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Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ)

M. de Bruin-Weller,[1] D. Thaçi,[2] C.H. Smith,[3] K. Reich,[4] M.J. Cork,[5] A. Radin,[6] Q. Zhang,[7] B. Akinlade,[6] A. Gadkari,[6] L. Eckert,[8] T. Hultsch,[9] Z. Chen,[6] G. Pirozzi,[10] N.M.H. Graham[6] and B. Shumel[6]

[1]University Medical Center Utrecht, Utrecht, the Netherlands
[2]University of Lübeck, Lübeck, Germany
[3]St. John's Institute of Dermatology, London, U.K.
[4]Dermatologikum and TFS Research Institute, Hamburg, Germany
[5]Sheffield Dermatology Research, The University of Sheffield, Sheffield, U.K.
[6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, U.S.A.
[7]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, U.S.A.
[8]Sanofi, Chilly-Mazarin, France
[9]Sanofi, Cambridge, MA, U.S.A.
[10]Sanofi, Bridgewater, NJ, U.S.A.

Summary

Background Atopic dermatitis is a chronic inflammatory skin disease that may require systemic therapy. Ciclosporin A (CsA) is a widely used, potent immunosuppressant but it is not effective in all patients with atopic dermatitis, and side-effects limit its use. Dupilumab, a fully human anti-interleukin 4 receptor-alpha monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of Type 2/Th2-mediated inflammation, and is approved in the U.S.A. and the European Union for the treatment of inadequately-controlled moderate-to-severe atopic dermatitis in adults.

Objectives To evaluate efficacy and safety of dupilumab with concomitant topical corticosteroids (TCS) in adults with atopic dermatitis with inadequate response to/intolerance of CsA, or for whom CsA treatment was medically inadvisable.

Methods In this 16-week, double-blind, randomized, placebo-controlled, phase III trial, patients were randomized 1 : 1 : 1 to subcutaneous dupilumab 300 mg weekly (qw) or every 2 weeks (q2w) or placebo. All received concomitant medium-potency TCS from Week −2 through Week 16; dosage could be tapered if lesions cleared, or stopped for adverse reactions to TCS.

Results In total, 390 patients were screened, 325 were randomized, and 318 completed the trial. Treatment groups had similar baseline characteristics. Significantly more patients in the dupilumab qw + TCS and q2w + TCS groups achieved ≥ 75% improvement from baseline in the Eczema Area and Severity Index at Week 16 vs. the placebo + TCS group (primary end point) (59·1% and 62·6% vs. 29·6%, respectively; $P < 0{\cdot}001$ vs. placebo + TCS, both doses). Other clinical outcomes and atopic dermatitis symptoms were significantly improved in the dupilumab qw + TCS and q2w + TCS groups, including pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life (QoL). Treatment groups had similar overall rates of adverse events (qw + TCS, q2w + TCS

Correspondence
Marjolein de Bruin-Weller.
E-mail: m.s.debruin-weller@umcutrecht.nl

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and placebo + TCS groups: 69·1%, 72·0% and 69·4%, respectively) and serious adverse events (1·8%, 1·9% and 1·9%, respectively). Conjunctivitis was more frequent with dupilumab + TCS; skin infections were more frequent with placebo + TCS.

Conclusions Dupilumab + TCS significantly improved signs and symptoms of atopic dermatitis and QoL in adults with a history of inadequate response to/intolerance of CsA, or for whom CsA treatment was medically inadvisable. No new safety signals were identified.

What's already known about this topic?

- Patients with atopic dermatitis that is inadequately controlled with topical therapy have few systemic treatment options.
- Ciclosporin A (CsA) is a systemic immunosuppressant approved for atopic dermatitis in most European countries and Japan, but not all patients respond, and side-effects limit its use.
- Dupilumab (monoclonal antibody against interleukin-4 receptor-alpha) with/without topical corticosteroids (TCS) is approved in the U.S.A. and the European Union for the treatment of adults with inadequately-controlled moderate-to-severe atopic dermatitis.

What does this study add?

- In this 16-week trial in adults with atopic dermatitis and history of inadequate response or intolerance to CsA, or for whom CsA treatment was medically inadvisable, dupilumab administered weekly or every 2 weeks with concomitant TCS significantly improved signs and symptoms and quality of life, with no new safety signals.
- These data support the use of dupilumab in this difficult-to-treat population.

Atopic dermatitis is a chronic pruritic inflammatory skin disease that features activation of Type 2/T-helper (Th2) immune responses, and an altered skin barrier and skin microbiome.[1–8] For patients with an inadequate response or intolerance to topical therapies, guidelines recommend systemic immunosuppressants [e.g. ciclosporin A (CsA), methotrexate, azathioprine or mycophenolic acid], although these treatments show variable efficacy/effectiveness and tolerability, and may be complicated by adverse effects and adverse medication interactions both in the short and long term.[9–18] Phototherapy is also recommended, but cannot be used as long-term treatment and has risks including burning, skin ageing, adverse medication interactions and skin cancer.[9–18]

Unlike other systemic immunosuppressants, CsA is approved in many European countries and Japan for severe atopic dermatitis when systemic therapy is required. CsA suppresses Th1, Th2 and Th17/22, affecting both humoral and cellular immune responses.[19,20] Long-term use (beyond 1 year) of CsA, as may be required in atopic dermatitis, is limited by risk of side-effects, although off-label use beyond 1 year has been reported.[17,21–39] Side-effects associated with CsA include hypertension, nephrotoxicity and subjective side-effects (e.g. headache, paraesthesia in fingers and toes, fatigue).[17,21–39] Its use is also limited by contraindications because of other medical conditions. Thus, patients with atopic dermatitis who are unresponsive to or who are unable to use topical medications or CsA have few treatment options. Given the chronicity of atopic dermatitis and the need for long-term pharmacological therapy, new treatment options with better benefit–risk profiles are needed.

Dupilumab, a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor-alpha, is a targeted agent that selectively inhibits signalling of IL-4 and IL-13, key cytokines of type 2/Th2 inflammation.[40] Dupilumab is approved in the U.S.A. for the treatment of adults with moderate-to-severe atopic dermatitis whose disease is inadequately controlled by topical therapies, or when such treatments are not advisable, and can be used with or without topical corticosteroids (TCS).[41] Dupilumab has also been approved by the European Medicines Agency for use in adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.[42]

In patients with moderate-to-severe atopic dermatitis who had inadequate response to topical medications, dupilumab alone or with TCS significantly improved clinical signs and symptoms of atopic dermatitis.[43–48] In these studies, adverse

events (AEs) that were more frequent with dupilumab included conjunctivitis and injection-site reactions, but there was no increase in infections or serious AEs (SAEs) compared with placebo.[43–47] In addition, dupilumab is being investigated in other Type 2/Th2 diseases. Positive data have been reported in clinical trials with dupilumab in patients with asthma,[49–51] chronic rhinosinusitis with nasal polyposis[52] and eosinophilic oesophagitis,[53] providing evidence of a common Type 2/Th2 mechanism underlying these diseases.

The present study expands upon previous studies of dupilumab in patients with moderate-to-severe atopic dermatitis by evaluating the efficacy and safety of dupilumab with concomitant TCS in patients with atopic dermatitis and a history of inadequate response or intolerance to CsA, or CsA-naïve patients for whom CsA treatment was medically inadvisable.

Patients and methods

Study design

LIBERTY AD CAFÉ (ClinicalTrials.gov Identifier: NCT02755649; EudraCT: 2015-002653-35) was a randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study (Fig. 1). Patients were enrolled at academic institutions, hospitals and clinics in 10 European countries in which systemic CsA has been approved for atopic dermatitis. Patients were recruited by individual sites, based on reviews of patient databases, referrals and advertising. See Appendix S2 (Supporting Information) for additional details about our methods.

Patients

Main inclusion criteria were: individuals ≥ 18 years of age with chronic atopic dermatitis according to American Academy of Dermatology consensus criteria;[1] where treatment with a potent TCS is indicated; there has been an inadequate response to TCS (as defined by investigator) within the 6 months before screening; a history of (i) prior CsA exposure and either inadequate response to CsA, requirement for CsA at doses or durations beyond those specified in prescribing information, or intolerance and/or unacceptable toxicity, or (ii) CsA-naïve and not eligible for CsA because of medical contraindications (e.g. uncontrolled hypertension on medication), use of prohibited concomitant medications, increased susceptibility to CsA-induced renal damage (elevated creatinine) and/or liver damage (elevated liver function tests), increased risk of serious infection or hypersensitivity to CsA active substance or excipients; an Eczema Area Severity Index (EASI) score ≥ 20 at screening and baseline; an Investigator's Global Assessment (IGA) score ≥ 3 [scale 0 (clear) to 4 (severe)] at screening and baseline; and ≥ 10% body surface area (BSA) of atopic dermatitis involvement at screening and baseline. (Appendix S2, full inclusion/exclusion criteria; see Supporting Information.)

Ethics

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements. All patients provided signed written informed consent prior to any study procedure. Prior to study initiation, institutional review boards (Table S1; see Supporting Information) and independent ethics committees reviewed and approved the protocol, the informed consent form and patient information. An independent data monitoring committee (IDMC) monitored patient safety.

