Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial

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Summary

Background Dupilumab (an anti-interleukin-4-receptor-α monoclonal antibody) blocks signalling of interleukin 4 and interleukin 13, type 2/Th2 cytokines implicated in numerous allergic diseases ranging from asthma to atopic dermatitis. Previous 16-week monotherapy studies showed that dupilumab substantially improved signs and symptoms of moderate-to-severe atopic dermatitis with acceptable safety, validating the crucial role of interleukin 4 and interleukin 13 in atopic dermatitis pathogenesis. We aimed to evaluate the long-term efficacy and safety of dupilumab with medium-potency topical corticosteroids versus placebo with topical corticosteroids in adults with moderate-to-severe atopic dermatitis.

Methods In this 1-year, randomised, double-blinded, placebo-controlled, phase 3 study (LIBERTY AD CHRONOS), adults with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids were enrolled at 161 hospitals, clinics, and academic institutions in 14 countries in Europe, Asia-Pacific, and North America. Patients were randomly assigned (3:1:3) to subcutaneous dupilumab 300 mg once weekly (qw), dupilumab 300 mg every 2 weeks (q2w), or placebo via a central interactive voice/web response system, stratified by severity and global region. All three groups were given concomitant topical corticosteroids with or without topical calcineurin inhibitors where inadvisable for topical corticosteroids. Topical corticosteroids could be tapered, stopped, or restarted on the basis of disease activity. Coprimary endpoints were patients (%) achieving Investigator's Global Assessment (IGA) 0/1 and 2-point or higher improvement from baseline, and Eczema Area and Severity Index 75% improvement from baseline (EASI-75) at week 16. Week 16 efficacy and week 52 safety analyses included all randomised patients; week 52 efficacy included patients who completed treatment by US regulatory submission cutoff. This study is registered with ClinicalTrials.gov, NCT02260986.

Findings Between Oct 3, 2014, and July 31, 2015, 740 patients were enrolled: 319 were randomly assigned to dupilumab qw plus topical corticosteroids, 106 to dupilumab q2w plus topical corticosteroids, and 315 to placebo plus topical corticosteroids. 623 (270, 89, and 264, respectively) were evaluable for week 52 efficacy. At week 16, more patients who received dupilumab plus topical corticosteroids achieved the coprimary endpoints of IGA 0/1 (39% [125 patients] who received dupilumab plus topical corticosteroids qw and 39% [41 patients] who received dupilumab q2w plus topical corticosteroids *vs* 12% [39 patients] who received placebo plus topical corticosteroids; p<0·0001) and EASI-75 (64% [204] and 69% [73] *vs* 23% [73]; p<0·0001). Week 52 results were similar. Adverse events were reported in 261 (83%) patients who received dupilumab qw plus topical corticosteroids, 97 (88%) patients who received dupilumab q2w, and 266 (84%) patients who received placebo, and serious adverse events in nine (3%), four (4%), and 16 (5%) patients, respectively. No significant dupilumab-induced laboratory abnormalities were noted. Injection-site reactions and conjunctivitis were more common in patients treated with dupilumab plus topical corticosteroids-treated patients than in patients treated with placebo plus topical corticosteroids.

Interpretation Dupilumab added to standard topical corticosteroid treatment for 1 year improved atopic dermatitis signs and symptoms, with acceptable safety.

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Introduction

Atopic dermatitis is a chronic, relapsing inflammatory skin disorder characterised by intense pruritus and excoriations, with erythematous, xerotic, lichenified, fissured skin, and increased risk of skin infections.[1–3] Atopic dermatitis affects 2–10% of adults worldwide, and in severe cases is associated with substantial psychosocial distress and systemic comorbidities.[4,5] As a chronic

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Research in context

Evidence before this study

Long-term treatment options are limited for patients with moderate-to-severe atopic dermatitis refractory to topical therapy. Long-term use of systemic corticosteroids and other systemic immunosuppressants is not recommended, due to risk of serious toxicities. Dupilumab is a fully human monoclonal antibody that binds specifically to the shared α chain subunit of the interleukin-4 and interleukin-13 receptors, thereby inhibiting the signalling of interleukin 4 and interleukin 13. Dupilumab showed efficacy and acceptable safety in randomised, placebo-controlled, double-blind early-phase studies of dupilumab monotherapy for 4 weeks or 12 weeks, and with concomitant topical corticosteroids for 4 weeks, and as monotherapy for 16 weeks in phase 2b and phase 3 studies in patients with moderate-to-severe atopic dermatitis. To identify randomised, controlled, blinded clinical trials of long-term (>16 weeks) systemic treatment in atopic dermatitis, we searched PubMed using the search terms: "atopic dermatitis", "eczema", "systemic", "cyclosporine", "ciclosporin", "methotrexate", "azathioprine", "mycophenolate", "methylprednisolone", "dexamethasone", "prednisolone", "prednisone", "corticosteroids", "glucocorticoids", "antibody", "clinical trial", and "human", published from Jan 1, 1995, to Jan 25, 2017. We identified four randomised, controlled long-term studies of ciclosporin with or without topical treatments. No other randomised, controlled studies of long-term systemic treatment were identified, and thus neither a meta-analysis nor a systemic review was done.

Added value of this study

LIBERTY AD CHRONOS is the first long-term, placebo-controlled, double-blinded study with dupilumab that allowed for the concomitant use of medium-potency or low-potency topical corticosteroids with or without topical calcineurin inhibitors as background therapy in patients with moderate-to-severe atopic dermatitis and inadequate response to topical medications. Patients were randomly assigned (3:1:3) to dupilumab 300 mg weekly, dupilumab 300 mg every 2 weeks, or placebo weekly; all patients used concomitant topical corticosteroids with or without topical calcineurin inhibitors, which could be tapered or stopped and restarted depending on need, or topical calcineurin inhibitors where inadvisable for topical corticosteroids. Our results show significant benefit of adding dupilumab to topical corticosteroids with or without topical calcineurin inhibitors over a broad range of efficacy outcomes. Both dupilumab plus topical corticosteroids dose groups, compared with placebo plus topical corticosteroids, improved multiple measures of clinical severity, reduced rates of atopic dermatitis flares, and improved pruritus and other patient-reported symptoms of atopic dermatitis, symptoms of depression and anxiety, and quality of life. Dupilumab plus topical corticosteroids had an acceptable safety profile with no clinically meaningful differences in laboratory values. No new safety signals were identified in this study, showing no additional safety concerns resulting from concomitant topical corticosteroids with or without topical calcineurin inhibitors with dupilumab.

Implications of all the available evidence

In view of the chronicity and dynamic nature of atopic dermatitis and the resulting need for long-term treatment, the 1-year safety and efficacy outcomes of this study provide critical evidence for assessment of the benefit-to-risk profile of dupilumab for long-term management of moderate-to-severe atopic dermatitis not adequately controlled with topical corticosteroids with or without topical calcineurin inhibitors alone. Dupilumab added to a background of concomitant topical medications improved multiple aspects of clinical and patient-reported outcomes considered to be crucial to positively modify the natural history of moderate-to-severe atopic dermatitis. Because these topical medications are a mainstay of treatment for moderate-to-severe atopic dermatitis per current treatment guidelines, their concomitant use (as needed) in this study closely mimics real-world treatment protocols and might provide relevant guidance on the use of a biological background therapy in adults with moderate-to-severe atopic dermatitis.

disease, moderate-to-severe atopic dermatitis often requires long-term treatment; however, data for efficacy and safety of long-term treatment with systemic immunosuppressive medications are limited.[6–16] Treatment guidelines recommend limiting treatment with high-potency topical corticosteroids with or without topical calcineurin inhibitors to a short period for acute atopic dermatitis flares uncontrolled by moisturisers and general skin care.[14,15,17–19] Systemic treatments, including corticosteroids and immunosuppressants (eg, ciclosporin, methotrexate, or azathioprine) or phototherapy are only recommended when atopic dermatitis is not controlled by topical medications or when topical corticosteroids cannot be tapered to safe maintenance levels.[14–20] Neither continuous use of high-potency topical corticosteroids nor systemic treatments are suitable for long-term treatment due to an unfavourable benefit-to-risk profile.[14–20] Therefore, there is a high unmet need for safe and effective long-term therapies for moderate-to-severe atopic dermatitis.

Dupilumab is a fully human monoclonal antibody that binds specifically to the shared α chain subunit of the interleukin-4 and interleukin-13 receptors (interleukin-4R-α), inhibiting the signalling of interleukin 4 and interleukin 13, type 2/Th2 inflammatory cytokines implicated in numerous allergic diseases ranging from asthma to atopic dermatitis.[21] In its first pivotal study in asthma, dupilumab showed substantial improvement in

lung function assessed by forced expiratory volume in 1 s (FEV_1) as well as 71–81% reduction in exacerbations,[22] while a phase 2 study in nasal polyposis with chronic rhinosinusitis also robustly satisfied all its primary endpoints.[23] Similarly, both in early-phase, randomised, placebo-controlled studies in which dupilumab was given either as monotherapy or concomitantly with topical corticosteroids,[24–26] as well as in two larger phase 3 studies in which dupilumab monotherapy was compared with placebo at 16 weeks in patients with moderate-to-severe atopic dermatitis and inadequate response to topical medications,[27] dupilumab resulted in clinically and significant improvements in clinical signs and symptoms of atopic dermatitis, with an acceptable safety profile. These clinical studies validate the crucial role of interleukin 4 and interleukin 13 in multiple allergic (type 2 immune) disease settings, and particularly in atopic dermatitis. Dupilumab has been approved by the US Food and Drug Administration (FDA) for use in adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

We aimed to assess efficacy and safety of 52 weeks of continuous treatment with two dose regimens of dupilumab with background therapy of concomitant medium-potency or low-potency topical corticosteroids with or without topical calcineurin inhibitors, in comparison to topical corticosteroids with or without topical calcineurin inhibitor treatment, in adults with moderate-to-severe atopic dermatitis who had a previously documented inadequate response to topical medication (topical corticosteroids with or without topical calcineurin inhibitors) or systemic treatment. Concomitant topical corticosteroids with or without topical calcineurin inhibitors could be tapered, stopped, or restarted as clinically required during the study. Efficacy at week 16 was the primary objective; key secondary objectives were safety and efficacy over the 52-week treatment period.

