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ORIGINAL RESEARCH

Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis and Prior Use of Systemic Non-Steroidal Immunosuppressants: Analysis of Four Phase 3 Trials

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ABSTRACT

Introduction: Dupilumab is approved as first-line systemic treatment for adults/adolescents with moderate-to-severe atopic dermatitis (AD) in Europe and elsewhere owing to its favourable benefit–risk profile. However, systemic non-steroidal immunosuppressants (NSISS) are often used as first-line therapy in clinical practice. Impact of prior therapy with NSISS on dupilumab's treatment effect vs. control has not been described previously. This study assessed

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dupilumab's efficacy vs. control in patients with moderate-to-severe AD, comparing treatment effect in patients with/without prior systemic NSISS therapy, in four phase 3 trials.

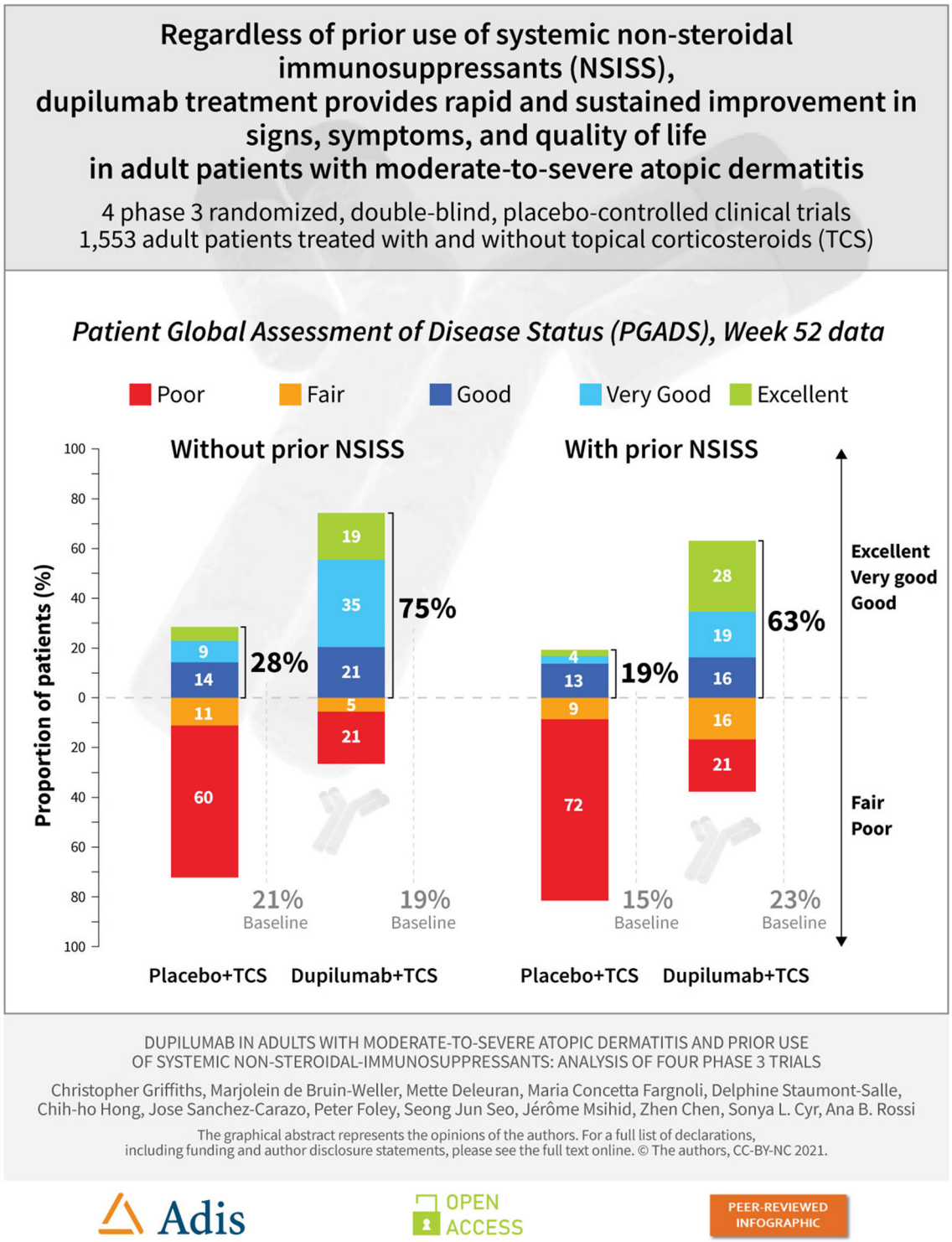
Methods: This post hoc analysis included 1553 patients randomized to placebo or dupilumab (300 mg q2w) as monotherapy for 16 weeks, or with concomitant topical corticosteroids (TCS) for 16/52 weeks, from four randomized, double-blind, placebo-controlled, phase 3 trials. Patients were stratified by prior use of systemic NSISS and dupilumab-treated patients were analysed against control groups (treated with placebo or placebo + TCS).

Results: Dupilumab-treated patients, regardless of prior treatment with NSISS, achieved a significantly higher percentage reduction from baseline in Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), Dermatology life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM) vs. control; significantly more achieved EASI score ≤ 7, Peak Pruritus Numerical Rating Scale ≤ 4, POEM ≤ 7, and DLQI ≤ 5 by week 4. These rapid, significant improvements were seen with or without concomitant TCS and sustained through end-of-treatment.

