ORIGINAL ARTICLE

Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis

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ABSTRACT

BACKGROUND

Prurigo nodularis is a chronic pruritic skin disease with multiple nodular skin lesions. Nemolizumab is a monoclonal antibody targeting the interleukin-31 receptor, which is involved in the pathogenesis of prurigo nodularis.

METHODS

We conducted a 12-week, randomized, double-blind, phase 2 trial of nemolizumab (at a dose of 0.5 mg per kilogram of body weight) administered subcutaneously at baseline, week 4, and week 8, as compared with placebo, in patients with moderate-to-severe prurigo nodularis and severe pruritus. Moderate-to-severe prurigo nodularis was defined as 20 or more nodules, and severe pruritus was defined as a mean score of at least 7 for the worst daily intensity of pruritus on the numerical rating scale (scores range from 0 [no itch] to 10 [worst itch imaginable]). The primary outcome was the percent change from baseline in the mean peak score for pruritus on the numerical rating scale at week 4. Secondary outcomes included additional measures of itching and disease severity. Safety assessments were performed through week 18.

RESULTS

A total of 70 patients were randomly assigned in a 1:1 ratio to receive nemolizumab (34 patients) or placebo (36). The initial pruritus score on the numerical rating scale was 8.4 in each group. At week 4, the peak pruritus score on the numerical rating scale was reduced from baseline by 4.5 points (change, −53.0%) in the nemolizumab group, as compared with a reduction of 1.7 points (change, −20.2%) in the placebo group (difference, −32.8 percentage points; 95% confidence interval, −46.8 to −18.8; P<0.001). Results for secondary outcomes were in the same direction as for the primary outcome. Nemolizumab was associated with gastrointestinal symptoms (abdominal pain and diarrhea) and musculoskeletal symptoms.

CONCLUSIONS

Nemolizumab resulted in a greater reduction in pruritus and severity of skin lesions than placebo in patients with prurigo nodularis but was associated with adverse events. Larger and longer trials are needed to determine the durability and safety of nemolizumab for the treatment of prurigo nodularis. (Funded by Galderma; ClinicalTrials.gov number, NCT03181503.)

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Prurigo nodularis is a subtype of chronic prurigo[1] that causes a highly pruritic, chronic disease characterized by hyperkeratotic, crusted or excoriated, light-red to bright-red nodules (lesions may be hyperpigmented depending on skin type).[1] Skin lesions may range in number from a few to hundreds, and they can range from a few millimeters to 2 to 3 cm in diameter. Prurigo nodularis can manifest in circumscribed areas, but in most cases it is generalized, with symmetric distribution of the lesions on the extensor surfaces of the arms and legs and on the trunk.[1]

Prurigo nodularis affects patients of either sex, with some predilection for elderly patients and for patients with dark skin, including persons of African ancestry.[2,3] It is typically refractory to treatment and may be associated with diabetes, chronic kidney disease, and human immunodeficiency virus infection.[3] The intensity of pruritus in prurigo nodularis is considered to be the highest among several types of chronic pruritic skin disease.[4-7] In one study, patients with prurigo nodularis had a higher intensity of pruritus, more frequent episodes of pruritus, and worse quality of life than did patients with pruritus due to other dermatoses.[6] In an international study involving patients with dermatologic conditions, 37% of the patients with prurigo nodularis had anxiety and 29% had depression; suicidal ideation was reported by 19% of the patients.[8]

The pathogenesis of prurigo nodularis is not well understood, but it has been considered to include a form of neuronal sensitization of itch-processing neurons and the development of an itch–scratch cycle.[1,4,7] Inflammatory pathways in the skin and neuronal plasticity play a role in prurigo nodularis,[4,5] with studies showing nerve-fiber alterations in the epidermis and dermis and the presence of inflammatory cells in the dermis. Pruritus in this disorder could be stimulated by the release of tryptase, interleukin-31, prostaglandins, eosinophil cationic protein, and neuropeptides from inflammatory cells, mast cells, and nerve fibers.[5,7] Up-regulation of interleukin-31 messenger RNA has been reported to be 50 times as high in prurigo nodularis lesions as in skin-biopsy samples from healthy persons.[9] Treatment of prurigo nodularis mainly targets the symptom of pruritus.[5,7,10-12]

Nemolizumab is a humanized antihuman interleukin-31 receptor A monoclonal antibody that inhibits the binding of interleukin-31 to its receptor and subsequent signal transduction. We conducted a phase 2 trial with a 12-week intervention period and 6-week follow-up period to assess the efficacy and safety of nemolizumab as compared with placebo in the treatment of prurigo nodularis. The primary objective was to evaluate the effect of nemolizumab on pruritus. Secondary objectives were to evaluate the effect of nemolizumab on prurigo nodularis skin lesions and on quality of life.