Methods

Study design and participants

This 1-year randomised, placebo-controlled, double-blind, multicentre, parallel-group phase 3 study (LIBERTY AD CHRONOS) was done at 161 sites (hospitals, clinics, and academic institutions) in Australia, Canada, Czech Republic, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Romania, South Korea, Spain, the UK, and the USA (appendix pp 3–6).

Key inclusion criteria included age 18 years or older; atopic dermatitis (American Academy of Dermatology Consensus Criteria[3]) present for 3 or more years before screening; documented history within 6 months before screening of inadequate response to medium-potency to high-potency topical corticosteroids (with or without topical calcineurin inhibitors as appropriate), or documented systemic treatment within the past 6 months, or both; and Investigator's Global Assessment (IGA) score of 3 or higher (moderate-to-severe on a scale of 0–4) and Eczema Area and Severity Index (EASI) score of 16 or higher at screening and baseline. Full inclusion and exclusion criteria are listed in the appendix (pp 7–9).

This study was done in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines (version R1), and applicable regulatory requirements. All patients provided signed written informed consent. The protocol and all relevant study forms were approved by all relevant institutional review boards and an independent ethics committee. An independent data monitoring committee monitored patient safety.

For the **study protocol** see http://dupilumab.regpha.com/R668-AD-1224_Protocol.pdf

Randomisation and masking

Patients were randomly assigned (3:1:3) to dupilumab 300 mg once weekly (qw), dupilumab 300 mg every 2 weeks (q2w), or placebo qw, using a central randomisation scheme provided by an interactive voice/web response system, stratified by baseline disease severity (moderate [IGA=3] *vs* severe [IGA=4]) and geographical region (Asia Pacific, eastern Europe, North America, and western Europe). Patients given dupilumab q2w received matching placebo in the weeks when dupilumab was not given. Blinded study drug kits with a medication numbering system were used. Placebo was provided in identical syringes. The study remained blinded to all individuals (including patients, investigators, and study personnel) until the time of prespecified unblinding, except for the statistician who provided the randomisation sequence, and independent data monitoring committee members. The study was unblinded after database lock, on May 18, 2016.

Procedures

Patients applied moisturisers at least twice daily for the 7 days immediately before randomisation and throughout the study. After a 35-day screening period, dupilumab or placebo was given subcutaneously for 52 weeks. All patients received concomitant topical corticosteroids; topical calcineurin inhibitors could be used in body locations considered inadvisable for topical corticosteroids. Rescue treatment, consisting of any locally approved treatments for atopic dermatitis, including topical or systemic medications or phototherapy, could be used after week 2. After the 52-week treatment period, patients entered a follow-up period of 12 weeks. Patients who completed the study, including those who flared (ie, had worsening of disease that required escalated treatment) during the follow-up, or who discontinued study drug but completed all study visits, were eligible to enter an open-label extension (LIBERTY AD OLE; NCT01949311).

See Online for appendix

On day 1, patients received a loading dose of 600 mg dupilumab or placebo. Starting on day 1, all patients used

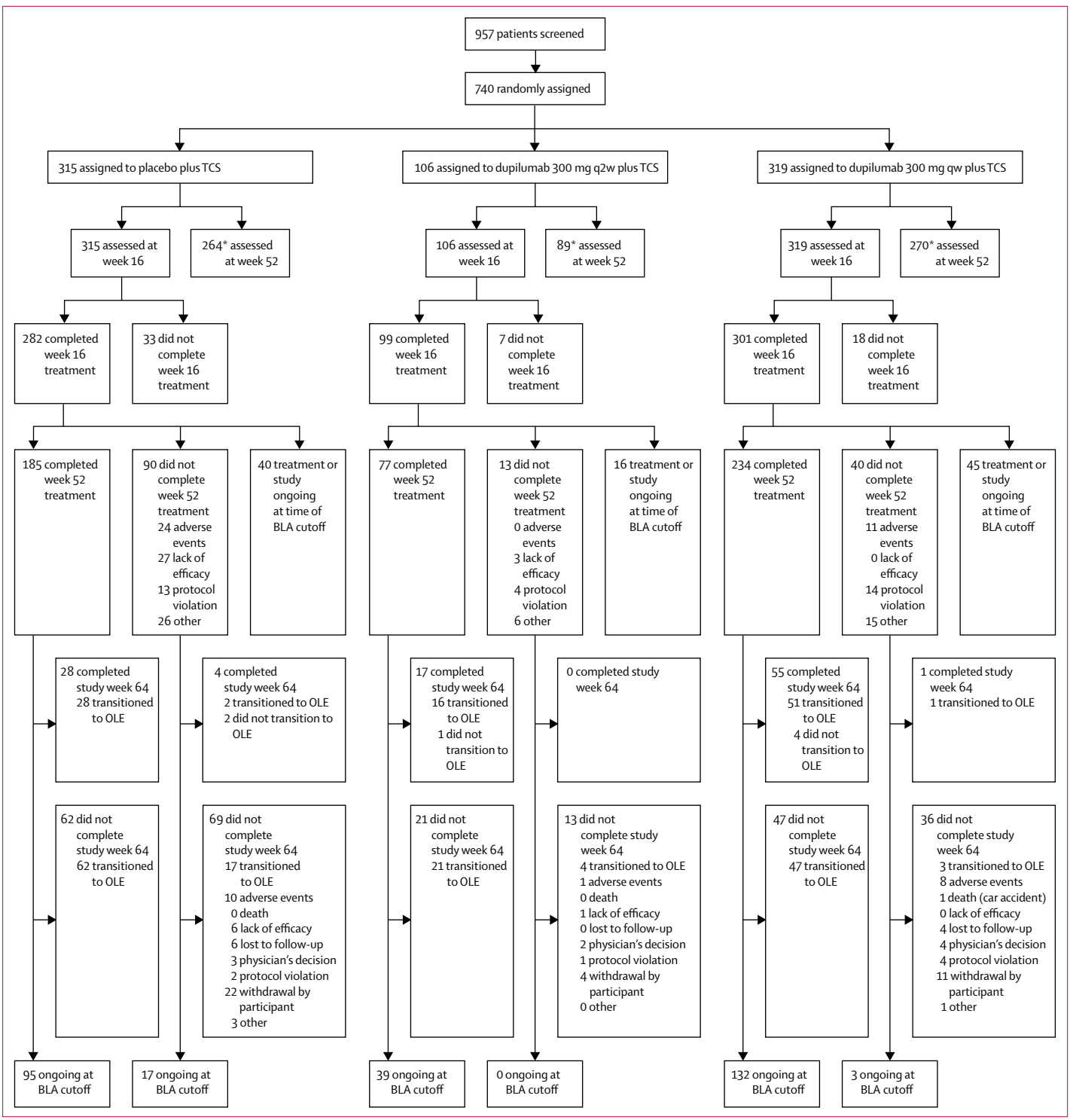


Figure 1: **Trial profile**
*Randomised by April 27, 2015. BLA=biologics licence application. OLE=open-label extension. q2w=every 2 weeks. qw=once weekly. TCS=topical corticosteroids.

once-daily medium-potency topical corticosteroids, or low-potency topical corticosteroids for sensitive skin areas (eg, face); potency per US classification (appendix p 14).[28] Topical calcineurin inhibitors could be used in place of topical corticosteroids in locations such as the face, intertriginous areas, and genital areas. After disease

was controlled (clear or almost clear), patients using medium-potency topical corticosteroids switched to low-potency topical corticosteroids for 7 days, then stopped; for sensitive skin locations, low-potency topical corticosteroids or topical calcineurin inhibitors could be tapered and stopped. If lesions returned, patients could retreat with topical corticosteroids with or without topical calcineurin inhibitors as before. Patients were clinically monitored for toxicity to topical corticosteroids, and stepped down or stopped as needed.

After week 2, patients with intolerable atopic dermatitis symptoms could receive rescue treatment with any locally approved atopic dermatitis treatments at the investigator's discretion. Patients receiving high-potency topical corticosteroids as rescue could continue with study drug. If rescue consisted of systemic medications or phototherapy, study drug was temporarily discontinued, but could be restarted after discontinuing systemic rescue treatment and a five half-lives washout period (systemic medications), or 1 month after completing phototherapy. Patients who received rescue treatment or discontinued study drug could continue study visits and assessments.

Patients were assessed for eligibility, medical history, demographics, comorbid type 2 immune diseases (ie, atopic or allergic disorders, such as asthma, allergic rhinitis, and food allergies), concomitant medications or procedures, adverse events, and efficacy outcomes at baseline (day 1); and safety (including laboratory assessments) and efficacy once weekly (weeks 1–4), then every 4 weeks (weeks 8–64). Study visits could be conducted by telephone at weeks 5, 7, 9–11, and 13–15 for patients who self-administered or whose caregiver administered study drug. See appendix p 9 for prohibited and permitted concomitant medications.

Outcomes

The two coprimary endpoints were the proportion of patients with both IGA 0/1 (clear/almost clear; 0–4 scale) and 2-point or higher reduction from baseline at week 16, and the proportion of patients achieving 75% improvement in EASI (EASI-75) from baseline to week 16.

Key secondary efficacy endpoints were: proportions of patients achieving: IGA 0/1 and 2-point or higher reduction from baseline at week 52, EASI-75 at week 52, peak pruritus numerical rating scale (NRS) improvement (reduction) of 4 points or higher (baseline to weeks 2, 4, 16, 24, and 52), and 3 points or higher (baseline to weeks 16 and 52); and peak pruritus NRS percentage change (baseline to weeks 16 and 52). For peak pruritus NRS, patients reported the intensity of their worst itch via an interactive voice/web response system on a scale of 0–10 (no itch to worst itch imaginable) during the previous 24 h daily (weeks 0–16) or weekly (weeks 17–52). For weeks with daily peak pruritus NRS score reporting (weeks 0–16), weekly scores were calculated by averaging daily scores. A responder on the peak pruritus NRS scale was defined on the basis of a 3-point or 4-point improvement from baseline.[29]

Other secondary efficacy endpoints included percentage change (baseline to weeks 16 and 52) in scores for EASI, Scoring Atopic Dermatitis (SCORAD), Global Individual Signs Score (GISS; erythema, infiltration or papulation, excoriations, and lichenification), and peak pruritus NRS (also to week 2); change (baseline to weeks 16 and 52) in peak pruritus NRS score, percent body surface area affected, Patient-Oriented Eczema Measure (POEM), Hospital Anxiety and Depression Scale (HADS) total score, Dermatology Life Quality Index (DLQI); proportion of topical atopic dermatitis medication-free days; and incidence rate of flares (ie, worsening of atopic dermatitis requiring re-institution, escalation, or intensification of atopic dermatitis treatment) through week 52.