Conclusions: Dupilumab treatment (monotherapy or + TCS) provides rapid, significant, sustained improvements in signs, symptoms, and quality of life in patients with moderate-to-severe AD compared with control, regardless of prior systemic NSISS use.

Clinical Trial Registration: LIBERTY AD SOLO 1: ClinicalTrials.gov identifier NCT02277743, EudraCT 2014-001198-15. LIBERTY AD SOLO 2: ClinicalTrials.gov identifier NCT02277769, EudraCT 2014-002619-40. LIBERTY AD CHRONOS: ClinicalTrials.gov identifier NCT02260986, EudraCT 2013-003254-24. LIBERTY AD CAFÉ: ClinicalTrials.gov identifier NCT02755649, EudraCT 2015-002653-35.

Graphic Abstract:



DUPILUMAB IN ADULTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS AND PRIOR USE OF SYSTEMIC NON-STEROIDAL-IMMUNOSUPPRESSANTS: ANALYSIS OF FOUR PHASE 3 TRIALS

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PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD), also known as eczema, is characterized by red, oozy, and dry skin that can become cracked and infected. Dupilumab is a drug that blocks key molecules that cause allergic conditions, such as AD. It has been shown to be effective in treating moderate-to-severe AD. Other drugs commonly used to treat AD include certain anti-inflammatory drugs, known as non-steroidal immunosuppressants (NSISS), such as cyclosporin. It is not known if patients treated in the past with NSISS get the same results from AD treatment with dupilumab. This analysis used data from four large studies that included patients with moderate-to-severe AD. The objective was to see if prior NSISS use impacted how dupilumab worked to control AD. The researchers looked at a range of measurements—including ones that were assessed by a patient's doctor such as measurements of AD skin lesions. Itching and how patients felt about their overall life quality were also analysed (which included items such as sleep, pain, ability to work or do normal leisure activities, etc.). The researchers found that if a patient had taken an NSISS for AD before taking dupilumab, it had no impact on the efficacy of dupilumab. All of the measurements evaluated improved significantly more in patients treated with dupilumab than in patients taking a placebo (dummy) medication. The benefits of treatment occurred within a few weeks of starting dupilumab treatment and remained until the end of the longest study included in this analysis, 1 year.

Keywords: Atopic dermatitis; Immuno suppressants; Clinical trial; Dupilumab

Key Summary Points

Why carry out this study?

Despite a questionable or poor risk–benefit profile, systemic non-steroidal immunosuppressants (NSISS) are frequently prescribed to treat adults with moderate-to-severe atopic dermatitis (AD) refractory to topical therapy.

Substantial evidence from large, randomized, double-blind, placebo-controlled clinical trials supports the use of dupilumab to treat adults with moderate-to-severe AD, with a favourable long-term safety profile.

What did the study ask?

This study assessed the impact of prior use of NSISS on the efficacy of dupilumab treatment.

What were the study outcomes/conclusions?

Regardless of prior systemic NSISS use, dupilumab provides rapid, significant, and sustained improvements in signs, symptoms, and quality of life in adult patients with moderate-to-severe AD.

What has been learned from the study?

Overall, these results indicate that adult patients with AD and a history of systemic NSISS use do not have a reduced response to dupilumab treatment, supporting its use both as a systemic first-line treatment and in patients where systemic NSISS have failed.

DIGITAL FEATURES

This article is published with digital features, including a video, graphical abstract, to facilitate understanding of the article. To view digital

features for this article go to https://doi.org/10.6084/m9.figshare.14627706.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, type 2 inflammation skin disease characterized by skin lesions and pruritus that can significantly impair quality of life [1]. The disease affects up to 20% of children and 2–8% of adults worldwide [2, 3]. Type 2 immunity evolved to promote barrier immunity on mucosal surfaces and eliminate helminth parasites, and is characterized by Th2 $CD4^+$ T cells, IL-C2 cells, and B cell production of IgE antibody subclass, recruitment of eosinophils, basophils, and mast cells, and release of signature cytokines that include interleukin (IL)-4, IL-5, IL-9, and IL-13 [4, 5].

The chronic nature of AD implies the need for long-term management, and topical treatments often provide inadequate control of moderate-to-severe AD [6–8]. Oral corticosteroids (OCS) are unsuitable for chronic or relapsing AD because of high likelihood of disease rebound [9]. Systemic non-steroidal immunosuppressants (NSISS), including cyclosporin A (CsA), methotrexate (MTX), mycophenolate mofetil, and azathioprine, are frequently prescribed to treat severe AD refractory to topical therapy (EUROSTAD [10]; TREAT [11, 12]); however, there is a lack of robust evidence from large, well-designed randomized clinical trials (RCT) to support their use, and their toxicity profile requires frequent laboratory monitoring, and long-term treatment is not recommended because of a poor benefit–risk profile [13–18]. Patients treated with these broad-spectrum NSISS can suffer relapses and substantial side effects, including nephrotoxicity, liver dysfunction, and an increased risk of infection and cancer, and they are contraindicated in many patients [13, 15–22].

Dupilumab, a fully human [23, 24] monoclonal antibody to the IL-4Rα, blocks the shared receptor component for IL-4 and IL-13, key and central drivers in type 2 inflammatory diseases [25]. Dupilumab is approved in several countries for adolescents and adults with type 2 inflammatory diseases, including AD and asthma, and in adults with chronic rhinosinusitis with nasal polyps. It is also approved in the USA for children 6–11 years with moderate-to-severe AD, and in Europe and other countries for children 6–11 years with severe AD. The dupilumab development programme included more than 4000 patients with moderate-to severe AD globally, and more than 10,000 patients in all indications..

