

Nemolizumab is Associated with a Rapid Improvement in Atopic Dermatitis Signs and Symptoms: Subpopulation (EASI ≥ 16) Analysis of Randomized Phase 2B Study

J. I. Silverberg, MD, PhD, MPH,¹ A. Pinter, MD,² A. Alavi, MD,³ C. Lynde, MD,⁴ J-D. Bouaziz, MD, PhD,⁵ A. Wollenberg, MD,⁶ D. F. Murrell, MD,⁷ S. Alpizar, MD,⁸ V. Laquer, MD,⁹ K. Chaouche, MD, PhD,¹⁰ F. Ahmad, MS,¹¹ J. M. Armstrong, PhD,¹⁰ C. Piketty, MD, PhD¹⁰

¹Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

²Department of Dermatology, Venereology, and Allergology, University Hospital Frankfurt am Main, Frankfurt am Main, GERMANY

³Department of Dermatology, Mayo Clinic, Rochester, Minnesota, USA

⁴Department of Medicine, University of Toronto, Toronto, Ontario, CANADA

⁵Department of Dermatology, Paris VII Sorbonne Paris Cité University Assistance Publique – Hôpitaux de Paris, Paris, FRANCE

⁶Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Munich, GERMANY

⁷Department of Dermatology, St George Clinical School, University of New South Wales, Sydney, AUSTRALIA

⁸ Clinical Research Trials of Florida, Tampa, FL, USA

⁹ First OC Dermatology, Fountain Valley, CA, USA

¹⁰Galderma, Entre-Deux-Villes, SWITZERLAND

¹¹Galderma Laboratories, Fort Worth, TX, USA

Corresponding author: Jonathan I. Silverberg, MD, PhD; 676 N St Clair St #1600, Chicago, IL 60611. Phone 312-695-8106; email: jonathanisilverberg@gmail.com

Conflicts of interest:

Dr Silverberg has received honoraria as a speaker/consultant for Galderma, Abbvie, AnaptysBio, Asana, Arena, Boehringer Ingelheim, Dermavant, Eli Lilly, GlaxoSmithKline, Glenmark, Kiniksa, Leo, Menlo, Novartis, Pfizer, Regeneron-Sanofi, and Realm and has received grants as an investigator from Galderma and GlaxoSmithKline. Dr Pinter has worked as an investigator and/or speaker and/or advisor for following pharmaceutical companies: AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Biontec, Boehringer-Ingelheim, Celgene, GSK, Eli-Lilly, Galderma, Hexal, Janssen, LEO-Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi-Genzyme, Schering-Plough und UCB Pharma. Dr Alavi has received honoraria as a consultant, speaker, or advisory board participant from AbbVie, Galderma, Janssen, LEO, Novartis, Sanofi, and Valeant; received grants from AbbVie; and was a research investigator with AbbVie, Aristea, Asana, Boehringer-Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly, Genetech, Glenmark, Incyte, InflaRx, Janssen, Kyowa, LEO, Novartis, Pfizer, Regeneron,

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and UCB. Dr Lynde has served as consultant, speaker, and investigator as well as participated in advisory boards for Valeant Pharma and Galderma, and has served as investigator for Xenon and Demira. Dr Bouaziz has received honoraria as advisor for Galderma. Dr Wollenberg has received grants, personal fees, and/or nonfinancial support from Almirall, Beiersdorf, Bioderma, Chugai, Galapagos, Galderma, Hans Karrer, Leo Pharma, Eli Lilly, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen, and Sanofi-Aventis. Dr Murrell has received grants as investigator and honoraria as advisor for Galderma, Sanofi, Anacor, Pfizer, Menlo, Pierre Fabre, and GlaxoSmithKline, Principiablo, and Argenix and has also served as an investigator for Regeneron and Medimmune. Dr Alpizar has received honoraria as a consultant for AstraZeneca and Galderma. Dr Laquer has received honoraria as a consultant for Abbvie, Leo Pharma, Novartis, Aqua, Pfizer, Biogen, Mayne, Intraderm, Celgene, and Allos; Dr Laquer has also served as an investigator from Ortho Dermatologics and Galderma. Dr Chaouche, Mr Ahmad, Dr Armstrong, and Dr Piketty are employees of Galderma.

Running Title: Nemolizumab in Atopic Dermatitis: EASI $\geq$ 16 Analysis

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ABSTRACT

Background: Nemolizumab is a humanized anti-IL-31 receptor blocker in phase 3 for atopic dermatitis (AD).

Objective: Analyze onset of action of nemolizumab 30 mg and compare efficacy and safety vs placebo (SC q4wk plus loading dose) in moderate-to-severe AD.

Methods: Post-hoc analysis of patients with Eczema Area and Severity Index (EASI) scores ≥ 16 from a phase 2b trial of moderate-to-severe AD. Endpoints were change in EASI score at week 16, peak pruritus numeric rating scale (PP-NRS), Investigator's Global Assessment (IGA), changes in sleep and responders with ≥ 4 -point improvement on PP-NRS.

Results: There was a significantly greater itch relief apparent by Day 2 (-22.8% vs -12.3% PP-NRS; $P=0.005$) which continued to improve through week 16 (-68.5% vs -30.9% PP-NRS; $P<0.001$). At week 16, PP-NRS ≥ 4 -point response of itch was observed in 68.0% nemolizumab vs 15.9% placebo patients ($P\leq 0.001$). There was also a rapid improvement of sleep disturbance with nemolizumab 30 mg, with a significant separation from placebo by day 3 (-26.6% vs -9.0%; $P<0.001$) which further improved till week 16 (-76.0% vs -36.5%; $P<0.001$). Also for the EASI score a separation between groups in favor of nemolizumab was observed by week 1 ($P\leq 0.001$), which increased through week 16 (-68.6% vs. -42.6%; $P=0.002$). Finally, the degree of response was greater in nemolizumab-treated patients; clinically relevant reductions of 75% EASI were observed in 50.0% of nemolizumab patients versus 15.9% of placebo patients, while 90% reductions were reported for 36.0% and 6.8% of patients, respectively ($P<0.001$ for both). IGA success (score of 0/1) was 32.0% for nemolizumab vs 6.8% for placebo ($P=0.002$).