METHODS

TRIAL DESIGN AND OVERSIGHT

This multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase 2 trial involved patients with moderate-to-severe prurigo nodularis and was conducted at centers in Austria, France, Germany, Poland, and the United States. The trial was conducted according to the principles of the Declaration of Helsinki, and the protocol (available with the full text of this article at NEJM.org) was approved by ethics committees at each institution. The trial was designed by the trial sponsor, Galderma, with input from the first three authors and from the last author, who is an employee of the sponsor. The data were gathered and analyzed by the sponsor. The first draft of the manuscript was prepared by the academic and industry authors, with professional writing assistance provided by the sponsor. Confidentiality agreements were in place between the authors and the sponsor. The authors vouch for the completeness and accuracy of the data, for the accurate reporting of adverse events, and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Eligible patients were adults who had had prurigo nodularis with severe pruritus for at least 6 months. Severe pruritus was defined as a mean score of at least 7 points over the previous week for the worst daily intensity of pruritus on the numerical rating scale (scores range from 0 [no itch] to 10 [worst itch imaginable]; a change of 4 points indicates a clinically important difference). Patients had to have moderate-to-severe prurigo nodularis, which was defined as prurigo nodular lesions on the upper limbs, with or without lesions on the trunk or lower limbs, and at least

20 nodules on the body, with lesions present on both sides of the body. The presence or absence of a background of atopy (medical history of atopic dermatitis, asthma, or allergic rhinitis) was recorded at inclusion.

Exclusion criteria were chronic pruritus due to a condition other than prurigo nodularis, lesions of prurigo on one side of the body only, or signs that were diagnostic of neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, delusional parasitosis, or dermatitis artefacta. Additional exclusion criteria and information about washout periods for previous treatment are provided in the Methods Section and Table S1 in the Supplementary Appendix, available at NEJM.org.

TRIAL TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive injections of either nemolizumab, administered subcutaneously at a dose of 0.5 mg per kilogram of body weight, or matching placebo. A total of three subcutaneous injections were administered — at baseline, at week 4, and at week 8. The week 12 trial visit was specified as the end of the intervention period. Patients had follow-up visits at 16 and 18 weeks.

Rescue therapy for pruritus could be added from day 29 onward at the discretion of the site investigators after the primary outcome of the trial was assessed at week 4. All efficacy and safety assessments were completed before the initiation of rescue therapy. Patients who received topical rescue therapies were allowed to continue nemolizumab or placebo, whereas those who received systemic therapy had to discontinue nemolizumab or placebo.

OUTCOME MEASURES

All outcome measures were assessed by trial investigators and study nurses or trained clinical coordinators, all of whom were unaware of the trial-group assignments, and some outcome data were captured in the patient's diary. The primary outcome was the percent change from baseline in the peak pruritus score on the numerical rating scale at week 4. We determined the peak score by assessing worst scores per 24 hours on the numerical rating scale over a period of 7 days; the highest score was determined as the peak score. We determined the mean pruritus score on the numerical rating scale by calculating the 24-hour average (mean) score on the numerical rating scale over a period of 7 days. Secondary outcomes were the changes from baseline in the peak and mean pruritus scores on the numerical rating scale at week 12, in the verbal rating scale score for itch (on a scale from 0 [no pruritus] to 4 [very severe pruritus]) at week 12, in the dynamic pruritus score for the change in itch (on a scale from 0 [strongly worsened pruritus] to 8 [almost no pruritus or no pruritus], with a score of 4 indicating no change) at week 4, in the investigator's global assessment of disease severity on the basis of the appearance of lesions (on a scale from 0 [clear] to 4 [severe]), and in a multidimensional, 7-item prurigo activity score[10] to monitor the stage of disease (number, distribution, and activity of prurigo lesions) at week 12. To assess changes in prurigo lesions, investigators were instructed to specify on the prurigo activity score tool a localization that was most representative of the patient's overall disease (left or right side of forearm, upper arm, lower leg, or upper leg or the ventral or dorsal side of trunk), and this area was used at all subsequent assessments. A response according to the investigator's global assessment was defined as a score of 0 or 1 plus an improvement of 2 points from baseline.

