

ORIGINAL ARTICLE

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

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ABSTRACT

BACKGROUND

Interleukin-31 may play a role in the pathobiologic mechanism of atopic dermatitis and pruritus. We wanted to assess the efficacy and safety of nemolizumab (CIM331), a humanized antibody against interleukin-31 receptor A, in the treatment of atopic dermatitis.

METHODS

In this phase 2, randomized, double-blind, placebo-controlled, 12-week trial, we assigned adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments to receive subcutaneous nemolizumab (at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kilogram every 8 weeks. The primary end point was the percentage improvement from baseline in the score on the pruritus visual-analogue scale (on which a negative change indicates improvement) at week 12. Secondary end points included changes in the score on the Eczema Area and Severity Index (EASI, on which a negative change indicates improvement), and body-surface area of atopic dermatitis.

RESULTS

Of 264 patients who underwent randomization, 216 (82%) completed the study. At week 12, among the patients who received nemolizumab every 4 weeks, changes on the pruritus visual-analogue scale were –43.7% in the 0.1-mg group, –59.8% in the 0.5-mg group, and –63.1% in the 2.0-mg group, versus –20.9% in the placebo group ($P < 0.01$ for all comparisons). Changes on the EASI were –23.0%, –42.3%, and –40.9%, respectively, in the nemolizumab groups, versus –26.6% in the placebo group. Respective changes in body-surface area affected by atopic dermatitis were –7.5%, –20.0%, and –19.4% with nemolizumab, versus –15.7% with placebo. Among the patients receiving nemolizumab every 4 weeks, treatment discontinuations occurred in 9 of 53 patients (17%) in the 0.1-mg group, in 9 of 54 (17%) in the 0.5-mg group, and in 7 of 52 (13%) in the 2.0-mg group, versus in 9 of 53 (17%) in the placebo group.

CONCLUSIONS

In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A. The limited size and length of the trial preclude conclusions regarding adverse events. (Funded by Chugai Pharmaceutical; XCIMA ClinicalTrials.gov number, NCT01986933.)

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ATOPIC DERMATITIS IS A CHRONIC Pruritic, inflammatory skin disease that is triggered by an immune response to antigenic substances, irritants, and mechanical irritation and which is often associated with a personal or family history of type 1 allergies, allergic rhinitis, or asthma.¹⁻⁴ Pruritus often causes patients to persistently scratch their skin, leading to sleep disturbance and exacerbation of atopic dermatitis. Pruritus has a negative effect on the patients' quality of life, with the intensity of pruritus directly affecting psychosocial well-being.⁵⁻⁹ Some patients have pruritus even if other symptoms are well controlled, and although topical glucocorticoids and antihistamines are approved for the treatment of pruritus, their effects in atopic dermatitis are limited or associated with long-term side effects.^{10,11} Thus, among patients with atopic dermatitis, the primary therapeutic objective should be to relieve pruritus, improve dermatitis, and enhance quality of life. Treatments for atopic dermatitis, such as emollients, topical glucocorticoids, and calcineurin inhibitors,^{2,12,13} that have been approved by the Food and Drug Administration have limited efficacy among the patients with moderate-to-severe atopic dermatitis.^{2,14} Although oral antihistamines are frequently prescribed for atopic dermatitis, such drugs have little to no antipruritic effect.^{12,15} There is, therefore, considerable demand for effective treatment options with a good safety profile and improved characteristics for administration.

Interleukin-31 plays a role in the pathogenesis of atopic dermatitis and, more specifically, in the occurrence of pruritus.¹⁶⁻²¹ Nemolizumab (CIM331),²² a humanized monoclonal antibody against interleukin-31 receptor A, binds to interleukin-31 receptor A on a number of cells, including neurons, to inhibit interleukin-31 signaling, which may alleviate pruritus.²³ In a phase 1 clinical study, a single dose of nemolizumab, administered subcutaneously, suppressed pruritus, consequently improved sleep disturbance, and reduced concomitant use of topical glucocorticoids in adult patients with moderate-to-severe atopic dermatitis.²⁴ In Exploring CIM331 in Atopic Dermatitis (XCIMA), a phase 2, randomized, double-blind, placebo-controlled, multicenter, multiple-dose trial, we evaluated the efficacy, safety, and side-effect profile of nemolizumab over a period of 12 weeks in adults with moderate-to-severe atopic dermatitis.