Nemolizumab was safe and well-tolerated in this population; nasopharyngitis and upper respiratory tract infection were the most common adverse events.

Conclusions: Nemolizumab resulted in very rapid, sustained improvements of inflammation, pruritus and sleep in patients with EASI ≥ 16 at baseline.

Trial registration: Clinicaltrials.gov NCT03100344

INTRODUCTION

Atopic dermatitis (AD), a common and debilitating inflammatory skin disease, is characterized by dysfunction of the immune system, skin barrier, and neuronal pathways.^{1,2} Eczema and itch are prominent clinical manifestations,^{1,3} and the itch-scratch cycle leads to further exacerbation of skin disease and sleep disturbances that can impact daytime functioning.^{3,4} AD negatively affects patients' overall quality of life,^{5,6} and the intensity of itch is correlated with impact on psychosocial well-being.⁷⁻¹⁰

Recent research showed that interleukin 31 (IL-31) plays a critical role in AD.¹ IL-31 is a cytokine that is expressed in many human tissues, including skin, and is involved in T_H2-inflammation.^{11,12} Furthermore IL-31 provides a link between the immune and neuronal systems to mediate inflammatory itch,^{11,13} and IL-31-specific activation of dendritic cells is thought to be part of a positive feedback loop in inflammatory skin diseases.¹⁴ Study of skin biopsies revealed increased IL-31 expression in the inflammatory infiltrates from AD patients compared with controls; increased IL-31 expression was not found in biopsies of patients with other T_H2-weighted inflammatory skin diseases such as contact dermatitis.¹⁵ Thus, it is important to investigate the therapeutic actions in AD of treatments targeted toward inhibiting IL-31.

Nemolizumab is a humanized anti-IL-31 receptor blocker that is currently in phase 3 studies for treatment of AD and prurigo nodularis. Phase 2 studies of nemolizumab showed important clinical benefit in reducing cutaneous signs of inflammation and itch in patients with EASI scores of 12 or higher.^{3,16,17} A phase 2b randomized controlled trial evaluated nemolizumab 10 mg, 30 mg, and 90 mg vs placebo with a background of topical corticosteroids (TCSs) in patients

with moderate-severe AD, and observed maximal efficacy with the 30 mg dose.¹⁶ In this 24 week study, nemolizumab improved Eczema Area and Severity Index (EASI), investigator global assessment (IGA), and peak pruritus numeric rating scale (PP-NRS). However, this study defined moderate-severe AD using an inclusion criterion of EASI ≥ 12 , which is lower than the threshold used in most other trials of emerging therapies for moderate-severe AD.¹⁶ To help clinicians evaluate the clinical profile of nemolizumab in context with other emerging therapies, a subgroup analysis was performed on 16-week data from the phase 2b study focusing on patients with EASI scores ≥ 16 who were treated with nemolizumab 30 mg or placebo, since this is more comparable to the baseline characteristics in studies of current and emerging therapies. This will also allow the phase 2 data to be interpreted in context of data from ongoing phase 3 studies in patients with baseline EASI ≥ 16 . Similarly, although the original primary study endpoint was at week 24, data from the week 16 visit are included here, to assess data similar to that generated by other recent investigations. Moreover we were interested in the velocity of the onset of action of nemolizumab and performed respective analyses on itch, sleep and lesions.

METHODS

Full details of the phase 2b study were published in Silverberg et al and are briefly summarized.¹⁶

Study design

This phase 2b study was a randomized, double-blind, multicenter, study in adults with moderate-to-severe AD and severe pruritus, inadequately controlled with topical therapies (NCT03100344). Patients received nemolizumab 30 mg every 4 weeks with a 60 mg loading dose or placebo, with concomitant mid-potency topical corticosteroids (TCS) introduced at screening visit, for 24 weeks. This post-hoc analysis evaluated efficacy in patients with baseline EASI scores ≥ 16 (nemolizumab: n=50, placebo: n=44) at week 16, as well as secondary endpoints.

Ethics

The study was performed following ethical principles of the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent before any study procedures were performed.

Patients

Detailed inclusion and exclusion criteria were previously reported.¹⁶ The main inclusion criteria were moderate-to-severe AD (Investigator's Global Assessment [IGA] score of 3 or 4), in patients aged ≥ 18 years, plus severe pruritus inadequately controlled by topical therapy. Severe pruritus was defined as a Pruritus Categorical Scale score ≥ 7 (range: 0-10) on ≥ 3 out of the 7

days prior to screening plus an average daily peak pruritus numeric rating scale (PP-NRS) of at least 7 during the week prior to baseline visit. Inadequate response to topical therapy within the past 6 months had to be documented and patients had to agree to using only authorized TCS throughout the study.

