ORIGINAL ARTICLE

Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus

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ABSTRACT

BACKGROUND

Nemolizumab is a subcutaneously administered humanized monoclonal antibody against interleukin-31 receptor A, which is involved in pruritus and inflammation in atopic dermatitis. In phase 2 studies, nemolizumab lessened the severity of atopic dermatitis.

METHODS

In a 16-week, double-blind, phase 3 trial, we randomly assigned Japanese patients with atopic dermatitis and moderate-to-severe pruritus and an inadequate response to topical agents in a 2:1 ratio to receive subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents. The primary end point was the mean percent change in the visual-analogue scale (VAS) score for pruritus (range, 0 to 100, with higher scores indicating worse pruritus) from baseline to week 16. Secondary end points included the time course of change in the VAS score for pruritus up to week 4, the change in the Eczema Area and Severity Index (EASI) score (range, 0 to 72, with higher scores indicating greater severity), a score of 4 or less on the Dermatology Life Quality Index (DLQI; range, 0 to 30, with higher scores indicating a greater effect on daily life), a score of 7 or less on the Insomnia Severity Index (ISI; range, 0 to 28, with higher scores indicating greater severity), and safety.

RESULTS

A total of 143 patients were randomly assigned to receive nemolizumab and 72 to receive placebo. The median VAS score for pruritus at baseline was 75. At week 16, the mean percent change in the VAS score was −42.8% in the nemolizumab group and −21.4% in the placebo group (difference, −21.5 percentage points; 95% confidence interval, −30.2 to −12.7; P<0.001). The mean percent change in the EASI score was −45.9% with nemolizumab and −33.2% with placebo. The percentage of patients with a DLQI score of 4 or less was 40% in the nemolizumab group and 22% in the placebo group; the percentage of patients with an ISI score of 7 or less was 55% and 21%, respectively. The incidence of injection-related reactions was 8% with nemolizumab and 3% with placebo.

CONCLUSIONS

In this 16-week trial, the use of subcutaneous nemolizumab in addition to topical agents for atopic dermatitis resulted in a greater reduction in pruritus than placebo plus topical agents. The incidence of injection-site reactions was greater with nemolizumab than with placebo. Longer and larger trials are necessary to determine whether nemolizumab has a durable effect and is safe for atopic dermatitis. (Funded by Maruho; JapicCTI number, 173740.)

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A Quick Take is available at NEJM.org

The inflammatory skin condition atopic dermatitis is a chronic, relapsing disease characterized by epidermal-barrier disruption, T-cell activation, and imbalance of the skin microbiome.[1,2] The pathogenesis of atopic dermatitis is primarily driven by type 2 helper T (Th2) lymphocytes, with considerable contributions from Th17 and Th22 cells, which release cytokines, resulting in elevated IgE production and skin inflammation.[3,4] One characteristic symptom of atopic dermatitis is pruritus, which diminishes quality of life.[5-7] Scratching that is associated with pruritus may induce mechanical damage to skin, which may in turn enhance inflammatory reactions and worsen pruritus (itch–scratch cycle).[8,9] Pruritus is also associated with poor sleep quality.[10]

Treatment guidelines for atopic dermatitis include topical glucocorticoids or topical calcineurin inhibitors to reduce inflammation.[5,11-14] Japanese guidelines also recommend the adjunctive use of oral antihistamines to reduce pruritus,[14] although a systematic review has suggested that the antipruritic effect of antihistamines is limited in patients with atopic dermatitis.[15]

Nemolizumab is a humanized monoclonal antibody against interleukin-31 receptor A that is administered subcutaneously.[16,17] Interleukin-31 plays a role in pruritus[18,19] and affects inflammatory response and epidermal-barrier disruption in atopic dermatitis.[19,20] In early-phase clinical studies involving adults with moderate-to-severe atopic dermatitis, nemolizumab showed efficacy in reducing pruritus and skin signs.[17,21-23]

Because patients with atopic dermatitis are likely to already be receiving therapy to control inflammation and pruritus, clinical trials that evaluate new therapies could include coadministration with topical agents or oral antihistamines. In this phase 3 trial, we evaluated nemolizumab, administered concomitantly with topical agents, in Japanese patients with atopic dermatitis and inadequately controlled moderate-to-severe pruritus.