Post-hoc efficacy endpoints included mean change in EASI score (baseline to weeks 16 and 52), and proportions of patients at weeks 16 and 52 achieving 50% or 90% improvement in EASI (EASI-50 or EASI-90), 2-point or higher improvement from baseline in IGA, 4-point or higher improvement (reduction) from baseline in POEM in patients with baseline POEM scores of 4 or higher, 4-point or higher improvement (reduction) from baseline in DLQI in patients with baseline DLQI scores of 4 or higher, and proportion of patients with HADS-A and HADS-D scores of less than 8, among patients who had HADS-A or HADS-D scores of 8 or higher at baseline. A 4-point improvement is considered the minimal clinically important difference (MCID) for POEM[30] and DLQI.[31] For HADS-A and HADS-D, a score of 8 or higher on either subscale is considered indicative of clinically relevant symptoms of anxiety or depression, respectively (appendix pp 9–11 and 15).[32]

Adverse events, serious adverse events, laboratory values, vital signs, and electrocardiogram (ECG) results were assessed over the 52-week treatment period. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.

Statistical analysis

The sample size was chosen to enable adequate characterisation of the long-term safety profile as well as efficacy of dupilumab in this patient population. Methodology for sample size determination is presented in the appendix (p 12).

The full analysis set included all randomised patients for efficacy analyses at prespecified timepoints before week 52 (appendix p 16). Efficacy analyses for week 52 and timecourse over each study visit were done in the subset of full analysis set patients (FAS-52) who were randomised by April 27, 2015, and would have completed the week 52 visit by April 27, 2016 (cutoff date for data submission to the US FDA). The safety analysis set

	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=106)	Dupilumab 300 mg qw plus TCS (n=319)
Age (years)	34·0 (25·0–45·0)	40·5 (28·0–49·0)	34·0 (26·0–45·0)
Sex			
Men	193 (61%)	62 (58%)	191 (60%)
Women	122 (39%)	44 (42%)	128 (40%)
Race			
White	208 (66%)	74 (70%)	208 (65%)
Black or African American	19 (6%)	2 (2%)	13 (4%)
Asian	83 (26%)	29 (27%)	89 (28%)
Other	5 (2%)	1 (1%)	9 (3%)
Atopic dermatitis disease duration (years)	26·0 (17·0–38·0)	28·0 (20·0–44·0)	26·0 (18·0–39·0)
BSA (%)	55·0% (40·0–75·0)	58·8% (43·5–78·5)	52·0% (36·0–71·5)
EASI score	29·6 (22·2–40·8)	30·9 (22·3–41·6)	29·0 (21·6–40·7)
IGA score*			
4	147 (47%)	53 (50%)	147 (46%)
3	168 (53%)	53 (50%)	172 (54%)
Peak pruritus NRS score	7·6 (6·3–8·6)	7·7 (6·6–8·5)	7·4 (6·0–8·6)
SCORAD—total score	64·1 (55·9–76·1)	69·7 (60·4–79·8)	65·3 (55·2–76·3)
POEM score	20·0 (16·0–25·0)	21·0 (16·0–25·0)	20·0 (16·0–25·0)
DLQI score	14·0 (9·0–20·0)	13·5 (8·0–20·0)	14·0 (8·0–20·0)
HADS—total score	11·0 (6·0–18·0)	12·5 (7·0–18·0)	12·0 (7·0–18·0)
HADS-A or HADS-D score ≥8	148 (47%)	59 (56%)	154 (48%)
GISS score	8·0 (7·0–10·0)	9·0 (7·0–11·0)	9·0 (8·0–10·0)
Comorbid type 2 immune diseases at baseline†			
Allergies (other than food allergy)	63% (200/315)	62% (68/110)	67% (211/315)
Allergic rhinitis	43% (134/315)	48% (53/110)	41% (130/315)
Asthma	41% (130/315)	41% (45/110)	37% (116/315)
Food allergy	30% (96/315)	35% (39/110)	36% (112/315)
Allergic conjunctivitis (keratoconjunctivitis)	22% (68/315)	28% (31/110)	23% (73/315)
Hives	11% (34/315)	13% (14/110)	11% (34/315)
Chronic rhinosinusitis	8% (26/315)	6% (7/110)	4% (12/315)
Nasal polyps	2% (7/315)	2% (2/110)	2% (5/315)
Eosinophilic oesophagitis	0	1% (1/110)	0

Data are median (IQR), n (%), or % (n/N). q2w=every 2 weeks. qw=once weekly. TCS=topical corticosteroids. BSA=body surface area. EASI=Eczema Area and Severity Index. IGA=Investigator's Global Assessment. NRS=numerical rating scale. SCORAD=Scoring Atopic Dermatitis. POEM=Patient-Oriented Eczema Measure. DLQI=Dermatology Life Quality Index. HADS=Hospital Anxiety and Depression Scale. HADS-A=HADS anxiety subscore. HADS-D=HADS depression subscore. GISS=Global Individual Signs Score. *IGA score of 4 denotes severe and 3 denotes moderate. †Safety analysis set.

Table 1: **Baseline demographics and clinical characteristics (full analysis set)**

included all randomised patients who received study drug, based on dose regimen received.

Binary endpoints were analysed using the Cochran-Mantel-Haenszel test adjusted by randomisation strata. Primary analyses of binary endpoints were by intention to treat; patients were categorised as non-responders after rescue treatment initiation or study withdrawal. Continuous efficacy endpoints were analysed using multiple approaches; in this paper, we present the last observation carried forward (LOCF) approach with an ANCOVA model, which captures the last value prior to rescue or dropout; additionally, in the appendix, we present a multiple imputation method with ANCOVA in which data after rescue treatment were set to missing and then missing data were imputed using multiple imputation, with treatment, randomisation strata, and the corresponding baseline value of the endpoint included in the model. Multiple additional prespecified sensitivity analyses were done on binary and continuous endpoints using various methods to handle missing data (appendix p 12).

As a multiplicity adjustment to control for overall type-1 error, a hierarchical testing procedure was used to assess the primary and secondary endpoints in a prespecified order (appendix pp 9–10). For each test within each dose regimen, if an endpoint was significant at the two-sided 0·025 level, then the next endpoint in the hierarchy was tested. If an endpoint did not achieve significance at 0·025 for a dose regimen, then for subsequent endpoints in that dose regimen, significance at a p value of less than 0·025 was considered nominal. The study was not powered for comparisons between dupilumab dose groups. See appendix pp 12–13 for further details of statistical analyses.

Data were analysed with SAS (version 9.2 or above).

This trial was registered with ClinicalTrials.gov, NCT02260986, and EudraCT, 2013-003254-24.

Role of the funding source

This study was funded by Sanofi and Regeneron Pharmaceuticals Inc. The funders participated in the conception and design of the study, analysis and interpretation of the data, drafting and critical revision of the report, and gave approval to submit. The corresponding author had full access to all data in the study and had full responsibility for the decision to submit for publication. All authors provided final approval to submit.

Results

Between Oct 3, 2014, and July 31, 2015, 740 patients were enrolled; 319 were randomly assigned to dupilumab 300 mg qw plus topical corticosteroids, 106 to dupilumab 300 mg q2w plus topical corticosteroids, and 315 to placebo plus topical corticosteroids, respectively (figure 1). Four patients who were originally randomised to the dupilumab qw plus topical corticosteroids group had at least three fewer dupilumab injections than planned through week 16, and therefore were analysed under the dupilumab q2w plus topical corticosteroids group for the safety analyses. Treatment groups had similar baseline demographics and disease characteristics (table 1). Comorbid type 2/Th2 immune diseases (ie, atopic or allergic disorders) were common. Of the 740 patients initially enrolled, 623 (270 in the dupilumab qw plus

topical corticosteroids group, 89 in the dupilumab q2w plus topical corticosteroids group, and 264 in the placebo plus topical corticosteroids group) were randomly assigned by April 27, 2015, and would have completed the 52-week treatment period at the time of data cutoff; these 623 patients were included in the week 52 efficacy analyses (figure 1). Almost all enrolled patients completed 16 weeks of treatment: 282 (90%) of 315 for placebo plus topical corticosteroids, 99 (93%) of 106 for dupilumab 300 mg q2w plus topical corticosteroids, and 301 (94%) of 319 for dupilumab 300 mg qw plus topical corticosteroids. However, only 185 (67%) of 275 placebo plus topical corticosteroids-treated patients evaluable at 52 weeks completed the study compared with 77 (86%) of 90 and 234 (85%) of 274 who completed in the dupilumab q2w plus topical corticosteroids and qw plus topical corticosteroids groups, respectively, consistent with increased satisfaction with dupilumab treatment.