METHODS

STUDY DESIGN AND OVERSIGHT

The trial was conducted from December 2013 through April 2015 in hospitals in the United States, Europe, and Japan in adults with moderate-to-severe atopic dermatitis. We screened patients during the period from 28 days to 8 days before randomization, which was followed by a run-in period for 7 days to perform baseline assessments. The double-blind, placebo-controlled treatment phase lasted for 12 weeks (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was conducted in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from the local ethics committee or institutional review board at each study center. All the patients provided written informed consent.

The trial was designed by the study sponsor, Chugai Pharmaceutical, with input from the first three and last authors; data were gathered and analyzed by Chugai Pharmaceutical. The first draft of the manuscript was prepared by the academic and industry authors, with professional medical writing and editorial assistance provided by Caudex Medical, funded by Chugai Pharmaceutical. The academic authors vouch for the completeness and accuracy of the data and data analyses and for the fidelity of the trial to the protocol, available at NEJM.org. Confidentiality agreements between the authors and Chugai Pharmaceutical regarding the data were established.

TRIAL PATIENTS

Patients between the ages of 18 and 65 years who had moderate-to-severe atopic dermatitis that was inadequately controlled by topical glucocorticoids or topical calcineurin inhibitors were included in the trial. To be eligible to participate, patients were required to have a score of at least 10 on the Eczema Area and Severity Index (EASI), which ranges from 0 to 72, with higher scores indicating worse disease severity; a score for pruritus of at least 50 mm on a visual-analogue scale, which ranges from 0 (no itch) to 100 mm (worst itch imaginable); and a score of at least 3 on the static Investigator's Global Assessment (sIGA), which ranges from 0 (clear) to 5 (very severe disease). Patients were excluded if they had active dermatologic diseases concomitant with atopic derma-

titis or if they had received systemic therapy for atopic dermatitis or ultraviolet radiation therapy within 4 weeks before randomization, potent or very potent topical glucocorticoids or topical calcineurin inhibitors within 2 weeks before randomization, or mild or moderately potent topical glucocorticoids or antihistamines (topical or systemic) within 1 week before randomization.

Patients underwent randomization with the use of a centralized interactive voice or online response system to receive nemolizumab (four treatment groups) or placebo in a 1:1:1:1 ratio, with treatment assignments stratified according to geographic region. Patients received subcutaneous nemolizumab at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight or placebo every 4 weeks or nemolizumab at a dose of 2.0 mg per kilogram every 8 weeks with placebo given at week 4 in an analysis that was exploratory in nature. During the trial, patients were permitted to use emollients and localized treatments (e.g., eye-drops). Patients who had no improvement on the pruritus visual-analogue scale and eczematous skin manifestations, as judged by the investigator, were permitted to use a potent topical glucocorticoid as rescue therapy at or after week 4.

OUTCOME MEASURES

The primary efficacy end point was the percentage improvement between baseline and week 12 in the score on the pruritus visual-analogue scale,²⁵ which was recorded daily by patients who used an electronic reporting tool in a double-blind manner. (On this scale, negative change indicates improvement.) Primary efficacy analyses compared each of the nemolizumab groups with placebo, except for the exploratory analysis in the group that received 2.0 mg of nemolizumab per kilogram every 8 weeks. Secondary efficacy outcomes at week 12 and at each time point (weeks 1, 2, 3, 4, 6, 8, and 10) included improvement from baseline in the EASI score; in the score on Scoring Atopic Dermatitis (SCORAD), which ranges from 0 to 103, with higher scores indicating more severe disease; on the sIGA score; on the body-surface area affected by atopic dermatitis; on the pruritus verbal rating scale, which describes pruritus intensity from 0 (none) to 4 (very severe) daily; and on the sleep-disturbance visual-analogue scale, which ranges from 0 (no sleep disturbance) to 100 (inability to sleep at all) daily; the proportion of patients with 25%, 50%, and