Methods

Trial Design and Oversight

This was a phase 3, 16-week, randomized, double-blind, parallel-group, multicenter, Japanese trial initiated on October 23, 2017 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); data analysis occurred in February 2019. After completion of the initial trial, eligible patients could enter a 52-week, open-label, long-term follow-up trial.

This trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and all other applicable regulatory requirements. Trial documentation was approved by the institutional review board at each participating center. Patients (or their legal guardians) provided written informed consent before the first dose of nemolizumab or placebo.

The trial protocol was developed by the sponsor, Maruho, with input from the first and last authors. Maruho paid for professional writing assistance and electronic patient diaries and analyzed the trial data. Nemolizumab and placebo were provided by the product manufacturer, Chugai Pharmaceutical. All the authors had access to all trial data and participated in the analysis of the data. All the authors have confidentiality agreements with the sponsor regarding proprietary information. The sponsor and all the authors vouch for the completeness and accuracy of the data, the complete reporting of adverse events, and the fidelity of the trial to the protocol (available at NEJM.org).

Patients

Inclusion criteria were an age of 13 years or older at the date of informed consent; a body weight of 30.0 to 120.0 kg; a confirmed diagnosis of atopic dermatitis as determined by investigators according to the criteria of Hanifin and Rajka,[24] with pruritus; inadequate pruritic response (score of ≥3 on a five-level itch scale; range, 0 to 4, with higher scores indicating worse itching[25]) to medium-potency[11,26] topical glucocorticoids or to topical calcineurin inhibitors administered at a stable dose for at least 4 weeks and to oral antihistamines administered at a stable dose for at least 2 weeks (or an inability to receive such therapies); a visual-analogue scale (VAS) score for pruritus of 50 or more on the day of randomization (range, 0 to 100, with higher scores indicating worse pruritus)[27]; and an Eczema Area and Severity Index (EASI) score of 10 or more on the day of randomization (range, 0 to 72, with higher scores indicating greater severity).[28] Exclusion criteria were any abnormal laboratory values or conditions that could confound the outcome of the trial or en-

danger the patient (for details, see the Supplementary Appendix).

TRIAL INTERVENTIONS

After a 28-day screening period, patients were randomly assigned in a 2:1 ratio through an interactive Web-response system to receive nemolizumab (60 mg) or placebo. Placebo was formulated to be identical to nemolizumab but without the active product. On the date of randomization and every 4 weeks thereafter to 16 weeks, nemolizumab or placebo was injected subcutaneously, by the investigating physician or by a nurse under the instruction of the investigator, into the abdomen of each patient, in a skin area unaffected by atopic dermatitis.

Concomitant stable atopic dermatitis medications (medium-potency topical glucocorticoids, topical calcineurin inhibitors, and oral antihistamines) remained unchanged during the use of nemolizumab or placebo. Concomitant use of lower-potency topical glucocorticoids[11,26] and moisturizing or protecting agents for atopic dermatitis–associated eczema was allowed. Prohibited concomitant therapies included antibody drugs (excluding nemolizumab), phototherapy and hyposensitization therapies, and systemic treatments. Higher-potency topical glucocorticoids were allowed as rescue therapy (at the investigator's discretion) when worsening atopic dermatitis–associated eczema was noted (details are available in the protocol).

TRIAL END POINTS

The primary efficacy end point was the percent change in the weekly mean VAS score for pruritus from baseline to week 16, with the percent change equivalent to the absolute point change on the 0-to-100 scale when the baseline score is 100. Scores were evaluated by patients daily and recorded in an electronic diary provided by the sponsor; weekly mean scores were calculated by averaging daily scores.

Secondary efficacy end points were the time course of percent change in the daily VAS score for pruritus up to week 4, the percent change in the EASI score from baseline to week 16, the percentage of patients with a score of 4 or less on the total Dermatology Life Quality Index (DLQI; range, 0 to 30, with higher scores indicating a greater effect on daily life),[29] the percentage of patients with a decrease of 4 or more points from baseline in the total DLQI score (considered to be the minimal clinically important difference),[30] and the percentage of patients with a score of 7 or less on the Insomnia Severity Index (ISI; range, 0 to 28, with higher scores indicating greater severity).[31]

