Assessment. n/N1=number of patients who achieved endpoint/number of patients in subgroup for each treatment group. NRS=Numerical Rating Scale. TCS=topical corticosteroid.

Figure S4: **Kaplan–Meier curve of time to first use of rescue treatment or withdrawal from study from baseline through week 16***



No. of patients at risk

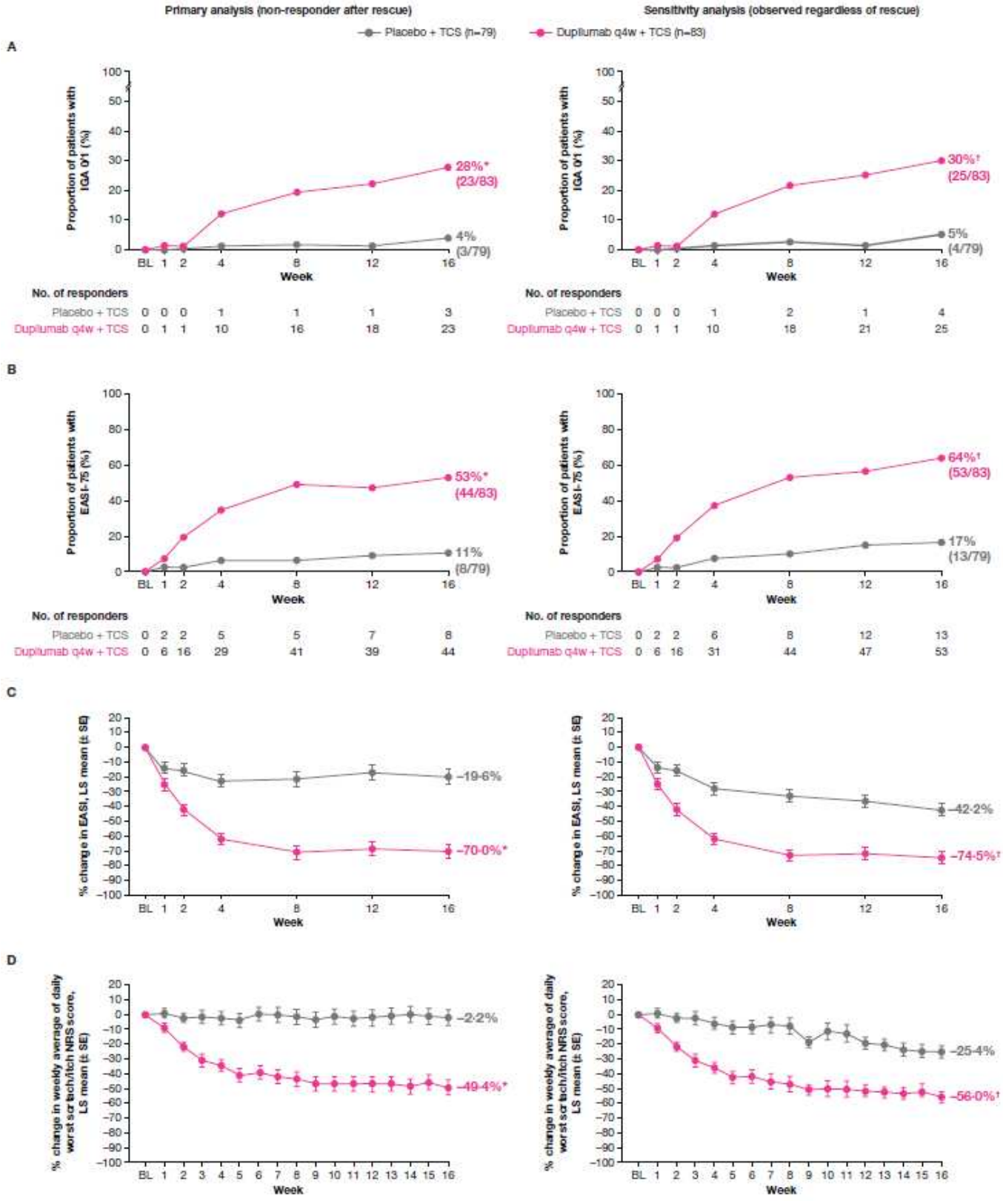
Placebo + TCS	79	79	78	70	62	53	48	47	44	37	34	34	31	28	28	28	28
Dupilumab q4w + TCS	83	83	83	80	79	78	74	73	73	71	70	69	69	68	67	67	67

AD=atopic dermatitis. q4w=every 4 weeks. TCS, topical corticosteroid.

