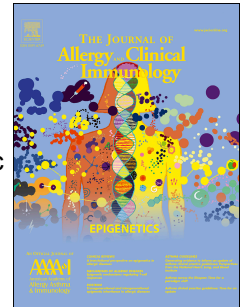


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Phase 2b Randomized Study of Nemolizumab in Adults with Moderate-Severe Atopic Dermatitis and Severe Pruritus

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PHASE 2B RANDOMIZED STUDY OF NEMOLIZUMAB IN ADULTS WITH MODERATE-SEVERE ATOPIC DERMATITIS AND SEVERE PRURITUS

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Running title: Nemolizumab in Moderate-Severe Atopic Dermatitis

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ABSTRACT

Background: Nemolizumab targets the interleukin 31 receptor alpha subunit (IL-31RA) involved in atopic dermatitis (AD) pathogenesis.

Objective: To evaluate a new dosing strategy of nemolizumab in AD.

Methods: A 24-week, randomized, double-blind, multicenter, study of nemolizumab (10, 30, 90 mg) SC injections q 4 weeks vs placebo, with topical corticosteroid in adults with moderate-to-severe AD, severe pruritus and inadequate control with topical treatment (n=226). Eczema Area and Severity Index (EASI), peak-pruritus numeric rating score (PP-NRS), and Investigator's Global Assessment (IGA) were assessed. Standard safety assessments were performed.

Results: Nemolizumab improved EASI, IGA and/or NRS-itch, with the 30 mg dose most effective. Nemolizumab 30 mg reduced EASI vs placebo at wk-24 (-68.8% vs. -52.1%; $p=0.016$); significant differences were observed by wk-8 ($p\leq 0.01$). With significant improvement ($p=0.028$) as early as wk-4, IGA 0/1 rates were higher for nemolizumab 30 mg vs. placebo at wk-16 (33.3% vs 12.3%; $p=0.008$) but not wk-24 owing to increased placebo/TCS effect (36.8% vs 21.1%; $P=0.06$). PP NRS was improved for nemolizumab 30 mg vs placebo at wk-16 (-68.6% vs -34.3%; $p<0.0001$) and wk-24 (-67.3% vs -35.8%; $p<0.0001$), with difference by wk-1 ($p<0.001$). NRS response rates (≥ 4 -point decrease) were higher for nemolizumab 30 mg vs placebo at wk-16 ($p\leq 0.001$) and wk-24 ($p\leq 0.01$). Nemolizumab was safe and well-tolerated. The most common adverse events were nasopharyngitis and upper respiratory tract infection.

Conclusions: Nemolizumab resulted in rapid and sustained improvements of cutaneous signs of inflammation and pruritus in AD, with maximal efficacy observed at 30 mg. Nemolizumab had an acceptable safety profile.

Clinicaltrials.gov trial registration number: NCT03100344

EUDRACT NUMBER: 2016-005025-37

Full study protocol is available in supplemental information

CAPSULE SUMMARY

This study evaluated nemolizumab plus topical corticosteroids in patients with AD and severe pruritus and found a significant effect on cutaneous signs of AD (by EASI and IGA), plus a rapid reduction of pruritus.

Key Messages

What's already known about this topic?

- There are patients with moderate-to-severe atopic dermatitis refractory to topical therapies who have limited treatment options.
- Nemolizumab is a humanized monoclonal antibody to the IL-31 receptor α .
- IL-31 has broad actions as a proinflammatory and immunomodulatory cytokine, linking the immune and neural systems to induce pruritus in AD.
- Nemolizumab monotherapy is effective in AD, with a notable marked rapid effect on pruritus, and an acceptable safety profile.

What does this study add?

- This placebo-controlled, double-blind study evaluated nemolizumab with concomitant use of topical corticosteroids in patients with moderate-to-severe AD and severe pruritus.
- Nemolizumab had a significant and clinically relevant effect on cutaneous signs of AD compared with placebo as assessed by EASI and IGA, with a rapid and sustained effect on pruritus.
- This study provides confirmation of the importance of IL-31 inhibitors in the management of AD.

INTRODUCTION

Nemolizumab is a humanized monoclonal antibody that targets the interleukin-31 receptor A (IL-31RA); it has been formulated for subcutaneous injection and studied in atopic dermatitis (AD).¹⁻³ IL-31 is a member of the IL-6 family of cytokines, which are central to the progression of chronic disease.⁴ Recent information has implicated IL-31 in the pathogenesis of AD.^{1, 5-10} IL-31 is responsible for a distinct transcriptional program in sensory neurons which causes nerve elongation and branching and may underly the tendency of AD patients to experience “increased sensitivity to minimal stimuli inducing sustained itch.”¹¹ Nemolizumab binds to the IL-31 receptor on a spectrum of cells, including neurons, which is potentially its mechanism in relieving pruritus.² IL-31 regulates brain-derived natriuretic peptide (BNP) in dorsal root ganglions and the skin, thereby regulating cytokine and chemokine release and controlling itch signaling pathways.¹² Thus, inhibition of IL-31 and its actions on BNP provides a novel therapeutic approach for AD. From a broader perspective, IL-31 helps drive T_H2-associated inflammation by modulating keratinocyte differentiation and the immune response via stimulation of proinflammatory cytokines.¹³ Increased skin barrier penetration of allergens and irritants has been shown to accompany IL-31 associated alteration of keratinocyte differentiation.¹³ Further, IL-31 can induce pathological remodeling of the skin through increase epidermal basal-cell proliferation, leading to epidermal thickening, and stimulate transepidermal water loss and additional impaired skin-barrier function.¹⁴

Pruritus is the most burdensome symptom of AD and drives the “itch-scratch cycle,” increasing skin barrier damage and resulting in sleeplessness, fatigue, and poor quality of life.^{2, 15, 16}

Pruritus can directly impair psychosocial well-being and quality of life, leading to increased

stress and depressive symptoms.¹⁷ Topical treatments for AD do not control disease – particularly pruritus – for all patients, and current systemic therapies are associated with long-term safety concerns.¹ There is a core group of patients for whom treatment options are limited and who need new safe and efficacious treatments.¹⁸

Nemolizumab targets the IL-31 pathway to manage both signs and symptoms of AD. In moderate-to-severe AD, nemolizumab monotherapy (phase 2a study) or combined therapy with topical corticosteroids (TCS; phase 1 study) was associated with rapid and sustained relief of pruritus and improvement of dermatitis.^{1,3} This phase 2b study assessed the efficacy and safety of nemolizumab in combination with TCS to determine optimal dose and duration of therapy. TCS were included because they are commonly used with systemic regimens for AD.¹⁹ While prior studies of nemolizumab in AD utilized a weight-based dosage, this study evaluated a more patient-centric dosing strategy including a loading dose to rapidly achieve steady-state drug concentrations (4 vs 10-12 weeks) and fixed-dose to allow potential use of a convenient auto-injector. This mirrors current development trends with biologic agents. We chose to assess nemolizumab in this more clinically relevant scenario. The loading dose and flat dose were selected based on the clinical pharmacokinetic profile of nemolizumab. The phase 2a study demonstrated that steady state concentrations were achieved at Week 16 of treatment without a loading dose. Pharmacokinetic models showed that the fixed doses of 10, 30, and 90 mg were expected to provide similar systemic exposure levels to those observed in the previous Phase 2a study. In addition, loading doses were added (20 mg for the 10 mg dose; 60 mg for the 30 mg dose) to rapidly achieve targeted systemic levels and ensure a fast onset of action.