	Week 16 (unless otherwise specified)			Week 52		
	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=106)	Dupilumab 300 mg qw plus TCS (n=319)	Placebo qw plus TCS (n=264)	Dupilumab 300 mg q2w plus TCS (n=89)	Dupilumab 300 mg qw plus TCS (n=270)
Coprimary endpoints						
Proportion of patients who achieved IGA score 0/1 and reduction of ≥2 points from baseline	12% (39)	39% (41); p<0·0001	39% (125); p<0·0001	13% (33)	36% (32); p<0·0001	40% (108); p<0·0001
Difference *vs* placebo plus TCS (95% CI)*	..	26 (16·3–36·3)	27 (20·3–33·3)	..	24 (12·7–34·2)	28 (20·4–34·6)
Proportion of patients who achieved EASI-75	23% (73)	69% (73); p<0·0001	64% (204); p<0·0001	22% (57)	65% (58); p<0·0001	64% (173); p<0·0001
Difference *vs* placebo plus TCS (95% CI)*	..	46 (35·7–55·7)	41 (33·7–47·8)	..	44 (32·5–54·7)	43 (34·9–50·1)
Secondary outcomes						
Proportion of patients who achieved peak pruritus NRS score improvement ≥4 points from baseline†	20% (59/299)	59% (60/102); p<0·0001	51% (150/295); p<0·0001	13% (32/249)	51% (44/86); p<0·0001	39% (97/249); p<0·0001
Difference *vs* placebo plus TCS (95% CI)*	..	39 (28·5–49·7)	31 (23·8–38·4)	..	38 (27·0–49·7)	26 (18·8–33·5)
Proportion of patients who achieved peak pruritus NRS score improvement ≥3 points from baseline‡	28% (85/306)	66% (69/105); p<0·0001	62% (193/309); p<0·0001	16% (40/256)	56% (49/88); p<0·0001	43% (112/261); p<0·0001
Difference *vs* placebo plus TCS (95% CI)*	..	38 (27·6–48·3)	35 (27·3–42·1)	..	40 (28·8–51·4)	27 (19·8–34·8)
Peak pruritus NRS score, LS mean % change from baseline	−28·6% (2·03)	−56·2% (3·38); p<0·0001	−54·8% (1·99); p<0·0001	−27·1% (2·66)	−56·2% (4·38); p=0·0001§	−54·4% (2·60); p<0·0001§
Proportion of patients who achieved peak pruritus NRS score improvement ≥4 points from baseline to week 24†	16% (48/299)	54% (55/102); p<0·0001	44% (129/295); p<0·0001	NA	NA	NA
Difference *vs* placebo plus TCS (95% CI)*	..	38 (27·3–48·4)	28 (20·7–34·7)	NA	NA	NA
Proportion of patients who achieved peak pruritus NRS score improvement ≥4 points from baseline to week 4†	16% (49/299)	37% (38/102); p<0·0001	27% (80/295); p=0·0021	NA	NA	NA
Difference *vs* placebo plus TCS (95% CI)*	..	21 (10·6–31·2)	11 (4·2–17·3)	NA	NA	NA
Proportion of patients who achieved peak pruritus NRS score improvement ≥4 points from baseline to week 2†	8% (24/299)	18% (18/102); p=0·0062	14% (40/295); p=0·03 (NS)	NA	NA	NA
Difference *vs* placebo plus TCS (95% CI)*	..	10 (1·6–17·6)	6 (0·6–10·5)	NA	NA	NA
Peak pruritus NRS score, LS mean % change from baseline to week 2	−19·8% (1·60)	−27·2% (2·68); p=0·0157§	−25·6% (1·58); p=0·0077§	NA	NA	NA
Peak pruritus NRS score, LS mean change from baseline	−2·1 (0·13)	−4·1 (0·21); p<0·0001	−4·1 (0·13); p<0·0001§	−2·1 (0·16)	−4·2 (0·26); p<0·0001§	−4·1 (0·16); p<0·0001§
EASI score, LS mean % change from baseline	−43·2% (2·26)	−76·7% (3·77); p<0·0001	−77·3% (2·22); p<0·0001§	−45·8% (2·70)	−78·3% (4·44); p<0·0001§	−80·3% (2·64); p<0·0001§
Percent BSA affected, LS mean change from baseline	−18·6 (1·13)	−38·6 (1·88); p<0·0001	−37·4 (1·11); p<0·0001§	−20·3 (1·33)	−41·5 (2·19); p<0·0001§	−39·9 (1·30); p<0·0001§
SCORAD score, LS mean % change from baseline	−31·8% (1·55)	−62·1% (2·61); p<0·0001	−63·3% (1·53); p<0·0001§	−34·1% (1·88)	−66·2% (3·14); p<0·0001§	−66·1% (1·85); p<0·0001§
DLQI score, LS mean change from baseline	−5·3 (0·31)	−9·7 (0·51); p<0·0001	−10·5 (0·30); p<0·0001§	−5·6 (0·36)	−10·9 (0·59); p<0·0001§	−10·7 (0·36); p<0·0001§
POEM score, LS mean change from baseline	−4·7 (0·38)	−12·4 (0·63); p<0·0001	−12·5 (0·37); p<0·0001§	−5·3 (0·46)	−13·7 (0·75); p<0·0001§	−12·7 (0·45); p<0·0001§
HADS total score, LS mean change from baseline	−3·6 (0·34)	−4·9 (0·56); p=0·03 (NS)	−5·2 (0·33); p=0·0004§	−3·4 (0·40)	−5·3 (0·65); p=0·0109§	−5·5 (0·39); p<0·0001§
GISS total score, LS mean % change from baseline	−28·2% (1·63)	−53·1% (2·73); p<0·0001§	−56·3% (1·62); p<0·0001§	−29·2% (2·01)	−58·3% (3·30); p<0·0001§	−59·7% (1·97); p<0·0001§

(Table 2 continues on next page)

	Week 16 (unless otherwise specified)			Week 52		
	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=106)	Dupilumab 300 mg qw plus TCS (n=319)	Placebo qw plus TCS (n=264)	Dupilumab 300 mg q2w plus TCS (n=89)	Dupilumab 300 mg qw plus TCS (n=270)
(Continued from previous page)						
Other secondary outcomes						
Proportion of patients with AD flares through week 52¶	NA	NA	NA	41% (130)	14% (15); p<0·0001§	13% (40); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	NA	NA	..	−28 (−36·04 to −19·23)	−29 (−35·14 to −22·01)
Proportion of topical TCS/TCI and systemic rescue medication-free days‖	7 (18·5)	12 (27·6); p=0·08 (NS)	16 (28·9); p<0·0001§	11 (23·7)	17 (30·1); p=0·07 (NS)	23 (33·7); p<0·0001§
Post-hoc analyses						
Proportion of patients who achieved EASI-50	37% (118)	80% (85); p<0·0001§	78% (249); p<0·0001§	30% (79)	79% (70); p<0·0001§	70% (189); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	43 (33·5–52·0)	41 (33·6–47·6)	..	49 (38·6–58·9)	40 (32·3–47·9)
Proportion of patients who achieved EASI-90	11% (35)	40% (42); p<0·0001§	43% (138); p<0·0001§	16% (41)	51% (45); p<0·0001§	51% (137); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	29 (18·6–38·5)	32 (25·7–38·6)	..	35 (23·8–46·3)	35 (27·8–42·6)
Proportion of patients who achieved ≥2-point reduction in IGA score	18% (58)	60% (64); p<0·0001§	55% (174); p<0·0001§	18% (47)	56% (50); p<0·0001§	53% (142); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	42 (31·7–52·2)	36 (29·2–43·1)	..	38 (27·1–49·7)	35 (27·3–42·3)
Proportion of patients who achieved ≥4-point improvement (MCID) in POEM**	37% (115/312)	77% (82/106); p<0·0001§	77% (246/318); p<0·0001§	26% (68/261)	76% (68/89); p<0·0001§	65% (174/269); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	41 (30·9–50·1)	41 (33·4–47·6)	..	50 (40·1–60·7)	39 (30·8–46·4)
Proportion of patients who achieved ≥4-point improvement (MCID) in DLQI††	43% (129/300)	81% (81/100); p<0·0001§	74% (231/311); p<0·0001§	30% (77/254)	80% (68/85); p<0·0001§	63% (167/264); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	38 (28·5–47·5)	31 (23·9–38·7)	..	50 (39·5–59·9)	33 (24·8–41·1)
Proportion of patients who achieved HADS-A and HADS-D scores <8‡‡	26% (39/148)	47% (28/59); p=0·0040§	47% (73/154); p=0·0003§	18% (24/133)	43% (23/53); p=0·0003§	45% (62/138); p<0·0001§
Difference *vs* placebo plus TCS (95% CI)*	..	21 (6·5–35·7)	21 (10·4–31·7)	..	25 (10·5–40·2)	27 (16·3–37·5)

Data are % (n), LS mean % change from baseline (SE) (LOCF), or % (n/N). Unless otherwise indicated, efficacy analyses were done using the full analysis set, which included all randomised patients (appendix). For week 52 outcomes, the population comprises those patients in the full analysis set who had completed 52 weeks of treatment and were evaluated for efficacy outcomes by the cutoff date for US Food and Drug Administration submission. Within each dose regimen, the primary and secondary endpoints were tested following a hierarchical testing procedure with a prespecified order; ie, inferential conclusions about successive endpoints required statistical significance of the prior one at the 0·025 significance level. All p values are two-sided and represent comparisons versus placebo plus TCS. AD=atopic dermatitis. BSA=body surface area. DLQI=Dermatology Life Quality Index. EASI=Eczema Area and Severity Index. EASI-50=≥50% improvement in EASI score from baseline. EASI-75=≥75% improvement in EASI score from baseline. EASI-90=≥90% improvement in EASI score from baseline. GISS=Global Individual Signs Score. HADS=Hospital Anxiety and Depression Scale. IGA=Investigator's Global Assessment. LOCF=last observation carried forward. LS=least squares. MCID=minimal clinically important difference. N=number of patients in baseline subgroup. NA=not applicable. NRS=numerical rating scale. NS=non-significant. POEM=Patient-Oriented Eczema Measure. q2w=every 2 weeks. qw=once weekly. SCORAD=Scoring Atopic Dermatitis. TCI= topical calcineurin inhibitors. TCS=topical corticosteroids. *Difference in proportions of patients between dupilumab plus TCS and placebo plus TCS. †Analysis for this endpoint was performed only for patients with baseline peak pruritus NRS score ≥4; n/N represents the number of patients with the outcome divided by the number of patients with baseline peak pruritus NRS scores ≥4 . ‡Analysis for this endpoint was performed only for patients with baseline peak pruritus NRS score ≥3; n/N represents the number of patients with the outcome divided by the number of patients with baseline peak pruritus NRS scores ≥3. §Nominally significant p value. ¶Safety analysis set. ‖The proportion was defined as the number of days that a patient used neither TCS nor TCI nor systemic rescue therapy divided by the observation study days. **Analysis for this endpoint was performed only for patients with baseline POEM scores ≥4; n/N represents the number of patients with the outcome divided by the number of patients with baseline POEM scores ≥4. ††Analysis for this endpoint was performed only for patients with baseline DLQI scores ≥4; n/N represents the number of patients with the outcome divided by the number of patients with baseline DLQI scores ≥4. ‡‡Analysis for this endpoint was performed only for patients with HADS-A or HADS-D ≥8 at baseline (ie, those with symptoms of anxiety or depression); n/N=number of patients with the outcome divided by the number of patients with HADS-A or HADS-D ≥8 at baseline.