Study procedures, randomization and treatments

The screening period ran from day −28 to baseline, and included a TCS standardization period, which ran from day −14 to baseline (Fig. 1). At baseline, patients were randomized (1 : 1 : 1) to receive 16 weeks of subcutaneous dupilumab 300 mg weekly (qw) or subcutaneous dupilumab 300 mg every 2 weeks (q2w) or placebo, using a central interactive voice-/web-response randomization system, stratified by baseline IGA score (3 or 4) and prior CsA exposure

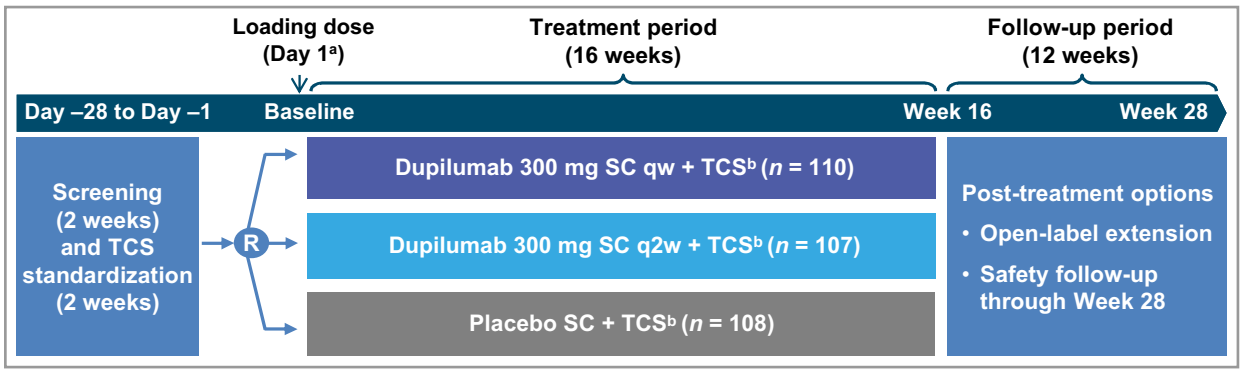

Fig 1. Study design. [a]Dupilumab 600 mg or matching placebo; [b]Patients were required to use TCS for the entire treatment period. q2w, every 2 weeks; qw, weekly; R, randomization (1 : 1 : 1); SC, subcutaneous; TCS, topical corticosteroids.

(yes/no). At baseline, patients received a loading dose of 600 mg dupilumab or matching placebo, followed thereafter by subcutaneous dupilumab 300 mg qw or q2w, or placebo.

For blinding purposes, patients assigned to dupilumab q2w + TCS received placebo on weeks when dupilumab was not administered. The blinded study drug (dupilumab or placebo) was provided in coded kits with a medication numbering system. Except for the statistician who provided the randomization sequence, the IDMC statistician and IDMC members, the study remained blinded to all individuals until prespecified unblinding. Emergency unblinding was permitted for a medical emergency, an SAE that was unexpected or for which a causal relationship to study drug could not be ruled out, or for any other significant medical event. During Weeks 17–28, patients were followed for safety or could enter an open-label extension study (R668-AD-1225; ClinicalTrials.gov: NCT01949311; EudraCT: 2013-001449-15).

During the initial 2 weeks of the screening period, patients could use TCS at investigator discretion. Starting at day −14, and during the study treatment period, all eligible patients applied medium-potency TCS once daily to active lesion areas, or low-potency TCS on areas of thin skin (e.g. face, neck, intertriginous and genital areas) or where continued treatment with medium-potency TCS was considered unsafe. Patients could stop TCS upon adverse reaction to the TCS. Patients achieving an IGA of 0 by Weeks 4, 8 or 12 could taper TCS to every other day.

After Week 4, patients who continued to have an IGA of 0 for 4 weeks could switch TCS to twice per week; if they did not continue to have an IGA of 0 they would revert to daily dosing. Patients with clear skin continued to apply TCS to lesion-prone areas at intervals of every other day (if prior to day 57) or twice weekly (after day 57), as described above.

During the safety follow-up, patients could remain on TCS at investigator discretion. Patients recorded TCS use in a medication diary; tubes were weighed at each visit through Week 16. Patients were instructed to apply emollients twice daily for the 7 days prior to randomization and throughout the study; stable doses of prescription moisturizers or moisturizers containing additives were permitted if initiated before screening.

Patients could receive rescue medication, including potent or very potent TCS, topical calcineurin inhibitors or systemic medication, if medically necessary (e.g. to control intractable atopic dermatitis symptoms), at investigator discretion. Patients who received rescue medication were considered treatment failures, but continued study visits and assessments; those on topical rescue medication could continue study treatment, whereas those on systemic rescue medication discontinued study treatment (Appendix S2, prohibited concomitant medications; see Supporting Information).

End points

The primary end point was the proportion of patients with ≥ 75% improvement from baseline in EASI score (EASI-75) at Week 16. Secondary end points were the following (all at Week 16, unless otherwise indicated): per cent change from baseline in EASI, SCORing Atopic Dermatitis (SCORAD), weekly average of peak daily pruritus numerical rating scale (NRS) (Weeks 2 and 16) and Global Individual Sign Score (GISS); change from baseline in per cent BSA affected by atopic dermatitis, Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM) and Hospital Anxiety and Depression Scale (HADS); mean weekly dose of TCS during the treatment period; and proportions of patients with ≥ 50% or ≥ 90% improvement from baseline in EASI score (EASI-50 or EASI-90), EASI-75 (among patients with prior CsA exposure), ≥ 4-point reduction in weekly average of peak daily pruritus NRS score (among patients with baseline pruritus NRS score ≥ 4), ≥ 50% improvement from baseline in SCORAD (SCORAD-50) and both IGA 0 or 1 (clear or almost clear) and a 2-point reduction in IGA from baseline.

Post hoc analyses included: mean change from baseline in EASI, SCORAD and pruritus NRS scores; mean change from baseline in SCORAD visual analogue scale for sleep; and proportions of patients reporting 'no problem' on the pain/discomfort subscale on the generic five-dimension three-level EuroQoL scale (among patients reporting moderate-to-severe pain/discomfort at baseline), reporting 'no days' or '1–2 days' for number of nights that sleep was disturbed in the past week (POEM item 2) (among patients reporting 3–7 nights with missed sleep the previous week at baseline), achieving ≥ 4-point improvement in DLQI score [minimal clinically important difference (MCID)] (among patients with baseline DLQI ≥ 4),[54] achieving ≥ 4-point improvement in POEM score (MCID) (among patients with baseline POEM ≥ 4)[55] and achieving HADS anxiety (HADS-A) and depression (HADS-D) scores < 8 (among patients with HADS-A or HADS-D ≥ 8 at baseline).[56]

Statistical analyses

Approximately 110 patients were planned for each treatment group – approximately 70 with previous exposure to CsA and 40 with no exposure (Appendix S3; see Supporting Information). Target accrual was approximately 330 patients (110 per arm, including 70 with prior CsA exposure and 40 with no prior CsA exposure); this provided 99% power for the primary end point, assuming EASI-75 rates of 60·1% in the dupilumab arms and 26·4% in the placebo group, based on results of a 16-week phase IIb study[44] and a 12-week phase IIa study[43] in patients with moderate-to-severe atopic dermatitis, by prior CsA use and CsA-naïve patients.

Significance was set to $P = 0{\cdot}05$, two-sided. To account for multiplicity arising from comparison of each of the dupilumab + TCS dose groups with placebo + TCS, efficacy analyses were carried out in sequential order, following an end point hierarchy for each dupilumab dose regimen (Appendix S3; see Supporting Information). The study was not powered for comparison of the two dupilumab dose regimens. Significance values were considered nominal for post hoc analyses.

For the primary efficacy end point and other binary end points, the Cochran–Mantel–Haenszel test adjusted by randomization strata [disease severity (IGA 3 or 4) and prior CsA use (yes/no)], was used to compare each dupilumab + TCS group with placebo + TCS. Patients were specified as being 'nonresponders' at rescue medication initiation. Continuous end points were analysed using multiple imputation with ANCOVA; data after rescue medication usage was set to missing, and imputed by multiple imputation. For post hoc responder analyses, values after first rescue treatment were set to missing; patients with missing scores at week 16 were considered to be 'nonresponders' (Appendix S3; see Supporting Information).

Safety assessments are reported for the 16-week treatment period, and include AEs, treatment-related AEs, SAEs and AEs leading to discontinuation or death. Efficacy assessments were based on the full-analysis set, which included all randomized patients, based on the treatment allocated as randomized (intention-to-treat). Safety analyses were based on the safety population, which included all randomized patients who received any study drug, based on the treatment received.

Analyses used SAS version 9.2 or above (SAS Institute, Cary, NC, U.S.A.).

Results

Patient disposition and baseline characteristics

Between January and December 2016, 390 patients were screened and 325 randomized to one of three groups: 300 mg dupilumab qw + TCS (n = 110), 300 mg dupilumab q2w + TCS (n = 107) or placebo + TCS (n = 108) (Fig. S1 and Table S2; see Supporting Information).

Baseline characteristics were similar among treatment groups overall (Table 1), and in subgroups based on prior CsA use (Table S3; see Supporting Information). Median atopic dermatitis duration was 30 years. At baseline, the median EASI score was 31·1–31·7, 75% of patients reported moderate or severe pain/discomfort, 59% reported sleep disruption in 3–7 nights over the past week and 65% had previously received CsA. Most patients completed the study treatment (98·2%, 100% and 95·4% in the qw + TCS q2w + TCS and placebo + TCS groups, respectively) by data cut-off (5 January 2017); 3 (3%) in the placebo + TCS group withdrew from study treatment because of lack of efficacy, and 2 (2%) each in the placebo + TCS and dupilumab qw + TCS groups withdrew because of AEs.

Efficacy

Primary end point

The proportion of patients achieving EASI-75 at Week 16 was significantly higher in the dupilumab qw + TCS and q2w + TCS groups vs. placebo + TCS (59·1% and 62·6% vs. 29·6%, respectively; $P < 0·001$, each dose group vs. placebo + TCS) (Table 2, Fig. 2a).