Exploratory efficacy end points were the change over time in the pruritus VAS score, itch score, EASI score, DLQI score, ISI score, modified EASI score,[32] score on the pruritus numerical rating scale (NRS; range, 0 to 10, with higher scores indicating worse pruritus),[33] score on the Patient-Oriented Eczema Measure (POEM; range, 0 to 28, with higher scores indicating greater severity),[34] static investigator's global assessment (sIGA) score (range, 0 to 5, with higher scores indicating greater severity of atopic dermatitis),[35] and score on the Work Productivity and Activity Impairment: Atopic Dermatitis questionnaire[36]; the mean percent change in the modified EASI score from baseline to week 16; and the percentage of patients with the following: a 50%, 75%, or 90% decrease in the pruritus VAS score, an itch score of 1 or less, a decrease of 4 or more points from baseline in the pruritus NRS score, a 50%, 75%, or 90% decrease in the EASI score, a decrease of 2 or more levels in the sIGA score (i.e., final score of ≤1), and a decrease of 4 or more points from baseline in the POEM total score (the minimal clinically important difference[37]). Patients used the electronic diary to input pruritus VAS scores, pruritus NRS scores, and itch scores by evaluating their mean pruritus severity in the previous 24 hours according to the range of the relevant scales. The mean daily quantity of topical agents used during the trial period was calculated. A post hoc efficacy analysis was performed to calculate the percentage of patients with a decrease of 6 points or more from baseline in the total ISI score.

During the 16-week trial period, safety end points (including adverse events that emerged during treatment) were evaluated, with severity assessed by the investigator, according to prespecified protocol definitions. In the safety assessment, worsening of atopic dermatitis could be reported as a protocol-defined adverse event.

STATISTICAL ANALYSIS

The required sample was calculated to be 204 (136 in the nemolizumab group and 68 in the placebo group) with the use of the POWER pro-

cedure in SAS software (t-test). This sample would provide 90% power to detect a difference (nemolizumab minus placebo) of –17 percentage points in the percent change from baseline in the pruritus VAS score, at a significance level of 5% (two-sided alpha level), under the assumption that the standard deviation in both trial groups was 35%.

Modified intention-to-treat methods were used for the analyses of the primary and secondary end points and included all randomly assigned patients who received at least one dose of nemolizumab or placebo and had data available for evaluation. The safety analysis set included all randomly assigned patients who received at least one dose of nemolizumab or placebo. All statistical analyses were performed with the use of SAS software, version 9.3 or higher (SAS Institute).

The analysis of the primary efficacy end point used a mixed-effects model for repeated measures (MMRM) that included data from weeks 1, 2, 4, 8, 12, and 16 to calculate the weekly mean VAS score for pruritus. For the secondary efficacy end points, no adjustments were made for multiple comparisons, and these are presented as point estimates with unadjusted confidence intervals, from which no clinical inferences can be made. Two prespecified sensitivity analyses were performed for the primary end point to account for missing data and the use of rescue medication: a tipping-point analysis that used the multiple-imputation method and an MMRM analysis that used all observed data regardless of the use of rescue medication.

For continuous end points, MMRM analysis, analysis of covariance, and intention-to treat analysis were applied. Binary end points were evaluated according to the between-group difference in the percentage of patients who met the