Table 2: **Efficacy outcomes**

Higher proportions of patients who received dupilumab plus topical corticosteroids versus those who received placebo plus topical corticosteroids achieved both coprimary endpoints (table 2, figures 2B, appendix p 28); these were intention-to-treat analyses with rescue and dropout considered as failures. For one coprimary endpoint, IGA 0/1 and 2-point or higher improvement in IGA from baseline at week 16 was achieved by 39% of patients (125 of 319) who received dupilumab qw plus topical corticosteroids and 39% of patients (41 of 106) who received dupilumab q2w plus topical corticosteroids versus 12% of patients (39 of 315) who received placebo plus topical corticosteroids (p<0·0001, each dose group *vs* placebo plus topical corticosteroids). For the other coprimary endpoint, an EASI-75 response at 16 weeks was achieved by 64% (204 of 319) of patients who received dupilumab qw plus topical corticosteroids and 69% (73 of 106) of patients who received dupilumab q2w plus topical corticosteroids versus 23% (73 of 315) of the control group (p<0·0001, each dose group *vs* placebo plus topical corticosteroids). The sensitivity analyses

supported the results of the primary analysis (appendix pp 17–18). The first key secondary endpoint, peak pruritus NRS improvement of 4 or higher at 16 weeks, was achieved by 51% (150 of 295) of the patients who received dupilumab qw plus topical corticosteroids and 59% (60 of 102) of the patients who received dupilumab q2w plus topical corticosteroids versus 20% (59 of 299) of patients in the control group ($p<0·0001$, each dose group *vs* placebo plus topical corticosteroids; table 2, figure 3B). Similar efficacy was observed at week 52: for IGA 0/1 and 2-point or higher improvement in IGA from baseline at 52 weeks—40% (108 of 270) and 36% (32 of 89) versus 13% (33 of 264), respectively ($p<0·0001$, each dose group *vs* placebo plus topical corticosteroids); for EASI-75 at 52 weeks—64% (173 of 270) and 65% (58 of 89) versus 22% (57 of 264; $p<0·0001$, each dose group *vs* placebo plus topical corticosteroids). The results for peak pruritus NRS improvement of 4 or higher at 52 weeks were 39% (97 of 249) and 51% (44 of 86) versus 13% (32 of 249; $p<0·0001$, each dose group *vs* placebo plus topical corticosteroids; table 2, figure 3B).

In addition, dupilumab plus topical corticosteroids resulted in higher EASI-50 and EASI-90 responses than did placebo plus topical corticosteroids at weeks 16 and 52 (table 2, figures 2A, C) and greater mean percentage reductions and mean reductions in EASI (table 2, figure 3A, appendix pp 19–20, 29–31). Dupilumab plus topical corticosteroids also improved all other measures of clinical severity at weeks 16 and 52 versus placebo plus topical corticosteroids, including the proportion of patients achieving 2-point improvement from baseline in IGA, percentage change from baseline in SCORAD scores, change from baseline in percentage of body surface area affected, and percentage change from baseline in GISS (tables 2, appendix pp 19–20, 32–38). Dupilumab plus topical corticosteroids reduced the number of atopic dermatitis flares over the 52-week treatment period compared with placebo plus topical corticosteroids (table 2).

Dupilumab plus topical corticosteroids improved pruritus; significant differences versus placebo were apparent as early as week 2 (table 2, figure 3B, appendix pp 19–20, 39–40). The proportions of patients who achieved 4-point or higher and 3-point or higher improvements in peak pruritus NRS were significantly greater with dupilumab plus topical corticosteroids than with placebo plus topical corticosteroids at all prespecified timepoints, except week 2 for 4-point or higher improvement for dupilumab qw plus topical corticosteroids (table 2, figure 3B).

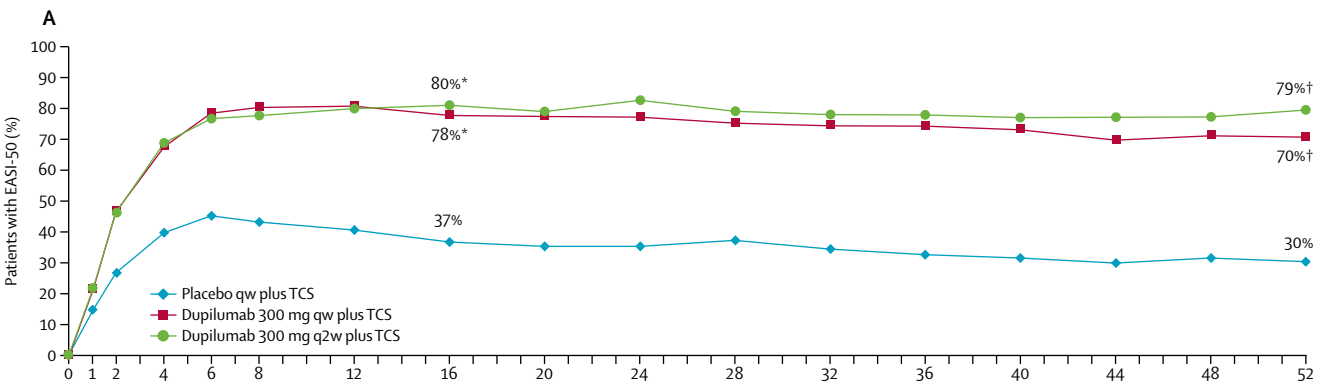
Dupilumab plus topical corticosteroids improved patient-reported symptoms of atopic dermatitis (including impact on sleep), as assessed by greater reductions in POEM scores versus placebo plus topical corticosteroids (tables 2, appendix pp 19–20, 41–42). In addition, among patients with baseline POEM scores 4 or higher, higher proportions of patients on dupilumab qw plus topical corticosteroids and q2w plus topical corticosteroids achieved 4-point or higher improvement (MCID) at weeks 16 and 52 (table 2).

DLQI scores, a measure of quality of life (QoL), improved from baseline to weeks 16 and 52 with dupilumab plus topical corticosteroids versus placebo plus topical corticosteroids (tables 2, appendix pp 19–20, 43–44). Among patients with baseline DLQI scores of 4 or higher, greater proportions in the dupilumab qw plus topical corticosteroids group and q2w plus topical corticosteroids group than in the placebo plus topical corticosteroids group achieved 4-point or higher improvement (MCID) in DLQI at weeks 16 and 52 (table 2).

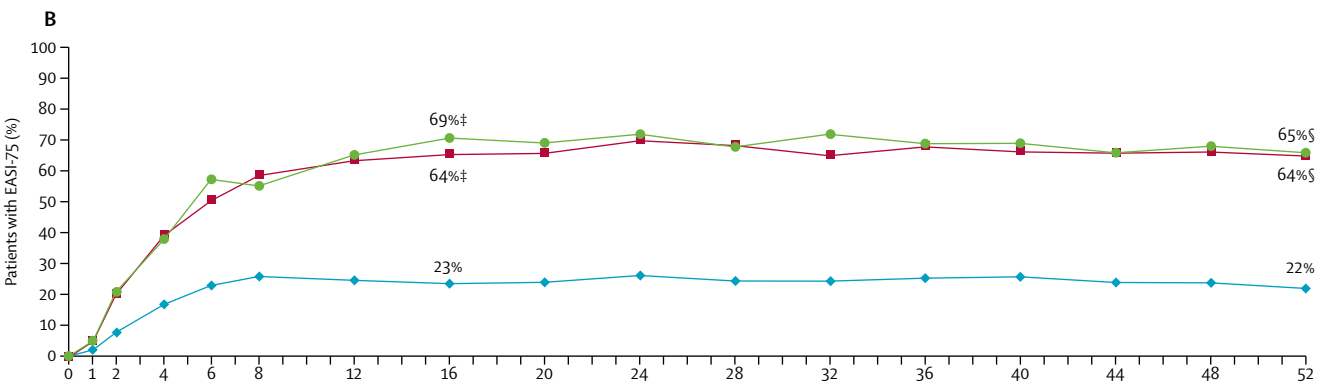
Dupilumab plus topical corticosteroids improved symptoms of anxiety and depression (table 2). In particular, dupilumab qw plus topical corticosteroids, but not q2w plus topical corticosteroids, improved HADS total score from baseline to week 16 versus placebo plus topical corticosteroids (table 2, appendix pp 19–20), although both dose regimens of dupilumab plus topical corticosteroids in the LOCF analysis improved HADS total score from baseline to week 52 compared with placebo plus topical corticosteroids (table 2). Among patients with HADS-A or HADS-D scores of 8 or higher at baseline (ie, those with clinically relevant symptoms of anxiety or depression), more patients in both dupilumab plus topical corticosteroids groups versus the placebo plus topical corticosteroids group achieved both HADS-A and HADS-D scores less than 8 (ie, absence of clinically relevant symptoms of anxiety and depression) at weeks 16 and 52 (table 2).

Patients who received dupilumab qw plus topical corticosteroids had more days free of topical corticosteroids with or without topical calcineurin inhibitors or systemic rescue medication use than those who received placebo plus topical corticosteroids (table 2), and both dupilumab plus topical corticosteroids groups had lower rates of rescue medication use (appendix p 21). Overall, rescue treatments were used by 55 (17%) of 315 patients who received dupilumab qw plus topical corticosteroids and 18 (16%) of 110 patients who received dupilumab q2w plus topical corticosteroids versus 164 (52%) of 315 in the placebo qw plus topical corticosteroids group. High-potency topical corticosteroids were the most frequently used rescue medications (appendix p 21).