75% improvement in scores on the pruritus visual-analogue scale, EASI, and SCORAD; and the proportion of patients with an improvement of at least 2 points on the sIGA and pruritus verbal rating scale. Patients used the electronic reporting tool to record their responses on the pruritus verbal rating scale and sleep-disturbance visual-analogue scale. The proportion of patients with changes in severity on the pruritus visual-analogue scale over time was also analyzed post hoc with the use of a bar chart.^{26,27} The EASI score is used to measure severity and extent of signs of atopic dermatitis.²⁸ SCORAD assesses the extent and severity of signs of atopic dermatitis through area and intensity assessment by the investigator and subjective symptoms reported by the patient.²⁹ The body-surface area that is affected by atopic dermatitis is assessed as part of SCORAD.

Exploratory efficacy outcomes included the patient-reported Dermatology Life Quality Index (which ranges from 0 to 30, with higher scores indicating a lower quality of life) at weeks 4, 8, and 12³⁰ and the daily measurement of sleep quality by means of actigraphy through week 4. (Actigraphy documents whole-body movement and is a validated motion-detection method for recording sleep measurements, including total sleep time, sleep efficiency [total sleeping time divided by the total time in bed], sleep onset latency, and waking after sleep onset.)^{31,32} We monitored adverse events and vital signs and performed physical examinations, respiratory assessments, and laboratory assessments through week 12 to evaluate the safety and side-effect profile of nemolizumab. We also measured anti-nemolizumab antibodies at baseline and at weeks 4, 8, and 12.

STATISTICAL ANALYSIS

We determined that a sample size of 43 patients per group would provide a power of 90% to detect a between-group difference of 25 percentage points in the change from baseline in the score on the pruritus visual-analogue scale, assuming a standard deviation of 35 for the change from baseline to week 12, using a two-sided t-test at the 0.05 significance level. On the basis of an expected dropout rate of 10%, a total of 50 patients per group underwent randomization. To account for multiplicity, we applied a hierarchical decision procedure with the sequence for the nemolizumab groups of 2.0 mg, 0.5 mg, and 0.1 mg per kilogram versus placebo every 4 weeks. For the

exploratory analysis of 2.0 mg of nemolizumab per kilogram every 8 weeks, the sample size was not determined on the basis of hypothesis testing but rather 50 patients were assigned, as in the other groups.

The intention-to-treat population included all the patients who received at least one dose of either nemolizumab or placebo. The per-protocol population, which excluded any patients with protocol violations and those who withdrew early from the trial, was a prespecified primary population for efficacy outcomes. A prespecified primary analysis was a pairwise comparison of each group that received nemolizumab every 4 weeks versus placebo at week 12 with the use of analysis of covariance. For the analysis specified in the protocol as the primary analysis, we excluded all the data that were measured during or after rescue therapy and imputed missing values using the last-observation-carried-forward method.

To provide more appropriate estimation of the effects of nemolizumab, we performed the intention-to-treat analyses and mixed-model repeated-measures analyses to estimate least-squares means for continuous end points and used a generalized linear mixed-model analysis with a logit link and binomial error for binary end points, results that are reported here. The model included fixed-effect terms for treatment, region (United States, Europe, and Japan), and week (categorical), baseline value, and treatment-by-week interaction. No imputation for missing data was applied. An unstructured covariance matrix was used to model the repeated-measures covariance. Mixed-model repeated-measures analysis was prespecified only for the primary end point.

Since a hierarchical decision procedure can be regarded as a closed testing procedure, there was no inflation of the alpha level owing to multiple comparisons, and the global two-sided alpha level of 0.05 was maintained. No formal statistical comparisons for the secondary outcome measures were planned or conducted. All the statistical analyses were performed with the use of SAS software, version 9.2 TS2M3.