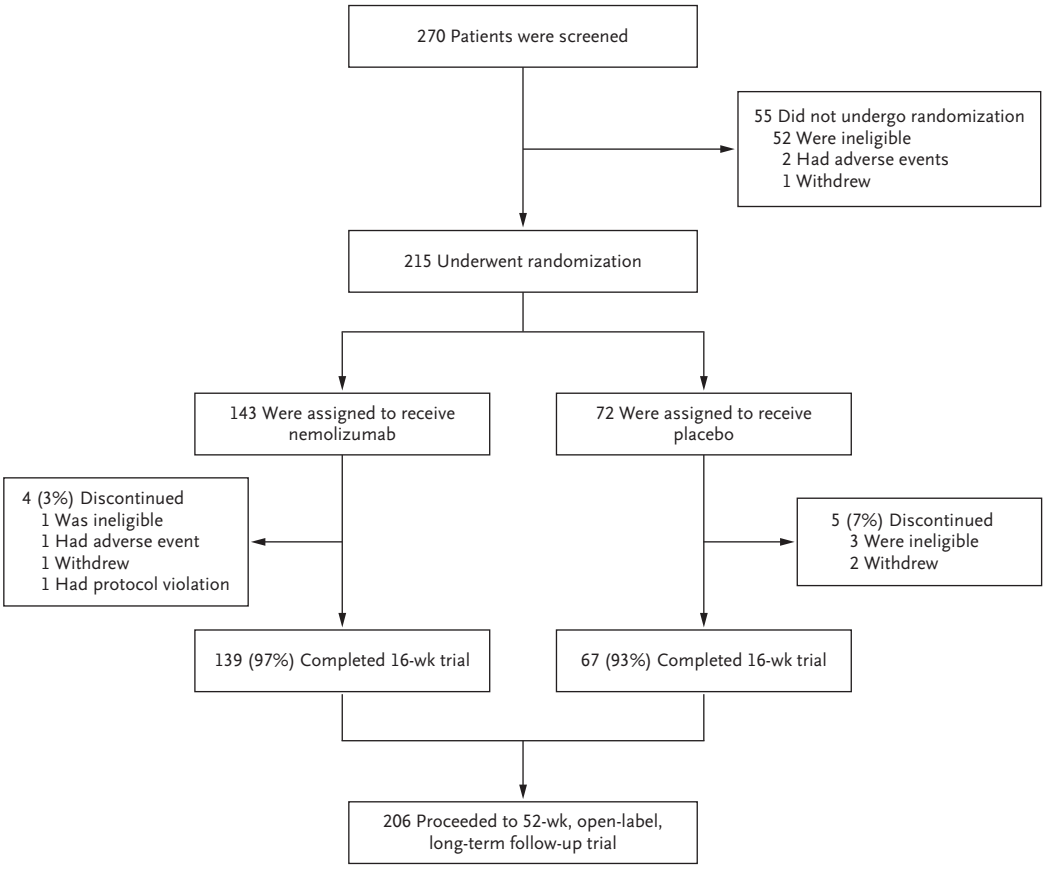

Figure 1. Screening, Randomization, and Follow-up.

end-point threshold. Missing data were not imputed for the continuous end points but were imputed as nonresponse for binary end points; the time course of the percent change in the daily VAS score for pruritus up to week 4 was analyzed with the use of last-observation-carried-forward analysis of covariance to derive estimates of least-squares mean. For evaluations of pruritus (VAS, NRS, and itch scores), data for patients who received rescue therapy owing to

Table 1. Baseline Demographic and Clinical Characteristics (Modified Intention-to-Treat Population).*

Characteristic	Nemolizumab (N=143)	Placebo (N=72)
Male sex — no. (%)	93 (65)	48 (67)
Median age (range) — yr	39.0 (13–73)	40.5 (13–80)
Median duration of disease (range) — yr	30.3 (1.1–61.3)	28.9 (1.3–59.9)
Median VAS score for pruritus (range)†	75.7 (49.7–100.0)	75.1 (53.3–100.0)
Median score on five-level itch scale (range)‡	3.0 (2–4)	3.0 (2–4)
Median EASI score (range)§	24.2 (10–65)	22.7 (10–58)
sIGA score — no. (%)¶		
0–3	82 (57)	45 (62)
≥4	61 (43)	27 (38)
DLQI score‖		
No. of patients with available data	136	69
Median (range)	12.0 (2–26)	12.0 (2–30)
ISI score**		
No. of patients with available data	142	72
Median (range)	12.0 (2–28)	12.0 (1–28)
POEM score††		
No. of patients with available data	142	72
Median (range)	22.0 (5–28)	20.5 (8–28)
Median no. of pruriginous lesions and papules (range)‡‡	8.0 (0–270)	11.0 (0–400)
Baseline treatment — no. (%)		
Topical therapy§§	143 (100)	72 (100)
Medium-potency topical glucocorticoid	139 (97)	70 (97)
Topical calcineurin inhibitor	59 (41)	29 (40)
Oral antihistamines§§	127 (89)	63 (88)
Nonsedating	126 (88)	61 (85)
Sedating	17 (12)	11 (15)