METHODS

The nemolizumab phase 2b study was conducted in North America (US, Canada), Europe (France, Germany, Poland), and Australia. This clinical study was conducted in accordance with the protocol, the Helsinki declaration (1964) and subsequent amendments, and the International Conference on Harmonization (ICH) good clinical practice (GCP), and in compliance with applicable regulatory requirements.

Study Design

This was a double-blind, randomized, placebo-controlled multicenter study of subcutaneous nemolizumab versus placebo. Nemolizumab was administered as a loading dose of 20 mg, 60 mg or 90 mg on day 1, followed by 10 mg, 30 mg, or 90 mg, respectively, every 4 weeks until week 20 (injections at weeks 4, 8, 12, 16 & 20) and a 12-week follow-up period until Week 32. All treatment arms also received background mid- or low-potency TCS started at the screening visit in a standardized regimen and moisturizer (either subjects preferred moisturizer or moisturizer suggested by the investigator).

Patient Population

Subjects had moderate-to-severe AD, defined as an IGA score of 3 or 4, and severe AD-associated pruritus uncontrolled by topical treatments. Severe pruritus was defined as Pruritus Categorical Scale score of severe on at least 3 of the last 7 days prior to screening and an average daily peak pruritus Numeric Rating Score (NRS) intensity ≥ 7 for 7 days prior to the baseline visit. Additional inclusion criteria were age ≥ 18 years, chronic AD present for ≥ 2 years, body

surface area (BSA) involvement $\geq 10\%$, and Eczema Area Severity Index (EASI) ≥ 12 . Patients also had documented inadequate response to topical treatments within the past 6 months and were currently using TCS, but also agreed to using only authorized TCS throughout the study and agreed to use a moisturizer at least once per day. Additional criteria and definitions of inadequate response to topical treatments are provided in the supplemental document.

Rescue therapy was allowed at any time during the study if deemed medically necessary by the investigator due to significant worsening of signs/symptoms of AD. It could take the form of higher potency or higher quantity of TCS, use of a topical calcineurin inhibitor, systemic treatment, phototherapy, or combinations of treatments. Study drug was continued unless there was a safety concern or rescue with systemic therapies. Subjects who received rescue therapies were considered treatment failures for the efficacy analysis.

Efficacy and Safety Assessments

The primary efficacy endpoint was percent change from baseline in EASI at week 24. Secondary endpoints were the proportion of subjects achieving IGA success (IGA clear/0 or almost clear/1) at week 24; other assessments at each visit included percent change in EASI, peak pruritus numerical rating scale (PP NRS) and proportion of subjects with improvement of PP NRS ≥ 4 , sleep disturbance NRS, change in SCORAD scores, and proportion of subjects achieving EASI 50%, 75%, or 90% reduction from baseline at week 24. Standard safety assessments were performed (specific information about additional safety and other assessments is provided in the supplemental document).

Quality of life was assessed using the Dermatology Life Quality Index (DLQI) and EuroQoL 5-Dimension (EQ5D) scales and Hospital Anxiety and Depression Scale (HADS). DLQI is a 10-item questionnaire focusing on how skin disease affects overall life quality; each question is rated on a scale of 0 (not at all) to 3 (very much). EQ5D is a two-part tool, with a visual analog score and descriptive questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mental health symptoms were assessed using the HADS. HADS is a 14-item instrument, with 7 questions each for anxiety and depression. Ratings are from 0 to 3, with a total score of 0 to 21 for each sub-scale.

Statistical Analysis

Statistical Analysis System (version 9.3, SAS Institute Inc, Cary, NC, USA) software was used and statistical analyses performed on following subject populations: intent-to-treat (ITT, all randomized subjects); per protocol (PP, ITT subjects who met all major protocol criteria), and safety (ITT subjects with at least one study drug application). All efficacy variables were summarized by treatment at each visit. The continuous data were summarized using means, medians, minimum, maximum, and standard deviations (SDs) and categorical variables were summarized by frequency and percentage for each response category. Primary and secondary continuous endpoints were analyzed using a Mixed-effect Model for Repeated Measures (MMRM) approach, including terms of treatment group and baseline IGA severity. All categorical endpoints were analyzed using Stratified Cochran Mantel-Haenszel test, time to event data were summarized and analyzed using Kaplan-Meier method. Multiple imputation (MI) and last observation carried forward (LOCF) methodologies were used as sensitivity analyses to impute the missing values. With binary endpoints, all missing values were treated as “non-

responder.” All efficacy data, except observed case, was set to missing after rescue medication use. Safety analyses were performed on the safety population. Adverse events were tabulated in frequency tables by System Organ Class and MedDRA Preferred term.

RESULTS

Patient Population

A total of 226 subjects were included in the intent-to-treat analysis with group sizes shown in Table 1; 225 of these were included in the safety population. Subject disposition is provided in the supplemental document. Baseline demographic and clinical disease characteristics were comparable between groups and are shown in Table 1.

Efficacy: AD and Inflammation

EASI

All nemolizumab doses showed greater improvement in mean percentage change in EASI at week 24 than placebo (Figure 1). At week 24, the greatest difference from baseline was seen with the nemolizumab 30 mg dose (-68.8% vs -52.1% Least Square [LS] mean reduction for placebo, $p=0.016$). A higher statistically significant difference was observed at week 16 with the 30 mg dose (-66.8% vs -43.1%; $p<0.01$).

The proportions of subjects reaching greater than 50%, 75% and 90% improvement in EASI from baseline were also analyzed (Figure 2). There were significantly more responders in all

nemolizumab treatment groups at most study visits, with best response rates occurring in the 30 mg dose group. At week 24, EASI50 was achieved in 66.7% vs. 43.9% of subjects in the nemolizumab 30 mg vs. placebo groups ($p=0.014$); EASI75 in 45.6% vs 26.3%, ($p=0.034$); and EASI90 in 29.8% vs 10.5%, respectively ($p=0.011$). At week 16, EASI50 was achieved in 59.6% vs. 36.8% of subjects in the nemolizumab 30 mg vs. placebo groups ($p=0.016$); EASI75 in 49.1% vs 19.3% ($p\leq 0.001$); and EASI90 in 33.3% vs 8.8%, respectively ($p=0.001$).

IGA Success

The proportion of subjects with IGA success over time is shown in Figure 3. Performance in the nemolizumab 30 mg and 90 mg treatment groups was very similar until week 12, after which the nemolizumab 30 mg dose was superior to the other nemolizumab doses. By week 24, 36.8% of subjects in the nemolizumab 30 mg dose achieved IGA success compared to 21.1% in the placebo group ($p=0.06$); at week 16, 33.3% of nemolizumab 30 mg subjects vs 12.3% of placebo subjects achieved IGA success ($p=0.008$).

