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Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study

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Background: Nemolizumab, an anti–IL-31 receptor A mAb, improved pruritus, dermatitis, and sleep in adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments in a phase II, 12-week, randomized, double-blind, placebo-controlled study (part A; NCT01986933).
Objective: We sought to assess the long-term efficacy and safety of nemolizumab injected subcutaneously every 4 weeks (Q4W) or every 8 weeks (Q8W) in a 52-week, double-blind extension (part B).
Methods: During part B, patients continued the previous nemolizumab dose (0.1, 0.5, or 2.0 mg/kg Q4W or 2.0 mg/kg Q8W). Part B end points included percentage improvement from baseline in pruritus visual analog scale and dermatitis scores (including the Eczema Area and Severity Index).
Results: Overall, 216 of 264 patients completed part A, and 191 entered part B; 131 completed part B. In 153 patients randomized to nemolizumab in part A, improvement from baseline in pruritus visual analog scale score was maintained/increased from weeks 12 to 64, with greatest improvement in the 0.5-mg/kg Q4W group (percentage change from baseline at week 64: −73.0, −89.6, −74.7, and −79.1 in the 0.1-, 0.5-, and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively). Improvement from baseline in dermatitis scores was also maintained/increased to week 64 (percentage change in Eczema Area and Severity Index score: −68.5, −75.8, −78.9, and −69.3 in the 0.1-, 0.5-, and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively). Over 64 weeks, 83% to 89% had 1 or more adverse events, with no new safety concerns identified.
Conclusion: Nemolizumab for up to 64 weeks was efficacious and overall well tolerated in patients with moderate-to-severe atopic dermatitis inadequately controlled by topical therapy. (J Allergy Clin Immunol 2018;142:1121-30.)

Key words: *Monoclonal antibody, IL-31, IL-31 receptor, atopic dermatitis, pruritus, nemolizumab*

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that leads to intensely pruritic disseminated skin lesions that result frequently in severe scratching.[1-4] Pruritus, the dominant symptom of AD, can drive the itch-scratch cycle, which further exacerbates the disease and leads to sleeplessness and fatigue, which significantly affect quality of life (QoL).[5,6] Topical glucocorticoids, calcineurin inhibitors, or both are typically used to manage AD; however, these agents are not sufficient to achieve

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Abbreviations used
AD: Atopic dermatitis
AE: Adverse event
BSA: Body surface area
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
IRR: Injection-related reaction
QoL: Quality of life
Q4W: Every 4 weeks
Q8W: Every 8 weeks
SAE: Serious adverse event
SCORAD: SCORing Atopic Dermatitis
sIGA: Static Investigator's Global Assessment
VAS: Visual analog scale
VRS: Verbal rating scale

symptom control in all patients, whereas systemic treatments have been associated with long-term safety concerns.[7-9] Despite the US Food and Drug Administration's recent approval of an anti–IL-4 receptor α mAb, dupilumab, for moderate-to-severe AD that is inadequately controlled by topical therapy, treatment options are limited, and there remains an unmet need for novel therapies with minimal long-term side effects.

Nemolizumab (CIM331) is an anti–IL-31 receptor A humanized mAb that blocks signaling mediated by IL-31, a proinflammatory cytokine associated with AD and pruritus.[10-13] IL-31 is also associated with disruption of the physical skin barrier, leading to greater penetration of allergens and pathogens.[14]

Building on the promising results of a phase I trial,[15] subcutaneous nemolizumab was assessed in a phase II, 12-week, randomized, double-blind, placebo-controlled, dose-finding study in patients with moderate-to-severe AD that was inadequately controlled by topical treatments (NCT01986933).[16] In the primary end point analysis, nemolizumab administered every 4 weeks (Q4W) significantly improved pruritus from baseline at week 12, as assessed by using the pruritus visual analog scale (VAS). Percentage reductions in pruritus VAS scores of −44% in the 0.1-mg/kg group, −60% in the 0.5-mg/kg group, and −63% in the 2.0-mg/kg group were reported versus −21% in the placebo group ($P < .01$ for all comparisons). Improvements in AD disease severity and body surface involvement, as well as sleep disturbance, were also observed at week 12 versus placebo.[16] Definitive conclusions about adverse events (AEs) could not be drawn because of the small patient sample and short follow-up period.