RESULTS

PATIENTS

Of the 264 patients who underwent randomization, 216 (82%) completed the 12-week study. Treatment discontinuations occurred in 9 of 53

patients (17%) in the 0.1-mg group, in 9 of 54 (17%) in the 0.5-mg group, and in 7 of 52 (13%) in the 2.0-mg group, versus in 9 of 53 (17%) in the placebo group. Adverse events were cited by 14 patients as the reason for withdrawal (Fig. S2 in the Supplementary Appendix). The per-protocol population included 229 patients. Reasons for exclusion from the per-protocol population included withdrawal from the trial before the evaluation of the pruritus visual-analogue scale at week 8, single-dose administration of either nemolizumab or placebo, or an inability to meet the inclusion criteria. The demographic and baseline characteristics across the nemolizumab and placebo groups were similar; the baseline scores on the pruritus visual-analogue scale represented intense itch, and sIGA scores, body-surface area affected by atopic dermatitis, and EASI scores reflected moderate-to-severe disease status (Table 1, and Table S1 in the Supplementary Appendix).

EFFICACY

At 12 weeks, among the patients who had received nemolizumab every 4 weeks, there was a significant, dose-dependent reduction in the least-squares mean percentage change from baseline in scores on the pruritus visual-analogue scale, as compared with placebo. The percentage reductions were -43.7% (95% confidence interval [CI], -53.4 to -34.0) with 0.1 mg of nemolizumab per kilogram ($P=0.002$), -59.8% (95% CI, -69.4 to -50.3) with 0.5 mg per kilogram ($P<0.001$), and -63.1% (95% CI, -72.9 to -53.3) with 2.0 mg per kilogram ($P<0.001$), as compared with -20.9% (95% CI, -31.4 to -10.5) with placebo (Fig. 1A). (An alternative approach to handling missing data in a prespecified primary analysis is shown in Fig. S3 in the Supplementary Appendix.) Weekly changes in the score on the pruritus visual-analogue scale are shown in Figure 1B, and daily changes during the first week in Figure S4 in the Supplementary Appendix.

At 12 weeks, among the patients who received nemolizumab every 4 weeks, the least-squares mean (\pm SE) percentage changes from baseline in the score on the pruritus verbal rating scale were $-36.8\pm 4.6\%$ with 0.1 mg per kilogram, $-50.9\pm 4.6\%$ with 0.5 mg per kilogram, and $-57.6\pm 4.6\%$ with 2.0 mg per kilogram, as compared with $-16.2\pm 5.0\%$ with placebo. The least-squares mean percentage changes in the EASI score were $-23.0\pm 7.5\%$ with

Table 1. Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo (N=53)	Nemolizumab			
		0.1 mg/kg (N=53)	0.5 mg/kg (N=54)	2.0 mg/kg (N=52)	2.0 mg/kg Every 8 Wk (N=52)
Male sex — no. (%)	25 (47)	28 (53)	22 (41)	31 (60)	29 (56)
Age — yr	37.0±13.1	33.5±10.3	33.7±11.7	34.4±11.9	35.8±13.6
Region — no. (%)					
United States	12 (23)	12 (23)	12 (22)	11 (21)	12 (23)
Europe	25 (47)	25 (47)	26 (48)	25 (48)	25 (48)
Japan	16 (30)	16 (30)	16 (30)	16 (31)	15 (29)
Weight — kg	74.1±22.2	73.9±22.1	72.3±19.4	71.6±15.9	71.9±19.7
Body-mass index†	26.2±7.0	25.4±6.3	25.6±6.4	24.8±5.1	25.4±6.2
Score on pruritus visual-analogue scale — mm‡	75.1±11.9	75.2±12.0	75.8±12.7	76.2±11.4	78.0±11.8
EASI score§	29.0±14.0	32.4±16.1	28.6±15.0	28.2±12.3	29.0±14.9
Body-surface area affected — %	44.8±26.2	55.9±27.1	45.5±25.2	48.8±25.0	45.8±26.3
Score on static Investigator's Global Assessment — no. (%)¶					
3	27 (51)	22 (42)	24 (44)	24 (46)	25 (48)
4	22 (42)	18 (34)	25 (46)	25 (48)	22 (42)
5	4 (8)	13 (25)	5 (9)	3 (6)	5 (10)
Dermatology Life Quality Index	15.6±6.1	15.5±6.2	14.5±6.4	15.7±5.9	16.2±7.5
Sleep measurements**					
Sleep onset latency — min	34.1±35.9	40.8±40.9	35.9±46.8	44.5±44.7	36.7±33.0
Total sleep time — min	330.2±89.0	312.4±80.0	327.2±98.0	323.0±100.2	322.2±77.6
Sleep efficiency — %	71.4±14.3	67.3±13.7	70.0±17.2	68.1±15.5	69.7±15.0
Waking after sleep onset — min	78.8±37.8	86.1±44.9	77.7±44.2	78.7±35.6	78.3±39.2