Secondary end points

Significantly more patients receiving dupilumab + TCS achieved EASI-50 and EASI-90 at Week 16 than placebo + TCS (Table 2; Fig. 2b, c). Among patients with prior exposure to CsA, significantly more receiving dupilumab + TCS achieved EASI-75 vs. placebo + TCS (Table 2; Fig. 2d). Dupilumab + TCS significantly improved EASI and SCORAD scores from baseline to Week 16 vs. placebo + TCS (Table 2, Fig. 3a, b; Table S4, Figs S2, S3; see Supporting Information), and significantly improved all other measures of clinical efficacy vs. placebo + TCS (Table 2, Fig. S4; see Supporting Information).

Dupilumab + TCS significantly improved weekly average peak pruritus NRS from baseline to Week 16 vs. placebo + TCS, with significant improvement by Week 2 (Table 2, Fig. 4a, Table S4, Fig. S5; see Supporting Information). Significantly more patients receiving dupilumab + TCS achieved ≥ 4-point reduction in pruritus NRS by Week 16 vs. placebo + TCS (Table 2, Fig. 4b).

Dupilumab + TCS significantly improved health-related quality of life (HRQoL), symptoms of atopic dermatitis, pain/discomfort, sleep and symptoms of anxiety and depression vs. placebo + TCS (Table 2, Table S4, Figs S6–8; see Supporting Information). Significantly higher proportions of patients on dupilumab + TCS achieved a ≥ 4-point improvement (MCID) in DLQI and POEM scores by Week 16 vs. placebo + TCS (Table 2, Fig. 5a, b). The proportion of patients who achieved HADS-A and HADS-D subscores < 8 (among patients with HADS-A or HADS-D ≥ 8 at baseline) by Week 16 was significantly higher in the dupilumab q2w + TCS group, but not the qw + TCS group, vs. placebo + TCS (Table 2, Fig. 5c). Results of sensitivity analyses were similar to the primary analyses (Table S5; Figs S2–5, 6b, 7b, 8b; see Supporting Information).

Medication use

The dupilumab + TCS groups used a lower mean weekly dose by weight of TCS vs. placebo + TCS (Table 2). Fewer patients receiving dupilumab + TCS vs. placebo + TCS used rescue medication (Table 3). The most frequently used rescue medication was potent TCS.

Safety

Similar proportions of patients in the dupilumab qw + TCS, q2w + TCS and placebo + TCS groups reported AEs (Table 4). Few patients permanently discontinued treatment because of AEs. Two patients in each treatment group experienced SAEs; none were considered related to study treatment. No deaths occurred during the study.

The dupilumab + TCS groups had higher rates of conjunctivitis and injection-site reactions than the placebo + TCS group, whereas the placebo + TCS group had higher rates of nonherpetic skin infections and atopic dermatitis exacerbations (Table 4, Tables S6, S7; see Supporting Information). There

Table 1 Baseline demographics and disease characteristics

	Placebo + TCS (n = 108)	Dupilumab q2w + TCS (n = 107)	Dupilumab qw + TCS (n = 110)
Age, years: median (IQR)	37·5 (29·0–49·0)	38·0 (25·0–47·0)	38·0 (29·0–48·0)
Ethnicity, n (%)			
White	104 (96·3)	104 (97·2)	105 (95·5)
Asian	2 (1·9)	2 (1·9)	2 (1·8)
Black	0	0	2 (1·8)
Other	2 (1·9)	0	1 (0·9)
Not reported/missing	0	1 (0·9)	0
Men, n (%)	68 (63·0)	65 (60·7)	66 (60·0)
Duration of atopic dermatitis, years: median (IQR)	28·5 (19·5–40·0)	29·0 (19·0–43·0)	32·0 (21·0–42·0)
EASI score, median (IQR)	31·7 (24·2–40·7)	31·6 (25·2–39·2)	31·1 (24·5–39·0)
IGA score			
Median (IQR)	3·0 (3·0–4·0)	3·0 (3·0–4·0)	3·0 (3·0–4·0)
Patients with IGA 4 (severe), n (%)	52 (48·1)	50 (46·7)	52 (47·3)
Peak weekly averaged pruritus NRS, median (IQR)	6·9 (4·9–8·1)	7·0 (5·4–8·0)	6·4 (5·2–7·7)
Body surface area, median (IQR)	53·0 (38·3–69·3)	55·0 (44·0–66·0)	55·8 (41·5–68·0)
SCORAD score, median (IQR)	67·5 (58·5–76·6)	66·7 (61·1–76·2)	66·1 (55·4–75·4)
Dermatology Life Quality Index, total score, median (IQR)	13·0 (7·0–19·5)	14·0 (8·0–22·0)	13·0 (7·0–21·0)
POEM score, median (IQR)	19·0 (14·0–24·0)	20·0 (15·0–24·0)	19·0 (14·0–24·0)
Hospital Anxiety and Depression Scale, total score, median (IQR)	13·0 (6·0–18·5)	13·0 (6·0–19·0)	12·0 (6·0–19·0)
Global Individual Sign Score, median (IQR)	9·0 (8·0–11·0)	9·0 (8·0–11·0)	9·0 (8·0–10·0)
5-dimension EuroQoL scale – pain/discomfort, n (%)			
I have no pain or discomfort	26 (24·1)	29 (27·1)	25 (22·7)
I have moderate pain or discomfort	73 (67·6)	69 (64·5)	75 (68·2)
I have extreme pain or discomfort	9 (8·3)	9 (8·4)	10 (9·1)
SCORAD sleep VAS, median (IQR)	3·8 (1·4–7·0)	4·5 (1·6–7·6)	4·25 (1·3–7·2)
POEM item 2: in last week sleep has been disturbed, n (%)			
Patients reporting, n	107	107	110
0 (no days)	12 (11·2)	17 (15·9)	24 (21·8)
1 (1–2 days)	35 (32·7)	24 (22·4)	19 (17·3)
2 (3–4 days)	19 (17·8)	21 (19·6)	15 (13·6)
3 (5–6 days)	18 (16·8)	12 (11·2)	22 (20·0)
4 (every day)	23 (21·5)	33 (30·8)	30 (27·3)
Atopic/allergic conditions, n (%)			
Food allergy	41 (38·0)	51 (47·7)	54 (49·1)
Other allergy[a]	71 (65·7)	76 (71·0)	76 (69·1)
Allergic rhinitis	61 (56·5)	60 (56·1)	63 (57·3)
Allergic conjunctivitis	59 (54·6)	44 (41·1)	40 (36·4)
Asthma	50 (46·3)	41 (38·3)	44 (40·0)
Chronic rhinosinusitis	10 (9·3)	7 (6·5)	8 (7·3)
Urticaria	9 (8·3)	8 (7·5)	10 (9·1)
Atopic keratoconjunctivitis	6 (5·6)	8 (7·5)	11 (10·0)
Nasal polyps	6 (5·6)	0	9 (8·2)
Eosinophilic oesophagitis	0	1 (0·9)	1 (0·9)
Previous use of systemic immunosuppressants for atopic dermatitis, n (%)[b]	84 (77·8)	84 (78·5)	84 (76·4)
Previous use of methotrexate, n (%)	7 (6·5)	10 (9·3)	13 (11·8)
Previous use of azathioprine, n (%)	6 (5·6)	7 (6·5)	13 (11·8)
CsA exposure, Yes: n (%)	72 (66·7)	69 (64·5)	69 (62·7)
Reasons for stopping the most recent CsA treatment			
CsA worked well	2 (2·8)	4 (5·8)	2 (2·9)
Inadequate efficacy	35 (48·6)	40 (58·0)	38 (55·1)
Because of important side-effects	45 (62·5)	32 (46·4)	34 (49·3)
To avoid important side-effects	7 (9·7)	5 (7·2)	7 (10·1)
Patient intolerance, discomfort or inconvenience	9 (12·5)	9 (13·0)	12 (17·4)
Other	4 (5·6)	9 (13·0)	8 (11·6)
Unknown	1 (1·4)	0	0

(continued)

Table 1 (continued)

	Placebo + TCS (n = 108)	Dupilumab q2w + TCS (n = 107)	Dupilumab qw + TCS (n = 110)
CsA exposure, No: n (%)	36 (33·3)	38 (35·5)	41 (37·3)
Reasons for no prior CsA			
Medical contraindication	27 (75·0)	27 (71·1)	24 (58·5)
Treatment with CsA is otherwise inappropriate	12 (33·3)	14 (36·8)	15 (36·6)
Risk of important side-effects is generally too high	5 (13·9)	5 (13·2)	6 (14·6)
CsA treatment is difficult to manage	0	0	1 (2·4)
Other	1 (2·8)	3 (7·9)	1 (2·4)

q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids; CsA, ciclosporin A; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing atopic dermatitis; VAS, visual analogue scale of 0–10 (higher numbers represent worse scores). [a]Includes allergies to medications, animals, plants, mould, dust mites and other; [b]Patients may have used more than one type of immunosuppressant prior to study entry.

were no clinically meaningful differences in laboratory values between treatment groups (data not shown).

Conjunctivitis [including Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA PTs) conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis] was reported in 16%, 28% and 11% of patients in the dupilumab qw + TCS, q2w + TCS and placebo + TCS groups, respectively; all but one event were mild or moderate (Table S6; see Supporting Information). Most conjunctivitis events (89%, 62% and 87%, respectively) were recovered/resolved or recovering/resolving by the end of treatment (Table S6; see Supporting Information).