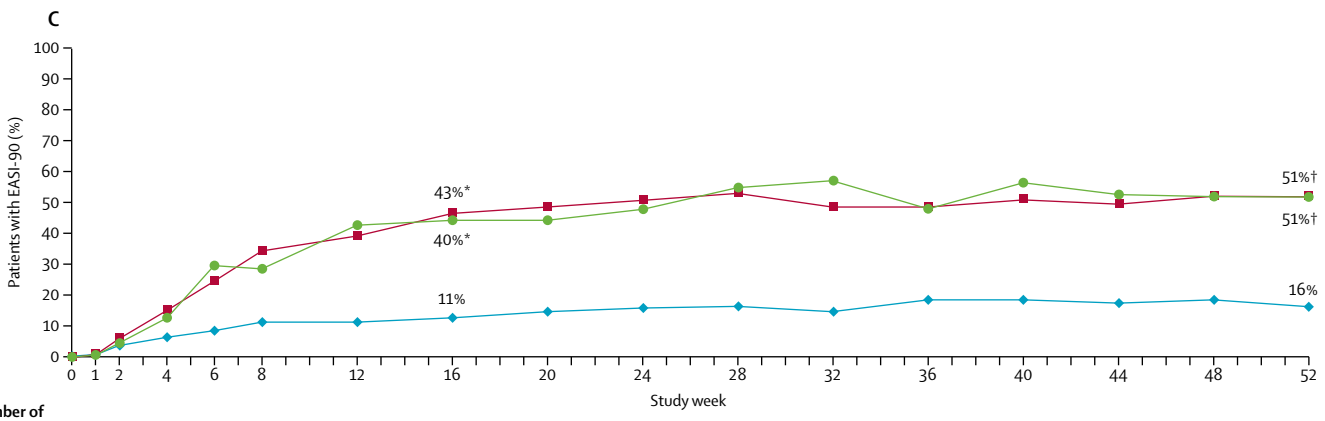
Overall rates of adverse events were similar across the treatment groups during the 52-week treatment period (table 3). The placebo plus topical corticosteroids group had higher overall rates of serious adverse events and discontinuations due to adverse events. Among patients on placebo plus topical corticosteroids who discontinued due to adverse events, 58% (14 of 24) discontinued due to atopic dermatitis flares. One patient in the dupilumab qw plus topical corticosteroids group died due to a motor vehicle accident; this was considered not related to study drug.



Number of patients	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52
Dupilumab qw (n=270)	58	123	182	211	216		217	209	208	207	202	199	199	195	186	189	189
Dupilumab q2w (n=89)	20	41	61	68	69		71	72	70	73	70	69	69	68	68	68	70
Placebo (n=264)	39	71	104	119	114		107	97	93	93	98	90	85	82	77	82	79



Number of patients	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52
Dupilumab qw (n=270)	15	56	106	136	158		171	176	177	188	184	174	182	177	176	177	173
Dupilumab q2w (n=89)	5	19	34	51	49		58	63	61	64	60	64	61	61	58	60	58
Placebo (n=264)	6	22	45	61	68		65	62	63	69	64	64	66	67	62	62	57



Number of patients	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52
Dupilumab qw (n=270)	2	17	40	66	92		105	124	130	135	141	130	130	135	131	138	137
Dupilumab q2w (n=89)	0	4	11	26	25		37	39	39	42	48	50	42	49	46	45	45
Placebo (n=264)	2	9	16	22	29		29	33	38	41	42	38	47	47	44	47	41

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The dupilumab plus topical corticosteroids groups had higher rates of injection-site reactions (MedDRA preferred term) than the placebo plus topical corticosteroids group; rates seemed to be dependent on dosing frequency (table 3). Injection-site reactions were mild or moderate, and rates declined over time (data not shown). Two patients withdrew due to mild injection-site reactions.

Incidence of conjunctivitis (including conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis [MedDRA preferred terms]) was higher in the dupilumab plus topical corticosteroids groups than in the placebo plus topical corticosteroids group (table 3). In most cases, additional workup and referral were not pursued. Most cases were mild (31 [51%] of 61 patients with conjunctivitis in the dupilumab qw plus topical corticosteroids group, two [13%] of 15 patients in the dupilumab q2w plus topical corticosteroids group, and 15 [60%] of 25 patients in the placebo plus topical corticosteroids group) or moderate (28 [46%] of 61, 13 [87%] of 15, and nine [60%] of 15 patients, respectively), and resolved with topical eye treatments during the study (data not shown). Two patients (1%) who received dupilumab qw plus topical corticosteroids and one patient (<1%) who received placebo plus topical corticosteroids had severe conjunctivitis: severe allergic conjunctivitis (one patient each in the dupilumab qw plus topical corticosteroids and placebo plus topical corticosteroids groups) and severe bacterial conjunctivitis (one patient in the dupilumab qw plus topical corticosteroids group; no bacterial cultures were obtained for this patient). Only one patient discontinued due to conjunctivitis: a patient in the dupilumab qw plus topical corticosteroids group with atopic keratoconjunctivitis in one eye.

Overall, similar proportions of patients in each treatment group reported herpesviral infections (table 3). Localised herpes simplex infections (eg, MedDRA preferred terms of oral herpes and herpes simplex) were more frequent in the dupilumab plus topical corticosteroids groups than in the placebo plus topical corticosteroids group, whereas herpes zoster and eczema herpeticum were more frequent in the placebo plus topical corticosteroids group (table 3). Systemic antiviral medications were used by 8% (26 of 315) of patients in the placebo plus topical corticosteroids group, 4% (4 of 110) of patients in the dupilumab q2w plus topical corticosteroids group, and 5% (16 of 315) of patients in the dupilumab qw plus topical corticosteroids group.

Higher rates of non-herpes viral skin infections were reported in the placebo plus topical corticosteroids group than in the dupilumab q2w plus topical corticosteroids and dupilumab qw plus topical corticosteroids groups (18% [56 of 315 patients] *vs* 11% [12 of 110 patients] and 8% [26 of 315 patients], respectively; table 3, appendix pp 22–23).

No clinically meaningful differences in laboratory values (appendix pp 24–27), vital signs, or ECG measures were noted between the dupilumab plus topical corticosteroids and placebo plus topical corticosteroids groups.

Figure 2: **Proportion of patients achieving EASI-50 (A), EASI-75 (B), and EASI-90 (C) response over time, from baseline to week 52; patients were considered non-responders after rescue treatment**

EASI=Eczema Area and Severity Index. EASI-50/75/90=proportion of patients who achieved 50%/75%/90% improvement in EASI score from baseline. FAS=full analysis set. FAS-52=patients in the full analysis set who had completed 52 weeks of treatment and were evaluated for efficacy outcomes by the cutoff date for US Food and Drug Administration submission. q2w=every 2 weeks. qw=once weekly. *Nominal p<0·0001, dupilumab plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). †Nominal p<0·0001, dupilumab plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS-52). ‡p<0·0001, dupilumab plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). §p<0·0001, dupilumab plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS-52).

Discussion

This 1-year study of dupilumab with concomitant topical medications is the first large, randomised, double-blinded, placebo-controlled study of long-term systemic treatment in patients with moderate-to-severe atopic dermatitis. Both dose regimens of dupilumab plus topical corticosteroids, when compared with placebo plus topical corticosteroids, improved atopic dermatitis lesions as assessed by IGA 0/1 response and EASI-75 at week 16 (coprimary endpoints). The improvement was sustained over the 52-week treatment period. Additionally, dupilumab plus topical corticosteroids improved several other measures of clinical signs and symptoms of atopic dermatitis including pruritus, as well as symptoms of anxiety and depression, and health-related quality of life (HRQoL), over the 52-week treatment period. Responses were similar for both dupilumab plus topical corticosteroids dose regimens. Efficacy outcomes at week 16 were consistent with those reported in previous studies.[24–27]

The coprimary endpoints are stringent measures of response required for regulatory approval and might not encompass all patients who experienced clinical benefits. Among patients treated with dupilumab plus topical corticosteroids, 39% achieved both IGA 0/1 and 2 point or higher improvement at week 16 versus 12% for placebo plus topical corticosteroids. However, this excludes patients with baseline IGA of 4 (severe disease) who achieved 2 point improvement to IGA of 2 (ie, mild disease). Looking at all patients who achieved 2 point or higher reduction in IGA score, increased responses were 55% and 60% versus 18% for dupilumab qw plus topical corticosteroids and dupilumab q2w plus topical corticosteroids versus placebo plus topical corticosteroids. Similarly, although 64–69% of patients who received dupilumab plus topical corticosteroids achieved EASI-75 versus 22–23% of patients who received placebo plus topical corticosteroids, this endpoint might also exclude some patients who experienced meaningful relief from signs and symptoms of atopic dermatitis. Most (70–80%) patients treated with dupilumab plus topical corticosteroids achieved EASI-50 at weeks 16 and