Here we describe a 52-week extension of that phase II trial to assess the long-term efficacy and safety of continuous subcutaneous nemolizumab when injected Q4W or every 8 weeks (Q8W).

METHODS

Study design

This phase II trial (NCT01986933) was performed in 2 parts (Fig 1). Part A, which was previously described,[16] was a 12-week evaluation of 4 dose regimens of nemolizumab, 0.1, 0.5, or 2.0 mg/kg administered subcutaneously Q4W and 2.0 mg/kg administered subcutaneously Q8W, or placebo administered subcutaneously Q4W. On completion of part A, patients entered the double-blind extension phase and continued to receive nemolizumab at the previously assigned dose for a further 52 weeks (weeks 12-64, part B). Patients randomized previously to placebo in part A were rerandomized to nemolizumab (0.1, 0.5, or 2.0 mg/kg subcutaneous Q4W) in part B at a 1:1:1 ratio by using a centralized interactive voice or online response system (placebo-treated patients were not rerandomized to nemolizumab 2.0 mg/kg Q8W). All patients were required to enter part B within 7 days of the final visit in part A. To maintain blinding in part B, the study monitoring team, study site personnel, and other site/company personnel remained blind to treatment allocation until the final database after study completion was locked.

The study was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Local ethics committee or institutional review board approval was obtained for each study center. Written informed consent was provided by all patients. The study was performed at 57 sites in the United Kingdom, Germany, Poland, Japan, and the United States between December 2013 and June 2016, and the database was unblinded on September 9, 2016, for analysis of part B.

Study population

Key inclusion criteria have been described previously (Fig 1).[16] Patients were required to have completed the part A treatment period and provided written informed consent for participation in the extension phase to enter part B. Patients who experienced a serious adverse event (SAE) considered related to nemolizumab during part A of the study were not eligible for part B.

Study procedures

In part B of the study, patients received treatment with 1 of 3 doses of nemolizumab (0.1, 0.5, or 2.0 mg/kg) administered subcutaneously Q4W or nemolizumab 2.0 mg/kg administered subcutaneously Q8W for 52 weeks. To maintain blinding, patients receiving nemolizumab Q8W were administered placebo at week 12 (last visit for part A), nemolizumab at week 16, and then alternating doses of placebo and nemolizumab. Patients were permitted to use emollients, localized treatments (eg, eye drops), mild topical glucocorticosteroids (including prednisolone), topical calcineurin inhibitors, and antihistamines (excluding nonselective H1 antihistamines). Patients with little or no improvement in pruritus VAS scores (range, 0 mm [no itch] to 100 mm [worst imaginable itch]) and static Investigator's Global Assessment (sIGA) scores (range, 0 [clear] to 5 [very severe disease]) in the opinion of the investigator were allowed to use a "potent" topical glucocorticosteroid,[17] such as mometasone furoate 0.1%, as a rescue therapy in part A (at or after week 4) and a "potent" or "very potent" topical glucocorticosteroid, such as clobetasol propionate 0.05%, in part B.

Study assessments

Baseline assessments for patients rerandomized from placebo to nemolizumab in part B were performed at the final visit of part A or at a separate visit. Patients attended study visits Q4W from week 12 to week 64 and a safety follow-up visit 12 weeks (±5 days) after the last dose of study drug. For consistency, patients were evaluated by the same assessor (when possible) at all visits. Assessor training was performed to minimize intersite and interinvestigator variation. Efficacy assessments were performed Q4W from week 16 to week 64 and at a withdrawal visit as soon as possible after drug discontinuation. The pruritus VAS, pruritus verbal rating scale (VRS; which measures pruritus intensity on a scale from 0 [no itch] to 4 [very severe itch]), and sleep disturbance VAS (which ranges from 0 [no sleep loss] to 100 [inability to sleep at all]) were completed by patients every 7 days during part B.