* Plus-minus values are means ±SD. Nemolizumab or placebo was administered once every 4 weeks, unless otherwise indicated. There were no significant differences between the groups. Percentages may not total 100 because of rounding.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the pruritus visual-analogue scale range from 0 (no itch) to 100 (worst imaginable itch).

§ Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating worse disease severity.

¶ Scores on the static Investigator's Global Assessment range from 0 (clear) to 5 (very severe disease).

|| Scores on the Dermatology Life Quality Index range from 0 to 30, with higher scores indicating a lower quality of life.

** Sleep measurements were recorded by means of actigraphy, which documents whole-body movement and is a validated motion-detection method for recording sleep measurements, including total sleep time, sleep efficiency (total sleeping time divided by the total time in bed), sleep onset latency, and waking after sleep onset.

0.1 mg per kilogram, $-42.3\pm 7.3\%$ with 0.5 mg per kilogram, and $-40.9\pm 7.5\%$ with 2.0 mg per kilogram, as compared with $-26.6\pm 8.1\%$ with placebo (Table 2, which excludes data after rescue therapy, and Table S2 in the Supplementary Appendix, which includes data after rescue therapy). The proportion of patients in each group who had a reduction of 25%, 50%, and 75% in the score on the pruritus visual-analogue scale, EASI, and

SCORAD and an improvement of at least 2 points on the sIGA at week 12 are shown in Tables S2 and S3 in the Supplementary Appendix. At week 12, the least-squares mean percentage changes in the body-surface area affected by atopic dermatitis were $-7.5\pm 9.7\%$ with 0.1 mg of nemolizumab per kilogram, $-20.0\pm 9.6\%$ with 0.5 mg per kilogram, and $-19.4\pm 9.7\%$ with 2.0 mg per kilogram, as compared with $-15.7\pm 10.5\%$ with placebo.