Outcomes assessed in this analysis

This analysis described the efficacy of nemolizumab 30 mg vs placebo after 16 weeks treatment. Percentage change from baseline at week 16 in EASI score was the study primary endpoint; to further assess the efficacy of nemolizumab in AD, secondary endpoints included percent change of EASI scores at each visit, the proportion of patients achieving EASI score reductions of 75% or 90% from baseline, IGA success rate (clear [0] or almost clear [1] with 2 point reduction), and change in body surface area (BSA involvement). The proportion of subjects with ≥ 4 -point improvement in PP-NRS score, and dynamic pruritus scale (DPS) scores were evaluated. The impact of nemolizumab on sleep was investigated via changes in sleep disturbance NRS.¹⁸ Additional assessments, including pruritus categorical scale (PCS), the Scoring Atopic Dermatitis (SCORAD) tool, Dermatology Life Quality Index (DLQI), and use of topical corticosteroids by group, are presented in the accompanying supplemental document. Standard safety assessments were performed, with details previously published.¹⁶

Statistical analysis

Statistical analysis details for the phase 2b study primary and secondary endpoints were published previously.¹⁶ All efficacy endpoints for this subpopulation (EASI ≥ 16) were summarized by treatment at individual study visits, and continuous data were described by

means, medians, min/max, and standard deviations. Categorical variables had frequency and percentage analyzed for each response category. Continuous efficacy endpoints were analyzed with a mixed-effects model for repeated measures approach, with terms for treatment group and baseline disease severity. Categorical endpoints were evaluated with stratified Cochran Mantel-Haenszel test, with time-to-event data described using the Kaplan-Meier method. Missing values for continuous endpoints were handled using MMRM approach, missing values were treated as “non-responders” for all binary endpoints. Safety analyses were performed for all patients who received at least one dose of study medication, and adverse events were tabulated by frequency using System Organ Class and MedDRA preferred terms. SAS software (v9.3, SAS Institute, Cary, NC) was used to perform the analysis.

RESULTS

Study population

The subgroup with baseline EASI $\geq$ 16 comprised 83.9% of all study patients (nemolizumab n=50/55 [90.9%], placebo n=44/57 [77.2%]). Demographics are shown in Table 1. There were 18 patients in each group with IGA 4, and 32 vs 26 patients with IGA 3 score at baseline in the nemolizumab 30 mg group. Additionally, there was a higher body surface area (BSA) involvement in the placebo group (53.1% compared with 44.3%).

TABLE 1 HERE

Efficacy: AD and inflammation

Change in EASI scores

The least square (LS) mean EASI score at week 16 was reduced by 68.6% in the nemolizumab group as compared with 42.6% in the placebo group (P=0.002). As shown in Figure 1, significant differences between groups in the EASI scores were observed by week 1 (P $\leq$ 0.001).

FIGURE 1 HERE

In addition, nemolizumab-treated patients were significantly more likely to achieve a 75% reduction in EASI score (EASI 75) (50.0% vs 15.9%) and a 90% reduction (EASI 90) at week 16 (36.0% vs 6.8%; P<0.001 for both comparisons).

IGA success rates

At week 16, IGA0/1 was achieved in 32.0% of nemolizumab subjects compared to 6.8% of those in the placebo group ($P=0.003$; delta 25.1%; 95% CI 10.1, 40.1). At all study visits, including week 1, IGA success rates in the nemolizumab 30 mg group were at least two-fold greater than those in the placebo group.

Reduction in AD-involved BSA

BSA reductions were noted at week 1 and continued throughout the study. By week 16, the percent change from baseline in BSA was -49.9% in the nemolizumab 30 mg group as compared with -28.1% in the placebo group ($P=0.053$).

Efficacy: Pruritus and sleep

Reduction in itch

Peak-pruritus NRS was improved for nemolizumab 30 mg vs placebo at week 16 (-68.5% vs -30.9%; $P<0.001$) (Figure 2) and there was greater itch relief apparent by Day 2 (-22.8% vs -12.3%; $P=0.005$). The absolute mean daily PP-NRS decreased in the nemolizumab group from 8.0 at baseline to 3.4 at Day 30 but remained relatively constant in the placebo group (8.0 at baseline to 6.5 at Day 30) (Figure S1). Significantly more patients achieved NRS response (≥ 4 -point) with nemolizumab 30 mg vs placebo at week 16 (68.0% vs 15.9%; $P<0.001$) and as shown in Figure 3 the difference in the proportion of PP NRS responders was statistically significant as early as day 4 (32.0% vs 6.8%; $p=0.003$). The delta between groups was 52.1 in favor of nemolizumab. A 3-point reduction was achieved in 74.0% of the nemolizumab group compared with 22.7% of the placebo group at week 16 ($P<0.001$), for a similar delta between groups of 51.3.

FIGURES 2-3 HERE

Reduction in weekly average itch in the nemolizumab groups was significantly greater than placebo in at all assessments. At week one, the LSmean change in weekly average PP NRS was -27.2% vs -9.8% for nemolizumab and placebo, respectively ($P<0.001$). Reductions in average PP NRS continued week over week in the nemolizumab group until week 16 (-68.5%); in comparison, reduction in weekly average PP NRS in the placebo group at week 16 was -30.9% ($P<0.001$). Of note, the proportion of patients with weekly average PP-NRS <2 at week 16 was 38.0% in the nemolizumab group and 4.5% in the placebo group ($P<0.001$).

Dynamic Pruritus Scale (DPS)

The Dynamic Pruritus Scale (DPS) assessed after the first study treatment injection at baseline showed that 25% of nemolizumab patients perceived improvement in itch at 4 hours compared with 17.9% of those in the placebo group. By 8 hours post-dose, 31.0% of nemolizumab and 23.5% of placebo patients perceived improvement; by 24 hours post-dose, improvement was apparent in 53.7% of nemolizumab and 36.4% of placebo patients; by 48 hours, improvement for nemolizumab and placebo was 75.6% vs 38.7%, respectively. At 72 hours, 73.7% of patients had some improvement in the nemolizumab group vs 34.4% in the placebo group.

Additional itch endpoints

The positive benefits of nemolizumab versus placebo in relieving itch were also demonstrated in the 5-D Itch Scale scores and the Pruritus Categorical Scale scores (details presented in the supplemental document).