Exploratory outcomes included changes in the Dermatology Life Quality Index (scores range from 0 to 30, with 30 representing the worst possible quality of life due to pruritus; a change in the score of ≥4 points is considered to be clinically important) and in the numerical rating scale score for sleep disturbance to determine sleep quality (on a scale from 0 to 10, with higher scores indicating worse sleep quality). Patients' assessments of the numerical rating scale score for pruritus, the verbal rating scale score for pruritus, and the numerical rating scale score for sleep disturbance were performed daily by the patients at home in the evening using a handheld device. The dynamic pruritus score was assessed 24 hours, 48 hours, and 72 hours after the first injection and at week 4 before the second injection. The Dermatology Life Quality Index was assessed at baseline and at weeks 4 and 12 or at early discontinuation of the trial. The investigator's assessments of the prurigo activity score and the investigator's global

assessment of disease severity were recorded at baseline; at weeks 4, 8, and 12; and at the follow-up visit at week 18. Detailed information about the assessment tools is provided in the protocol.

Safety was assessed by the collection of reports of adverse events by investigators or trial personnel at each trial visit, by laboratory safety testing, and by physical examination and assessment of vital signs, electrocardiogram, and respiratory measures (clinical examination) and peak expiratory flow. All assessments except respiratory assessments were performed in all patients; respiratory assessments were performed only in patients with a medical history of asthma. The safety population was defined as all the patients who underwent randomization and received at least one dose of nemolizumab or placebo.

STATISTICAL ANALYSIS

We calculated that, with an effect size of 0.857, a power of 90%, and a type I error of 5% (two-sided), the trial would need to enroll at least 30 patients per group. The sample-size estimate was increased to 35 patients per group to accommodate withdrawals and protocol deviations, for a total of 70 patients to undergo randomization. The intention-to-treat population, which included all the patients who underwent randomization, was used for all the efficacy analyses. The primary efficacy analysis of the percent change from baseline to week 4 in the weekly mean of the peak numerical rating scale scores for pruritus (weekly mean of the worst scores, indicating peak pruritus) was analyzed with the use of analysis of variance, including the trial group as factor and the presence or absence of a background of atopy and the country of investigational site as cofactors.

All the efficacy data collected after the use of rescue therapy were treated as missing data. The original plan was to impute missing data with the use of the last-observation-carried-forward and multiple-imputation approaches, with missing-at-random assumptions for the primary outcome. Missing data were imputed post hoc with the use of multiple-imputation missing-at-nonrandom assumptions for the primary and secondary outcomes, and the results presented here reflect the use of this method with the exception of the dynamic pruritus score and the Dermatology Life Quality Index, for which observed cases were presented. No adjustments for multiplicity were made for the secondary efficacy outcomes, and so the results are presented as point estimates with unadjusted confidence intervals only; no conclusions regarding treatment effect can be made from these data. The statistical analysis plan is available with the protocol.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

From October 2017 through September 2018, a total of 70 patients were randomly assigned to a trial group (34 patients to the nemolizumab group and 36 to the placebo group). All the patients were enrolled at the European trial centers, and no patients were enrolled at centers in the United States (see the Supplementary Appendix). The randomization and follow-up of the patients are shown in Figure 1. The demographic and disease characteristics of the patients were similar in the two groups at baseline, except that there was a higher percentage of men and a higher percentage of patients with severe disease according to the investigator's global assessment in the nemolizumab group than in the placebo group (Table 1).

OUTCOMES

At week 4, the percent change from baseline in the peak pruritus score on the numerical rating scale (primary outcome) was a reduction by 4.5 points (change, −53.0%) in the nemolizumab group, as compared with a reduction by 1.7 points (change, −20.2%) in the placebo group (difference, −32.8 percentage points; 95% confidence interval [CI], −46.8 to −18.8; P<0.001) (Table 2). For the primary outcome, responses were missing for two patients in the nemolizumab group and for three in the placebo group. Similar results were obtained with the use of multiple imputation (missing-at-random and last-observation-carried-forward analyses) (Table S2).