*During the 16-week treatment period, 16 (16/83; 19%) patients in the dupilumab group and 49 (49/78; 63%) patients in the placebo group used at least one rescue medication. The most commonly used dermatological rescue medication by therapeutic class was dermatological preparations of corticosteroids. Systemic corticosteroids were used for rescue of exacerbation of AD in 2 (2/78; 3%) patients in the placebo group and 1 (1/83; 1%) patient in the dupilumab group.

Figure S5: **Sensitivity analyses**

(A) Proportion of patients with an IGA score of 0/1 through week 16; (B) proportion of patients with EASI-75 through week 16; (C) LS mean percent change in EASI from baseline through week 16; (D) LS mean percent change in weekly mean of daily worst scratch/itch NRS score from baseline through week 16.

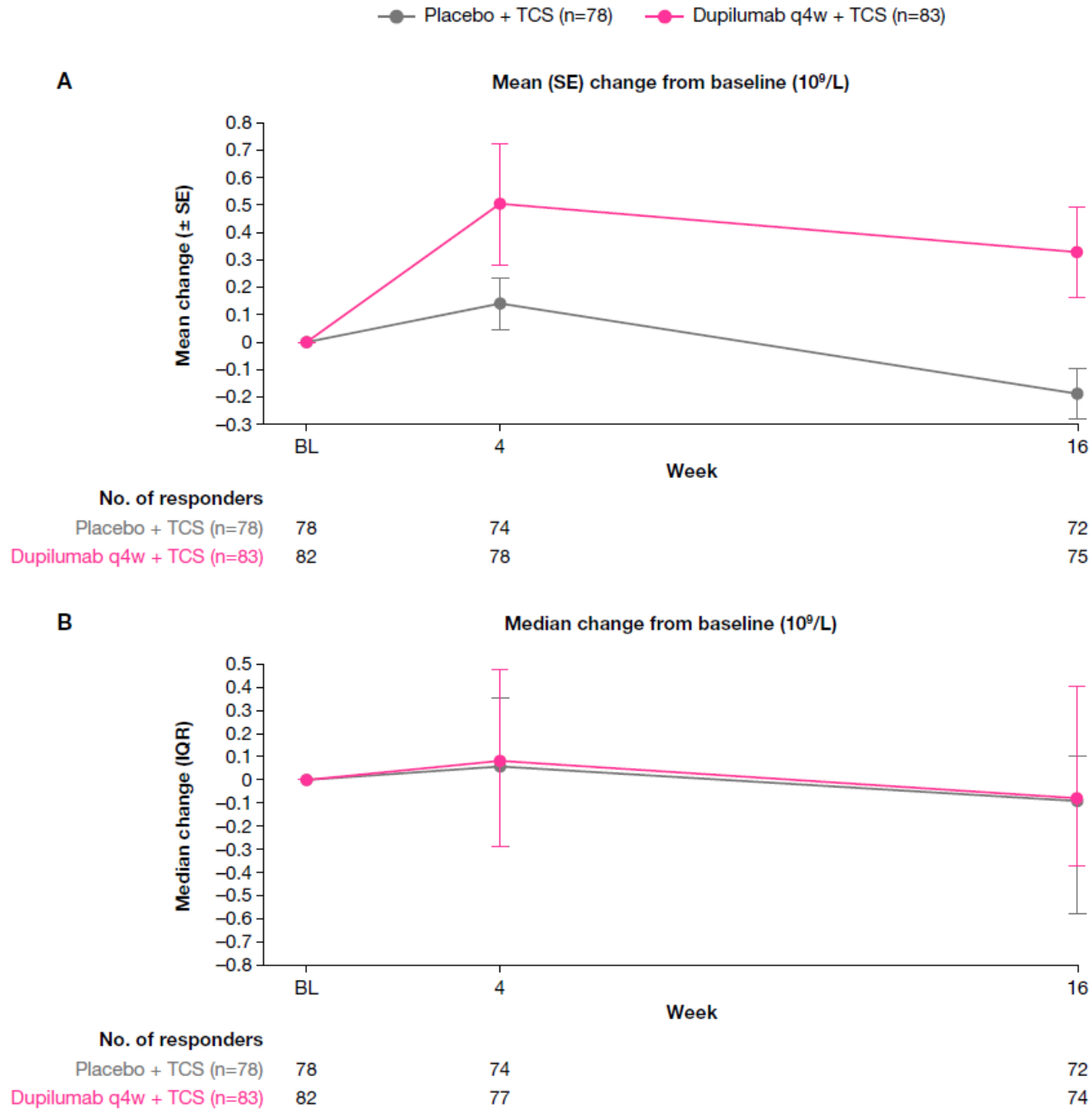


IGA score range: 0–4; EASI score range: 0–72; worst scratch/itch NRS score ranges: 0–10.