Improvements in sleep

Weekly Sleep disturbance NRS was improved for nemolizumab 30 mg vs placebo at week 16 (-76.0% vs -36.5%; $P<0.001$) with significant separation from placebo by week 1 (-28.0% vs -7.5%; $P<0.001$). The percentage change in LS-Mean sleep NRS on a daily basis from Day 0 to Day 15 is presented in Figure 4. There was greater sleep disturbance improvement apparent by Day 3 (-26.6% vs -9.0%; $P<0.001$). By day 30, 13 (26.0%) of patients in the nemolizumab group reported a score of 0 or 1 compared with 4 (9.1%) of patients in the placebo group ($P=0.039$). Also at Day 30, there were 26 (52.0%) patients with ≥ 4 -point improvement in sleep NRS in the nemolizumab group and 7 (15.9%) in the placebo group ($P<0.001$).

FIGURE 4 HERE

Composite responders

Notably, 32.0% of nemolizumab patients achieved combined IGA success, ≥ 4 -point improvement in average PP-NRS and EASI-75 score at Week 16 compared to only 2.3% of placebo patients ($P<0.001$).

Safety

Nemolizumab was safe and well-tolerated, with details previously published.¹⁶ Among patients with EASI ≥ 16 , 87.2% of nemolizumab and 79.1% of placebo-treated patients had at least one treatment emergent adverse event. Serious adverse events were uncommon, occurring in one patient each in the nemolizumab and placebo groups, and severe adverse events were more common in the placebo group (6 patients) than in the nemolizumab group (4 patients). The most common adverse events were nasopharyngitis and upper respiratory tract infection (Tables S1 and 2).

DISCUSSION

An EASI threshold of ≥ 16 has recently become a standard inclusion criteria in clinical trials for treatments of moderate-severe AD,¹⁹ and will be used in nemolizumab phase 3 clinical trials. As such, we performed a subgroup analysis of the phase 2b AD study to provide estimates of efficacy and safety in a cohort that is more comparable to other therapeutics. In this subpopulation of subjects in the nemolizumab phase 2 study with EASI ≥ 16 , the baseline mean EASI score was 27.48, which compares with the baseline EASI scores in other studies of moderate-severe AD. A decrease of 72% in mean EASI score at Week 16 compares well with dupilumab plus TCS at 77% (CHRONOS study).¹⁹ IGA success with nemolizumab in this study was 32.0% (delta between active drug and placebo group = 25.2), which is comparable to the 39% (delta between active drug and placebo group = 26.3) reported with dupilumab in the CHRONOS study.²⁰ It should be noted that there have been no head-to-head comparative studies of nemolizumab and dupilumab, and the number of participants in this phase 2b study was relatively small. These limitations should be considered when evaluating efficacy data.

The daily PP-NRS scores show a robust reduction in pruritus as early as 2 days after initiation of nemolizumab therapy. Patients reported clinically meaningful reductions in pruritus after the first nemolizumab dose. At day 2, the LS mean PP-NRS was reduced by 25.5% ($P < 0.001$) and the improvement in itch steadily increased until week 16, when it was reduced by 68.6%. There was significant separation in sleep disturbance NRS scores as early as day 3 between nemolizumab and placebo, indicating a positive effect on another major issue that most patients with moderate-to-severe AD face. Finally, a substantial group of nemolizumab patients (32.0%) had a robust

composite response including IGA success, clinically relevant reduction in itch (≥ 4 points on PP-NRS), and 75% or greater reduction in EASI score; this is in comparison to just 2.3% of patients in the placebo group.

When the analysis is confined to subjects with EASI ≥ 16 , the placebo responses are lower compared to the overall population, resulting in larger deltas between placebo and nemolizumab, which is also consistent with data from other newer agents. Similarly, the response to corticosteroids is flattened in the placebo population with more severe illness.

A head-to-head randomized clinical trial of nemolizumab with other treatments has not yet been conducted. In a population of AD patients with EASI ≥ 16 , the efficacy of nemolizumab at improving AD lesions (IGA and EASI) is in the same range to data from the published literature about dupilumab; further, the efficacy of nemolizumab in improving pruritus (proportion of patients with NRS response ≥ 4) suggests greater effect compared with published data on dupilumab. The rapid effect on pruritus is an important finding, as pruritus is the most common and most burdensome symptom in AD patients². Nemolizumab resulted in robust and sustained improvements of AD lesions and symptoms in patients with more severe AD, with favorable benefit-risk profile.