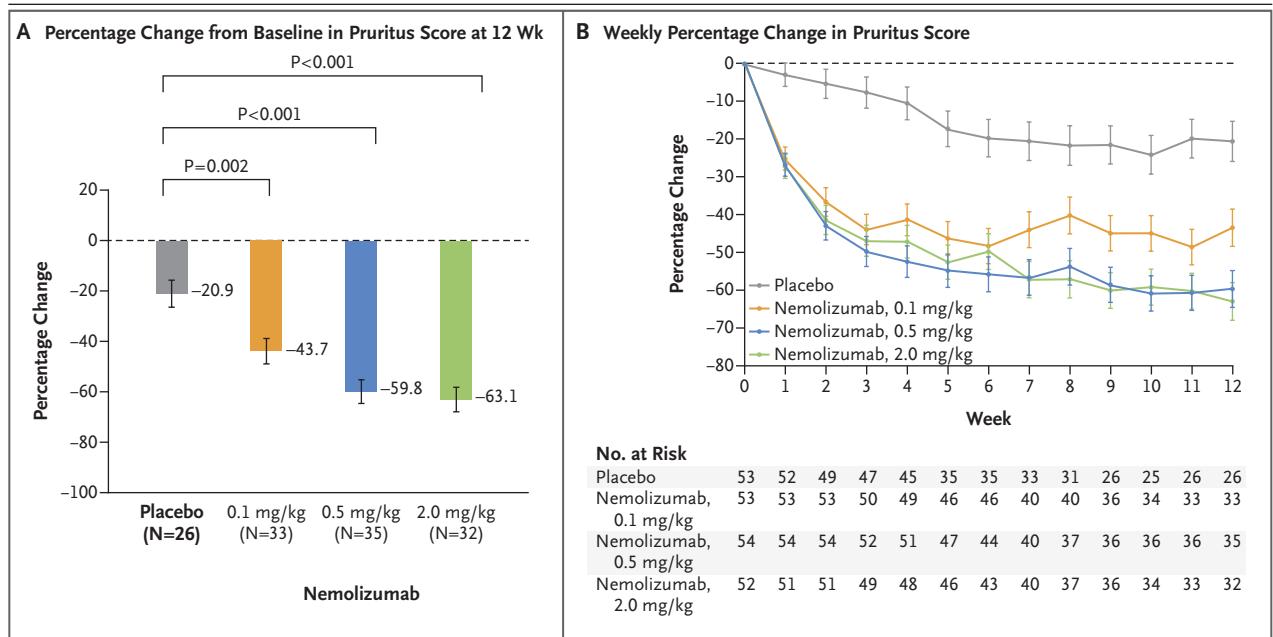


Figure 1. Percentage Change from Baseline in Pruritus Scores.

Shown is the least-squares mean percentage change from baseline in the score on the pruritus visual-analogue scale among patients with atopic dermatitis who were assigned to receive subcutaneous nemolizumab at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight or placebo every 4 weeks. Panel A shows the percentage change at 12 weeks in the intention-to-treat population (the primary end point), and Panel B shows the weekly percentage change during the study period. Data for patients who received rescue therapy for symptoms were excluded from these analyses. The I bars represent standard errors.

The least-squares mean percentage changes from baseline in improvements in sleep disturbance on the visual-analogue scale at week 12 were $-52.3 \pm 5.8\%$ with 0.1 mg of nemolizumab per kilogram, $-59.1 \pm 5.8\%$ with 0.5 mg per kilogram, and $-62.6 \pm 5.9\%$ with 2.0 mg per kilogram, as compared with $-31.9 \pm 6.3\%$ with placebo. Findings for exploratory end points including other sleep measures and scores on the Dermatology Life Quality Index are shown in Figures S5, S6, and S7 in the Supplementary Appendix.

SAFETY AND SIDE-EFFECT PROFILE

A total of 187 patients had at least one adverse event, with a similar number of adverse events in the placebo group and in each of the nemolizumab groups (Table 3). Among the patients who received nemolizumab every 4 weeks, serious adverse events occurred in 1 patient in the 0.1-mg group, no patients in the 0.5-mg group, and 3 patients in the 2.0-mg group, as compared with 1 patient in the placebo group; such events were reported in 2 patients in the exploratory group that received 2.0 mg of nemolizumab per kilogram every 8 weeks (Ta-

ble 3, and Table S4 in the Supplementary Appendix). Of the serious adverse events, three were an exacerbation of atopic dermatitis.

Discontinuations because of adverse events occurred in 5 patients in the 0.1-mg group, 3 patients in the 0.5-mg group, and 4 patients in the 2.0-mg group, as compared with 1 patient in the placebo group; 3 patients in the exploratory group that received 2.0 mg of nemolizumab per kilogram every 8 weeks discontinued treatment owing to adverse events. Ten patients who discontinued treatment had adverse events related to atopic dermatitis (e.g., exacerbation of atopic dermatitis or dermatitis exfoliativa) (Table 3, and Table S5 in the Supplementary Appendix).