For the secondary outcomes of the change from baseline in the peak and mean pruritus scores on the numerical rating scale at week 12, between-group differences favored nemolizumab; however, no conclusions can be made from these results because the confidence intervals for between-group differences were not adjusted

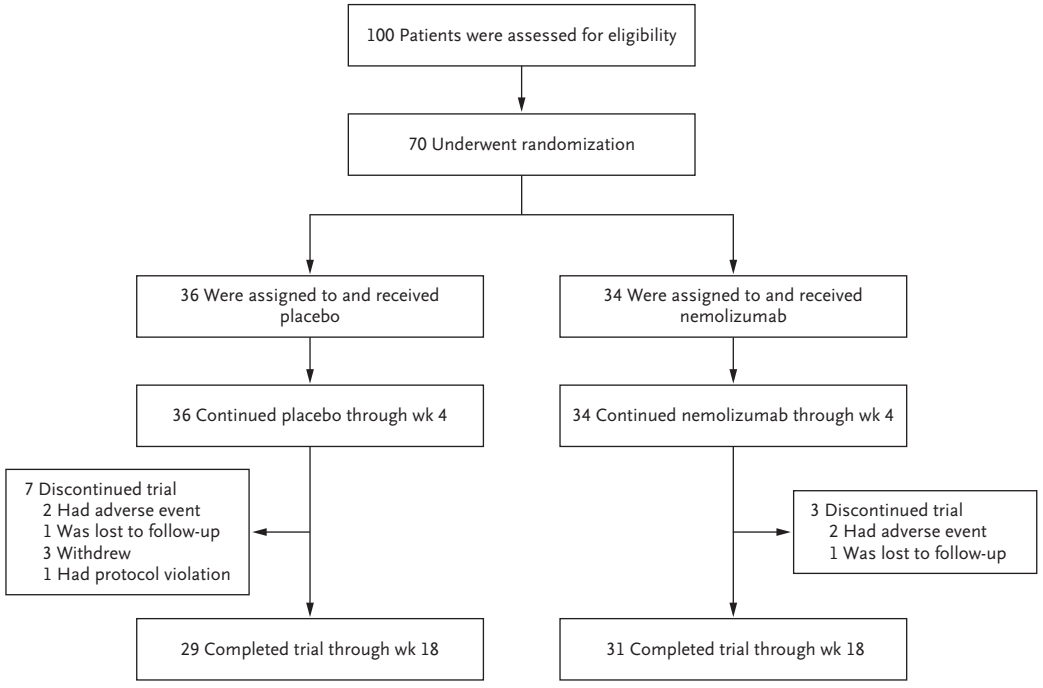

Figure 1. Randomization and Follow-up of the Patients.

for multiplicity. A numerical reduction in these scores was observed at week 1 and at all the other visits (weeks 2 to 18) (Fig. 2 and Fig. S1 and Table S3). The reduction in the pruritus score on the numerical rating scale was independent of the presence or absence of a background of atopy although the number of patients with atopy was small (five in the nemolizumab group and six in the placebo group).

Reductions were observed in pruritus intensity as assessed on the verbal rating scale for pruritus and the dynamic pruritus score. At week 12, the peak score for pruritus intensity on the verbal rating scale was reduced by 1.9 points (change, –56.7%) in the nemolizumab group and by 0.9 points (change, –27.7%) in the placebo group (difference, –29.0 percentage points; unadjusted 95% CI, –46.2 to –11.9) (Table 2). Changes in the peak and mean pruritus scores on the verbal rating scale at all trial visits are provided in Figure S2 and Table S4. The distribution of dynamic pruritus scores was numerically better in the nemolizumab group than in the placebo group at all evaluated time points (Table S5); 29% of the patients in the nemolizumab group reported no or almost no pruritus by week 4, as compared with none of the patients in the placebo group.