In dupilumab AD clinical trials, a large proportion of patients had prior treatment with at least one systemic NSISS agent. Here we analyse the efficacy of dupilumab vs. control in these patients, using clinically meaningful endpoints recommended by a global consensus of dermatologists [26], comparing the results achieved in dupilumab-treated vs. placebo/control-treated patients with prior use of NSISS and patients naïve to NSISS use.

The objective of this study was to assess dupilumab treatment effect in patients with moderate-to-severe AD, comparing patients with and without prior systemic NSISS use vs. control groups.

METHODS

Study Design

This post hoc analysis includes data from four randomized, double-blind, placebo-controlled, parallel-group, international phase 3 clinical trials: LIBERTY AD SOLO 1 (NCT02277743) and LIBERTY AD SOLO 2 (NCT02277769), for which data have been pooled [27]; LIBERTY AD CAFÉ (NCT02755649) [28]; and LIBERTY AD CHRONOS (NCT02260986) [29]. Detailed methodology, primary efficacy, and safety results have been reported previously [27–29].

SOLO 1 and SOLO 2 were two identically designed phase 3 trials that evaluated the efficacy and safety of dupilumab monotherapy treatment (300 mg weekly [qw] or every 2 weeks [q2w]) for 16 weeks in adult patients with moderate-to-severe AD. A 35-day screening and washout period preceded study drug administration. The CAFÉ and CHRONOS studies evaluated dupilumab treatment (300 mg qw or q2w)

with concomitant topical corticosteroids (TCS) in adults with moderate-to-severe AD for 16 and 52 weeks, respectively. A 35-day screening and washout period for systemic treatments preceded study drug administration, TCS were allowed during this period. CAFÉ included only adult patients with AD and an inadequate response or intolerance to CsA or for whom this treatment was medically inadvisable.

Baseline data for patient demographics, characteristics, and prior use of NSISS from all four clinical trials were very similar, and thus pooled. Efficacy data at 16 weeks from CAFÉ and CHRONOS were pooled to assess dupilumab treatment with concomitant TCS. Of dupilumab-treated patients, all analyses included only patients randomized to the approved dupilumab dosing regimen of 300 mg q2w [30, 31]. Patients have been stratified by at least one prior or no prior use of systemic NSISS. Around 10–11% of patients with previous treatment with NSISS received at least two NSISS (Table S1 in the supplementary material).

These trials were approved by respective institutional review boards and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. All patients provided written informed consent before participating in the trial.

This analysis includes results for change from baseline in Eczema Area and Severity Index (EASI; range 0–72), SCORing AD (SCORAD; range 0–103), Dermatology Life Quality Index (DLQI; range 0–30), Patient-Oriented Eczema Measure (POEM; range 0–28); percentage of patients achieving: $\geq$ 3-point improvement in Peak Pruritus Numerical Rating Scale (NRS), $\geq$ 75% improvement from baseline in EASI (EASI-75), EASI $\leq$ 7, Peak Pruritus NRS $\leq$ 4, POEM $\leq$ 7, DLQI $\leq$ 5; analysis of patients overall well-being related to the disease (PGADS) and patient perception of treatment effect (PGATE) on a 5-point Likert t scale (poor, fair, good, very good, and excellent).

Statistical Analysis

Efficacy analyses were performed separately in each subgroup (patients with or without prior systemic NSISS use) on the full analysis set, which included all randomized patients. For continuous outcomes, patients missing an assessment or who received rescue treatment were censored and set to missing and then imputed using the multiple imputation method; p values were assessed using an analysis of covariance model at each visit with baseline measurement as a covariate and the treatment, region, baseline Investigator's Global Assessment (IGA) strata (IGA = 3 vs. IGA = 4) and study identifier (for the SOLO studies only) as fixed factors. For responder endpoints, patients missing an assessment or who received rescue treatment were censored and set to missing; p values were derived by Cochran–Mantel–Haenszel (CMH) test stratified by baseline disease severity and study identifier at each visit. For PGADS and PGATE, patients missing an assessment or who received rescue treatment were set to worst class (poor). Means were calculated using the least-squares (LS) method. As all analyses were conducted post hoc, all p values should be considered to be nominal. Analyses were performed using SAS V9.4 or higher.

RESULTS

Patients

A total of 1553 patients randomized to placebo/control or dupilumab treatment were included in this analysis, then stratified by prior or no prior systemic NSISS use. Baseline demographics were very similar between patients with a history of prior NSISS treatment and those naïve to such treatment (Table 1). Patients who had prior use of systemic NSISS presented with, on average, numerically slightly higher disease severity at baseline, except for itch (Peak Pruritus NRS), which was similar (Table 1).