Exacerbation of atopic dermatitis, nasopharyngitis, upper respiratory tract infection, peripheral edema, and increased creatine kinase levels were the most common adverse events in this study. Exacerbation of atopic dermatitis and peripheral edema were more common in the nemolizumab groups than in the placebo group. Increased levels of creatine kinase were observed in more than 5% of the patients in some groups, with no sig-

Table 2. Changes from Baseline in Secondary Outcome Measures at 12 Weeks.*

Outcome Measure	Placebo (N=53)	Nemolizumab		
		0.1 mg/kg (N=53)	0.5 mg/kg (N=54)	2.0 mg/kg (N=52)
Change in score on pruritus visual-analogue scale				
No. of patients	26	33	35	32
Percent change	-20.9±5.3	-43.7±4.9	-59.8±4.8	-63.1±5.0
Change in EASI score				
No. of patients	26	33	35	32
Percent change	-26.6±8.1	-23.0±7.5	-42.3±7.3	-40.9±7.5
Change in SCORAD score†				
No. of patients	23	27	30	27
Percent change	-18.5±5.2	-27.5±4.9	-37.7±4.8	-39.8±4.9
Improvement of ≥2 points in score on static Investigator's Global Assessment				
No. of patients	26	33	35	32
Patients with improvement — %	11	14	38	25
Change in body-surface area affected by atopic dermatitis				
No. of patients	26	33	35	32
Percent change	-15.7±10.5	-7.5±9.7	-20.0±9.6	-19.4±9.7
Change in sleep-disturbance score on visual-analogue scale‡				
No. of patients	26	33	34	32
Percent change	-31.9±6.3	-52.3±5.8	-59.1±5.8	-62.6±5.9

* Plus–minus values are means ±SE. Nemolizumab or placebo was administered once every 4 weeks in each group.

† Scores on Scoring Atopic Dermatitis (SCORAD) range from 0 to 103, with higher scores indicating greater disease severity. SCORAD assesses the extent and severity of signs of atopic dermatitis through area and intensity assessment by the investigator and subjective symptoms reported by the patient.

‡ Sleep-disturbance scores on the visual-analogue scale range from 0 to 100 mm, with higher scores indicating greater sleep disturbance.

nificant differences observed between the nemolizumab groups and the placebo group. Antibodies against nemolizumab were detected in 3 patients after nemolizumab administration, and all antibodies were confirmed to be non-neutralizing.

DISCUSSION

In this phase 2 trial, we examined a treatment targeting interleukin-31 signaling for the treatment of atopic dermatitis. We found improvement in the primary outcome of pruritus for all the groups that received nemolizumab every 4 weeks, as compared with placebo, among patients with

moderate-to-severe atopic dermatitis. Although this trial has limitations, most notably the small number of patients and short duration, it provides evidence supporting the role of interleukin-31 in the pathobiologic mechanism of atopic dermatitis. Conclusions regarding adverse events cannot be made, given the small patient sample. Study limitations also include the dropout rate, with discontinuations being attributed mainly to exacerbations of atopic dermatitis. These exacerbations may have been caused by delayed rescue therapy because the patients did not meet the rescue criteria, as defined in the protocol, regarding the score on the pruritus visual-analogue scale

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N = 53)	Nemolizumab			
		0.1 mg/kg (N = 53)	0.5 mg/kg (N = 54)	2.0 mg/kg (N = 52)	2.0 mg/kg Every 8 Wk (N = 52)
Total no. of adverse events	105	110	80	99	90
Patients with ≥ 1 adverse event — no. (%)	36 (68)	38 (72)	36 (67)	40 (77)	37 (71)
Patients with ≥ 1 serious adverse event — no. (%)	1 (2)	1 (2)	0	3 (6)	2 (4)
Related to atopic dermatitis	0	0	0	2 (4)	1 (2)
Not related to atopic dermatitis	1 (2)	1 (2)	0	1 (2)	1 (2)
Patients with adverse event leading to withdrawal from treatment — no. (%)	1 (2)	5 (9)	3 (6)	4 (8)	3 (6)
Related to atopic dermatitis	0	2 (4)	3 (6)	2 (4)	3 (6)
Not related to atopic dermatitis	1 (2)	3 (6)	0	2 (4)	0
Exacerbation of atopic dermatitis — no. (%)†	7 (13)	11 (21)	10 (19)	11 (21)	9 (17)
Nasopharyngitis — no. (%)†	8 (15)	9 (17)	6 (11)	5 (10)	7 (13)
Upper respiratory tract infection — no. (%)†	6 (11)	4 (8)	1 (2)	4 (8)	5 (10)
Peripheral edema — no. (%)†	0	2 (4)	3 (6)	5 (10)	2 (4)
Elevation in blood creatine kinase — no. (%)†	3 (6)	2 (4)	2 (4)	4 (8)	3 (6)

* Nemolizumab or placebo was administered once every 4 weeks, unless otherwise indicated.