Herpes viral infections were reported in 7%, 5% and 6% of patients in the dupilumab qw + TCS, q2w + TCS and placebo + TCS groups, respectively (Table S8; see Supporting Information). The more serious forms of herpes viral infections (e.g. eczema herpeticum, ophthalmic herpes simplex and ophthalmic herpes zoster) occurred only in the placebo + TCS group. No localized herpes infections were severe and all but one had recovered/resolved by the end-of-treatment visit.

Discussion

Treatment options are limited for patients with atopic dermatitis who previously failed to respond to CsA or experienced CsA-related AEs, or for whom CsA use is inadvisable because of concomitant medical conditions or risk of drug interactions. This study demonstrates that dupilumab + TCS significantly improves skin lesions, pruritus and other symptoms of atopic dermatitis including pain/discomfort and sleep disruption, symptoms of anxiety and depression and HRQoL in this difficult-to-treat patient population. No new safety signals were identified in this study. Significantly more patients receiving dupilumab + TCS achieved EASI-75 at Week 16 (primary efficacy end point) vs. placebo + TCS. Among patients receiving dupilumab + TCS, 85% achieved a 50% reduction from baseline in EASI at Week 16 – a clinically meaningful response in this patient population with a high baseline burden of disease. Results in the subgroup of patients with prior exposure to CsA were consistent with the overall population. Outcomes for the two dupilumab dose regimens were generally similar. These results are consistent with those of previous studies of dupilumab in patients with moderate-to-severe atopic dermatitis inadequately controlled with topical medications.[43–48]

This study expands upon the previous studies in two principal ways. Firstly, unlike previous studies, the patients in this study were candidates for systemic treatment, and had either not responded to or had experienced intolerance to CsA, or for whom use of CsA treatment was medically inadvisable. Secondly, this study evaluated dupilumab on a background of treatment with TCS and patients could not discontinue TCS, unless for safety reasons, unlike in previous studies of dupilumab with concomitant TCS use, in which TCS could be stopped if lesions cleared.[43–48]

Patients with moderate-to-severe atopic dermatitis who need systemic therapy experience a significant burden of disease.[57–61] Atopic dermatitis symptoms can profoundly affect sleep, daily functioning, mental/emotional state, concomitant medication use and HRQoL, particularly in patients with untreated or inadequately treated atopic dermatitis.[57–61] Improvement in patient-reported outcomes was significant in both the dupilumab + TCS treatment groups, except for the proportion of patients who achieved HADS-A and HADS-D scores < 8 (among patients with HADS-A or HADS-D ≥ 8 at baseline), which was significantly greater with dupilumab q2w + TCS, but not qw + TCS; however, both dupilumab + TCS dose regimens showed significant improvement in mean change in HADS score from baseline.

Improvement in pruritus was rapid; divergence between dupilumab + TCS and placebo + TCS was significant by Week 2. By significantly improving a wide range of atopic dermatitis symptoms (including pruritus, pain/discomfort and sleep), in addition to aspects of mental health and HRQoL, dupilumab + TCS improved not only skin lesions but also the broader burden associated with moderate-to-severe atopic dermatitis in this patient population, consistent with previous studies.[43–48]

The choice of TCS background therapy as a control was consistent with European guidelines for patients eligible for

Table 2 Efficacy outcomes

	Placebo + TCS (n = 108)	Dupilumab q2w + TCS (n = 107)	Dupilumab qw + TCS (n = 110)
Primary efficacy outcome			
Proportion of patients who achieved EASI-75 at Week 16, n (%)	32 (29·6)	67 (62·6)***	65 (59·1)***
Secondary efficacy outcomes			
EASI score: LS mean per cent change from baseline at Week 16, % ± SE	−46·6 ± 2·76	−79·8 ± 2·59***	−78·2 ± 2·55***
Weekly average of peak pruritus NRS score: LS mean per cent change from baseline at Week 16, % ± SE	−25·4 ± 3·39	−53·9 ± 3·14***	−51·7 ± 3·09***
SCORAD score: LS mean per cent change from baseline at Week 16 ± SE	−29·5 ± 2·55	−62·4 ± 2·48***	−58·3 ± 2·45***
Weekly average of peak pruritus NRS score: proportion of patients who achieved improvement (reduction) ≥ 4 points from baseline to Week 16, n/N1 (%)[a]	13/91 (14·3)	43/94 (45·7)***	38/94 (40·4)***
Per cent body surface area affected: LS mean change from baseline at Week 16 ± SE	−19·6 ± 1·80	−39·2 ± 1·72***	−37·5 ± 1·69***
IGA: Proportion of patients who achieved both IGA of 0 or 1 and reduction from baseline of ≥ 2 points at Week 16, n (%)	15 (13·9)	43 (40·2)***	43 (39·1)***
DLQI: LS mean change from baseline at Week 16 ± SE	−4·5 ± 0·49	−9·5 ± 0·46***	−8·8 ± 0·45***
POEM: LS mean change from baseline at Week 16 ± SE	−4·3 ± 0·62	−11·9 ± 0·60***	−11·4 ± 0·59***
Proportion of patients with prior history of CsA who achieved EASI-75 at Week 16, n (%)	19 (26·4)	40 (58·0)***	39 (56·5)***
Mean weekly dose (g) of TCS use ± SE	25·1 ± 1·48	15·0 ± 1·51***	17·5 ± 1·49***
HADS: LS mean change from baseline at Week 16 ± SE	−2·3 ± 0·56	−6·1 ± 0·54***	−5·2 ± 0·53***
Other secondary efficacy outcomes			
Proportion of patients who achieved SCORAD-50 at Week 16, n (%)	28 (25·9)	71 (66·4)***	61 (55·5)***
GISS: LS mean change from baseline at Week 16 ± SE	−29·0 ± 2·75	−55·2 ± 2·66***	−53·3 ± 2·65***
Weekly average of peak pruritus NRS score: LS mean per cent change from baseline at Week 2, % ± SE	−10·0 ± 2·24	−17·2 ± 2·25*	−19·7 ± 2·21**
Post hoc efficacy outcomes[b]			
Proportion of patients who achieved EASI-50 at Week 16, n (%)	47 (43·5)	91 (85·0)***	94 (85·5)***
Proportion of patients who achieved EASI-90 at Week 16, n (%)	13 (12·0)	49 (45·8)***	41 (37·3)***
Proportion of patients with ≥ 4-point improvement in DLQI score at Week 16, n/N2 (%)	42/95 (44·2)	85/97 (87·6)***	77/99 (77·8)***
Proportion of patients with ≥ 4-point improvement in POEM score at Week 16, n/N3 (%)	45/107 (42·1)	89/106 (84·0)***	84/109 (77·1)***
Proportion of patients with HADS-A and HADS-D < 8 at Week 16, n/N4 (%)	22/60 (36·7)	35/56 (62·5)**	26/56 (46·4)[NS]
EQ-5D item 4 (pain/discomfort): proportion of patients reporting 'no problem' at Week 16, n (%)	40 (37·0)	75 (70·1)***	69 (62·7)***

TCS, topical corticosteroids; q2w, every 2 weeks; qw, weekly; EASI, Eczema Area and Severity Index; EASI-75, ≥ 75% improvement from baseline in EASI score; SE, standard error; LS, least squares; NRS, numerical rating scale; SCORAD, SCORing Atopic Dermatitis; N1, number of patients with peak pruritus NRS score ≥ 4 at baseline; IGA, Investigator's Global Assessment; DLQI, Dermatology Life Quality Index; POEM, Patient-Oriented Eczema Measure; CsA, ciclosporin A; HADS, Hospital Anxiety and Depression Scale; SCORAD-50, ≥ 50% improvement from baseline in SCORAD score; GISS, Global Individual Sign Score; EASI-50, ≥ 50% improvement from baseline in EASI score; EASI-90, ≥ 90% improvement from baseline in EASI score; N2, number of patients with DLQI score ≥ 4 at baseline; N3, number of patients with POEM score ≥ 4 at baseline; N4, number of patients with HADS-A or HADS-D ≥ 8 at baseline; NS, not significant; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; EQ-5D, 5-dimension EuroQoL scale. [a]Analysis was conducted in the population of patients with peak pruritus NRS score ≥ 4 at baseline; [b]all P-values for post hoc outcomes are nominal. *P < 0·05 vs. placebo + TCS; **P < 0·01 vs. placebo + TCS; ***P < 0·001 vs. placebo + TCS.