Table 1 Baseline demographics, disease characteristics and prior systemic non-steroidal immunosuppressants (NSISS) use. Baseline data is pooled from patients from the individual studies: SOLO1, SOLO2, CAFÉ, and CHRONOS

Baseline demographics and disease characteristics				
	0 prior systemic NSISS		**≥ 1 prior systemic NSISS**	
	Control (*N* = 606)	**Dupilumab 300 mg q2w (*N* = 444)**	**Control (*N* = 277)**	**Dupilumab 300 mg q2w (*N* = 226)**
Age, mean (SD), years	37.4 (13.7)	38.0 (14.4)	38.7 (13.4)	39.3 (13.3)
Sex, male, *n* (%)	332 (54.8)	253 (57.0)	179 (64.6)	141 (62.4)
Race, *n* (%)				
White	407 (67.2)	326 (73.4)	207 (74.7)	172 (76.1)
Black/African American	49 (8.1)	20 (4.5)	6 (2.2)	5 (2.2)
Asian	133 (21.9)	85 (19.1)	58 (20.9)	44 (19.5)
Other	17 (2.8)	13 (2.9)	6 (2.2)	5 (2.2)
Weight, kg, mean (SD)	76.0 (18.8)	76.5 (18.0)	76.1 (17.5)	74.6 (17.4)
Duration of AD, years, mean (SD)	28.1 (14.2)	27.7 (15.2)	29.1 (15.0)	30.0 (15.6)
EASI (0–72), mean (SD)	32.9 (13.6)	31.5 (12.6)	34.3 (13.1)	35.0 (13.0)
Patients with IGA score 4, *n* (%)	275 (45.4)	188 (42.3)	149 (53.8)	138 (61.1)
Peak Pruritus NRS (0–10), mean (SD)	7.2 (1.9)	7.3 (1.9)	7.4 (1.9)	7.3 (1.7)
SCORAD total score (103), mean (SD)	67.0 (13.9)	66.2 (13.6)	68.8 (13.9)	70.5 (13.4)
POEM (0–28), mean (SD)	19.8 (5.9)	19.6 (6.2)	21.1 (6.2)	21.2 (5.4)
DLQI (0–30), mean (SD)	14.2 (7.5)	14.2 (7.3)	15.8 (7.3)	15.4 (7.3)

Distribution of patients with ≥ 1 prior use of systemic NSISS		
	Control, *n* (%)	**Dupilumab 300 mg q2w, *n* (%)**
Pts with ≥ 1 prior use of ISS	277 (100.0)	226 (100.0)
Cyclosporin	226 (81.6)	186 (82.3)
Methotrexate	72 (26.0)	51 (22.6)
Azathioprine	48 (17.3)	34 (15.0)
Mycophenolate mofetil	30 (10.8)	34 (15.0)

AD atopic dermatitis, *EASI* Eczema Area and Severity Index, *DLQI* Dermatology Life Quality Index, *IGA* Investigator's Global Assessment, *NSISS* non-steroidal immunosuppressants, *NRS* numerical rating scale, *POEM* Patient-Oriented Eczema Measure, *q2w* every 2 weeks, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