At baseline, the mean number of prurigo lesions in a selected area that was representative of overall disease (as described in the Methods section) was 17.1 in the nemolizumab group and 22.4 in the placebo group. By week 12, the reduction in the mean lesion count was greater in nemolizumab group than in the placebo group (least-squares mean, –12.6 vs. –6.1 lesions; difference, –6.5 lesions; unadjusted 95% CI, –12.5 to –0.6). At the last follow-up visit (week 18), the least-squares mean change in the lesion count was –13.3 in the nemolizumab group and –7.5 in the placebo group. The proportions of healed prurigo lesions according to the prurigo activity score at all visits at which an assessment was performed are shown in Table S6; at week 4, a total of 75% or more healed lesions were reported in 24% of the patients in the nemolizumab group and in 11% of those in the placebo group.

The percentage of patients with a response according to the investigator's global assessment at week 12 was 23% in the nemolizumab group and 4% in the placebo group (Table 2). Figure S3

shows the distribution of the investigator's global assessments in the nemolizumab group and the placebo group at each trial visit, the proportions of patients who had a response according to the investigator's global assessment at each visit during which this was assessed, and an example of a patient in the nemolizumab group who had a clinical response according to the investigator's global assessment.

Sleep quality was assessed during the first 4 weeks after the initiation of nemolizumab or placebo (Fig. S4). The numerical rating scale score for sleep quality in the nemolizumab group showed numerical improvements starting at week 1 after the first treatment (least-squares mean, –23.4, vs. –5.1 in the placebo group). At week 4, the least-squares mean change from baseline in the numerical rating scale score for sleep quality, a prespecified secondary outcome, was –3.8 points (change, –56.4%) in the nemolizumab group and –1.6 points (change, –26.6%) in the placebo group (difference, –29.8 percentage points; unadjusted 95% CI, –47.5 to –12.0).

At week 12, the least-squares mean change from baseline in the Dermatology Life Quality Index was –10.4 in the nemolizumab group and –8.0 in the placebo group. The distribution of scores in the two trial groups at each assessed visit is shown in Table S7. In a post hoc analysis, the percentage of patients with a response according to the Dermatology Life Quality Index, defined as a reduction of 4 points or more (minimal clinically important difference), was higher in the nemolizumab group than in the placebo group both at week 4 and at week 12 (59% vs. 31% at both time points).

Rescue medication, including topical glucocorticoids and immunosuppressive drugs (administered at the discretion of the investigator), was used in two patients receiving nemolizumab and in four receiving placebo. Among these patients, systemic rescue medication was used in two patients in the nemolizumab group and in three in the placebo group.

SAFETY

The percentage of patients with adverse events was 68% in the nemolizumab group and 67% in the placebo group (Table 3). Four patients in the nemolizumab group and three in the placebo group had serious adverse events. The serious adverse events were as follows: one case of pso-

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

Characteristic	Placebo (N=36)	Nemolizumab (N=34)
Age — yr		
Mean	52.4±17.5	59.7±13.2
Range	20–77	26–85
Male sex — no. (%)	14 (39)	15 (44)
Race — no. (%)†		
White	35 (97)	33 (97)
Black	1 (3)	1 (3)
Weight — kg	80.3±20.7	81.6±21.8
Background of atopy — no. (%)‡		
Present	6 (17)	5 (15)
Absent	30 (83)	29 (85)
Estimated no. of nodules on body — no. (%)		
20–100	21 (58)	21 (62)
>100	15 (42)	13 (38)
Counted no. of nodules in representative area§	22.4±17.5	17.1±13.4
Numerical rating scale score for pruritus¶		
Weekly peak score	8.4±1.2	8.4±1.2
Weekly mean score	7.9±1.3	7.8±1.7
Prurigo nodularis per investigator's global assessment — no. (%)‖		
Moderate	22 (61)	16 (47)
Severe	14 (39)	18 (53)
Dermatology Life Quality Index**	15.8±6.0	16.9±7.5

* Plus–minus values are means ±SD. The characteristics of the patients were similar at baseline in the two groups, except that there was a higher percentage of men and a higher percentage of patients with severe disease according to the investigator's global assessment in the nemolizumab group than in the placebo group.

† Race was reported by the patient.

‡ Background of atopy was defined as a medical history of atopic dermatitis, asthma, or allergic rhinitis.

§ The counted number of nodules in a representative area was used for assessing the prurigo activity score. To assess changes in prurigo lesions, investigators were instructed to specify a localization that was most representative of the patient's overall disease (left or right side of forearm, upper arm, lower leg, or upper leg or the ventral or dorsal side of trunk), and this area was used at all subsequent assessments.