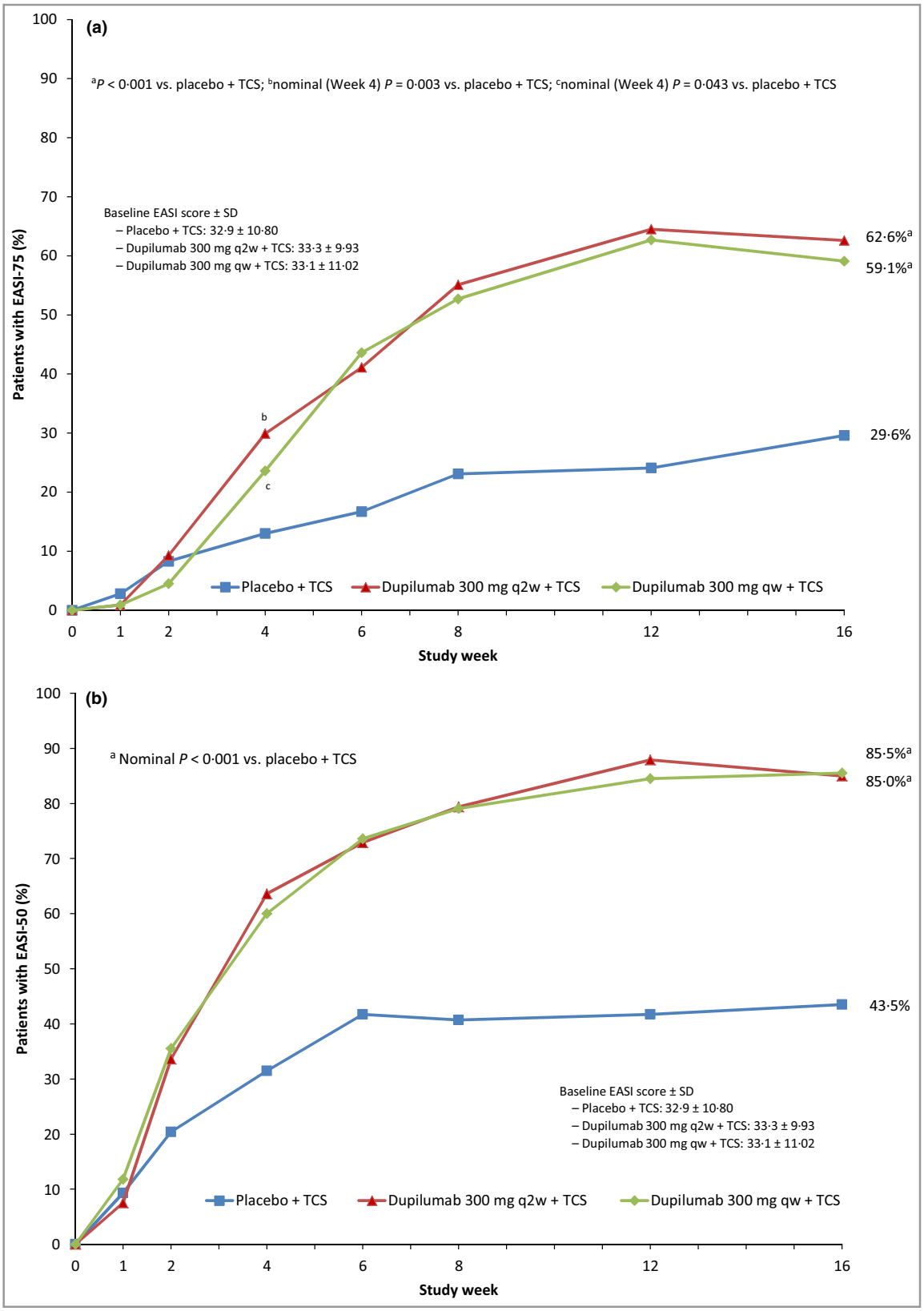

Fig 2. (a) Proportion of patients achieving EASI-75 (primary end point); (b) proportion of patients achieving EASI-50; (c) proportion of patients achieving EASI-90; (d) proportion of patients with prior CsA use achieving EASI-75. CsA, ciclosporin A; EASI, Eczema Area and Severity Index; EASI-50, ≥ 50% improvement in EASI score; EASI-75, ≥ 75% improvement in EASI score; EASI-90, ≥ 90% improvement in EASI score; q2w, every 2 weeks; qw, weekly; SD, standard deviation; TCS, topical corticosteroids.