SCORAD

At week 24, all three doses improved SCORAD score compared to placebo, with the highest difference in the nemolizumab 30 mg group. The LS mean absolute change in SCORAD at week 24 was -25.0 for placebo compared with -34.6 ($p=0.016$) for nemolizumab 10 mg, -37.8 ($p=0.001$) for nemolizumab 30 mg, and -32.5 ($p=0.058$) for nemolizumab 90 mg.

Efficacy: Pruritus

Pruritus

The LS mean percent change of peak pruritus numeric rating score (PP-NRS) is presented in Figure 4A. All doses of nemolizumab were associated with a rapid decrease in pruritus scores, with statistically significant differences from placebo starting as early as week 1. By week 2, all nemolizumab doses were greater than placebo ($p \leq 0.001$). The most marked effects on peak pruritus scores were seen in the nemolizumab 30 mg arm compared to placebo (-67.3% vs -35.8% at week 24, $p < 0.001$). The proportion of subjects with improvement in weekly average PP-NRS ≥ 4 from baseline was significantly greater in the nemolizumab groups vs. placebo treatment beginning at week 1, when 17.5% of subjects in the nemolizumab 30 mg dose responded compared to 5.3% in the placebo group (Fig 4B).

Efficacy: Additional Parameters*Sleep*

The LS mean percentage change in weekly average sleep disturbance NRS at week 24 was -67.5% with nemolizumab 10 mg, -74.8% for nemolizumab 30 mg, and -68.1% for nemolizumab 90 mg compared with -43% for placebo ($p \leq 0.001$ for all). As shown in Figure 5, a statistically significant difference from placebo was apparent as early as week 1 with all nemolizumab doses compared to placebo.

Quality of Life Assessments

Nemolizumab positively affected quality of life as assessed by DLQI and the VAS section of EQ5D. DLQI scores decreased significantly in all nemolizumab groups ($p \leq 0.001$) compared to placebo by week 2 in and were greater than placebo at 12 weeks in the 30 mg group

($p=0.043$). At week 24, DLQI scores were 4.8 in the nemolizumab 10 mg group (Mean -11.6 change, $p=0.018$), 4.9 in the nemolizumab 30 mg group (mean -10.5 change, $p=0.022$), 5.6 in the nemolizumab 90 mg group (mean -10.9) compared with 8.5 in the placebo group (mean -8.6 change). The change from baseline in overall EQ5D Index score at week 24 was not significantly different for any nemolizumab group versus placebo, although there were positive trends in specific dimensions. Nemolizumab 30 mg therapy was associated with significantly superior effects on mobility ($p=0.038$) and the 10 mg dose was superior to placebo in mobility ($p=0.083$), self-care ($p=0.043$), and pain/discomfort ($p=0.036$). The changes in VAS score were significantly different for the 10 and 30 mg doses ($p=0.023$ and 0.047 , respectively).

Mental health symptoms

The mean HADS scores were comparable among groups at baseline, and by week 24 had decreased by a mean of -7.1 in the nemolizumab 10 mg group, -4.3 in the nemolizumab 30 mg group, and -4.6 in the nemolizumab 90 mg group and -4.2 in the placebo group. Nemolizumab did not have a significantly different effect on the absolute scores on the HADS Anxiety subscale at week 12 or 24. There were significant differences from baseline on the HADS Depression subscale at week 24 in the nemolizumab 10 mg group ($p=0.007$) and 30 mg group ($p=0.048$). Similarly, significant differences were not apparent in the group of subjects with HADS Anxiety subscore ≥ 11 nor those with HADS Depression subscore ≥ 11 at baseline.

Use of background TCS

The use of medium- and low-potency TCS during the treatment period was higher in the placebo group than in all nemolizumab groups at each monthly checkpoint. The total mean use of TCS

from baseline to week 24 was 139.88 g in the nemolizumab 10 mg group, 167.53 in the 30 mg group, and 163.43 in the 90 mg group compared with 232.75 g in the placebo group. Note that subjects who received rescue treatment or discontinued the study were excluded from all TCS use analyses. The majority of subjects used the medium potency TCS and placebo subjects used almost twice the amount compared to nemo group. There was a 30-40% reduction in TCS use in the nemolizumab groups vs placebo group.

Use of Rescue Medication

Rescue medication was required during the treatment period by a total of 34 subjects; 6 in the nemolizumab 10 mg group, 7 in the 30 mg group, 8 in the 90 mg group and 13 in the placebo group. As shown in Table 2, use of both topical and systemic rescue medications were more common in the placebo group compared with nemolizumab groups.

Safety

A total of 185 patients had at least one adverse event, and the number of treatment-emergent adverse events (TEAEs) was similar in placebo and all nemolizumab groups. Nemolizumab at all doses was well-tolerated with few serious or severe adverse events; serious TEAEs were reported in 3 (5.5%) of nemolizumab 10 mg subjects, 2 (3.5%) in each of the 30-mg and 90-mg arms, and 1 (1.8%) of placebo subjects. Severe TEAEs occurred in 6 (10.7%) of the placebo group, 3 (5.5%) of nemolizumab 10-mg group, 5 (8.8%) in the nemolizumab 30-mg group, and 2 (3.5%) in the nemolizumab 90-mg group.

There were few adverse events leading to discontinuation (2 in the 30 mg group, 4 in the 10 mg group, and 7 in the 90 mg group vs 4 in the placebo group). A summary of the treatment-emergent adverse events (TEAEs) occurring in 5% or more subjects is shown in Table 3. Selected TEAEs of interest are shown in Table 4. In subjects with a history of asthma a higher incidence of asthma event was observed with nemolizumab in a dose-dependent fashion. All asthma events were mostly mild in severity and there were no *de novo* cases of asthma associated with nemolizumab. One severe event was observed in nemolizumab 90 mg arm. All events were reversible under treatment. There was a low incidence of peripheral edema observed in both placebo (n=2, 3.6%) and nemolizumab (n=8, 4.7%) patients, with no serious cases. Overall, the occurrence of the selected TEAEs of interest was acceptable and comparable in the nemolizumab and placebo groups.

Clinical laboratory data showed no significant changes in liver enzymes (ALT, AST, BUN, or alkaline phosphatase) through week 24. However, two subjects treated with nemolizumab (one in the 10 mg arm and the other in the 90 mg arm) discontinued early due to elevated creatine kinase. There were no signals of impact on C reactive protein, electrolytes, cholesterol or glucose.

DISCUSSION

This study demonstrated that treatment with nemolizumab resulted in rapid improvement in AD lesions, as assessed by EASI and IGA, when compared to placebo. In addition to improvements in inflammatory signs of AD, all assessments of pruritus showed a highly significant, fast-onset and sustained effect of nemolizumab. The primary endpoint, percent change in EASI at week 24

was statistically significant versus placebo for the nemolizumab 30 mg dose ($p=0.016$) and borderline statistically significant for the 10 mg dose ($P=0.051$). Though effects on itch and skin lesions have a separate timeline, data from this study clearly demonstrate a reduction in skin lesions and a greater improvement in pruritus. All doses except the 90 mg dose showed improvements in IGA response rates to week 24. Response after week 16 does not appear to increase, but remained within expected variability. A similar observation can be made for the 90 mg dose, with slightly higher variability which is likely due to a higher rate of missing responses in this group. The data from this study did not demonstrate a significant dose-response relationship between the 10 mg and 90 mg dose for clinical efficacy endpoints; this has been observed with other recent drug candidates, most recently with omalizumab.²⁰⁻²³ Therefore, the dose-response profile of the phase 2b study was further investigated using pharmacokinetic-pharmacodynamic (PK/PD) models. The dose response fit with a $E_{\max}$ or $I_{\max}$ model, and the maximum nemolizumab effect was observed at serum concentration close to the observed serum concentration for the 30 mg dose (data not shown).