¶ The weekly numerical rating score for pruritus was assessed over a period of 7 days before the baseline visit. Scores range from 0 (no itch) to 10 (worst itch imaginable). We determined the peak score by assessing worst scores per 24 hours on the numerical rating scale over a period of 7 days; the highest score was determined as the peak score. We determined the mean pruritus score on the numerical rating scale by calculating the 24-hour average (mean) score on the numerical rating scale over a period of 7 days.

‖ The investigator's global assessment of disease severity on the basis of appearance of lesions was scored on a scale from 0 (clear) to 4 (severe). A score of 3 indicated moderate severity.

** Values for the Dermatology Life Quality Index range from 0 to 30, with higher values indicating worse quality of life; a change of at least 4 points is considered to be a clinically important difference.

Table 2. Efficacy Assessments (Intention-to-Treat Population).*

Outcome	Placebo (N=36)	Nemolizumab (N=34)	Difference (95% CI)
Primary outcome			
Numerical rating scale score for pruritus: change from baseline in peak score at wk 4			
Least-squares mean absolute score change	−1.7	−4.5	
Least-squares mean percent change	−20.2	−53.0	−32.8 (−46.8 to −18.8)†
Secondary outcomes			
Numerical rating scale score for pruritus			
Change from baseline in peak score at wk 12			
Least-squares mean absolute score change	−2.1	−5.1	−3.0 (−4.4 to −1.7)
Least-squares mean percent change	−25.7	−61.9	−36.1 (−52.3 to −20.0)
Change from baseline in mean score at wk 12			
Least-squares mean absolute score change	−2.6	−5.0	−2.4 (−3.8 to −1.0)
Least-squares mean percent change	−35.4	−67.5	−32.1 (−49.8 to −14.4)
Verbal rating scale score for pruritus			
Change from baseline in peak score at wk 12			
Least-squares mean absolute change	−0.9	−1.9	−0.9 (−1.5 to −0.4)
Least-squares mean percent change	−27.7	−56.7	−29.0 (−46.2 to −11.9)
Change from baseline in mean score at wk 12			
Least-squares mean absolute change	−1.0	−2.0	−1.0 (−1.5 to −0.5)
Least-squares mean percent change	−31.1	−66.2	−35.1 (−51.9 to −18.3)
Dynamic pruritus score at wk 4 — no. (%)‡			
0	0	0	
1	0	1 (3)	
2	0	1 (3)	
3	2 (6)	0	
4	22 (61)	5 (15)	
5	1 (3)	2 (6)	
6	2 (6)	2 (6)	
7	3 (8)	11 (32)	
8	0	10 (29)	
Percent of healed prurigo lesions at wk 12 — no. (%)§			
100%	1 (3)	2 (6)	
75–99%	2 (6)	9 (26)	
50–74%	7 (19)	16 (47)	
25–49%	9 (25)	5 (15)	
0–24%	12 (33)	0	
Response according to investigator's global assessment at wk 12 — %¶	4	23	18 (2 to 37)

* For the primary outcome, responses were missing for two patients in the nemolizumab group and for three in the placebo group. Missing data were accounted for with the use of multiple imputation with an assumption that data were missing not at random. Secondary outcomes were not adjusted for multiplicity. Differences between percentages are shown in percentage points. Data for all trial visits are provided in Figures S1 and S2 and in Tables S3 through S5.

† P<0.001.

‡ Dynamic pruritus scores range from 0 to 8. A score of 4 indicates no change from baseline; scores below 4 indicate a worsened condition (with 0 indicating strongly worsened pruritus), and scores above 4 indicate an improvement in condition (with 8 indicating improvement to no pruritus or almost no pruritus). Observed values are presented; data were missing for 2 patients (6%) in the nemolizumab group and for 6 (17%) in the placebo group.

§ The prurigo activity score questionnaire is a 7-item tool for objective monitoring of pruriginous lesions over time in patients with chronic prurigo. One of the items, shown here, monitors the percentage of healed lesions as compared with lesions at baseline. Observed values are presented; data were missing for 2 patients (6%) in the nemolizumab group and for 6 (17%) in the placebo group.