* Nemolizumab (60 mg) and placebo were administered every 4 weeks. All the patients in each group were Asian (100%).
† Scores on the visual-analogue scale (VAS) for pruritus range from 0 to 100, with higher scores indicating worse pruritus. The score for each patient was the average measurement during the previous 24 hours.
‡ Scores range from 0 to 4, with higher scores indicating worse itching.
§ Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating greater severity.
¶ Scores on the static investigator's global assessment (sIGA) range from 0 to 5, with higher scores indicating greater severity of atopic dermatitis.
‖ Scores on the Dermatology Life Quality Index (DLQI) range from 0 to 30, with higher scores indicating a greater effect on daily life.
** Scores on the Insomnia Severity Index (ISI) range from 0 to 28, with higher scores indicating greater severity.
†† Scores on the Patient-Oriented Eczema Measure (POEM) range from 0 to 28, with higher scores indicating greater severity.
‡‡ No patients with prurigo nodularis were enrolled. Pruriginous lesions and papules of 7 to 8 mm were assessed and counted by dermatology specialists and were confirmed to be symptomatic of atopic dermatitis.
§§ The use of multiple agents was allowed.

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Nemolizumab (N=143)	Placebo (N=72)	Difference (95% CI)
			percentage points
Primary end point: percent change in pruritus VAS score from baseline to wk 16	−42.8±2.6	−21.4±3.6	−21.5 (−30.2 to −12.7)†
Secondary end points‡			
Percent change in pruritus VAS score from baseline to day 29	−34.4±2.2	−15.3±3.0	−19.3 (−26.6 to −11.9)
Percent change in EASI score from baseline to wk 16	−45.9±3.3	−33.2±4.7	−12.6 (−24.0 to −1.3)
Percentage of patients with a DLQI score of ≤4 at wk 16 (no./total no.)§	40 (51/129)	22 (15/67)	17 (2 to 31)
Percentage of patients with a decrease of ≥4 points in the DLQI score from baseline to wk 16 (no./total no.)¶	67 (89/133)	50 (34/68)	17 (3 to 31)
Percentage of patients with an ISI score of ≤7 at wk 16 (no./total no.)‖	55 (59/108)	21 (12/56)	33 (17 to 48)

* Plus–minus values are least-squares means ±SE. Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of nemolizumab or placebo and who had data available for evaluation. For evaluations of pruritus VAS scores, data for patients who received rescue therapy owing to exacerbations of atopic dermatitis were handled as missing values. For other evaluations (of EASI, DLQI, and ISI scores), data after receipt of rescue therapy were included in the analysis. Because the pruritus VAS score was evaluated by patients daily, the weekly mean scores were used in the analysis. CI denotes confidence interval.

† P<0.001.

‡ For the secondary end points, there were no adjustments for multiple comparisons, and therefore no clinical inferences can be drawn from these data.

§ Analysis for this end point was performed only for patients with a DLQI score of 5 or more at baseline.

¶ Analysis for this end point was performed only for patients with a DLQI score of 4 or more at baseline. A change of 4 points is considered to be the minimal clinically important difference.

‖ Analysis for this end point was performed only for patients with an ISI score of 8 or more at baseline.

exacerbations of atopic dermatitis were handled as missing values. For other evaluations, data after receipt of rescue therapy were included in the analysis. The statistical analysis plan and its amendments are available with the protocol at NEJM.org.

RESULTS

PATIENTS

Overall, 215 patients were enrolled and randomly assigned in a 2:1 ratio to receive nemolizumab or placebo (143 to nemolizumab and 72 to placebo); all the patients received at least one dose of nemolizumab or placebo and were included in the modified intention-to-treat analysis and safety analysis (Fig. 1). The baseline characteristics of the patients were similar in the two groups (Table 1 and Table S1). The median baseline disease-severity scores in the entire cohort were 75.4 for the pruritus VAS score, 3.0 for the score on the five-level itch scale, and 23.2 for the EASI score. All the patients (100%) had previously received topical agents, and 88% had received oral antihistamines (Table 1). The number of patients lost to follow-up at week 16 was 3 in each group. The percentages of patients who used topical rescue medication at any point up to week 16 were 17% (25 of 143 patients) in the nemolizumab group and 18% (13 of 72 patients) in the placebo group.

EFFICACY

At week 16, the least-squares mean percent change from baseline in the pruritus VAS score (primary end point) was −42.8% in the nemolizumab group and −21.4% in the placebo group (Table 2). The least-squares mean difference between the two groups was −21.5 percentage points (95% confidence interval [CI], −30.2 to −12.7; P<0.001). The results of sensitivity analyses were similar to those of the primary analysis (data not shown).