EASI=Eczema Area and Severity Index. EASI-75=at least 75% improvement from baseline in EASI. IGA=Investigator's Global Assessment. LS=least squares. NRS=Numerical Rating Scale. q4w=every 4 weeks. SE=standard error. TCS=topical corticosteroid.

*p<0·0001. †Nominal p<0·0001.

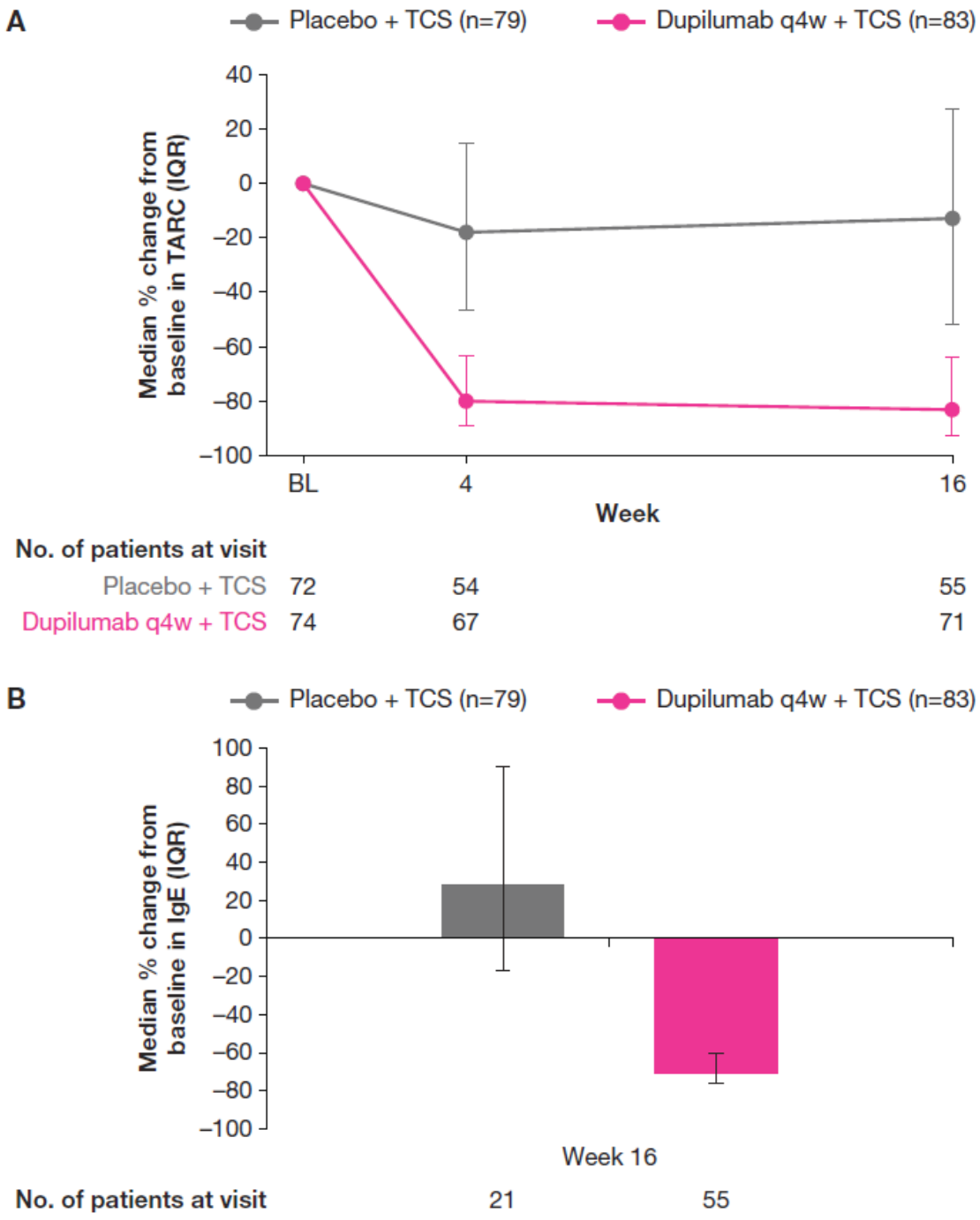
Figure S6: **Change from baseline in blood eosinophil counts through week 16**



BL=baseline. IQR=interquartile range. q4w=every 4 weeks. SE, standard error.