¶ A response according to the investigator's global assessment was defined as a score of 0 or 1 plus an improvement of 2 points from baseline. The values shown are the averages over the multiple imputed data sets for the trial. Therefore, it is not possible to show the exact numbers of patients with a response.

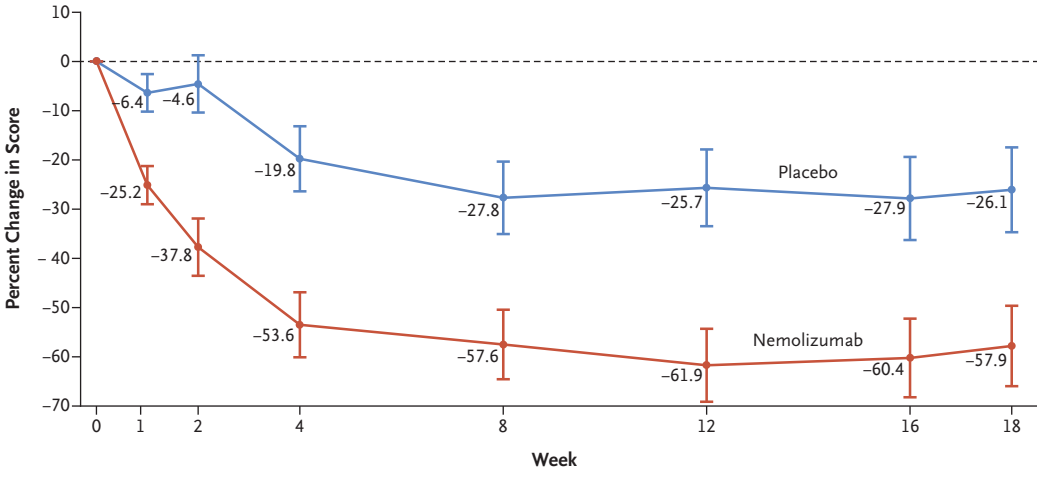

Figure 2. Percent Change from Baseline in the Weekly Peak Pruritus Score on the Numerical Rating Scale (Intention-to-Treat Population).

Shown is the percent change from baseline (dotted line) in the mean peak pruritus score on the numerical rating scale score in the two trial groups. Scores on this scale range from 0 (no itch) to 10 (worst itch imaginable). Missing data were imputed under an assumption of missing not at random. I bars indicate the standard error.

riasiform rash (with histologic testing showing an eczematous reaction) in the nemolizumab group and three cases of atopic dermatitis in the placebo group; one clavicular fracture in the nemolizumab group and one spinal fracture in the placebo group; two cases of musculoskeletal pain (one case of fibromyalgia in the nemolizumab group and one case of back pain in the placebo group); and one case of bladder lithiasis in the nemolizumab group. (Atopic dermatitis, back pain, and spinal fracture occurred in a single patient.) Two patients in each group discontinued nemolizumab or placebo owing to adverse events; one of the patients in the placebo group who discontinued had a serious adverse event.

In the nemolizumab group, gastrointestinal symptoms, including abdominal pain and diarrhea, occurred in seven patients (21%); musculoskeletal or connective-tissue disorders occurred in six (18%; arthralgia, back pain, muscle spasms, jaw pain, fibromyalgia, and spinal pain in one patient each); injury, poisoning, or procedural complications occurred in four (12%); and bronchitis occurred in two (6%). Table 3 summarizes the adverse events that occurred in at least 5% of the patients in either trial group; a complete listing of adverse events is provided in Table S8. No safety signals were observed in the laboratory tests, physical examinations, or the vital-sign or respiratory assessments (Table S9), and no safety signals were observed in the electrocardiographic assessments (data not shown).