To facilitate comparisons with the majority of AD studies week 16 data are presented, however, the week 24 endpoint was important to better illustrate how nemolizumab performs over a longer period of time. There was also statistically significant separation from placebo in secondary endpoints, including IGA response, EASI50, EASI75, EASI90, PP NRS, sleep NRS, and multiple QOL domains, with greatest differences seen at week 16 and the 30 mg dose showing superior to the three doses (10, 30 and 90mg tested). Further studies will use week 16 as the primary endpoint, consistent with most other clinical trials of new therapies in AD.

The efficacy shown in this study was greater than the results found in the nemolizumab phase 2a study at 12 weeks, particularly with the 30 mg dose. The phase 2a study was a study of nemolizumab monotherapy administered on a weight-based dosing schedule versus placebo.² The current data bring new information about the efficacy of nemolizumab in AD with use of a fixed-dose of nemolizumab plus loading dose at baseline, for a longer duration, and in combination with background (low and mid-potency) TCS. Rapid inhibition of pruritus in AD is an important treatment goal. Pruritus relief is expected to contribute to breaking the “itch-scratch cycle” and thus improve the skin condition in AD subjects. In the Nemolizumab phase 2b study, steady-state condition was achieved by Week 4, due to loading doses of 20 mg and 60 mg administered in the 10 mg and 30 mg study arms, respectively. For the 90-mg arm, steady state was reached at approximately Week 16 of treatment, in full accordance with Phase 2a results. It is our opinion that the use of loading dose to achieve more rapid steady state and a fixed dose improved the effects of nemolizumab on the inflammatory aspects of AD, while retaining the expeditious reduction in pruritus seen in earlier studies. There was a relatively high response rate in the placebo arm, which mirrors the normal TCS response; we feel that this is not a confounder for the study, but rather would more closely mimic usual clinical practice should nemolizumab be approved in the management of AD. The study population in the trial represents a difficult to treat population in AD, these patients are in need of new therapeutic options. Given the pivotal role of IL-31, it was hypothesized that patients with more severe itch would derive greatest benefit. This was incorporated into the study design to more closely mimic clinical realities.

There was a slightly higher incidence of TEAEs and serious TEAEs with nemolizumab compared with placebo. There was no imbalance in the incidence of skin infections between

active and placebo groups, but there was a higher incidence of non-skin infections with nemolizumab vs placebo. Notably, these infections were primarily nasopharyngitis, upper respiratory tract infections and gastroenteritis. A dose-dependent increase of asthma events in subjects with pre-existing asthma was reported, with mostly mild and very few moderate events that were manageable and reversible. All events were observed in subjects with pre-existing asthma and treatment was adjusted to the course of the disease, most of the cases were mild with PEF decreased in 13/24 cases. Some of these events may have occurred because effective treatment with nemolizumab led to improved overall well-being, and increased activity levels that, in turn, triggered asthma symptoms. Some of the cases of worsening may have been caused by respiratory infections, and it is reassuring that there were no de novo cases of asthma associated with nemolizumab. This safety profile is consistent with that reported by Ruzicka et al, except exacerbation of AD occurred more frequently in the placebo group in our study whereas it occurred more often in the nemolizumab groups in the earlier study.² In addition, higher rates of peripheral edema in nemolizumab groups² were not found in this study.

Study limitations include a small sample size, as it was a phase 2b study. This makes it difficult to interpret some of the rare safety events.

In conclusion, of the three doses evaluated, the 30 mg Q4W dose of nemolizumab was the most effective, and was associated with the highest overall efficacy on AD clinical signs and pruritus. Treatment with nemolizumab achieved fast onset and sustained effect on pruritus. Nemolizumab had an acceptable safety profile.

Acknowledgments: The authors would like to thank the Nemolizumab Study Team and all investigators in Europe, North America, and Australia (listed in the supplemental document) who participated in this clinical trial as well as colleagues in Galderma International, Galderma R&D in Sophia Antipolis, and Galderma Laboratories. We also acknowledge the writing support of Valerie Sanders of Sanders Medical Writing in the United States.

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Table 1. Patient demographics and baseline characteristics (ITT population).

	Placebo (N=57)	Nemolizumab 10 mg (N=55)	Nemolizumab 30 mg (N=57)	Nemolizumab 90 mg (N=57)	Total (N=226)
Gender					
Male	31 (54.4%)	29 (52.7%)	29 (50.9%)	26 (45.6%)	115 (50.9%)
Female	26 (45.6%)	26 (47.3%)	28 (49.1%)	31 (54.4%)	111 (49.1%)
Race					
White	45 (78.9%)	38 (69.1%)	40 (70.2%)	44 (77.2%)	167 (73.9%)
Black/African American	8 (14.0%)	3 (5.5%)	10 (17.5%)	8 (14.0%)	29 (12.8%)
Asian	4 (7.0%)	11 (20.0%)	6 (10.5%)	4 (7.0%)	25 (11.1%)
Other	0	3 (5.4%)	1 (1.8%)	1 (1.8%)	5 (2.2%)
Ethnicity					
Hispanic/Latino	5 (8.8%)	2 (3.6%)	2 (3.5%)	2 (3.5%)	11 (4.9%)
Non-Hispanic/Latino	52 (91.2%)	53 (96.4%)	55 (96.5%)	55 (96.5%)	215 (95.1%)
Age (years)					
Mean (SD)	40.9 (15.01)	35.3 (14.83)	40.2 (16.64)	40.9 (14.95)	39.3 (15.45)
Range	18-72	18-82	18-80	19-77	18-82
Weight					
Mean (SD) (kg)	80.58 (18.84)	73.72 (14.63)	76.90 (18.61)	80.49 (22.77)	77.96 (19.05)
Mean EASI (SD)	26.96 (12.44)	24.80 (10.20)	25.87 (10.53)	24.24 (10.41)	25.48 (10.92)
IGA					
3 (moderate)	38 (66.7%)	37 (67.3%)	39 (68.4%)	37 (64.9%)	151 (66.8%)
4 (severe)	19 (33.3%)	18 (32.7%)	18 (31.6%)	20 (35.1%)	75 (33.2%)
Mean AD involvement of BSA (SD)	45.6 (22.60)	40.4 (15.66)	42.4 (17.10)	37.6 (18.08)	41.5 (18.65)
Weekly PP NRS					
Mean $\pm$ SD	8.16 $\pm$ 1.17	8.62 $\pm$ 1.05	8.22 $\pm$ 1.39	8.22 $\pm$ 1.29	8.30 $\pm$ 1.24
Range	(3.6-10.0)	(5.4-10.0)	(0.6-10.0)	(2.4-10.0)	(0.6-10.0)
Weekly avg pruritus NRS					
Mean $\pm$ SD	7.52 $\pm$ 1.52	8.01 $\pm$ 1.28	7.62 $\pm$ 1.56	7.76 $\pm$ 1.39	7.72 $\pm$ 1.44
Sleep NRS	7.7 $\pm$ 1.75	8.2 $\pm$ 1.27	7.6 $\pm$ 1.80	7.9 $\pm$ 1.43	N/A
Mean SCORAD $\pm$ SD	67.90 $\pm$ 12.33	66.02 $\pm$ 11.37	67.01 $\pm$ 11.43	66.04 $\pm$ 11.33	66.74 $\pm$ 11.57
Mean DLQI	17.0 $\pm$ 6.60	16.5 $\pm$ 6.41	15.6 $\pm$ 7.28	16.6 $\pm$ 7.36	N/A
Mean HADS	12.2 $\pm$ 8.23	14.6 $\pm$ 6.79	12.1 $\pm$ 7.26	14.0 $\pm$ 8.36	N/A