Figure S7: **Biomarker analysis**

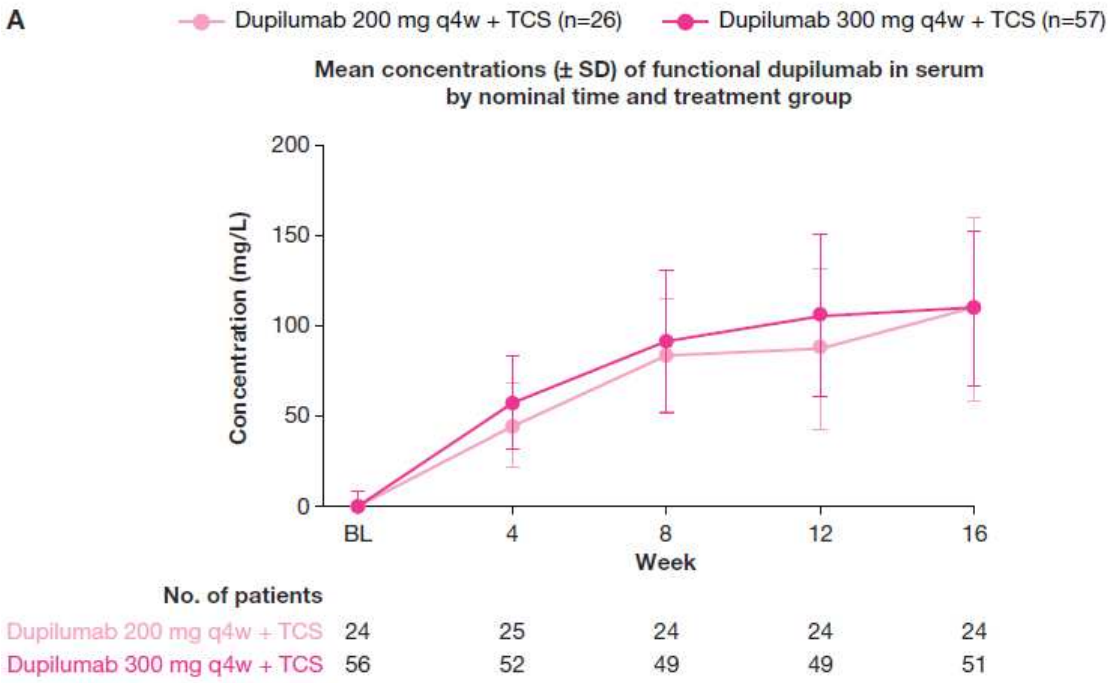
(A) Median percent change from baseline in serum TARC over time; (B) median percent change from baseline in serum total IgE at week 16.

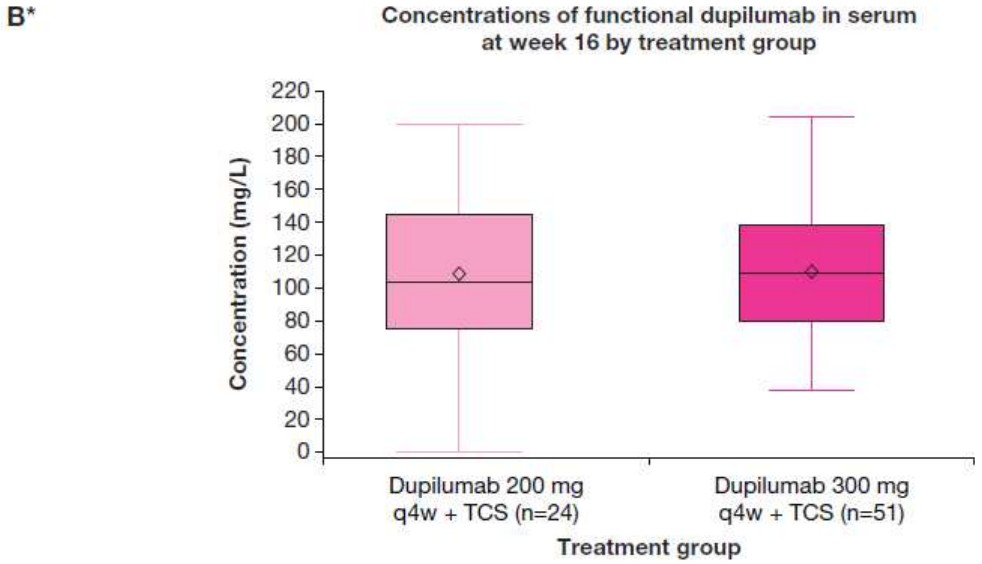


IQR=interquartile range. q4w=every 4 weeks. TARC=thymus and activation-regulated chemokine. TCS=topical corticosteroid.

Figure S8: **Concentrations of functional dupilumab**

(A) Concentrations of functional dupilumab over time; (B) concentrations of functional dupilumab at week 16.





BL=baseline. q4w=every 4 weeks. SD=standard deviation. TCS=topical corticosteroid.
*Boxes represent interquartile range, center line is median, diamond is mean, and bars represent minimum and maximum values.

4. References

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