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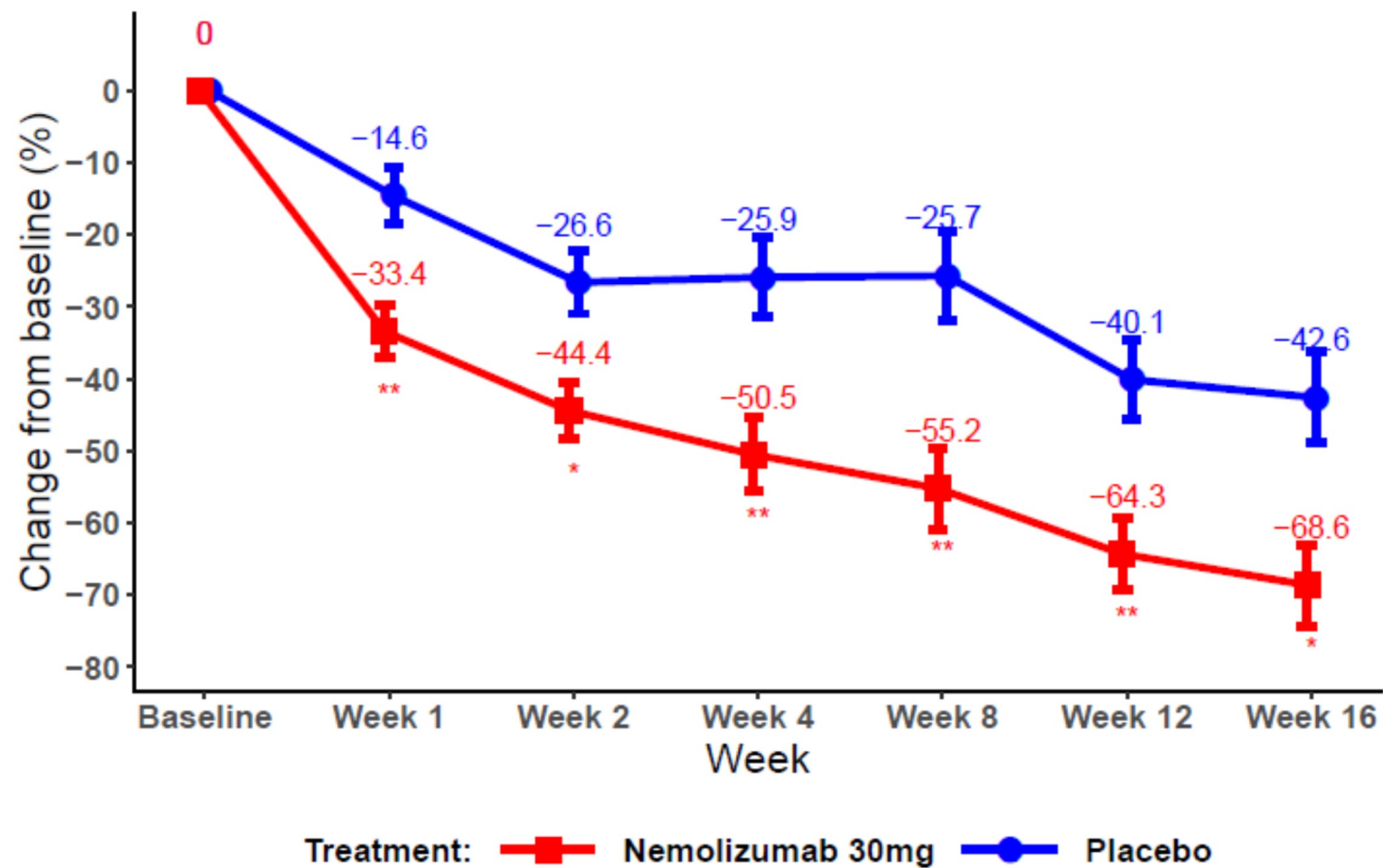
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Table 1. Patients' demographics and baseline characteristics (EASI ≥ 16 subgroup)

	Placebo (N=44)	Nemolizumab 30 mg (N=50)
Gender		
Male	27 (61.4%)	27 (54.0%)
Female	17 (38.6%)	23 (46.0%)
Race		
White	34 (77.3%)	35 (70.0%)
Black/African American	6 (13.6%)	8 (16.0%)
Asian	4 (9.1%)	6 (12.0%)
Other	0	1 (2.0%)
Ethnicity		
Hispanic/Latino	2 (4.5%)	2 (4.0%)
Non-Hispanic/Latino	42 (95.5%)	18 (96.0%)
Age (years)		
Mean (SD)	39.6 (14.74)	40.1 (16.56)
Range	18 - 72	18 - 80
Weight		
Mean (SD) (kg)	81.16 (19.53)	76.73 (19.13)
Mean EASI (SD)	30.91 (11.45)	27.48 (10.24)
IGA		
3 (moderate)	26 (59.1%)	32 (64.0%)
4 (severe)	18 (40.9%)	18 (36.0%)
Mean AD involvement of BSA (SD)	53.1% (20.18)	44.3% (16.80)
Weekly PP-NRS		
Mean $\pm$ SD	8.23 $\pm$ 1.17	8.33 $\pm$ 0.93
Range	(3.6-10.0)	(6.3-10.0)
Weekly avg pruritus NRS		
Mean $\pm$ SD	7.59 $\pm$ 1.45	7.68 $\pm$ 1.26
Sleep NRS	7.7 $\pm$ 1.63	7.7 $\pm$ 1.53
Mean SCORAD $\pm$ SD	71.23 $\pm$ 12.01	68.44 $\pm$ 11.35
Mean DLQI	17.3 $\pm$ 6.71	15.3 $\pm$ 6.78
Mean HADS	11.9 $\pm$ 8.14	11.8 $\pm$ 7.23