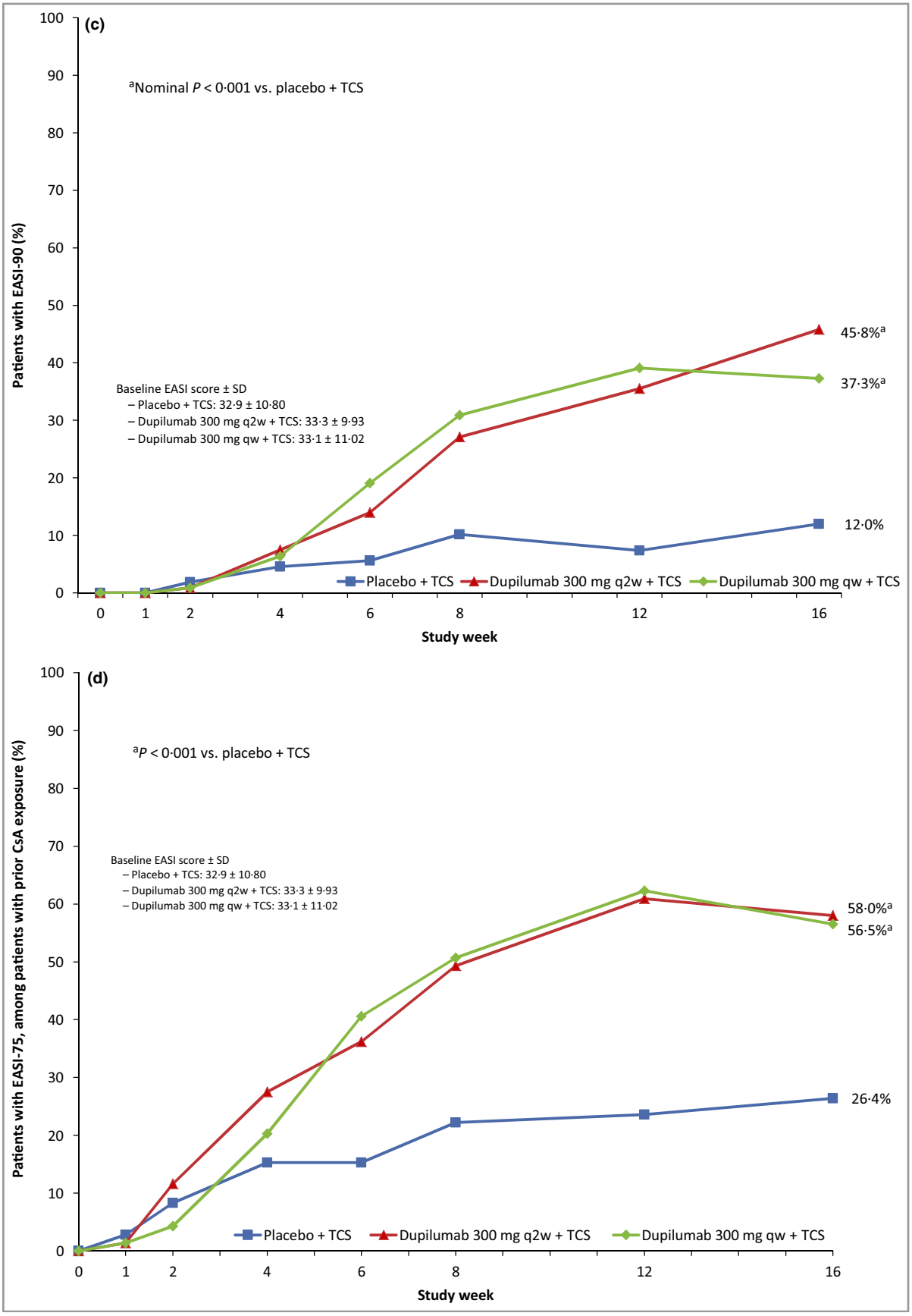

Fig 2. Continued

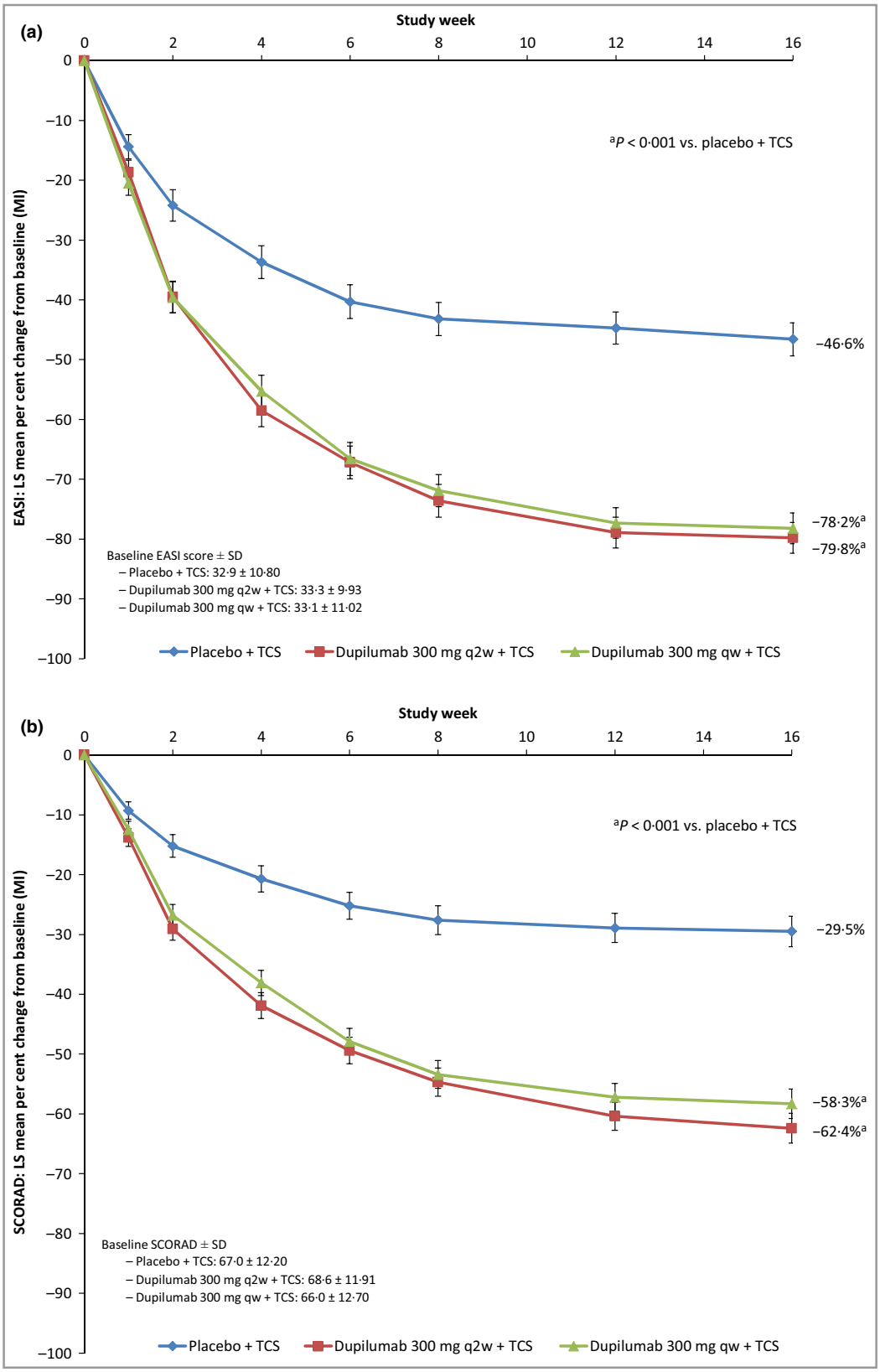

Fig 3. (a) EASI: LS mean per cent change from baseline, multiple imputation with censoring after rescue treatment use; (b) SCORAD: LS mean per cent change from baseline, multiple imputation with censoring after rescue treatment use. Error bars are ± SE. EASI, Eczema Area and Severity Index; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

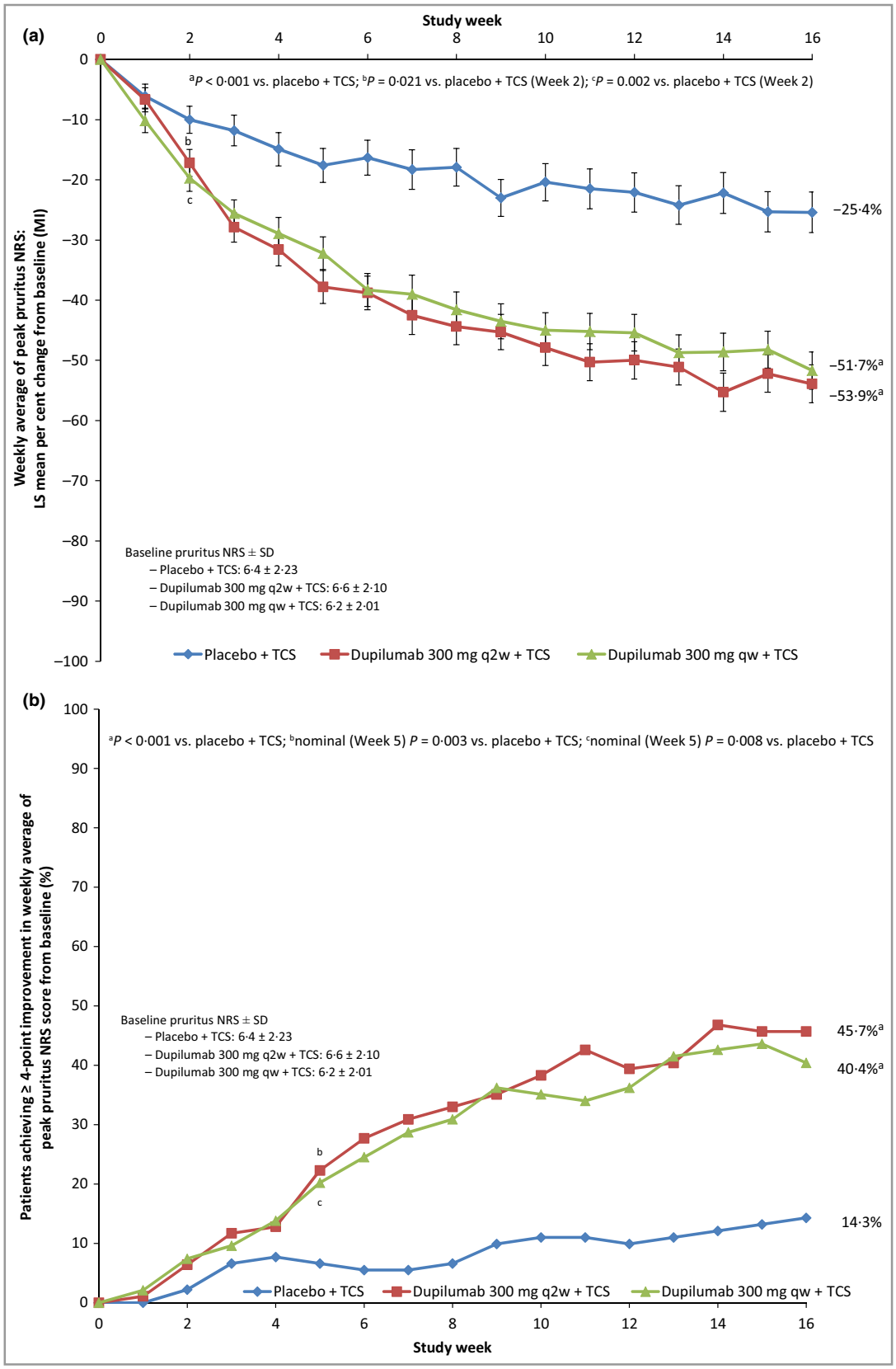

Fig 4. Weekly average of peak pruritus NRS: (a) LS mean per cent change from baseline, multiple imputation with censoring after rescue treatment use; (b) proportion of patients achieving ≥ 4-point reduction (improvement) from baseline. Error bars are ± SE. LS, least squares; MI, multiple imputation; NRS, numerical rating scale; q2w, every 2 weeks; qw, weekly; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

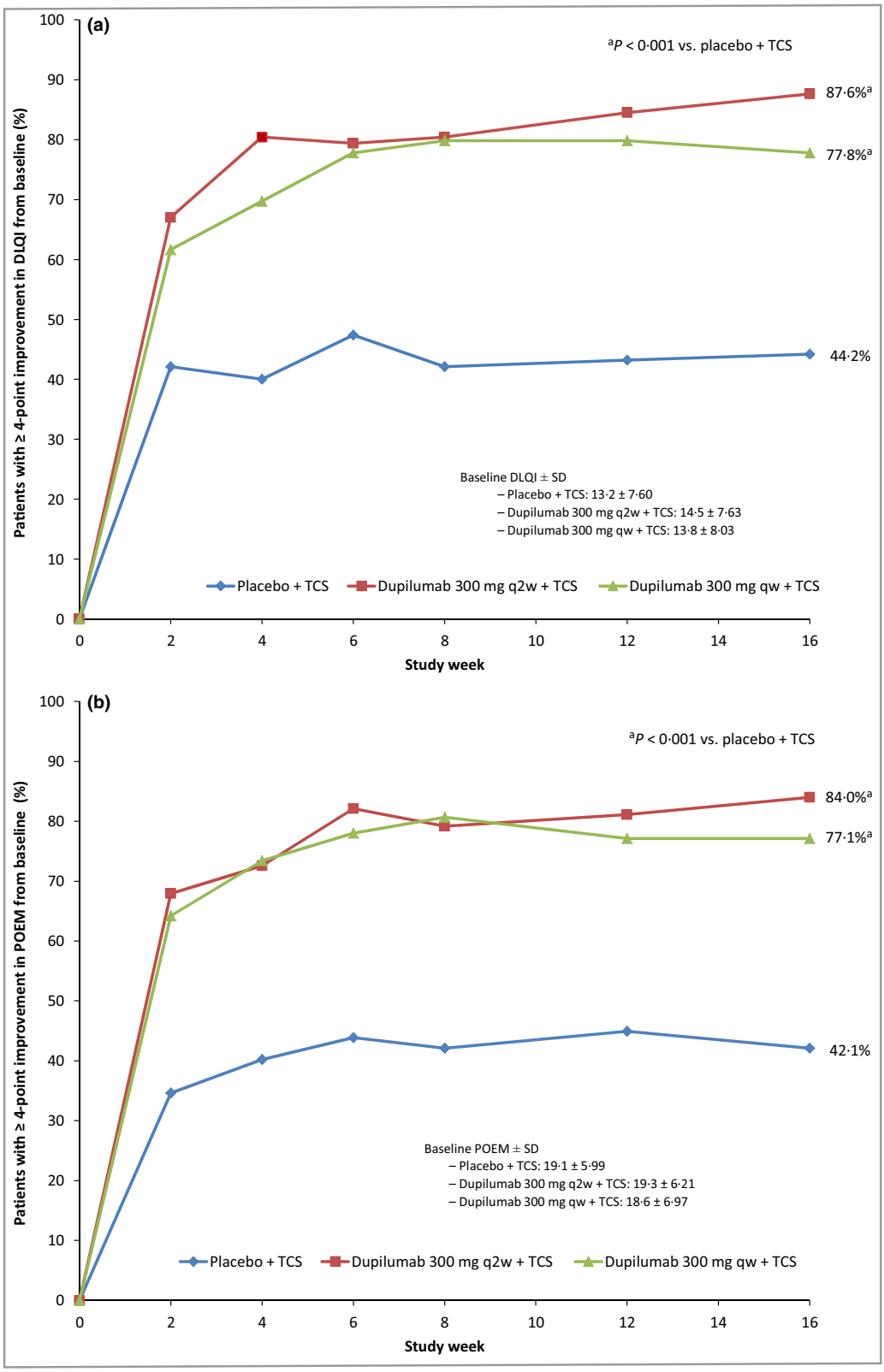

Fig 5. (a) DLQI: proportion of patients achieving ≥ 4-point reduction (improvement) from baseline (among patients with DLQI ≥ 4 at baseline); (b) POEM: proportion of patients achieving ≥ 4-point reduction (improvement) from baseline (among patients with POEM ≥ 4 at baseline); (c) proportion of patients with HADS-A and HADS-D < 8 at Week 16 among patients with HADS-A or HADS-D ≥ 8 at baseline. DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; POEM, Patient-Oriented Eczema Measure; q2w, every 2 weeks; qw, weekly; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