Study end points

The primary efficacy end point, percentage improvement from baseline at week 12 in pruritus VAS score, was assessed during part A. Secondary efficacy end points assessed in part B (weeks 12-64) included improvement from baseline values in the following: pruritus VAS score, Eczema Area and Severity Index (EASI) score (range, 0-72, with higher scores indicating worse disease severity), SCORing Atopic Dermatitis (SCORAD; range, 0-103, with

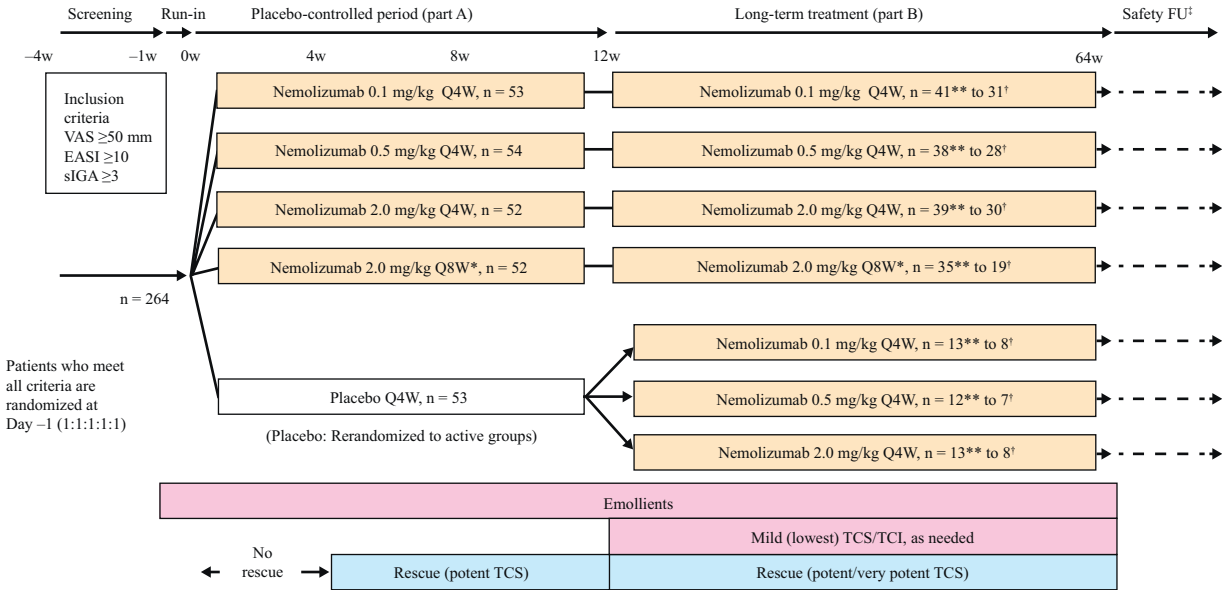

FIG 1. Study design. *Patients in the nemolizumab 2.0 mg/kg Q8W group received placebo at week 4 during part A; during part B, patients received placebo at week 12, nemolizumab at week 16, and then alternating doses of placebo and nemolizumab. **Number of patients who randomized to part B. †Number of patients at week 64. ‡Safety follow-up was performed 12 weeks after the last dose of study drug. *FU*, Follow-up; *TCI*, topical calcineurin inhibitor; *TCS*, topical glucocorticosteroid; *w*, week.

higher scores indicating more severe disease), body surface area (BSA) of AD involvement, and sleep disturbance VAS score. Secondary end points also included the proportion of patients with 25%, 50%, and 75% improvement from baseline in pruritus VAS and EASI scores; the proportion of patients with a 2-point or greater improvement from baseline in sIGA and pruritus VRS scores; and the proportion of patients receiving rescue therapy. The proportion of patients who achieved a pruritus VAS score of less than 30 mm (no or mild itch)[18] was explored in a *post hoc* analysis.

Exploratory efficacy outcomes in part B included the frequency, duration, and amount of topical glucocorticosteroid used as a rescue therapy and Dermatology Life Quality Index score (DLQI; measured on a scale of 0-30, with higher scores representing greater impairment). A change in DLQI score of 4 points or greater, which was considered a minimal clinically important difference,[19] was explored in a *post hoc* analysis. The long-term safety profile was also evaluated.