DISCUSSION

In this phase 2 trial involving adults with moderate-to-severe prurigo nodularis, nemolizumab therapy resulted in greater reductions in signs and symptoms of the disorder than placebo. Treatment with nemolizumab was associated with reductions in pruritus as gauged by the primary outcome of the peak pruritus score on the numerical rating scale at week 4. There were improvements as compared with placebo in secondary pruritus outcomes, which included assessments of peak and mean intensity of itch, overall disease severity, and the investigator's global assessment. However, the analyses were not adjusted for multiplicity, and no clinical inferences can be made from them. Changes in quality of life and sleep disturbance were assessed by the Dermatology Life Quality Index and the numerical rating scale score for sleep quality, respectively; quality of life and sleep quality improved during the trial in both groups but to a larger degree in the nemolizumab group than in the placebo group; however, conclusions should not be made from these data because of the same limitation regarding a lack of multiplicity adjust-

Table 3. Adverse Events (Safety Population).*

Adverse Event	Placebo (N=36)	Nemolizumab (N=34)
Total no. of adverse events	69	77
Any adverse event — no. of patients (%)	24 (67)	23 (68)
Adverse event leading to withdrawal from trial — no. of patients (%)	2 (6)	2 (6)
Injection-related reaction — no. of patients (%)	0	1 (3)
Infection or infestation — no. of patients (%)	12 (33)	10 (29)
Nasopharyngitis	4 (11)	5 (15)
Conjunctivitis	2 (6)	3 (9)
Bronchitis	0	2 (6)
Cystitis	2 (6)	0
Postoperative wound infection	2 (6)	0
Skin or subcutaneous-tissue event — no. of patients (%)	12 (33)	10 (29)
Neurodermatitis or atopic dermatitis	5 (14)	5 (15)
Alopecia	2 (6)	0
Contact dermatitis	0	2 (6)
Worsening of pruritus	2 (6)	0
Gastrointestinal event — no. of patients (%)	5 (14)	7 (21)
Abdominal pain	0	2 (6)
Diarrhea	0	2 (6)
Musculoskeletal or connective-tissue event — no. of patients (%)		
Any	5 (14)	6 (18)
Arthralgia	2 (6)	1 (3)
General disorder or administration-site condition — no. of patients (%)†	4 (11)	5 (15)
Injury, poisoning, or procedural complication — no. of patients (%)†	2 (6)	4 (12)
Clavicle fracture	0	1 (3)
Eye injury	0	1 (3)
Muscle strain	1 (3)	0
Renal or urinary event — no. of patients (%)†	2 (6)	2 (6)
Nervous system disorder — no. of patients (%)†	1 (3)	2 (6)
Dizziness	0	1 (3)
Headache	1 (3)	0
Tremor	0	1 (3)
Respiratory, thoracic, or mediastinal event — no. of patients (%)		
Any	3 (8)	0
Cough	2 (6)	0
Blood or lymphatic system event — no. of patients (%)		
Any	2 (6)	0
Lymphadenopathy	2 (6)	0
Metabolism or nutrition disorder — no. of patients (%)		
Any	0	2 (6)
Increased appetite	0	2 (6)
Vascular disorder — no. of patients (%)‡	2 (6)	0

* The safety population comprised patients who underwent randomization and received at least one dose of nemolizumab or placebo. Shown here are the adverse events that occurred in 5% of the patients in either trial group.
† No individual disorder or condition occurred in at least 5% of the patients in either group.
‡ Hot flush and hypotension were reported in one patient each.

ments. The patients in the trial had had disease for longer than 6 months; in the nemolizumab group, more than one third of the patients were clear or almost clear of lesions within a period of 3 months, and itch began to abate within the first week.

There were more instances of abdominal symptoms, including abdominal pain and diarrhea, and musculoskeletal symptoms (nonspecific bodily pains) in the nemolizumab group than in the placebo group. There were two cases of bronchitis in the nemolizumab group. Injection-site reactions occurred in one patient treated with nemolizumab.

This trial supports the role of the pruritogen interleukin-31 in the pathophysiology of prurigo nodularis.[1,13] In the skin, interleukin-31 is expressed by activated CD4+ T cells that regulate proinflammatory pathways, especially inflammation related to type 2 helper T cells.[14] Interleukin-31, when bound to its receptor complex, has been shown to be a mediator of pruritus,[14,15] especially in atopic dermatitis and prurigo nodularis.[13] Inhibition of interleukin-31 signaling may be a target for treatment in these pruritic skin diseases.[16-18]

In this phase 2 trial, nemolizumab resulted in a greater reduction in pruritus and severity of skin lesions in patients with prurigo nodularis over a period of 4 weeks but was associated with abdominal and nonspecific musculoskeletal symptoms. Longer and larger trials are needed to determine the durability and safety of nemolizumab for the treatment of prurigo nodularis.

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