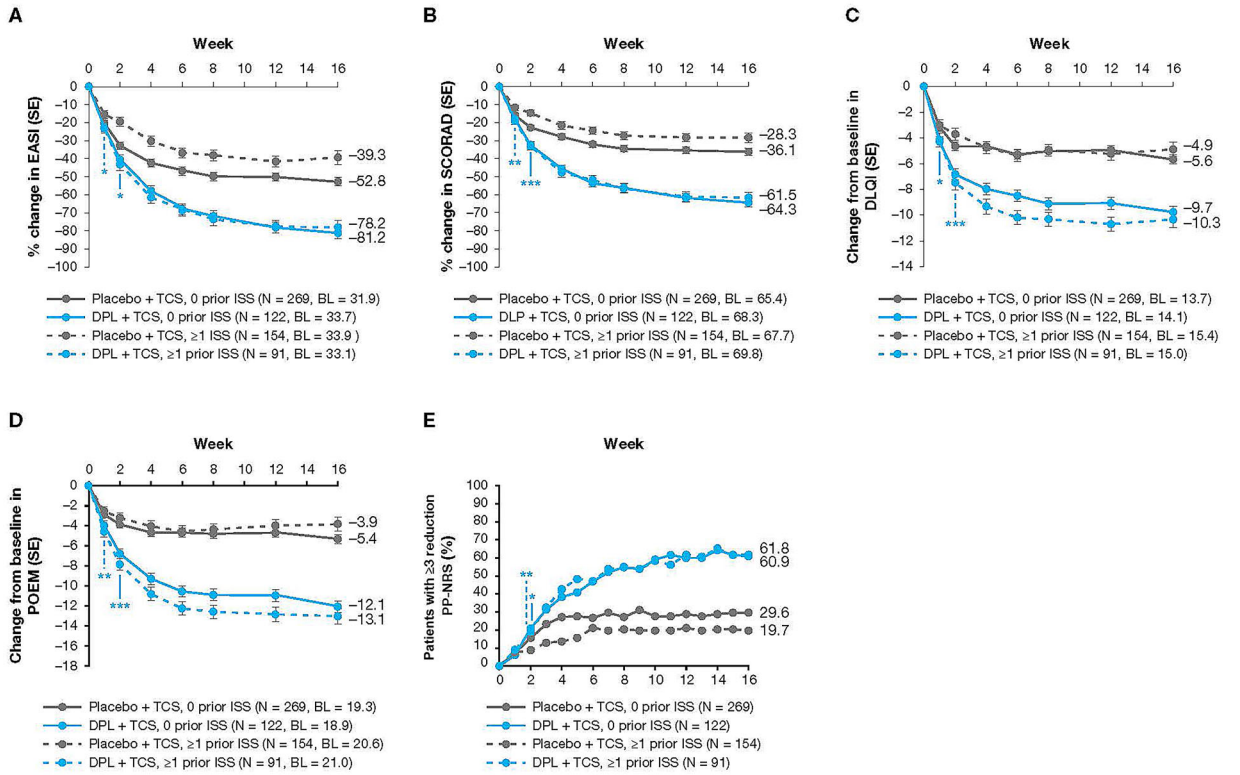

Fig. 1 Efficacy of short-term (16 weeks) dupilumab 300 mg q2w with concomitant TCS therapy for patients with atopic dermatitis with or without prior use of non-steroidal immunosuppressants (pooled analysis from CAFÉ and CHRONOS trials). **a** LS mean percentage change from baseline in EASI. **b** LS mean percentage change from baseline in SCORAD. **c** LS mean change from baseline in DLQI. **d** LS mean change from baseline in POEM. **e** Percentage of patients achieving ≥ 3-point improvement in Peak Pruritus NRS from baseline. $^{*}p < 0.05$ vs. placebo; $^{**}p < 0.01$ vs. placebo; $^{***}p < 0.001$ vs. placebo. AD atopic dermatitis, BL baseline, EASI Eczema Area and Severity Index, DPL dupilumab, DLQI Dermatology Life Quality Index, ISS immunosuppressant, NSISS non-steroidal immunosuppressants, POEM Patient-Oriented Eczema Measure, PP-NRS Peak Pruritus NRS, q2w every 2 weeks, SCORAD SCORing Atopic Dermatitis, SE standard error, TCS topical corticosteroids

Dupilumab Efficacy in Patients With or Without Prior Systemic NSISS Use

All dupilumab-treated patient groups in this analysis, regardless of concomitant TCS use or prior use of systemic NSISS, when compared vs. control, achieved a significantly higher percentage reduction from baseline in EASI by week 4; and SCORAD, DLQI, and POEM by week 2; (Figs. 1, 2, and 3); ≥ 3-point improvement in Peak Pruritus NRS by week 2, and 4 point improvement by week 3; DLQI score ≤ 5 by week 2; and EASI score ≤ 7 and POEM score ≤ 7 by week 4 (Figs. 1, 2, and 3).

By week 16 of dupilumab with concomitant TCS treatment (pooled analysis of CAFÉ and CHRONOS trials), patients in both populations achieved significant ($p < 0.001$) improvements in EASI, SCORAD, DLQI, POEM, and Peak Pruritus NRS.

Further improvements in these outcome measures were seen following long-term treatment of dupilumab with concomitant TCS (52 weeks, CHRONOS). Patients achieved an LS mean percentage reduction in EASI from baseline (vs. placebo with TCS) of − 89.0% vs. − 66.6%, 95% LSMCI (− 32.20, − 12.45) and − 84.1% vs. − 55.6%, 95% LSMCI