† This adverse event was reported in at least 5% of the patients who received nemolizumab.

(50 mm or more), despite active dermatitis. The proportion of patients who received rescue therapy was 26.4% in the group receiving 0.1 mg of nemolizumab per kilogram, 27.8% in the 0.5-mg group, and 26.9% in the 2.0-mg group, as compared with 39.6% in the placebo group; in the exploratory group that received 2.0 mg of nemolizumab per kilogram every 8 weeks, the proportion was 28.8%.

The incidence and types of adverse events that were associated with nemolizumab were similar to those in the placebo group with the exception of exacerbations in atopic dermatitis and peripheral edema, which were more common among the patients receiving nemolizumab.

Atopic dermatitis is initially associated with a selective expansion of type 2 helper T (Th2) cells, and skin lesions are associated with the activation of Th2, Th22, and Th17 cytokines.³³ In chronic atopic dermatitis, an intensification of Th2 and Th22 activation occurs with the appearance of a

Th1 component.³⁴ The detailed mechanisms underlying dermatitis and pruritus are complex and not fully understood, but there is evidence that interleukin-31 may play a role in the development of pruritus. Several studies have shown that dorsal-root ganglion neurons express interleukin-31 receptor A,^{17,18,35} and interleukin-31 stimulation evokes Ca²⁺ influx in dorsal-root ganglion neurons,¹⁷ findings that strongly indicate a direct effect of interleukin-31 in the induction of itch. However, in a recent study, interleukin-31 did not induce immediate itch in patients with atopic dermatitis and in healthy controls after skin challenge.³⁶ Interleukin-31 may contribute to the pathogenesis of atopic dermatitis by various mechanisms other than, or in addition to, pruritus induction — for example, by effects on the physical and antimicrobial skin barrier³⁷ or by promoting the growth of sensory nerves.³⁸ We can assume that in addition to the direct inhibition of interleukin-31 activity, some indirect inhibition may

be involved in the mode of action of nemolizumab,²² but further research on the function of interleukin-31 is needed. Pruritus has been shown to aggravate atopic dermatitis and have a negative effect on patients' quality of life,⁵ including loss of sleep, depression, aggressiveness, body disfigurement, and suicidal thoughts.³⁹⁻⁴¹ In our trial, we used actigraphy to objectively monitor sleep quality and also assessed patients' quality of life. However, we can make no inferences from the results, since the analyses were exploratory, with no formal testing planned (Figs. S5, S6, and S7 in the Supplementary Appendix).

The trial was not designed to formally compare responses between the various dose groups, but the largest reduction in the primary outcome (the least-squares mean percentage change from baseline in the score on the pruritus visual-analogue scale at 12 weeks) occurred in the group receiving 0.5 mg of nemolizumab per kilogram every 4 weeks, the dose that appeared to present the best benefit-risk profile. The apparent lack of incremental benefit of the higher dose is puzzling, since we might expect, at the very least, a faster onset of action. In exploratory exposure-response analyses, the percentage change from baseline in the score on the pruritus visual-analogue scale tended to be stable when the serum level of nemolizumab was more than 2.6 μg per milliliter, which corresponded to the mean dose achieved with 0.5 mg per kilogram. However, there was large variability among the patients (Fig. S8 in the Supplementary Appendix).

In conclusion, we found that the monthly administration of nemolizumab reduced pruritus in patients with moderate-to-severe atopic dermatitis. The results of this phase 2 trial support future studies of the role of interleukin-31 and its inhibition for the control of pruritus.

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