Note: Percentages are based on the number of subjects having a non-missing value in the respective treatment arm.

Table 2. Rescue medication use (ITT population).

	Placebo (N=57)	Nemolizumab 10 mg (N=55)	Nemolizumab 30 mg (N=55)	Nemolizumab 90 mg (N=55)	Total (N=226)
Subjects with ≥ 1 rescue medication and/or procedure					
During treatment period	13 (22.8%)	6 (10.9%)	7 (12.3%)	7 (14.0%)	34 (15.0%)
During follow-up period	4 (7.0%)	4 (7.3%)	5 (8.8%)	6 (10.5%)	19 (8.4%)
Topical rescue medication (n)	23	10	9	8	50
Systemic rescue medication (n)	7	3	1	2	13

[1] The treatment period is defined as from date of the randomization to date of week 24 (for completer) or 4 weeks after the last study drug injection (for subjects who early discontinued study drug).

[2] The follow-up period is defined as from date of week 24 (for completer) or 4 weeks after the last study drug injection (for subjects who early discontinued study drug) to date of week 32 / final visit.

[3] Rescue medication data are for treatment period only.

*Percent of all rescue medication (topical and systemic).

Table 3. TEAEs occurring in $\geq 5\%$ by system organ class and preferred term, all causes (SAF population).

	Plc (N=56)	Nemolizumab			
		10 mg (N=55)	30 mg (N=57)	90 mg (N=57)	All (N=169)
At least 1 TEAE	43 (76.8%)	47 (85.5%)	47 (82.5%)	48 (84.2%)	142 (84%)
Infection and Infestation*	23 (41.4%)	34 (61.8%)	34 (59.6%)	34 (59.6%)	102 (60.4%)
Nasopharyngitis	12 (21.4%)	18 (32.7%)	14 (24.6%)	13 (22.8%)	45 (26.6%)
URTI	1 (1.8%)	4 (7.3%)	6 (10.5%)	4 (7%)	14 (8.3%)
Gastroenteritis	0	0	3 (5.3%)	4 (7%)	7 (4.1%)
Sinusitis	0	3 (5.5%)	3 (5.3%)	1 (1.8%)	7 (4.1%)
Oral herpes	1 (1.8%)	2 (3.6%)	1 (1.8%)	3 (5.3%)	6 (3.6%)
UTI	3 (5.4%)	3 (5.5%)	1 (1.8%)	2 (3.5%)	6 (3.6%)
Rhinitis	3 (5.4%)	0	3 (5.3%)	1 (1.8%)	4 (2.4%)
Herpes infection	5 (8.9%)	4 (7.3%)	3 (5.3%)	5 (8.7%)	12 (7.1%)
Skin and SC tissue disorders	20 (35.7%)	18 (32.7%)	23 (40.4%)	23 (40.4%)	64 (37.9%)
Dermatitis atopic	18 (32.1%)	12 (21.8%)	14 (24.6%)	16 (28.1%)	42 (24.9%)
Dry Skin	0	0	3 (5.3%)	0	3 (1.8%)
Respiratory, thoracic & mediastinal disorders	7 (12.5%)	6 (10.9%)	13 (22.8%)	12 (21.1%)	31 (18.3%)
Asthma flare	1 (1.8%)	2 (3.6%)	7 (12.3%)	10 (17.5%)	19 (11.2%)
Cough	2 (3.6%)	1 (1.8%)	3 (5.3%)	2 (3.5%)	6 (3.6%)

Table 4. Selected TEAEs (Safety Population).

	Placebo (N=56)	Nemolizuma b 10 mg (N=55)	Nemolizumab 30 mg (N=55)	Nemolizumab 90 mg (N=55)	All nemo (N=169)
Number of selected TEAEs	74	75	77	74	226
Subjects with selected TEAEs	31 (55.4%)	37 (67.3%)	37 (64.9%)	37 (64.9%)	112 (66.3%)
AD exacerbation	9 (16.1%)	3 (5.5%)	7 (12.3%)	7 (12.3%)	17 (10.1%)
Injection-related reaction	5 (8.9%)	1 (1.8%)	2 (3.5%)	2 (3.5%)	5 (3%)
Local	3 (5.4%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	3 (1.8%)
Systemic	2 (3.6%)	1 (1.8%)	0	1 (1.8%)	2 (1.2%)
Peripheral edema	2 (3.6%)	2 (3.6%)	4 (7.0%)	2 (3.5%)	8 (4.7%)
Skin infection	7 (12.5%)	7 (12.7%)	9 (15.8%)	6 (10.5%)	22 (13%)
Non-skin infection	21 (37.5%)	31 (56.4%)	31 (54.4%)	31 (54.4%)	93 (55%)
Headache	7 (12.5%)	6 (10.9%)	4 (7.0%)	4 (7.0%)	14 (8.3%)
Subjects with selected serious TEAEs	0	1 (1.8%)	2 (3.5%)	2 (3.5%)	5 (3.0%)
Serious AD exacerbation	0	0	1 (1.8%)	0	1 (0.6%)

FIGURE LEGENDS

Figure 1. Mean % change from baseline in EASI over time (ITT population).

Figure 2. Proportion of EASI50, 75, and 90% responders (ITT Population).

Figure 3. Proportion of subjects achieving IGA success (Clear/almost clear plus 2-grade improvement).

Figure 4. (A) The least squares mean percent change in PP-NRS from baseline to week 24 (ITT population) and (B) proportion of subjects with an improvement of weekly average peak pruritus NRS ≥ 4 (ITT Population). Any subject with missing visit or rescue dosing were treated as a non-responder.

Figure 5. Change in sleep NRS over time.