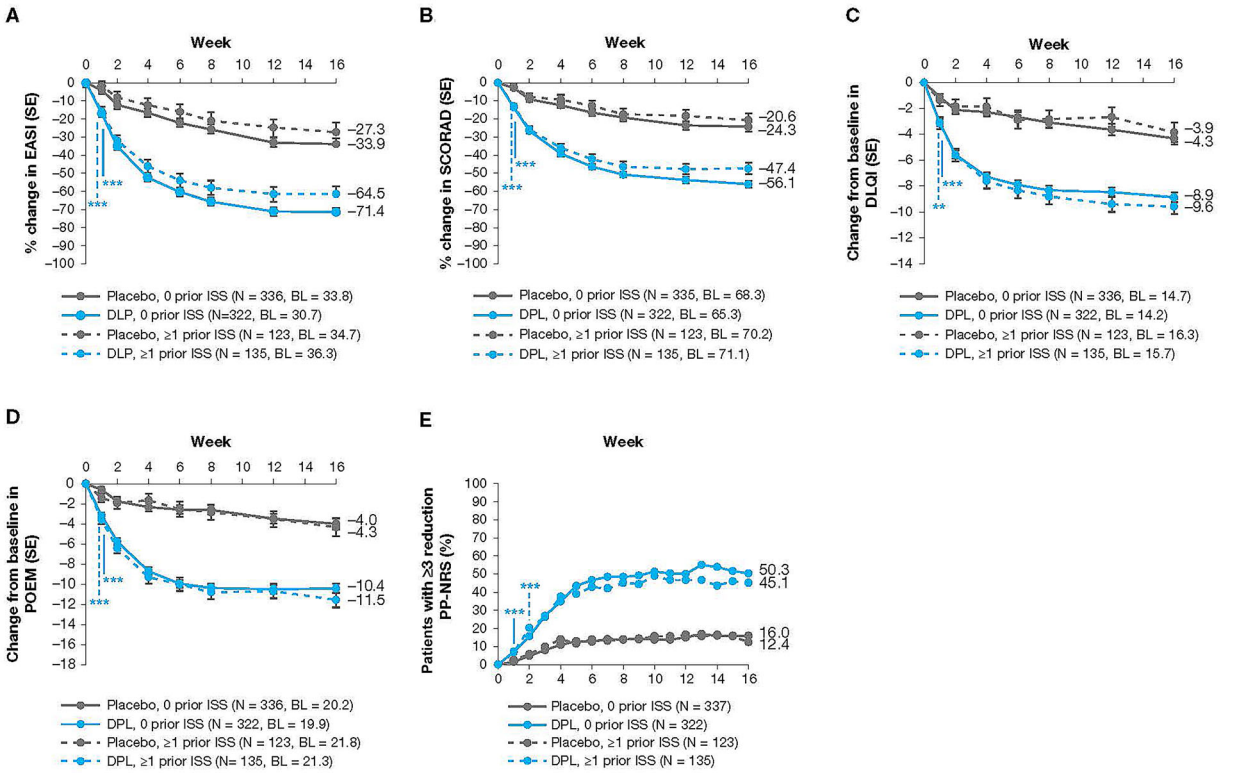

Fig. 2 Efficacy of dupilumab 300 mg q2w monotherapy for atopic dermatitis patients with or without prior use of non-steroidal immunosuppressants (SOLO 1 & SOLO 2). **a** LS mean percentage change from baseline in EASI. **b** LS mean percentage change from baseline in SCORAD. **c** LS mean change from baseline in DLQI. **d** LS mean change from baseline in POEM. **e** Percentage of patients achieving ≥ 3-point improvement in Peak Pruritus NRS from baseline. $^{*}p < 0.05$ vs. placebo; $^{**}p < 0.01$ vs. placebo; $^{***}p < 0.001$ vs. placebo. AD atopic dermatitis, BL baseline, EASI Eczema Area and Severity Index, DPL dupilumab, DLQI Dermatology Life Quality Index, ISS immunosuppressant, NSISS non-steroidal immunosuppressants, POEM Patient-Oriented Eczema Measure, PP-NRS Peak Pruritus NRS, q2w every 2 weeks, SCORAD SCORing Atopic Dermatitis, SE standard error, TCS topical corticosteroids

(– 47.28, – 9.68); – 73.0% vs. – 49.6%, 95% LSMCI (– 32.54, – 14.24); and – 67.5% vs. – 43.5% 95% LSMCI (– 37.81, – 10.04) in SCORAD; and an LS mean reduction of – 10.2 vs. – 6.8, 95% LSMCI (– 5.002, – 1.888) and – 12.2 vs. – 7.2, 95% LSMCI (– 7.354, – 2.548) in DLQI; – 12.7 vs. – 6.1, 95% LSMCI (– 8.918, – 4.278) and – 15.8 vs. – 5.1, 95% LSMCI (– 14.029, – 7.365) in POEM (Fig. 2d); and 56.5% vs. 19.0%, 95% CI risk difference (23.97–50.94) and 48.8% vs. 11.3%, 95% CI risk difference (21.40–53.63) achieved ≥ 3-point improvement in Peak Pruritus NRS, in the NSISS and the at least one prior use of a systemic NSISS populations, respectively.

In both the short- and long-term studies, following treatment with placebo plus concomitant TCS, patients with at least one prior use of a systemic NSISS achieved consistent lower improvements in signs (EASI), SCORAD and itch (Peak Pruritus NRS) than patients naïve to systemic NSISS.

Significant improvements ($p < 0.001$) in outcome measures were also evident in patients after receiving 16 weeks of dupilumab monotherapy (pooled SOLO 1 and SOLO 2 trials) regardless of prior use of NSISS (Fig. 2).