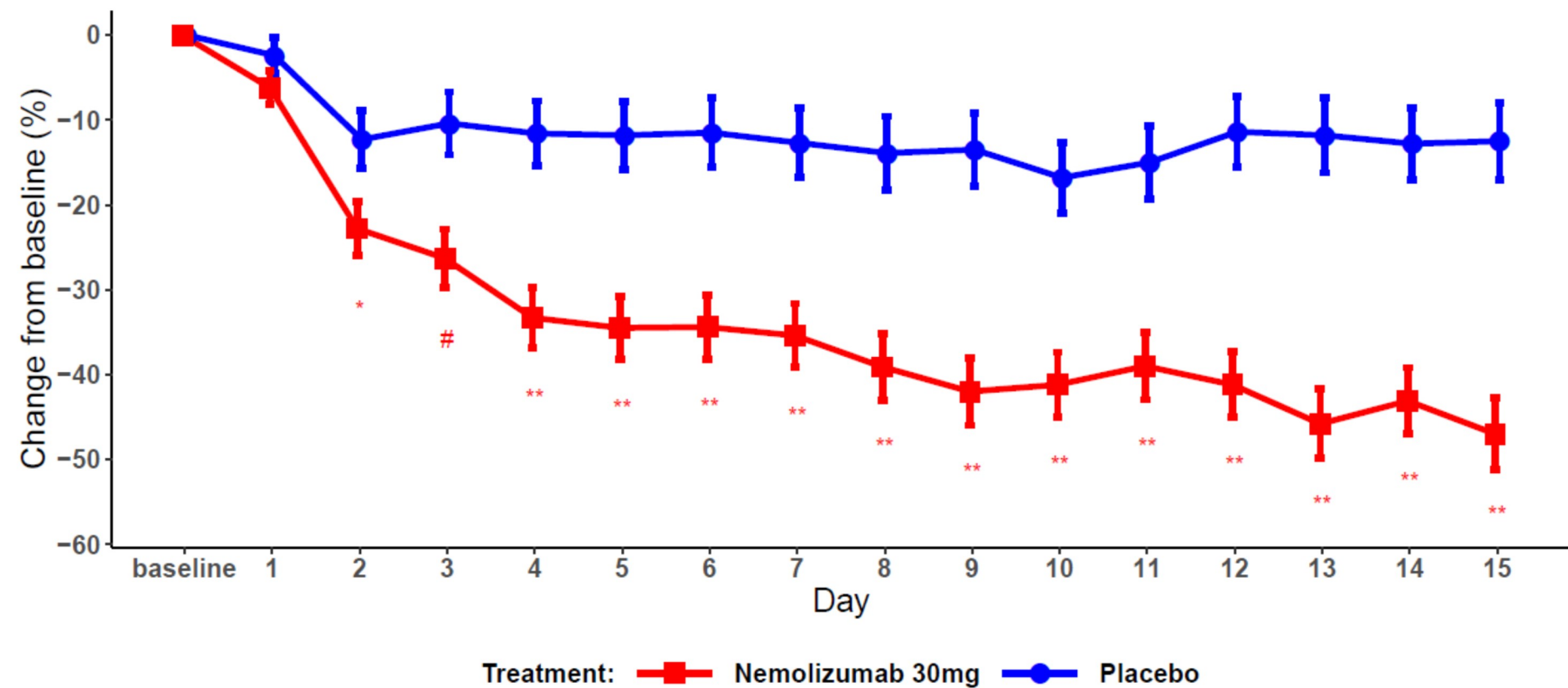
SD = standard deviation; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; AD = atopic dermatitis; BSA = body surface area; PP-NRS = peak pruritus numerical rating scale; NRS = numerical rating scale; SCORAD = SCORing Atopic Dermatitis; DLQI = Dermatology Life Quality Index; HADS = Hospital Anxiety and Depression Scale.