With respect to secondary outcomes, from which no clinical conclusions can be drawn because of the lack of a plan for adjustment for multiple comparisons, the time course of the percent change in the pruritus VAS score from baseline to week 16 is shown in Figure 2A and Figure S2. The percent change in the daily VAS score for pruritus from baseline to week 4 is shown in

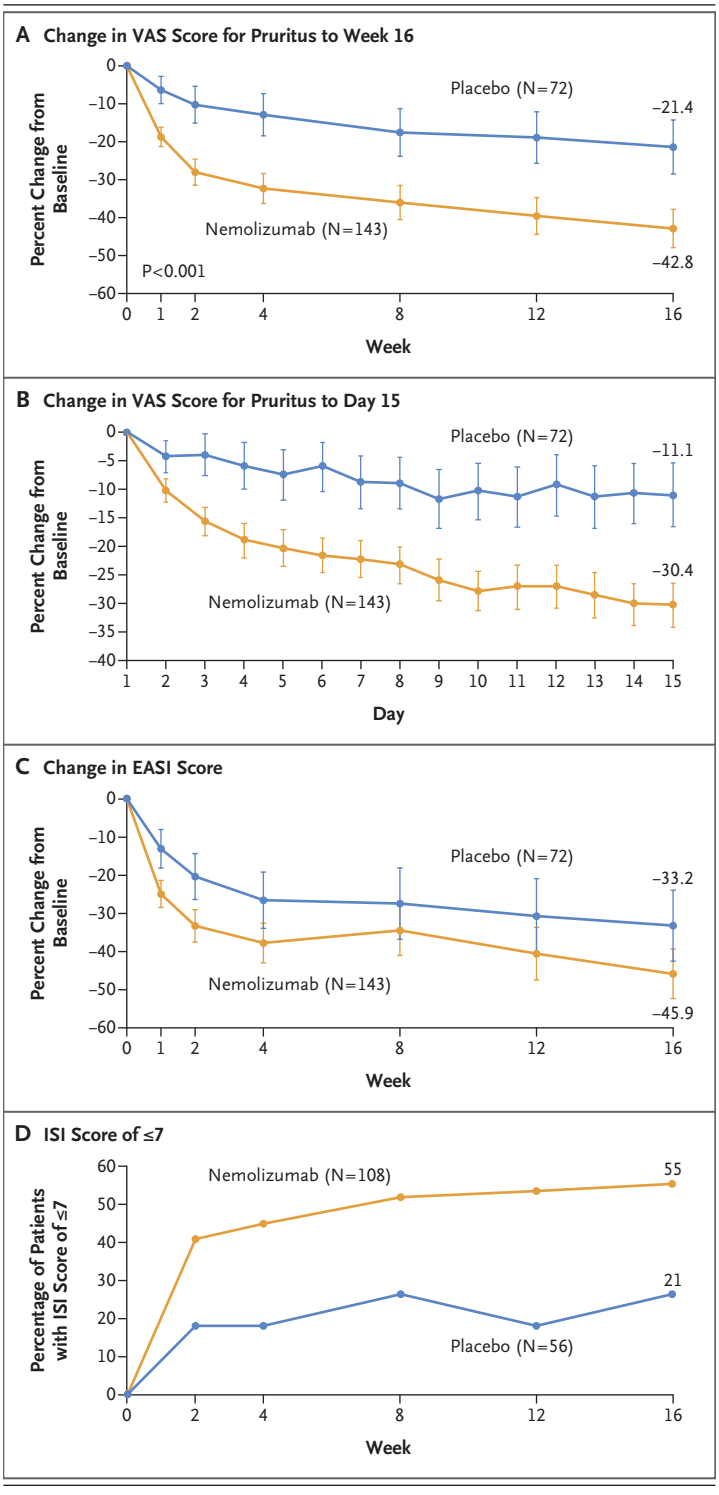

Figure 2. Efficacy Outcomes (Modified Intention-to-Treat Population).