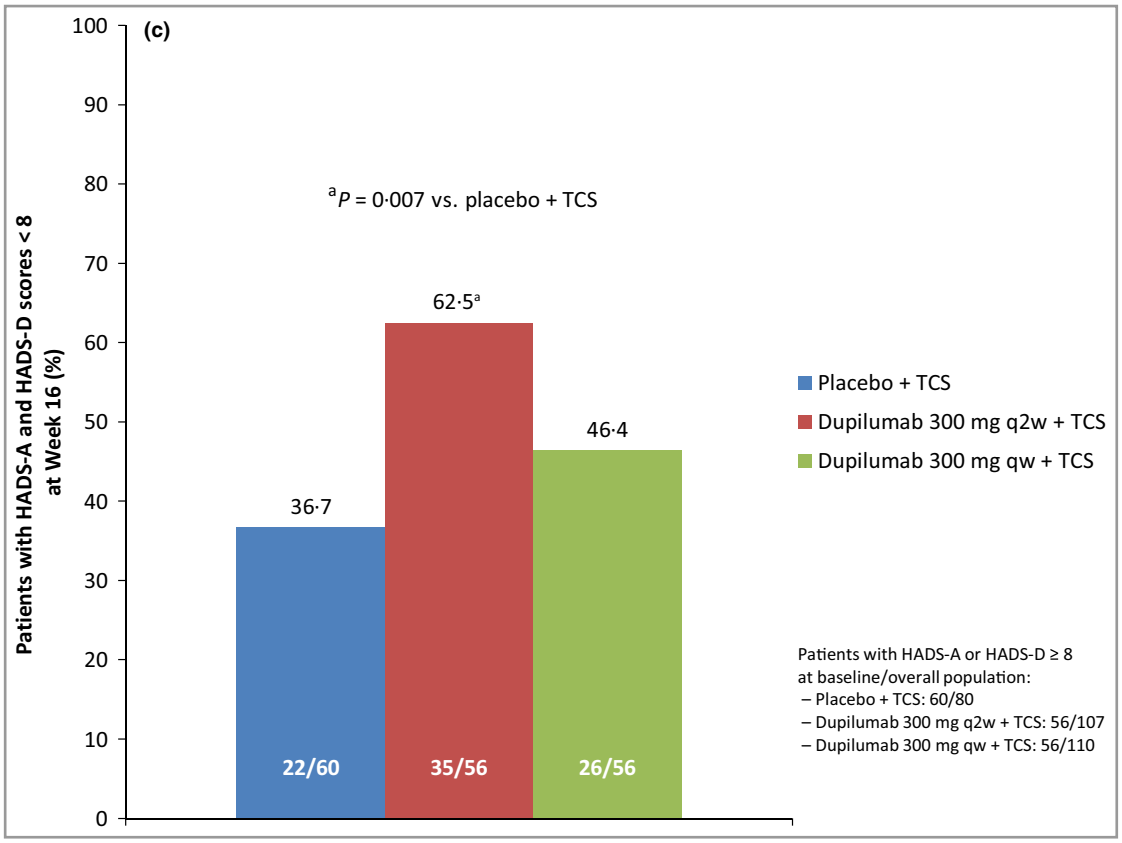

Fig 5. Continued

Table 3 Use of rescue medication during the study

	Placebo + TCS (n = 108)	Dupilumab q2w + TCS (n = 107)	Dupilumab qw + TCS (n = 110)
Patients requiring ≥ 1 rescue medication	19 (17·6)	4 (3·7)	5 (4·5)
TCS	16 (14·8)	3 (2·8)	4 (3·6)
Potent (group III)	11 (10·2)	3 (2·8)	2 (1·8)
Very potent (group IV)	7 (6·5)	0	2 (1·8)
Immunosuppressants	3 (2·8)	0	1 (0·9)
Oral ciclosporin A	3 (2·8)	0	0
Selective immunosuppressants	0	0	1 (0·9)
Non-TCS topical preparations (e.g. TCI)	0	1 (0·9)	0
Systemic glucocorticoids	2 (1·9)	0	0

Data are n (%). TCS, topical corticosteroids; q2w, every 2 weeks; qw, weekly; TCI, topical calcineurin inhibitors.

systemic CsA,[11,12,16] and reflects real-world practice. Patients receiving placebo + TCS used significantly more background TCS and rescue medication than the dupilumab + TCS groups, another indicator of better disease control with dupilumab + TCS compared with background TCS alone.

Several factors may help to account for the effect of placebo + TCS treatment on efficacy. Some 'placebo + TCS effect' may appear because of the natural waxing and waning clinical course of atopic dermatitis. In addition, the protocol requirement for patients with an inadequate response to TCS is not the same as no response to TCS. As noted, patients in the placebo group applied TCS and emollients in a continuous manner in a controlled setting under the supervision of a principal investigator. This alone may be responsible for an approximate 10% improvement in the per cent change in EASI score, as can be seen by comparing the Week 16 placebo response in LIBERTY AD CHRONOS (−48·4%)[47] with the Week 16 response in the monotherapy LIBERTY AD SOLO 1 (−37·6%) and LIBERTY AD SOLO 2 (−30·9%) trials.[46] The effect would be expected to be greater in a trial requiring continuous use of TCS (unlike CHRONOS, in which patients could stop TCS if their lesions cleared). This suggests that even patients who were candidates for systemic therapy could still obtain some benefit from continuous treatment with TCS. Nonetheless, in CAFÉ the significantly greater efficacy of dupilumab + TCS than placebo + TCS demonstrates that dupilumab provides clinically meaningful improvement over any improvement provided by background therapy with TCS in this patient population.

Treatment groups had similar overall rates of AEs and SAEs; no new safety signals were identified. Dupilumab + TCS was

Table 4 Adverse events

Number (%) of patients with:	Placebo + TCS (n = 108)	Dupilumab q2w + TCS (n = 107)	Dupilumab qw + TCS (n = 110)
≥ 1 adverse event	75 (69·4)	77 (72·0)	76 (69·1)
Any drug-related adverse event	20 (18·5)	36 (33·6)	37 (33·6)
Any adverse event causing permanent discontinuation of study drug	1 (0·9)	0	2 (1·8)
Any death	0	0	0
Any serious adverse event[a]	2 (1·9)	2 (1·9)	2 (1·8)
Any drug-related serious adverse event	0	0	0
Any serious adverse event causing permanent discontinuation of study drug	0	0	1 (0·9)
Adverse events (MedDRA PTs) reported by ≥ 2% of patients in any treatment group			
Infections and infestations[b]	44 (40·7)	49 (45·8)	47 (42·7)
Nasopharyngitis[c]	18 (16·7)	22 (20·6)	17 (15·5)
Conjunctivitis[c]	3 (2·8)	12 (11·2)	8 (7·3)
Oral herpes[c]	0	3 (2·8)	5 (4·5)
Gastroenteritis[c]	1 (0·9)	2 (1·9)	3 (2·7)
Respiratory tract infection viral[c]	1 (0·9)	0	4 (3·6)
Upper respiratory tract infection[c]	1 (0·9)	1 (0·9)	3 (2·7)
Pharyngitis[c]	3 (2·8)	1 (0·9)	2 (1·8)
Respiratory tract infection[c]	0	0	3 (2·7)
Herpes simplex[c]	3 (2·8)	1 (0·9)	1 (0·9)
Skin and subcutaneous tissue disorders[b]	21 (19·4)	22 (20·6)	21 (19·1)
Dermatitis atopic[c]	16 (14·8)	8 (7·5)	9 (8·2)
Eye disorders[b]	15 (13·9)	21 (19·6)	18 (16·4)
Allergic conjunctivitis[c]	7 (6·5)	16 (15·0)	10 (9·1)
Lacrimation increased[c]	1 (0·9)	1 (0·9)	3 (2·7)
Eye pruritus[c]	0	0	3 (2·7)
General disorders and administration site conditions[b]	12 (11·1)	9 (8·4)	21 (19·1)
Fatigue[c]	1 (0·9)	4 (3·7)	3 (2·7)
Injection-site reaction[c]	0	1 (0·9)	4 (3·6)
Injection-site erythema[c]	1 (0·9)	1 (0·9)	3 (2·7)
Injection-site swelling[c]	1 (0·9)	0	3 (2·7)
Oedema peripheral[c]	3 (2·8)	0	2 (1·8)
Nervous system disorders[b]	12 (11·1)	14 (13·1)	14 (12·7)
Headache[c]	9 (8·3)	10 (9·3)	10 (9·1)
Respiratory, thoracic and mediastinal disorders[b]	14 (13·0)	14 (13·1)	14 (12·7)
Rhinitis allergic[c]	1 (0·9)	7 (6·5)	4 (3·6)
Cough[c]	1 (0·9)	4 (3·7)	3 (2·7)
Oropharyngeal pain[c]	2 (1·9)	3 (2·8)	1 (0·9)
Rhinorrhoea[c]	3 (2·8)	0	3 (2·7)
Asthma[c]	3 (2·8)	1 (0·9)	1 (0·9)
Gastrointestinal disorders[b]	16 (14·8)	9 (8·4)	9 (8·2)
Diarrhoea[c]	2 (1·9)	3 (2·8)	2 (1·8)
Abdominal pain[c]	4 (3·7)	0	4 (3·6)
Musculoskeletal and connective tissue disorders[b]	12 (11·1)	4 (3·7)	10 (9·1)
Myalgia[c]	0	0	4 (3·6)
Back pain[c]	3 (2·8)	1 (0·9)	2 (1·8)
Vascular disorders[b]	1 (0·9)	4 (3·7)	3 (2·7)
Hypertension[c]	1 (0·9)	1 (0·9)	3 (2·7)
Blood and lymphatic system disorders[b]	4 (3·7)	4 (3·7)	1 (0·9)
Lymphadenopathy[c]	4 (3·7)	2 (1·9)	0
Skin infections (adjudicated; excluding herpetic infections)	9 (8·3)	2 (1·9)	4 (3·6)
Treatment-emergent conjunctivitis	12 (11·1)	30 (28·0)	18 (16·4)
Conjunctivitis	3 (2·8)	12 (11·2)	8 (7·3)
Conjunctivitis allergic	7 (6·5)	16 (15·0)	10 (9·1)
Adenovirus conjunctivitis	0	1 (0·9)	0
Conjunctivitis bacterial	2 (1·9)	1 (0·9)	0
Conjunctivitis viral	1 (0·9)	1 (0·9)	0