Fig 1



* $p \leq 0.01$; ** $p \leq 0.001$

Fig 2



* $p \leq 0.01$; # $p \leq 0.05$; ** $p \leq 0.001$

Fig 3

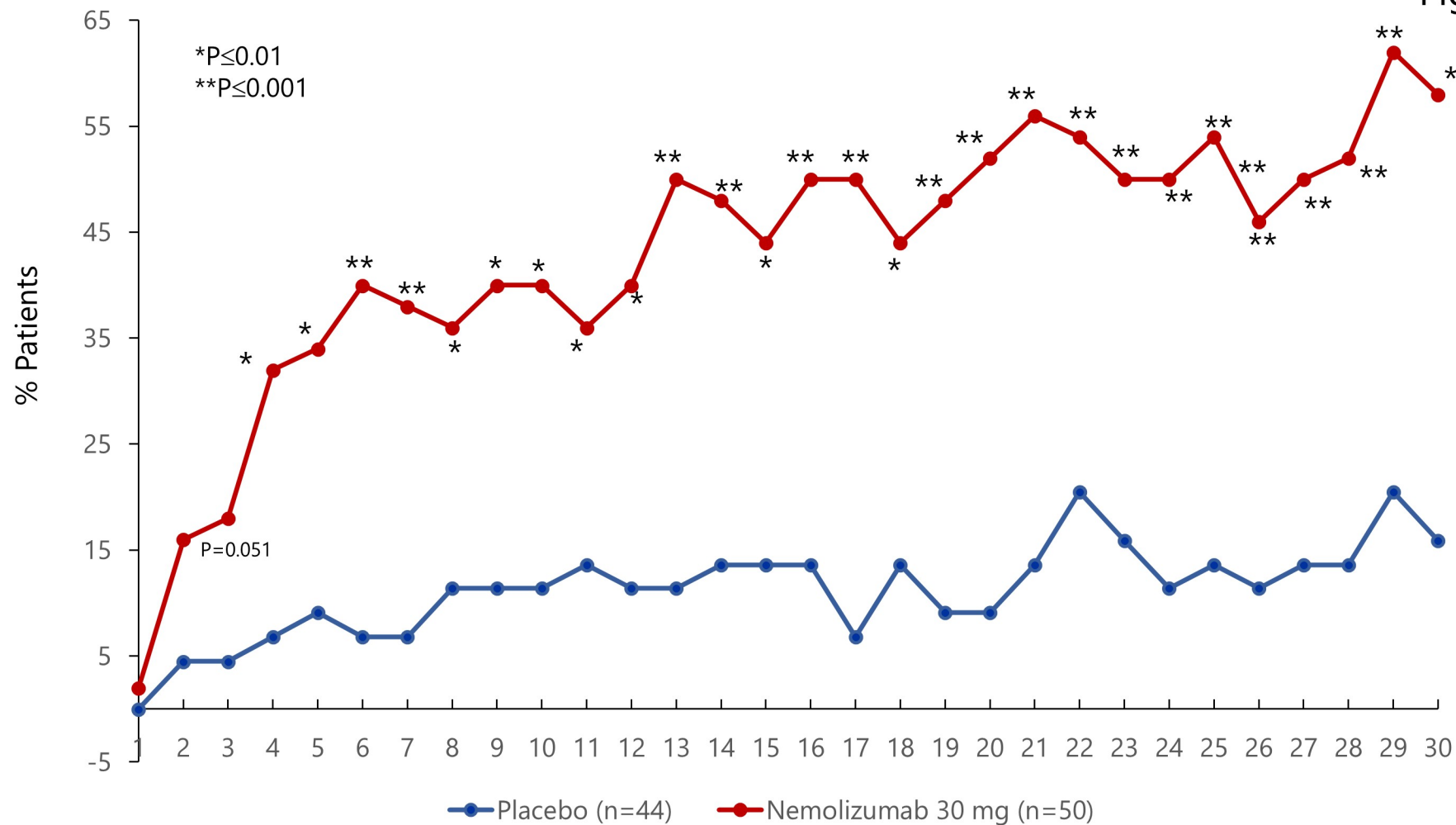
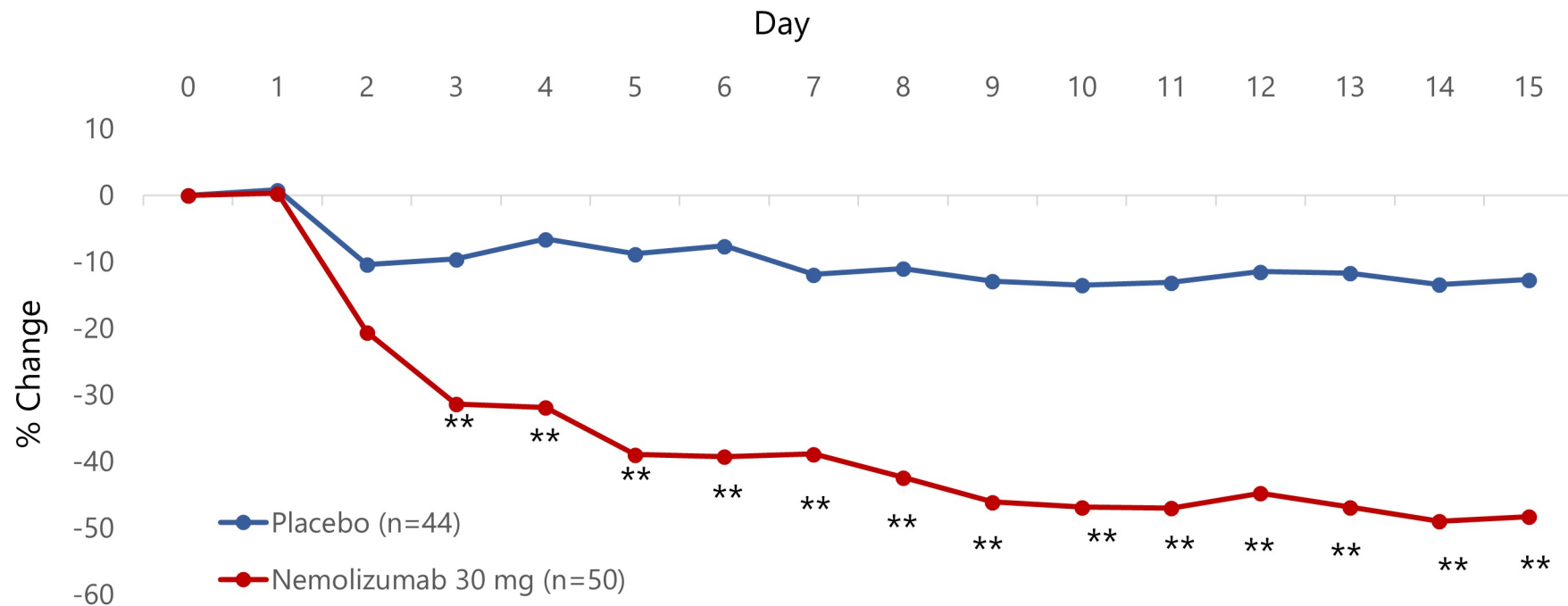


Fig 4



**P<0.001 all visits starting Day 3

**Nemolizumab is Associated with Early Improvement in Atopic Dermatitis Patients:
Subpopulation (EASI $\geq$ 16) Analysis of Phase 2B Study**

J. I. Silverberg, MD, PhD, MPH,¹ A. Pinter, MD,² A. Alavi, MD,³ C. Lynde, MD,⁴ J-D. Bouaziz, MD, PhD,⁵ A. Wollenberg, MD,⁶ D. F. Murrell, MD,⁷ S. Alpizar, MD,⁸ V. Laquer, MD,⁹ M. Braeutigam, MD,¹⁰ F. Ahmad, MS,¹¹ J. Armstrong, PhD,¹⁰ C. Piketty, MD, PhD¹⁰

¹Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

²Department of Dermatology, Venereology, and Allergology, Goethe-Universität Frankfurt am Main, Frankfurt am Main, GERMANY

³Department of Medicine, University of Toronto, Toronto, Ontario, CANADA

⁴Department of Medicine, University of Toronto, Toronto, Ontario, CANADA

⁵Department of Dermatology, Paris VII Sorbonne Paris Cité University Assistance Publique – Hôpitaux de Paris, Paris, France

⁶Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Munich, GERMANY

⁷Department of Dermatology, St George Clinical School, University of New South Wales, Sydney, AUSTRALIA