Panel A shows the primary efficacy end point: the percent change in the weekly mean visual-analogue scale (VAS) score for pruritus (with higher scores indicating worse pruritus) from baseline to week 16. Panel B shows the percent change in the daily mean VAS score for pruritus from baseline to day 15; for the prespecified secondary end point of the percent change up to week 4, the least-squares mean difference between the nemolizumab group and the placebo group was −19.3 percentage points (95% confidence interval, −26.6 to −11.9). Panel C shows the percent change in the Eczema Area and Severity Index (EASI) score (with higher scores indicating greater severity) from baseline to week 16. In Panels A through C, data are shown as least-squares means, and I bars indicate 95% confidence intervals. Panel D shows the percentage of patients with a score of 7 or less on the Insomnia Severity Index (ISI; range, 0 to 28, with higher scores indicating greater severity) from baseline to week 16.

Table 2 (least-squares mean difference between the nemolizumab group and the placebo group, −19.3 percentage points; 95% CI, −26.6 to −11.9). Figure 2B shows the data from the first 15 days of this period, highlighting that changes were reported as early as day 2 (−10.3% in the nemolizumab group and −4.4% in the placebo group). Figure 2C shows the time course of the percent change in the EASI score. The least-squares mean percent change at week 16 was −45.9% in the nemolizumab group and −33.2% in the placebo group. The percentage of patients with a DLQI score of 4 or less was 40% in the nemolizumab group and 22% in the placebo group, and the percentage of patients with a decrease of 4 or more points in the DLQI score was 67% and 50%, respectively, at week 16 (Table 2). An ISI score of 7 or less was achieved in 55% of the patients in the nemolizumab group and 21% of those in the placebo group (Fig. 2D). Results for exploratory end points and post hoc analysis of ISI scores are provided in Tables S2 and S3 and Figure S3.

SAFETY

Overall, 71% of the patients in each group reported adverse events that emerged during treatment (Table 3 and Table S4); most were mild or moderate in severity as determined by the investigators. Severe adverse events were reported by three patients (2%) in the nemolizumab group: Meniere's disease, acute pancreatitis, and atopic dermatitis (in one patient each). Three patients who received nemolizumab reported a total of four treatment-related adverse events resulting in discontinuation of the drug: atopic dermatitis, Meniere's disease, alopecia, and peripheral edema.

Table 3. Adverse Events (Safety Analysis Set).*

Adverse Event	Nemolizumab (N=143)	Placebo (N=72)
	no. of patients (%)	
Any adverse event	101 (71)	51 (71)
Severe	3 (2)†	0
Moderate	32 (22)	14 (19)
Mild	90 (63)	45 (62)
Serious adverse event	3 (2)	2 (3)
Treatment modification		
Discontinuation	3 (2)	0
Dose interruption	3 (2)	2 (3)
Dose reduction	0	0
Adverse events of special interest		
Injection-related reaction	12 (8)	2 (3)
Asthma	0	0
Worsening of atopic dermatitis‡	34 (24)	15 (21)
Skin infection	10 (7)	7 (10)
Elevated creatine kinase	4 (3)	1 (1)
Musculoskeletal and connective-tissue symptoms	7 (5)	6 (8)
Death	0	0
Adverse events reported by ≥3% of patients in either group§		
Dermatitis atopic‡	33 (23)	15 (21)
Nasopharyngitis	18 (13)	11 (15)
Cytokine abnormal	10 (7)	0
Blood creatine kinase increased	5 (3)	1 (1)
Acne	2 (1)	3 (4)

* Shown are adverse events that emerged during treatment. Multiple occurrences of an event for a single patient are counted only once. The severity of adverse events was assessed by the investigator, according to definitions prespecified in the protocol, as mild (the event causes discomfort, but without limiting normal activities of daily living), moderate (discomfort affects normal activities of daily living), or severe (the event disturbs work or normal activities of daily living).

† Meniere's disease, pancreatitis acute, and dermatitis atopic (preferred terms in the Japanese translation of the *Medical Dictionary for Regulatory Activities* [MedDRA], version 20.1) occurred in one patient each.

‡ Atopic dermatitis ("dermatitis atopic" according to the preferred term in MedDRA) could be reported as a safety outcome in individual patients; however, it was not considered as an efficacy outcome, which involved a reduction in the severity of atopic dermatitis in the overall population.

§ Events are shown according to the preferred term in the Japanese translation of the MedDRA, version 20.1.