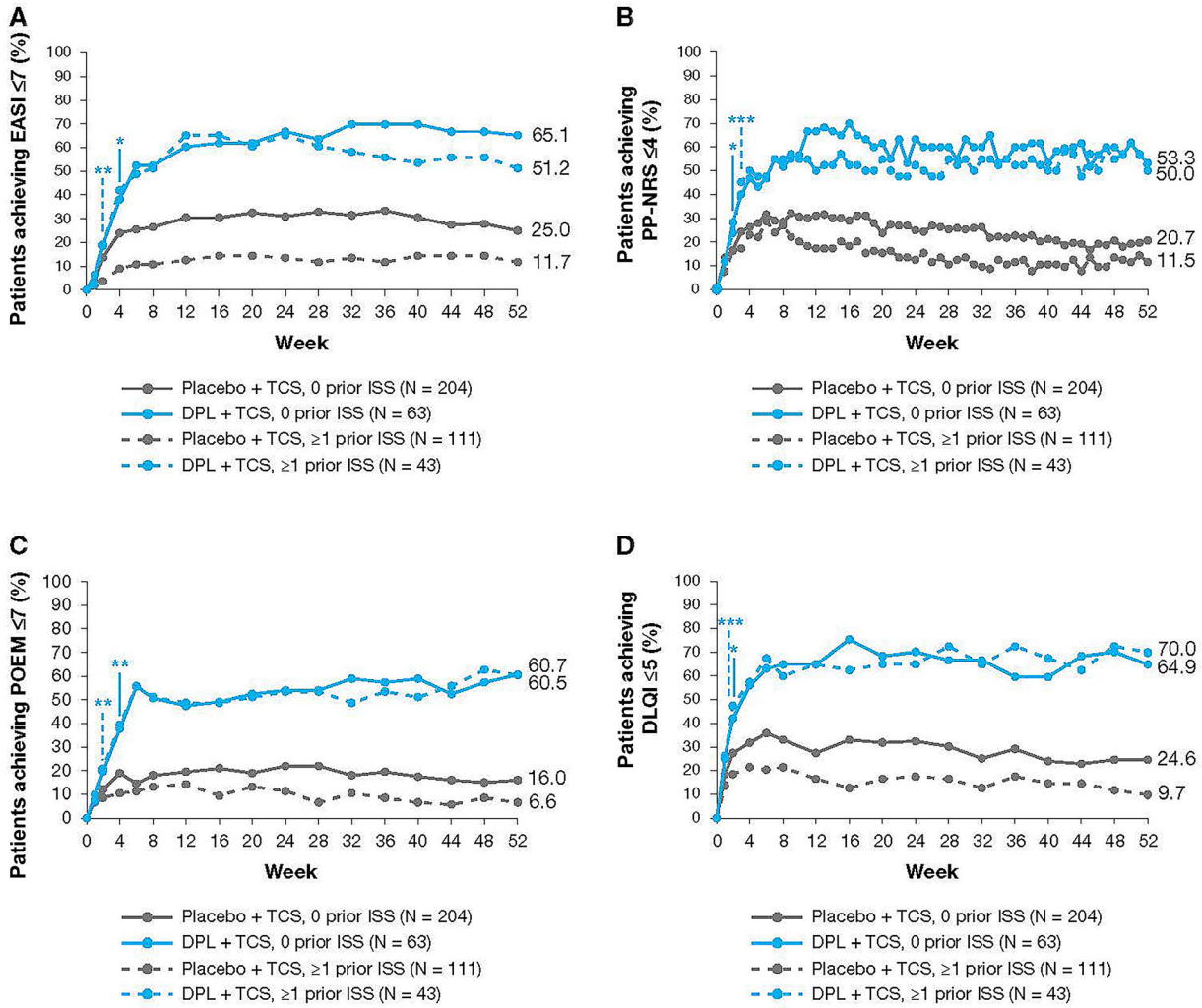

Fig. 3 Clinically meaningful responses following dupilumab 300 mg q2w with concomitant TCS therapy over 52 weeks (CHRONOS) with or without prior use of non-steroidal immunosuppressants. **a** Percentage of patients achieving EASI score of ≤ 7. **b** Percentage of patients achieving Peak Pruritus NRS of ≤ 4. **c** Percentage of Patients achieving POEM score of ≤ 7. **d** Percentage of Patients achieving DLQI score of ≤ 5. $^{*}p < 0.05$ vs. placebo; $^{**}p < 0.01$ vs. placebo; $^{***}p < 0.001$ vs. placebo. AD atopic dermatitis, BL baseline, EASI Eczema Area and Severity Index, DPL dupilumab, DLQI Dermatology Life Quality Index, ISS immunosuppressant, NSISS non-steroidal immunosuppressants, POEM Patient-Oriented Eczema Measure, PP-NRS Peak Pruritus NRS, q2w every 2 weeks, TCS topical corticosteroids

In a set of clinically meaningful response analyses (Fig. 3), by week 8 the majority of patients receiving dupilumab and TCS (CHRONOS), with or without prior systemic NSISS treatment, achieved scores corresponding to minimal/mild or absent disease: EASI score ≤ 7, Peak Pruritus NRS ≤ 4, POEM score ≤ 7, and DLQI score ≤ 5. These improvements were maintained until the end of treatment (52 weeks). In addition, by week 2, over 60% of patients receiving dupilumab with concomitant TCS, regardless of their prior use of NSISS, rated their overall well-being in relation to their skin condition as "good", "very good", or "excellent" (Fig. 4). For patients receiving placebo and TCS only, numerically fewer patients with a history