TCS, topical corticosteroids; q2w, every 2 weeks; qw, weekly; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class. [a]Serious adverse events were acute pancreatitis and hepatotoxicity (1 patient each in the dupilumab q2w + TCS group), ureteric calculus and atopic dermatitis (1 patient each in the dupilumab qw + TCS group) and hemiparesis and emphysema (1 patient each in the placebo + TCS group); [b]MedDRA SOC; SOCs listed are those for which at least one associated PT was reported in ≥ 2% of patients in any treatment group; [c]MedDRA PT.

not associated with increased overall risk of infections. Conjunctivitis and injection-site reactions were more frequent with dupilumab + TCS, whereas skin infections and atopic dermatitis exacerbations were more frequent with placebo + TCS, consistent with previous studies of dupilumab in atopic dermatitis.[43,44,46,47] Decreased incidence of nonherpetic skin infections in dupilumab-treated patients in this study, as in previous studies, adds to the body of evidence suggesting that dupilumab may restore skin barrier function.

Conjunctivitis rates in this study, especially MedDRA PTs of conjunctivitis and allergic conjunctivitis, were higher in all treatment groups than in previous studies.[44,46,47] In addition, more patients in this study reported a history of allergic conjunctivitis at baseline (36·4%, 41·1% and 54·6% in the dupilumab qw + TCS, q2w + TCS and placebo + TCS groups, respectively) compared with previous studies (e.g. LIBERTY AD CHRONOS, 21·6–28·2%).[44,46,47] This may partly be because of an increased awareness of conjunctivitis following publication of previous studies, in addition to the regional distribution of study sites (most patients were from Germany and Poland), compared with previous studies, which were conducted not only in Europe, but also in countries in North America and the Asia-Pacific. However, most conjunctivitis events were of mild or moderate severity and resolved while patients were still on treatment. No patient withdrew from study treatment because of an AE of conjunctivitis.

Interestingly, dupilumab is not associated with increased conjunctivitis rates in studies in other diseases, including asthma[49–51] and chronic rhinosinusitis with nasal polyposis,[52] suggesting that the increased rates of conjunctivitis in atopic dermatitis studies may reflect a unique interaction between atopic dermatitis- and dupilumab-related mechanisms. Further evaluations of conjunctivitis are ongoing to better characterize the aetiology, clinical features and most effective treatments.

As a chronic disease, atopic dermatitis requires long-term treatment options. In the present study, dupilumab + TCS was evaluated for 16 weeks. Safety and efficacy of dupilumab + TCS in the present study are similar to those observed at 52 weeks in a subset of patients in the CHRONOS study (n/N = 126/623) with baseline characteristics similar to the patient population in the present study.[47,62] Safety of dupilumab beyond 1 year is being evaluated in the open-label extension study.

Oral CsA is a broad immunosuppressant prescribed for patients with severe atopic dermatitis whose disease warrants systemic treatment. Although it may be effective in the short term in patients with severe atopic dermatitis, use of CsA is limited because of the risk of several types of side-effects, and the label restricts use to 1 year.[21–39] In addition, cessation of CsA treatment can lead to disease rebound, which is difficult to manage. Concern about these issues has led to reluctance among some physicians to initiate CsA therapy. The data from this 16-week clinical trial show that dupilumab is highly efficacious and well tolerated among patients not adequately controlled with or intolerant to CsA, or for whom CsA is medically inadvisable, giving physicians an important new treatment option. No blood monitoring is required for dupilumab;[41,42] however, blood monitoring may be required in some regions based on local guidelines.

This study had limitations. It was not designed to compare the two dupilumab dose regimens; however, results were similar for both regimens. In addition, the study was not designed to compare CsA-treated and CsA-naïve subgroups. In both subgroups, patients had been considered for CsA treatment, but CsA-naïve patients did not receive CsA because it was considered medically inadvisable (e.g. because of pre-existing hypertension or use of statins).

In conclusion, 16 weeks of dupilumab + TCS compared with placebo + TCS significantly improved signs and symptoms of atopic dermatitis and HRQoL, reduced use of concomitant TCS and rescue medications, and had an acceptable safety profile in adults with atopic dermatitis with a history of inadequate response or intolerance to CsA, or for whom CsA was medically inadvisable. These data support the use of dupilumab + TCS as a targeted biological therapy in this difficult-to-treat population.

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Appendix

Conflicts of interest: M.d.B.-W. is principal investigator, advisory board member and consultant for Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme; and principal investigator and advisory board member for AbbVie. D.T. has received honoraria for participation on advisory boards, as a speaker, and for consultancy from AbbVie, Almiral, Amgen, Biogen-Idec, Bristol-Myers Squibb, Celgene, Dignity, Dr. Reddy, Galapagos, Galderma, Janssen, Leo, Maruho, Mitsubishi, Lilly, Novartis, Pfizer, Sandoz-Hexal, Regeneron Pharmaceuticals, Inc., Sanofi, UCB and Xenoport; and received research grants from Celgene and Novartis. C.H.S. is a principal investigator for Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. K.R. is an advisor and/or paid speaker for and/or has participated in clinical trials for AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Takeda, UCB Pharma and Xenoport. M.C. is an investigator for/received honoraria from Astellas, Johnson and Johnson, Leo Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi and Stiefel-GSK; served on advisory boards for/received honoraria from Amgen, Astellas, Bayer, Johnson and Johnson, Merck Sharp & Dohme, Leo Pharmaceuticals, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Stiefel-GSK and Unilever; served as a consultant for/received honoraria from Amgen, Astellas, Johnson and Johnson, Leo Pharmaceuticals, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Stiefel-GSK, Unilever; gave lectures for/received honoraria from Astellas, Johnson and Johnson, Leo Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi and Stiefel-GSK; and received research grants/honoraria from Bayer and Merck Sharp & Dohme. B.A., Z.C., A.G., N.M.H.G., A.R., B.S. and Q.Z. are all employees and shareholders of Regeneron Pharmaceuticals, Inc. L.E., T.H., and G.P. are all employees of and may hold stock and/or stock options in Sanofi.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Study investigators.

Appendix S2 Additional methods.

Appendix S3 Additional statistical methods.

Table S1 Institutional review boards and independent ethics committees.

Table S2 Recruitment by country.

Table S3 Baseline characteristics: subgroups based on prior ciclosporin A use (a); subgroups based on baseline disease severity (Investigator's Global Assessment score 3 or 4) (b).

Table S4 Mean change from baseline at Week 16 in Eczema Area and Severity Index, SCORing Atopic Dermatitis, weekly

average of peak pruritus numerical rating scale, Dermatology Life Quality Index and Patient-Oriented Eczema Measure; multiple imputation method with censoring after rescue treatment.

Table S5 Sensitivity analyses of the proportion of patients who achieved EASI-75 at Week 16 (primary end point).

Table S6 Incidence of conjunctivitis and keratitis according to treatment group.

Table S7 Incidence of skin infection according to treatment group (Medical Dictionary for Regulatory Activities high level terms and preferred terms).

Table S8 Incidence of herpes virus infection according to treatment group.

Fig S1. CONSORT diagram of patient disposition.

Fig S2. Eczema Area and Severity Index: least squares mean per cent change (± SE) from baseline (last observation carried forward).

Fig S3. SCORing Atopic Dermatitis (SCORAD): least squares mean per cent change in SCORAD from baseline (last observation carried forward).

Fig S4. Per cent body surface area affected by atopic dermatitis: least squares mean change (± standard error) from baseline; (a) multiple imputation, (b) last observation carried forward.

Fig S5. Peak weekly pruritus numerical rating scale: least squares mean per cent change (± standard error) from baseline (last observation carried forward).

Fig S6. Dermatology Life Quality Index: least squares mean change from baseline; (a) multiple imputation, (b) last observation carried forward.

Fig S7. Patient-Oriented Eczema Measure: least squares mean change from baseline, multiple imputation (a); last observation carried forward (b).

Fig S8. Hospital Anxiety and Depression Scale total score: least squares mean change from baseline; multiple imputation (a), last observation carried forward (b).