ABBREVIATIONS USED

AD	Atopic dermatitis
BNP	Brain-derived natriuretic peptide
EASI	Eczema Area and Severity Index
IGA	Investigator Global Assessment
IL-31	Interleukin-31
MMRM	Mixed-effect Model for Repeated Measures
NRS	Numeric rating scale
SCORAD	SCORing of Atopic Dermatitis
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event

Fig 1

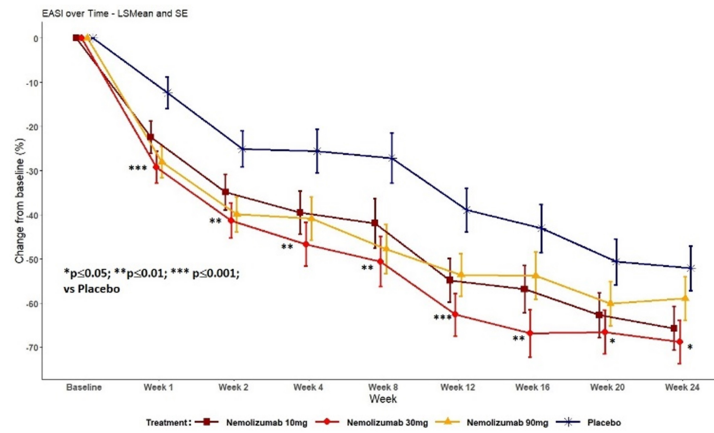


Fig 2

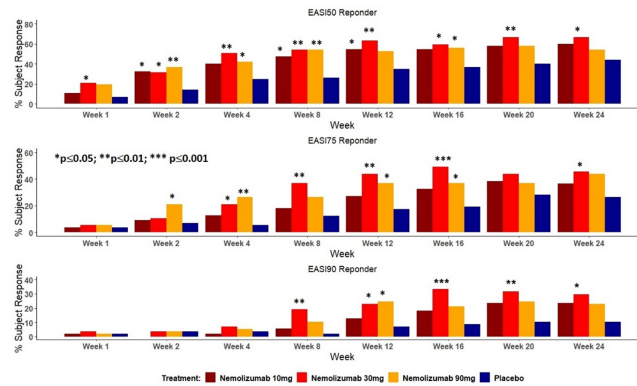


Fig 3

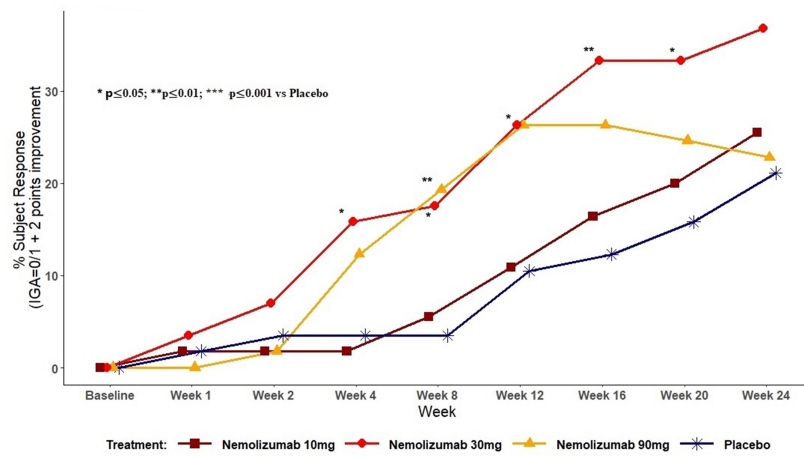


Fig 4A

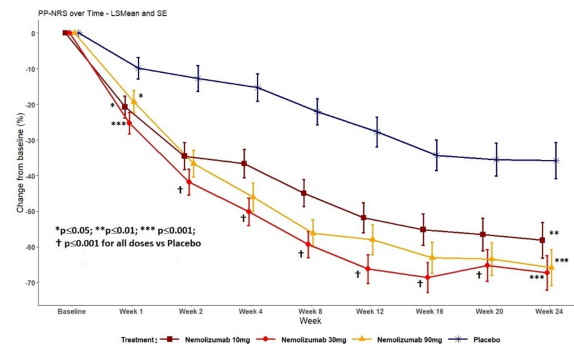


Fig 4B

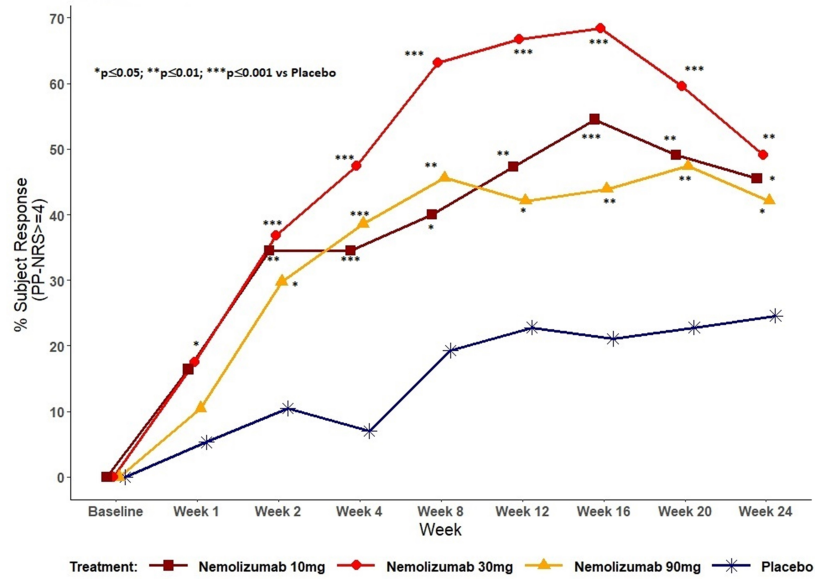
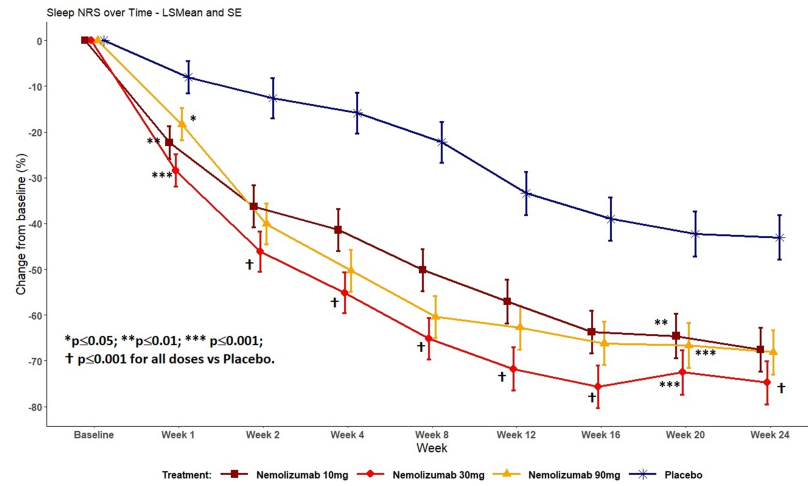
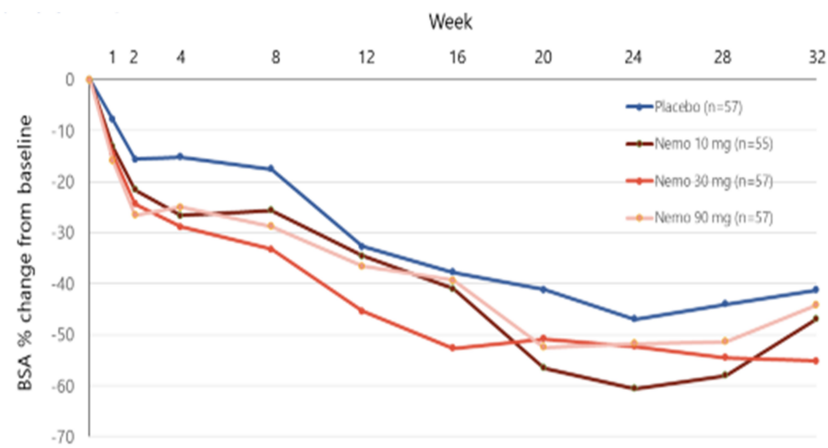