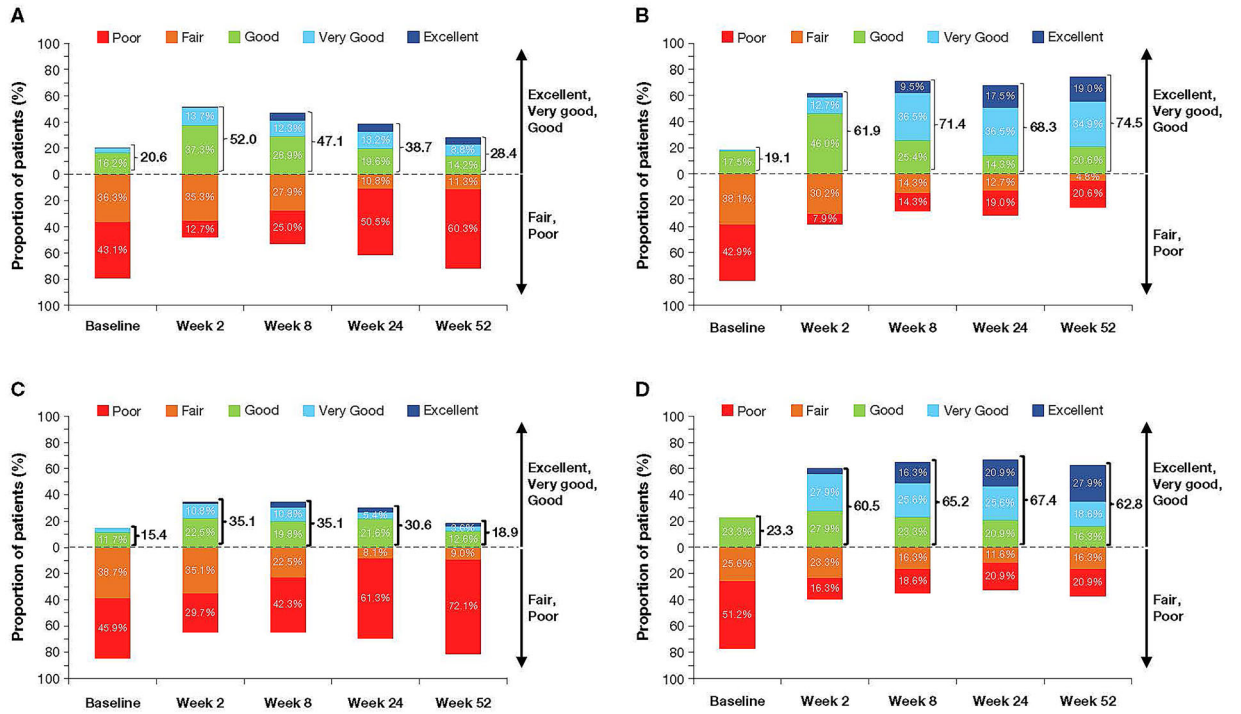

Fig. 4 Patient Global Assessment of Disease Status following dupilumab 300 mg q2w with concomitant TCS therapy over 52 weeks (CHRONOS). Patients were asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing" and rated on a 5-point scale. **a** Patients with 0 prior systemic NSISS use receiving placebo and TCS. **b** Patients with 0 prior systemic NSISS use receiving dupilumab and TCS. **c** Patients with at least one prior systemic NSISS use receiving placebo and TCS. **d** Patients with at least one prior systemic NSISS use receiving dupilumab and TCS. NSISS non-steroidal immunosuppressants, PGADS Patient Global Assessment of Disease Status, q2w every 2 weeks, TCS topical corticosteroids

of prior systemic NSISS use achieved these clinically meaningful responses, compared with patients naïve to NSISS.

During dupilumab with concomitant TCS treatment (CHRONOS 52 weeks), over half of patients in both populations (those with or without prior use of systemic NSISS) achieved EASI-75 (by week 6, data not shown), and more than 3/4 rated their satisfaction with treatment as "good", "very good", or "excellent" (by week through to end of treatment, data not shown).

DISCUSSION

In this analysis, dupilumab therapy (with or without concomitant TCS therapy) resulted in rapid, consistent, and significant improvements in signs and symptoms of AD, as well as improvements in quality of life (QoL) compared to control arms (placebo/placebo + TCS). Improvements were achieved by patients naïve to systemic NSISS, and also by patients with a history of use of these agents. In both patient populations, these improvements were sustained throughout 1 year (end of treatment).

A majority of patients treated with dupilumab (with or without prior NSISS use) achieved clinically meaningful responses corresponding to absent or mild/minimal disease signs and symptoms, and low or no impact in QoL by the end of the treatment period. Most patients considered their general well-being in relation to their AD as good, very good, or excellent, and were very satisfied with the treatment effect.

Of note, as observed in the control groups, patients with prior systemic NSISS use were consistently less responsive to TCS treatment without dupilumab. These patients had poorer improvements in signs and symptoms compared to the NSISS-naïve patients. These data suggest that patients may become less responsive to TCS treatment following prior use of systemic NSISS, or that these patients constitute a more "difficult to treat with TCS" population, and thus had previously been recommended systemic therapy. Interestingly, however, patients with prior use of NSISS were generally not more "difficult to treat" with dupilumab, compared with those naïve to systemic NSISS.

AD can have a profound impact on a patient's QoL from direct and indirect effects of signs and symptoms [32, 33]. Even with slightly higher baseline disease severity in terms of subjective QoL impairment (DLQI) and patient-reported symptoms (POEM), numerically higher improvements in DLQI and POEM were observed in patients with a history of systemic NSISS use compared with those patients naïve to these agents, suggesting a greater perceived relief. Relief was also evident in pruritus. Comparable baseline severity in Peak Pruritus NRS between patients with or without prior use of systemic NSISS was matched with comparable improvements following dupilumab treatment, with the majority of patients achieving absent or mild pruritus at end of treatment, independent of prior treatment with NSISS.

The similar baseline disease severity between patients with or without prior use of systemic NSISS is likely a consequence of clinical trial entry criteria. In dupilumab phase 3 trials, the AD severity of patients at baseline was similar to that of patients who are candidates for systemic therapy in EU registries (BioDay [34]; EUROSTAD [10]; TREAT [12]). In a retrospective Korean study, baseline severity of disease was higher in NSISS-experienced patients (EASI 31.7 in the prior NSISS group vs. 26.9 in the NSISS-naïve group) [35]. Therefore, patients in this analysis are likely representative of patients with AD who are candidates for systemic treatment in the real-world population, many of whom will have had prior NSISS therapy.

In the absence of a head-to-head study comparing dupilumab vs. any systemic NSISS, an indirect comparison of dupilumab and CsA published by Ariëns et al. in 2019 [36] suggests a higher relative efficacy of dupilumab vs. CsA. The study found that 74% of patients treated with dupilumab achieved EASI-75 at 24–30 weeks, vs. only 40% of those treated with CsA. In addition, registry studies show higher adherence to dupilumab treatment, compared to CsA and methotrexate [34, 37]. Ongoing registry studies (EUROSTAD [10]; TREAT [12]) are further investigating long-term response and adherence to systemic treatments.

The results from these analyses involving 1553 patients from four robust RCTs are supported by real-world cases of dupilumab treatment [38], where dupilumab has provided better short- and long-term control of a patient's AD compared with systemic NSISS [37, 39] and has been similarly effective in patients who have failed to respond to CsA [37, 39, 40] and even in a cohort of patients who failed treatment on two or more NSISS [34].

Limitations of the study include the post hoc nature of the analyses.

CONCLUSIONS

Taken together, these results indicate that a patient's prior history of use of systemic NSISS does not impact the efficacy of dupilumab treatment for moderate-to-severe AD, supporting its use both as a systemic first-line treatment and in patients in whom systemic NSISS have been used. Dupilumab brings a new perspective to systemic treatment of this patient population, offering the prospect of long-term control [41] and flare prevention [42].

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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