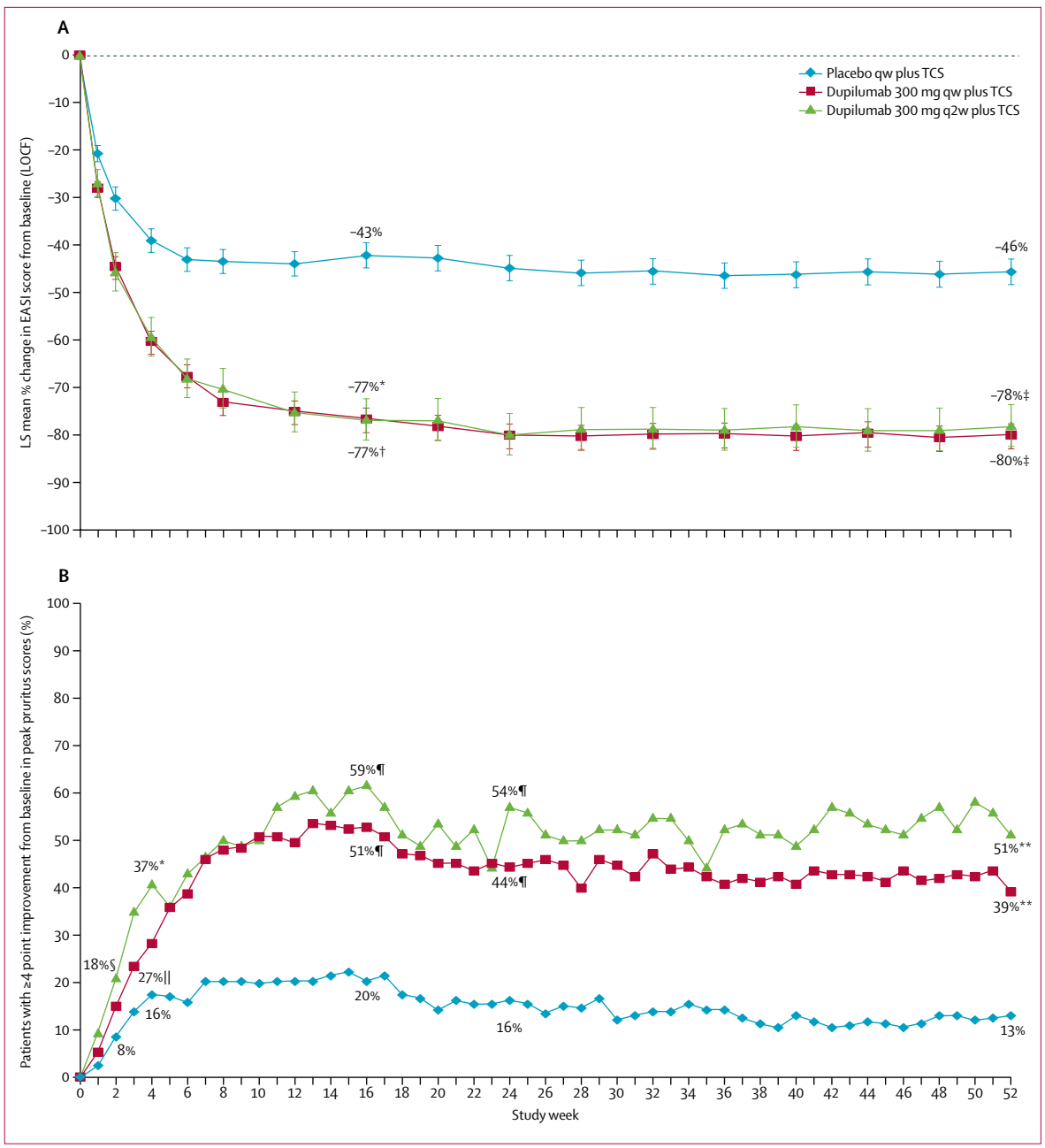

Figure 3: **Least squares mean percent change in EASI score over time (LOCF; A) and proportion of patients who achieved ≥4-point improvement from baseline in peak pruritus NRS scores (B), from baseline to week 52**

EASI=Eczema Area and Severity Index. FAS=full analysis set. FAS-52=patients in the full analysis set who had completed 52 weeks of treatment and were evaluated for efficacy outcomes by the cutoff date for US Food and Drug Administration submission. LOCF=last observation carried forward. NRS=numerical rating scale. q2w=every 2 weeks. q2=weekly. *p<0·0001, dupilumab q2w plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). †Nominal p<0·0001, dupilumab qw plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). ‡Nominal p<0·0001, dupilumab q2w plus topical corticosteroids *vs* placebo plus topical corticosteroids and dupilumab qw plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS-52). §p=0·0062, dupilumab q2w plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). ¶p<0·0001, dupilumab q2w plus topical corticosteroids and dupilumab qw plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). ||p=0·0021, dupilumab qw plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS). **p<0·0001, dupilumab q2w plus topical corticosteroids *vs* placebo plus topical corticosteroids and dupilumab qw plus topical corticosteroids *vs* placebo plus topical corticosteroids (FAS-52).

52, versus 30–37% of patients treated with placebo plus topical corticosteroids. Because of the high disease burden in this patient population (mean baseline EASI scores of 29–31), even 50% improvement from baseline reflects a clinically meaningful response, considering that the MCID for EASI is 6·6.[30]

	n			n per 100 patient-years		
	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=110)	Dupilumab 300 mg qw plus TCS (n=315)	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=110)	Dupilumab 300 mg qw plus TCS (n=315)
Adverse events						
Total number of adverse events	1493	478	1482	532·38	476·23	507·73
Total number of serious adverse events	22	5	10	7·85	4·98	3·43
Patients with adverse events						
≥1 adverse event	84% (266)	88% (97)	83% (261)	321·38	383·68	322·89
Death†	0	0	<1% (1)	0	0	0·34
≥1 serious adverse event	5% (16)	4% (4)	3% (9)	5·86	4·05	3·12
Adverse events leading to treatment discontinuation	8% (24)	2% (2)	3% (9)	8·52	2·70	2·81
Adverse events (SOC‡–PT§)						
Infections and infestations‡	58% (182)	57% (63)	53% (166)	108·08	101·50	94·33
Nasopharyngitis§	19% (61)	23% (25)	19% (60)	24·80	29·23	23·67
Upper respiratory tract infection§	10% (32)	10% (11)	14% (43)	12·27	11·89	16·17
Sinusitis§	3% (9)	2% (2)	6% (18)	3·26	2·00	6·43
Influenza§	5% (17)	4% (4)	3% (9)	6·24	4·06	3·13
Eye disorders‡	15% (46)	31% (34)	32% (102)	17·99	43·63	44·85
Conjunctivitis¶‖	8% (25)	14% (15)	19% (61)	9·42	16·36	23·81
Skin and subcutaneous tissue disorders‡	53% (167)	28% (31)	33% (103)	96·50	38·27	45·84
Atopic dermatitis§	46% (144)	18% (20)	17% (52)	73·37	22·61	19·96
General disorders and administration site conditions‡	16% (50)	26% (29)	26% (81)	20·32	36·24	35·20
Injection site reaction§	8% (24)	15% (16)	19% (60)	9·19	17·94	24·45
Respiratory–thoracic and mediastinal disorders‡	17% (53)	12% (13)	14% (45)	21·35	14·20	16·94
Asthma§	6% (19)	5% (5)	1% (2)	7·06	5·15	0·69
Nervous system disorders‡	12% (38)	9% (10)	12% (38)	14·94	10·80	14·37
Headache§	6% (19)	5% (5)	8% (24)	7·12	5·19	8·78
Non-herpetic skin infections**	18% (56)	11% (12)	8% (26)	59·3	36·1	27·4
Any herpes infections¶	8% (25)	7% (8)	7% (22)	25·6	24·0	22·7
Oral herpes§	3% (9)	4% (4)	5% (15)	3·26	4·10	5·30
Herpes simplex§	1% (2)	3% (3)	2% (5)	0·72	3·03	1·73
Herpes virus infection§	<1% (1)	1% (1)	1% (2)	0·36	1·00	0·69
Herpes zoster§	2% (5)	1% (1)	<1% (1)	1·80	1·00	0·34
Eczema herpeticum§	2% (6)	1% (1)	0	2·17	1·01	0
Genital herpes§	<1% (1)	0	<1% (1)	0·36	0	0·34
Herpes ophthalmic§	1% (2)	0	<1% (1)	0·72	0	0·34
Ophthalmic herpes simplex§	0	0	<1% (1)	0	0	0·34
Ophthalmic herpes zoster§	<1% (1)	0	0	0·36	0	0

MedDRA=Medical Dictionary for Regulatory Activities. PT=preferred term. q2w=every 2 weeks. qw=once weekly. SOC=system organ class. TCS=topical corticosteroids. *Safety analyses were done with the safety analysis set, which included all randomised patients who received a dose of any study drug (appendix p 13). The adverse events included here that are listed as number of patients (%) according to the PTs in the MedDRA version 18.0 were those that occurred in at least 5% of the patients in any study group, with the exception that all herpesviral PTs are listed. Adverse events were defined as any untoward medical occurrence; serious adverse events as any adverse event that results in death, is life-threatening, requires hospital admission or prolongation of existing hospital admission, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is an important medical event. †One patient died as a result of a motor vehicle accident; this was considered to be not related to study drug. ‡Adverse event reported at the PT level of the MedDRA hierarchy. §Adverse event reported at SOC level of the MedDRA hierarchy. ¶Adverse event reported at the high-level term level of the MedDRA hierarchy. ||Conjunctivitis (high-level term) includes the PTs conjunctivitis allergic, conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis. **Adjudicated.

Table 3*: Adverse events reported in patients in any treatment group during the 52-week treatment period (safety analysis set)

Dupilumab plus topical corticosteroids provided long-term benefits for pruritus and other patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and HRQoL. Pruritus is a prominent and often debilitating symptom of atopic dermatitis, with a substantial effect on psychosocial well-being of patients.[33,34]

Improvement in pruritus was rapid, with a significantly higher proportion of patients who received dupilumab plus topical corticosteroids versus patients who received placebo plus topical corticosteroids achieving peak pruritus NRS improvement of 4 or higher by week 2 (dupilumab q2w plus topical corticosteroids) or week 4 (dupilumab qw plus topical corticosteroids). These differences were sustained through to week 52. Divergence between dupilumab plus topical corticosteroids and placebo plus topical corticosteroids was also apparent as early as week 2 in peak pruritus NRS percentage improvement from baseline. For patients with moderate-to-severe atopic dermatitis, pruritus and sleep loss are among the most important symptoms to assess treatment response.[35] Improvement in pruritus is also associated with improvement in QoL.[26,33,34,36] Symptoms of depression and anxiety are common in patients with moderate-to-severe atopic dermatitis and might be an additional consequence of unremitting pruritus and poor sleep.[33,37]

Dupilumab plus topical corticosteroids reduced use of rescue treatments, including topical corticosteroids, oral corticosteroids, and systemic immunosuppressants. Although about 16% of patients treated with dupilumab plus topical corticosteroids received rescue treatment versus more than 50% of patients treated with placebo plus topical corticosteroids, all prespecified sensitivity analyses that included all observed data (regardless of rescue medication use) also remained significant and were consistent with the primary analyses.

The 52-week duration of this study allowed assessment of the effect of dupilumab plus topical corticosteroids on atopic dermatitis flares. Dupilumab plus topical corticosteroids reduced flare rates, and fewer patients experienced adverse events of atopic dermatitis exacerbation versus placebo plus topical corticosteroids. The broad medical and psychosocial effect of flares on patients' QoL, which might include increased need for higher-potency topical corticosteroids or systemic immunosuppressive medications, underscores the importance of minimising flares and improving long-term control of disease activity.