⁸ Clinical Research Trials of Florida, Tampa, FL, USA

⁹ First OC Dermatology, Fountain Valley, CA, USA

¹⁰ Galderma, Entre-Deux-Villes, SWITZERLAND

¹¹Galderma Laboratories, Fort Worth, TX, USA

ADDITIONAL EFFICACY ANALYSES

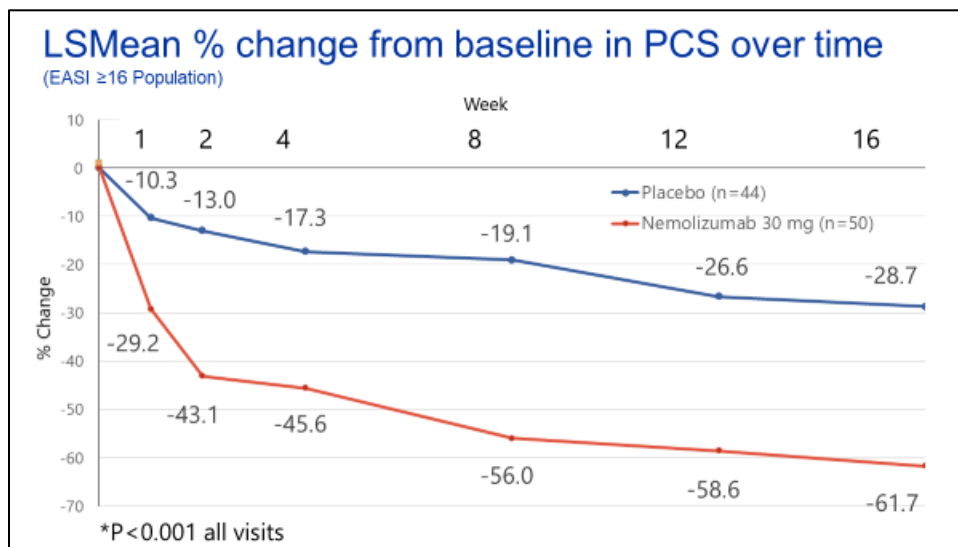
5-D Itch Scale

The absolute change from baseline in 5-D Itch Scale was significantly superior in the nemolizumab group at week 2 (the only post-baseline assessment), with a reduction of -6.9 compared to -2.9 in the placebo group ($P<0.001$).

Pruritus Categorical Scale

PCS success (score of 0-1) at week 16 was achieved in 74.0% of nemolizumab 30 mg patients compared to 18.2% of placebo patients ($P<0.001$). Significant differences between groups occurred at all time points, beginning at week 1 ($P<0.001$, Fig S1).

Figure S1. LSMean percent change from baseline in PCS at each study visit.



SCORAD

There was a steady reduction in SCORAD scores across study visits in the nemolizumab group, with significant difference from placebo at all visits beginning with the week 1 visit (LSMean -26.7% vs -13.3%, respectively, $P<0.001$). At week 16, SCORAD improvements were -57.1% in the nemolizumab 30 mg group compared with -28.2% in the placebo group ($P<0.001$).

DLQI

DLQI was assessed at week 2 and 12, and the improvement in score was superior with nemolizumab 30 mg at both timepoints. At week 2, LSMean DLQI was reduced by -9.0 in the nemolizumab group versus -4.5 in the placebo group ($P<0.001$), while at week 12 the reductions were -9.8 vs -6.2, respectively ($P=0.02$). The proportion of patients achieving a reduction of at least 4 points in DLQI score at week 12 was numerically superior in the nemolizumab group but not statistically different (56.0% vs 45.5% in placebo group $P=NS$).

Use of TCS

Use of medium and low potency TCSs decreased in both groups on a monthly basis from baseline through week 16; however, the reduction was greater in the nemolizumab 30 mg group (51.19 at baseline to 24.72 at week 16 vs placebo 55.66 at baseline and 40.13 at week 16).

A rescue therapy was used in 6 (12%) of the patients in the nemolizumab 30 mg group compared to 12 (27.3%) in the placebo group ($p=0.06$).

SAFETY ANALYSIS

A summary of the adverse events in the EASI-16 population is presented in Table S1. Six patients in the placebo group had severe adverse events, which included 5 subjects with AD and one patient with nasopharyngitis. In the nemolizumab group, four patients had severe AEs, which were one case of AD worsening, one prurigo, one intervertebral disc disorder, and one musculoskeletal pain. Table S2 presents the incidence of the most common AEs ($\geq 5\%$ of patients) for all causalities.

Table S1. Summary of adverse events in EASI-16 patients.

	Placebo (N=43)	Nemolizumab 30 mg (N=50)
Number AEs	128	151
Patients with ≥ 1 AE	34 (79.1%)	41 (82.0%)
Patients with Treatment-emergent serious AEs	1 (2.3%)	1 (2.0%)
Patients with severe AEs	6 (14.0%)	4 (8.0%)
AE leading to study discontinuation	0	1 (2.0%)

Table S2. Incidence of AEs occurring in $\geq 5\%$ of patients.

	Placebo (N=43)	Nemolizumab 30 mg (N=50)
Infections and infestations	15 (34.9%)	24 (48.0%)
Nasopharyngitis	9 (20.9%)	13 (26.0%)
Upper respiratory tract infection	1 (2.3%)	5 (10.0%)
Sinusitis	0	3 (6.0%)
Rhinitis	2 (4.7%)	3 (6.0%)
Folliculitis	2 (4.7%)	3 (6.0%)
Skin and subcutaneous tissue disorders	17 (39.5%)	14 (28.0%)
AD	17 (39.5%)	12 (24.0%)
Dry skin	0	3 (6.0%)
Respiratory, thoracic, and mediastinal disorders	2 (4.7%)	10 (20.0%)
Asthma	1 (2.3%)	7 (14.0%)
Cough	1 (2.3%)	3 (6.0%)
Gastrointestinal disorders	5 (11.6%)	5 (10.0%)
Diarrhea	3 (7.0%)	3 (6.0%)
Nausea	2 (4.7%)	1 (2.0%)

Abdominal pain	1 (2.3%)	3 (6.0%)
Nervous system disorders	4 (9.3%)	4 (8.0%)
Headache	4 (9.3%)	4 (8.0%)
Musculoskeletal and connective tissue disorders	1 (2.3%)	3 (6.0%)
Back pain	1 (2.3%)	3 (6.0%)