The most commonly reported adverse event of special interest was worsening atopic dermatitis, occurring in 24% of the patients in the nemolizumab group and 21% of those in the placebo group; one patient discontinued nemolizumab as a result. The incidence of injection-related reactions was 8% with nemolizumab and 3% with placebo. Musculoskeletal and connective tissue symptoms occurred in 5% of the patients in the nemolizumab group and 8% of those in the placebo group. Cytokine abnormalities such as an increased level of thymus and activation-regulated chemokine (TARC) occurred only in the nemolizumab group. The median change in the TARC level from baseline to week 16 and the lack of association of these changes with the EASI score are shown in Figures S4 and S5.

DISCUSSION

In the current trial, nemolizumab resulted in a greater reduction in pruritus than placebo over a period of 16 weeks in patients with atopic dermatitis who had not had an adequate response to topical agents and antihistamines. The secondary end-point results with respect to quality of life, sleep, and signs or extent of atopic dermatitis were in the same direction as the primary end-point results, but no inferences can be made from these results because there was no plan for adjustment for multiple comparisons. Nemolizumab plus topical agents may ameliorate both pruritus and signs of eczema and may lessen the severity of atopic dermatitis by disrupting the itch–scratch cycle. Safety results in our trial indicated that some patients reported worsening atopic dermatitis as an adverse event, although those patients had reductions in pruritus as measured by the VAS score. This worsening of atopic dermatitis as a safety outcome was not correlated with the efficacy outcome of a reduction in pruritus, and the mechanisms underlying this dichotomy are unclear.

In a previous phase 2a monotherapy trial involving patients with atopic dermatitis, all nemolizumab doses were associated with greater reductions in pruritus at week 12 than placebo.[21] Nemolizumab showed a lesser magnitude of efficacy in the current trial than in the phase 2a trial. A phase 2b trial showed a change in pruritus according to the NRS score, which precludes direct comparisons with the primary end point in the current trial; in the phase 2b trial, a between-group difference in the NRS score was reported at week 24.[22] Although there are variations among these trials in the numerical differences in end-

point results when comparing nemolizumab with placebo, all three trials showed an effect in reducing pruritus. The possible reasons for the between-trial differences include heterogeneity in inclusion criteria and differences in primary and secondary end points, nemolizumab dosage, trial duration, the ethnic groups of the patients, and concomitant treatments.

Several immunotherapies are currently being developed for the treatment of atopic dermatitis, and their availability varies according to country. Dupilumab, which has been shown in phase 3 clinical trials to be effective in patients with atopic dermatitis,[38] has been investigated mainly in conjunction with other therapies.[39] Dupilumab and nemolizumab have different treatment profiles. Nemolizumab was developed as an inhibitor of interleukin-31 signaling,[16,17] and interleukin-31 plays a role in the generation of pruritus in patients with atopic dermatitis[18,19]; moreover, interleukin-31 also has a proinflammatory role and is involved in the regulation of the cutaneous barrier.[19,20] Targeting interleukin-31 aims to decrease pruritus and signs of skin inflammation, which may result in reduced severity of eczema. In contrast, dupilumab targets interleukin-4 and interleukin-13, drivers of atopic dermatitis. In trials of dupilumab,[38,40] the primary end points were based on signs of atopic dermatitis (primarily eczema scores), and pruritus scores — such as the one used in the current trial as a primary end point — were secondary end points.

Adverse events with nemolizumab included injection-related reactions. Cytokine abnormalities (increased TARC level) occurred in the nemolizumab group after treatment; however, most were not accompanied by a worsening of signs of or the extent of atopic dermatitis. This trial has limitations, including the short duration of treatment; the inclusion of only Japanese patients; the enrollment of patients with an age of 13 years, even though there is a high prevalence of atopic dermatitis among children[5]; and the inability to draw conclusions from secondary end-point results because of the lack of a plan for adjustment for multiple comparisons.

This phase 3 trial involving patients with atopic dermatitis showed that nemolizumab, when used with topical agents, provided a greater reduction in pruritus than placebo plus topical agents. The incidence of injection-related reactions was higher with nemolizumab than with placebo. This trial did not assess the durability or safety of the drug beyond 16 weeks for atopic dermatitis with pruritus.

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Dr. Kabashima reports receiving consulting fees from Maruho; and Ms. Matsumura and Mr. Komazaki, being employed by Maruho. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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