Fig 5



Suppl Fig 1



Nemolizumab Phase 2b Study Supplemental document

Enrollment Period and Registration Information

The first patient was enrolled in the study titled “A Randomized, Double-blind, Multi-center, Parallel-group, Placebo-controlled Dose-ranging Study to Assess the Efficacy and Safety of **Nemolizumab** (CD14152) in Moderate-to-severe Atopic Dermatitis Subjects With Severe Pruritus Receiving Topical Corticosteroids” (NCT03100344 and EUDRACT NUMBER: 2016-005025-37) on July 6, 2017. The study was registered on Clinicaltrials.gov on March 29, 2017.

The clinical study protocol and forms were reviewed and approved by the following institutional review boards and independent ethics committees: Belberry Limited in Australia, Schulman/Advarra and Health Research Ethics Board of Alberta in Canada, The Ethics Committee at the LMU Munich in Germany, the Comité de Protection des Personnes Ile de France III, Paris in France, the Ethics Committee at the Lower Silesian Chamber of Physicians in Wroclaw, Poland, and Schulman/Advarra and Northwestern University in the United States.

Important Protocol Changes

There were no major or important protocol changes for this study.

Randomization and Sample Size Calculation

Randomization was generated by the Clinical Research Organization. Treatment was assigned centrally via Interactive Response Technology (IRT). All eligible subjects were randomly assigned to one of the four treatment groups in a 1:1:1:1 ratio. A randomization number was allocated to each eligible subject at baseline by the IRT system, and randomization was stratified by baseline IGA score.

Sample size was estimated using a multiple comparison procedures-modeling (MCP-Mod) approach by selecting a set of candidate dose response shapes based on primary endpoint response (percent change in EASI). Assuming placebo response of 35%, standard deviation 45%, and a maximum treatment difference of 30%, it was calculated that 50 subjects per arm would provide at least 90% power to detect a statistically significant dose-response for at least one model at 1-sided significance level of 0.025.

Additional Inclusion/Exclusion Criteria and Treatment Washout Periods

Additional inclusion criteria included:

- Female subjects had to fulfill one of the following
 - Be of non-childbearing potential demonstrated by absence of menstrual bleeding for 1 year prior to screening, without any other medical reason, hysterectomy or bilateral oophorectomy
 - If of childbearing potential, agree to a true abstinence or to use an effective or highly effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration

- Be willing and able to comply with all of the time commitments and procedural requirements of the trial protocol
- Understand and sign an Informed Consent Form prior to any investigational procedure
- No active or latent tuberculosis

Exclusion criteria were as follow:

- Body weight <45 kg
- Medical history of asthma that fulfilled any one or more of the scenarios described
 - Had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit
 - Poorly-controlled asthma (ie, symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit
 - Peak expiratory flow (PEF) <80% of the predicted value
- Cutaneous bacterial or viral infection within 1 week before the screening visit or during the run-in period
- Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 1 week before the screening visit or during the run-in period, unless completely resolved and subject had discontinued treatment at least 1 week prior to baseline visit
- Required rescue therapy during the run-in period, or expected to require 3 rescue therapy shortly after the baseline visit
- Positive serology results for hepatitis B or C, or human immunodeficiency virus at screening (positive HBcAb and a negative HBsAg were allowed if HBsAb was positive)
- Elevated alanine aminotransferase or aspartate aminotransferase ≥ 3 at screening
- Elevated creatinine phosphokinase >upper limit of normal at the screening visit, unless not confirmed on a repeat assessment within 2 weeks
- Neutrophil count $<1.5 \times 10^3/\mu\text{L}$ at the screening visit
- Prior treatment with nemolizumab
- Pruritus that responded to treatment with potential anti-pruritic effect (eg, antihistamines) and pruritus not associated with AD.
- Pregnancy or planning to become pregnant
- History of lymphoproliferative disease or malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, actinic keratoses or squamous cell carcinoma in situ (Bowen's disease) that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit or (2) carcinoma in situ of the cervix, or non-invasive malignant colon polyps that have been removed
- History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, et, monoclonal antibody)
- History of intolerance to low or mid potency topical corticosteroids (TCS) or for whom TCS is not advisable
- Known or suspected immunosuppression

- History of or current confounding skin condition (such as Netherton Syndrome, psoriasis, cutaneous T-Cell Lymphoma, contact dermatitis, chronic actinic dermatitis, or dermatitis herpetiformis)
- Any medical or surgical condition that could interfere with the assessments or interpretation of study results
- Any uncontrolled or serious disease that could put the subject at significant risk
- Planned or expected to have a major surgical procedure during the clinical trial
- Unwilling to refrain from prohibited medications during the trial
- Current or recent participation in any other clinical trial
- Vulnerable subject as defined in ICH/GCP

Table S1. Treatment washout periods

Topical treatments • Topical calcineurin inhibitor (TCI) • Any topical treatment for AD other than moisturizer and topical corticosteroid (TCS) (eg, Rx moisturizer)	Timeframe • 2 weeks • 2 weeks
Systemic treatments • Specific or non-specific desensitization therapy • Corticosteroids • Immunosuppressive/immunomodulatory drugs • Phototherapy • Biologic therapies • Vitamin D newly initiated or change in dose • Drugs with sedative effect such as benzodiazepines, sedating antihistamines, imidazopyridines, barbiturates or sedative anti-depressants (stable treatment with anti-histamines devoid of sedative effect was allowed) • Live vaccine • Non-live vaccine	Timeframe • 4 weeks • 4 weeks • 8 weeks or 5 half life • 4 weeks • 8 weeks or 5 half life • 2 weeks • 1 week • 4 weeks • 1 week

Definition of Inadequate Response to Topical Medications

1) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a daily regimen of a medium/high potency TCS for >4 weeks or maximum duration per PI

Or

2) Requirement of a long term treatment (>4 weeks) with a high potency TCS to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2)

AND

3) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) with TCI, when applicable

4) Subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) are also considered as inadequate responders to topical

treatments. Subjects will be considered as having inadequate response to topical treatments if they fulfill any of the three scenarios below or any combination of these three scenarios: 1 and 3, 2 and 3, 4

Safety Assessments

The following assessments were performed:

- Adverse Events (AEs) including Adverse Event of Special Interest (AESI) and selected AEs at all visits
- Physical examination and vital signs at all visits
- Clinical laboratory values at screening, baseline, weeks 4, 8, 12, 16, 20, 24 & 32 (follow-up)
- Electrocardiogram (ECG) at screening, baseline, weeks 1, 12 & 24
- Respiratory assessment at all visits in all subjects, and Peak Expiratory Flow (PEF) in subjects with a medical history of asthma

Adverse Events of Special Interest

The adverse events of special interest were defined as:

- Elevated ALT or AST (>3 ULN) in combination with elevated bilirubin >2 ULN, whether or not considered related to study drug by investigator
- Newly diagnosed asthma or worsening of asthma
- Elevated CPK (≥ 2.5 ULN) if considered to be related to study drug by investigator

Additional Assessments

Quality of life was assessed by the Dermatology Life Quality Index (DLQI; baseline, weeks 2, 12, and 24), the Hospital Anxiety and Depression Scale, number of missed work/school days, and EuroQoL 5-dimension at baseline and week 24.