Statistical analyses

Determination of sample size has been described previously.[16] Secondary and exploratory end points in part B were summarized by using descriptive statistics, and no formal statistical comparisons were performed in part B. No imputation was performed for missing data. Data measured during or after rescue therapy were included in the analyses. The intent-to-treat population, which included all randomized patients who had received at least 1 dose of nemolizumab in part A or B and had at least 1 postdose efficacy assessment, was used for efficacy analyses. All patients who had received at least 1 dose of nemolizumab in part A or B were included in the safety analyses. Efficacy and safety analyses were performed separately for patients who received nemolizumab throughout the 64-week study period (patients randomized to nemolizumab in part A and B) and patients who switched from placebo to nemolizumab at week 12 (patients randomized to placebo in part A and rerandomized to nemolizumab in part B).

RESULTS

In total, 264 patients were randomized to part A; of these, 216 completed part A, and 191 participated in part B, including 38 rerandomized from the placebo group (see Fig E1 in this article's Online Repository at www.jacionline.org). Of the 191 patients who participated in part B, 131 (69%) completed part B. The most common reasons for discontinuation from part B were patient withdrawal from the study (33/191 [17%]), followed by lack of efficacy (10/191 [5%]) and AEs (8/191 [4%]). The intent-to-treat population included 248 patients (211 patients randomized to nemolizumab in part A and 37 patients rerandomized to nemolizumab who received placebo in part A [1 rerandomized patient had no evaluable postdose efficacy data]). The safety population included 249 patients (211 randomized to nemolizumab in part A and 38 rerandomized to nemolizumab who received placebo in part A). Overall, 84% (222/264) of patients who entered the study in part A or B completed a safety follow-up 12 weeks after the last dose of study medication.

Baseline demographics and disease characteristics

Demographics and baseline characteristics for patients participating in part A have been reported.[16] Patients had intense itch at baseline according to the pruritus VAS scale score and moderate-to-severe disease according to the sIGA, BSA affected by AD, and EASI scores.[16] Mean baseline total serum IgE levels are reported in Table E1 in this article's Online Repository at www.jacionline.org. The most common current accompanying allergy was allergic rhinitis (n = 91), and the most frequent history of allergy was asthma (n = 34). Demographics, baseline characteristics, and baseline severity of AD among patients receiving placebo in part A who were rerandomized to nemolizumab Q4W in part B were similar between groups.

Efficacy

The improvement from baseline in pruritus VAS score observed in part A was maintained or increased from week 12