The safety profile was generally consistent with previous studies,[24,25,27] and there were no new safety signals in this study. Dupilumab plus topical corticosteroids was not associated with increased overall risk of infections (including serious or opportunistic infections), and infection rates were generally consistent with shorter-term studies.[24,25,27] The reduced incidence of non-herpetic skin infections in patients treated with dupilumab plus topical corticosteroids compared with patients treated with placebo plus topical corticosteroids is consistent with previous clinical studies and the suggestion that dupilumab might reduce skin infection risk in patients with atopic dermatitis.[27] Mechanisms could be related to restoration of skin barrier function, reduced scratching (via decreased pruritus), or improved antimicrobial or innate immune responses. Dupilumab might be the first targeted immune biologic that is neither immunosuppressive nor associated with increased risk of infection, but rather restorative of barrier and immune function. Further mechanistic studies are needed to explore this possibility and its mechanism. Increased incidence of mild-to-moderate conjunctivitis in the dupilumab plus topical corticosteroids groups was generally consistent with similar incidence of conjunctivitis in previous studies in atopic dermatitis.[24,25,27] Why conjunctivitis incidence is increased in patients with atopic dermatitis treated with dupilumab is unclear. A higher incidence of conjunctivitis was not noted in patients treated with dupilumab in studies in patients with asthma or nasal polyposis with chronic rhinosinusitis,[22,23,38] suggesting that mechanisms unique to atopic dermatitis could be involved.

Topical medications and moisturisers alone are often ineffective in patients with high atopic dermatitis burden, and phototherapy or systemic immunosuppressive medications might be needed to achieve disease control.[14,15,18,19] Corticosteroids broadly affect inflammatory processes associated with atopic dermatitis, but long-term continuous use is restricted by risk of local and systemic toxicity.[14,15,18,19,39,40] Nonetheless, topical corticosteroids as adjunctive therapy used concomitantly with dupilumab might offer some added benefit for treatment of residual localised disease. Patients in this study had previously shown inadequate response to topical corticosteroids, but addition of concomitant topical corticosteroids with or without topical calcineurin inhibitors to dupilumab resulted in efficacy that was generally as good or better than dupilumab monotherapy in previous studies.[24–27] For example, week 16 EASI-75 responses and EASI percentage improvement in the present study were about 10% greater in all three treatment groups than week 16 responses in two previous phase 3 studies of dupilumab monotherapy (SOLO 1 and SOLO 2).[27] Although results of the present study and SOLO results cannot be directly compared due to slight differences in study populations, our results suggest that there might be a small but consistent added clinical benefit of concomitant topical corticosteroids with or without topical calcineurin inhibitors.[27] Participation in a clinical study might reinforce regular use of topical treatments (provided free of charge in this study), which could account at least in part for responses in patients treated with placebo plus topical corticosteroids.

Few long-term studies of systemic immunosuppressive treatments, such as ciclosporin, in moderate-to-severe atopic dermatitis have been reported; of these, none were double blinded and placebo controlled. For example, in a 6-month randomised, open-label study in patients with moderate-to-severe atopic dermatitis, ciclosporin combined with topical corticosteroids with or without topical calcineurin inhibitors improved responses versus ciclosporin monotherapy, despite ciclosporin dose reduction in the combination group.[8] In a single-blinded, randomised study in patients

with severe atopic dermatitis, 30 weeks of either ciclosporin or enteric-coated mycophenolate mofetil showed similar levels of efficacy, although more patients on mycophenolate required oral corticosteroid rescue treatment.[11] Previous prospective long-term studies of ciclosporin in severe atopic dermatitis were hampered by high dropout rates, open-label design, intermittent dosing, or unclear outcome measures.[6,7,12] Other long-term efficacy and safety data of systemic immunosuppressive drugs in atopic dermatitis are only available from retrospective daily practice drug survival studies; for example, in a retrospective cohort study of ciclosporin in 356 patients with severe atopic dermatitis, most patients discontinued ciclosporin due to inefficacy or adverse events, or both, after 1 year.[9] Long-term drug survival studies of azathioprine, enteric-coated mycophenolate, and methotrexate in atopic dermatitis also reported high discontinuation rates after 1 year due to adverse events, inefficacy, or both.[10,13] In view of the toxicities of systemic immunosuppressants, guidelines limit their treatment duration, and most of these drugs (except ciclosporin in some countries) are not approved for atopic dermatitis treatment.[14–17,41] Thus, treatment options are limited for patients with inadequate response to topical corticosteroids.

This study has limitations. For some efficacy outcomes, such as the proportion of patients achieving IGA 0/1 and 2 point or higher improvement in IGA from baseline, EASI-75, and peak pruritus NRS improvement of 4 or higher and 3 or higher, the dupilumab q2w plus topical corticosteroids group showed greater variability over time compared with the dupilumab qw plus topical corticosteroids group, which might reflect the smaller sample size (33%) of the dupilumab q2w plus topical corticosteroids group. Additionally, quantification of the use of concomitant topical medication was difficult, because there are logistical and technical barriers to accurately and consistently measure leftover content in tubes of topical corticosteroids across more than 150 study sites.

In conclusion, adding dupilumab to standard-of-care treatment with topical corticosteroids with or without topical calcineurin inhibitors over 52 weeks improved efficacy across multiple measures of clinical severity, which included the primary and coprimary endpoints, signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and HRQoL. Significant improvements in pruritus occurred as early as week 2. Dupilumab plus topical corticosteroids also reduced the incidence of flares and use of topical and systemic rescue treatments. No new safety signals were associated with long-term treatment, and there were no clinically meaningful differences in laboratory values between dupilumab plus topical corticosteroids and placebo plus topical corticosteroids, and no additional safety concerns with the addition of concomitant topical corticosteroids with or without topical calcineurin inhibitors. The emerging benefit-to-risk profile in this 52-week study supports the role of dupilumab as a primary targeted biologic therapy for up to 1 year in patients with moderate-to-severe atopic dermatitis who are not controlled with topical medications alone. These results validate the fundamental role for interleukin 4 and interleukin 13 in the pathogenesis of atopic dermatitis and add to the possibility that these cytokines are crucially involved in related allergic or atopic (type 2/Th2 immune) diseases that are associated with atopic dermatitis.

Contributors

AB, VM, NMHG, GP, NS, and GDY contributed to the concept and design of the study; AB, MdBW, MG, JCC, JW, DP, ELS, KAP, HC-HH, DR, CEMG, PF, EP, TE, PHP, RMP, JCC, KE, and LK acquired data; all authors contributed to data analysis and interpretation, critical revision of the publication, final approval to submit, and were accountable for the accuracy and integrity of the publication.

Declaration of interests

AB has been a scientific adviser and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc, Sandoz, Sanofi Genzyme, Sun Pharma, UCB, and Valeant; and has received payment as a speaker for Lilly, Regeneron Pharmaceuticals Inc, and Sanofi Genzyme. MdBW has been a consultant for Regeneron Pharmaceuticals Inc, and Sanofi Genzyme; has been an advisory board member for AbbVie, Anacor, Regeneron Pharmaceuticals Inc, and Sanofi Genzyme; and has been a principal investigator for AbbVie, Novartis, Regeneron Pharmaceuticals Inc, Roche, and Sanofi Genzyme. MG has been an investigator for AbbVie, Galderma, GlaxoSmithKline, Pfizer, Regeneron Pharmaceuticals, Inc, Roche, and Sanofi Genzyme; a speaker for AbbVie and Sanofi Genzyme; and an advisory board member or consultant for AbbVie, Pfizer, Regeneron Pharmaceuticals Inc, and Sanofi Genzyme. JCC has been a consultant and speaker for AbbVie, Actelion, Celgene, Janssen, Lilly, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, and Sun Pharmaceutical; and an investigator for Actelion, Boehringer Ingelheim, Corrona, Cutanea, Dermira, Galderma, GlaxoSmithKline, Janssen, Lilly, Novartis, Merck, Pfizer, Regeneron Pharmaceuticals Inc, PSOLAR, Sun Pharmaceuticals, and Valeant.JW has been a speaker for Celgene, Eli Lilly, Janssen, and Regeneron Pharmaceuticals, Inc; served on advisory boards for AbbVie, Celgene, Eli Lilly, Janssen, Regeneron Pharmaceuticals, Inc., and Sun Pharma; and has been a principal Investigator for AbbVie, Actavis, Allergan, Actelion, Amaranth, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Coherus, Eli Lilly, Foamix, Genentech, GSK, Inventiv, Janssen, Leo Pharma, Maruho, Merck, Novartis, Novum, Oncobiologics, Pfizer, Regeneron Pharmaceuticals, Inc., Stiefel, Symbio, Tigercat, Topstone, and Valeant. DP has been a consultant for Bickel Biotechnology, Biofrontera AG, Celgene, Dermira, DUSA, Leo Pharma, Novartis, Promius, Regeneron Pharmaceuticals, Inc, TheraVida, and Valeant Pharmaceuticals International; a principal investigator for Abbott Laboratories, Amgen, Bickel Biotechnology, Celgene, Eli Lilly, Leo Pharma, Novartis, Novo Nordisk A/S, Ortho Dermatologics, Peplin, Pfizer, Photocure ASA, Regeneron Pharmaceuticals, Inc, Stiefel, and Valeant; an investigator for Promius; and an advisory board member for Pfizer. ELS has received grants/research support from Amgen, Celgene, Chugai, Galderma, and Regeneron Pharmaceuticals Inc; and has been a consultant for Anacor, Asubio, Celgene, Galderma, Genentech, Medicis, and Merck. KAP has been a consultant and investigator for Akros, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Dermira, Dow Pharma, Genentech, Merck Serono, Mylan, Roche, Sanofi-Aventis/Genzyme, Takeda, and UCB; a speaker, consultant, and investigator for AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Valeant; an investigator for Allergan, Anacor, Coherus, GlaxoSmithKline, and MedImmune; a consultant for AstraZeneca, Baxter, CanFite, Meiji Seika Pharma, and Mitsubishi Pharma; and a speaker and consultant for Devonian. HC-HH

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