Laboratory Assessments

The following standard laboratory tests were performed:

- Hematology: White blood cell count with differentials (including eosinophils), red blood cell count, hemoglobin, hematocrit, mean cell volume, and platelet count
- Blood chemistry: sodium, potassium, calcium, chloride, glucose, urea, creatinine, AST/ALT, alkaline phosphatase, total and direct bilirubin, CPK, high sensitivity C-reactive protein, fibrinogen, gamma-glutamyl transpeptidase, lactate dehydrogenase, total protein, albumin, uric acid, total cholesterol, low-density lipoprotein, high density lipoprotein, and triglycerides
- Urinalysis: blood proteins, leukocytes, glucose, ketones, nitrites, bilirubin, urobilinogen, pH, and specific gravity
- Pregnancy test: all women of childbearing potential had a serum pregnancy test at the screening visit and urine pregnancy tests at subsequent visits.
- Virology: HBsAg, HBsAb, hepatitis C, HIV-1 and -2 antibody
- Tuberculosis test

Table S2. Subject Disposition (ITT Population)

	Placebo (N=57)	Nemolizumab 10 mg (N=55)	Nemolizumab 30 mg (N=57)	Nemolizumab 90 mg (N=57)	Total (N=226)
Subjects randomized	57	55	57	57	226
Completed treatment*	40 (70.2%)	43 (78.2%)	50 (87.7%)	43 (75.4%)	176 (77.9%)
Temporarily discontinued treatment	0	1 (1.8%)	3 (5.3%)	1 (1.8%)	5 (2.2%)
Permanently discontinued treatment	14 (24.6%)	12 (21.8%)	6 (10.5%)	13 (22.8%)	45 (19.9%)
Reasons for discontinuation from study					
Adverse event	0	3 (5.5%)	2 (3.5%)	3 (5.3%)	8 (3.5%)
Lack of efficacy	2 (3.5%)	0	0	0	2 (0.9%)
Protocol violation	1 (1.8%)	0	0	0	1 (0.4%)
Withdrawal by subject	10 (17.5%)	7 (12.7%)	4 (7.0%)	8 (14.0%)	29 (12.8%)
Lost to follow up	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	4 (1.8%)

* Completed week 24 visit; There are 4 subjects (5469-002, 5604-002, 5850-004, 5850-005) who completed all injections but not the week 24 visit. These subjects were not counted as having completed treatment nor were they counted as having permanently discontinued study drug.

Additional Assessments

Body Surface Area

All three doses of nemolizumab reduced BSA significantly more than placebo (suppl Fig. 1). The mean percentage reduction from baseline in BSA for nemolizumab groups were clinically relevant at weeks 16 and 24, suggesting the quantity and quality of skin lesions improved compared over the study duration. However, there was also a high placebo response, which diluted the difference between active and placebo groups.

Suppl Fig 1. Mean percent change in body surface area at each visit (ITT population).

Table S3. Complete Listing of Study Investigators**Australia**

FREEMAN Michael	Benowa, Queensland
MURRELL Dedee	Kogarah, Sydney NSW
RUBEL Diana	PHILLIP ACT
SINCLAIR Rodney	East Melbourne VIC

Canada

ALAVI Afsaneh	Richmond Hill, ON
GOODERHAM Melinda	Peterborough, ON
LYNDE Charles	Markham, ON
METELITSA Andrei	Calgary, AB
PAPP Kim	Waterloo, ON
POULIN Yves	Ste-Foy, QC
ROBERN Michael	Ottawa, ON
SAPRA Sheetal	Oakville, ON
YANG William	Ottawa, ON

France

BOUAZIZ Jean-David	Paris
GROB Jean-Jacques	Marseille
LACOUR Jean-Philippe	Nice
PAUL Carle	Toulouse
SENECHAL Julien	Bordeaux
STAUMONT-SALLE Delphine	Lille

Germany

LEITZ Nicolas	Stuttgart
PAUSER Sylvia	Osnabrück
PINTER Andreas	Frankfurt
REICH Kristian	Hamburg
SCHAKEL Knut	Heidelberg
SCHWARZ Beate	Baden-Württemberg
SIMON Margrit	Berlin
STAUBACH -RENN Petra	Mainz
STICHERLING Michael	Erlangen
WEIRICH Oliver	Darmstadt
WERFEL Thomas	Hannover
WOLLENBERG Andreas	München
WORM Margitta	Berlin

Poland

AMBROZIAK Marcin	Warszawa
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BYSTRZANOWSKA Dorota	Warszawa
GEBSKA Edyta	Katowice
JUSZKIEWICZ-BOROWIEC Maria	Lublin
NARBUTT Joanna	Lodz
PULKA Grazyna	Krakow
SLOWINSKA Monika	Warszawa
SYGULA Ewa	Katowice
WEGLOWSKA Jolanta	Wrocław

US

ABRAMOVITS William	Dallas, TX
ALEXIS Andrew	New York, NY
ALLISON Dale	Waco, TX
ALPIZAR Sady	Tampa, FL
BROWNING John	San Antonio, TX
CALL Robert	Richmond, VA
DHAWAN Sunil	Fremont, CA
DIMITROPOULOS Vassilios	Darien, IL
FORMAN Seth	Tampa, FL
FRANKEL Ellen	Johnston, RI
GARCIA-SEPTIEN Ramon	Miami, FL
HOOPER Deirdre	New Orleans, LA
JOHNSON Sandra	Fort Smith, AR
LACQUER Vivian	Fountain Valley, CA
LUGO-SOMOLINOS Aida	Chapel Hill, NC
MCCUNE Mark	Overland Park, KS
PAULL William	Columbus, GA
PICKETT-BAISDEN Tina	Farmington Hills, MI
SADICK Neil	New York, NY
SHER Lawrence	Rolling Hills Estates, CA
SILVERBERG Jonathan*	Chicago, IL
SOONG Weily	Birmingham, AL
SOUNG Jennifer	Santa Ana, CA
STOLL David	Beverly Hills, CA
WEINBERG Jeffrey	Forest Hills, NY
WEISMAN Jamie	Sandy Springs, GA
YAMAUCHI Paul	Santa Monica, CA

*Coordinating Investigator