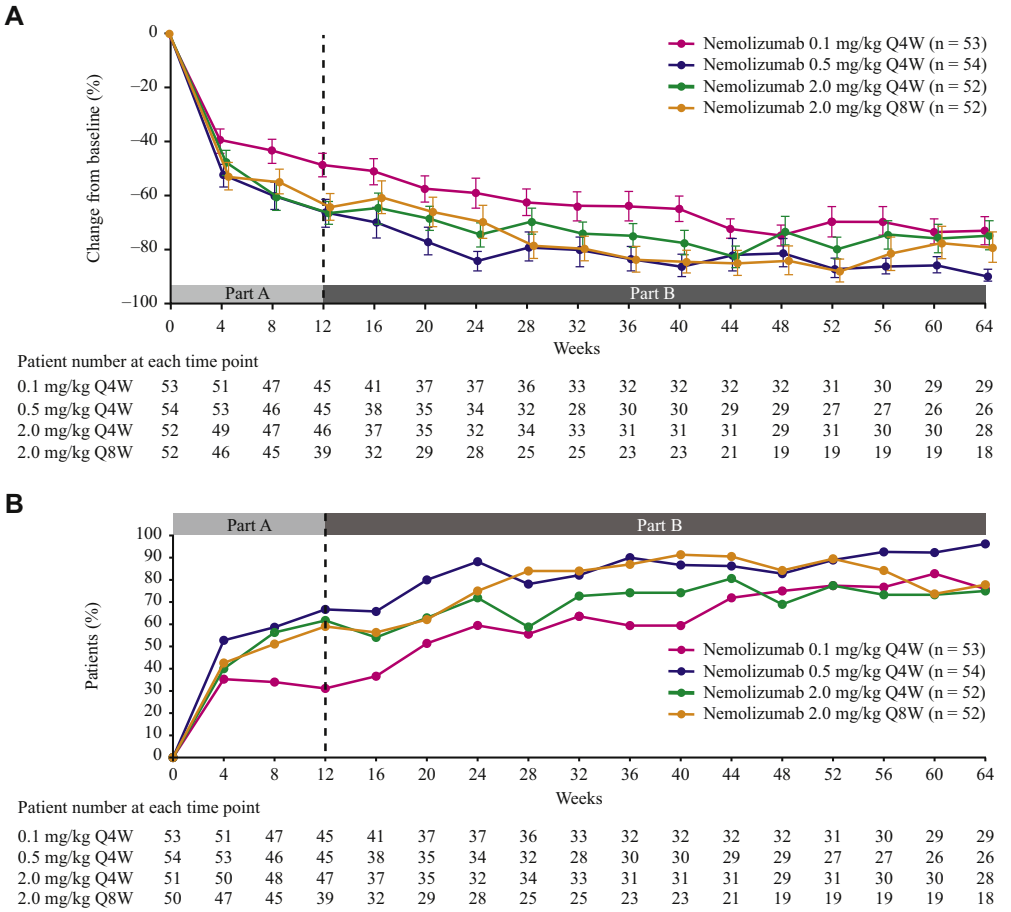

FIG 2. Pruritus VAS (ITT population who received nemolizumab in part A, including data after rescue therapy). **A,** Percentage change from baseline in pruritus VAS score. Data are presented as means (SEs). **B,** Proportion of patients with a pruritus VAS score of less than 30 mm (*post hoc* analysis). *ITT,* Intent-to-treat.

to week 64 in patients randomized to receive nemolizumab throughout the 64-week study period (Fig 2, *A*). The greatest improvement throughout the study was observed in the 0.5-mg/kg nemolizumab group (Table I). The proportion of patients who achieved a pruritus VAS score of less than 30 mm was maintained until week 64 (Fig 2, *B*, and Table I). The mean ± SD percentage change from baseline in EASI score, SCORAD score, BSA affected, and sleep disturbance VAS score and the proportion of patients with a 2-point or greater improvement in sIGA or pruritus VRS scores were also maintained or increased from week 12 to week 64 in patients who had received nemolizumab in part A (Fig 3, *A-C*, and Table I). Approximately two thirds (68%, 68%, and 66%) of patients in the 0.1-, 0.5-, and 2.0-mg/kg Q4W nemolizumab groups, respectively, and almost three quarters (74%) of patients in the 2.0-mg/kg Q8W group who remained on therapy at week 64 had a 75% improvement in EASI score (Table II).

In patients who received placebo in part A and switched to nemolizumab at week 12, a response to treatment in pruritus VAS score was seen by week 16 (ie, 4 weeks after switch to active treatment) and maintained through week 64 (1 year after the switch to active treatment, see Table E2 in this article's Online Repository at www.jacionline.org). Generally, mean ± SD percentage change from week 12 baseline to week 16 in SCORAD score, EASI score, BSA affected, and sleep disturbance VAS score indicated improvement that was maintained or increased from week 16 to week 64 (see Table E2). However, these data were affected by outlier values in the small number of patients included in each group, with a high degree of variability seen at each visit (see Table E2).

Topical glucocorticosteroid use

In patients randomized to receive nemolizumab throughout the 64-week study period, median duration of topical glucocorticosteroid use was lower with increasing nemolizumab dose at or greater than 0.5 mg/kg, from 27.0 weeks (range, 1-62 weeks) in the 0.1-mg/kg Q4W group to 8.0 weeks (range, 1-57 weeks) and 7.5 weeks (range, 1-59 weeks) in the 0.5- and 2.0-mg/kg Q4W groups, respectively, and 3.0 weeks (range, 1-48 weeks) in the 2.0-mg/kg Q8W group (see Table E3 in this article's Online Repository at www.jacionline.org). Median cumulative dose of topical glucocorticosteroid therapy was also lower with increasing nemolizumab dose at or greater than 0.5 mg/kg, from 137.4 g (range, 2-2,245 g) in the 0.1-mg/kg Q4W group to 60.7 g (range, 2-822 g), 55.8 g (range, 1-1,174 g), and 44.7 g (range, 10-250 g) in the 0.5- and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively (see Table E3). However, there was a high degree of variation between patients for duration and dose of topical glucocorticosteroid

TABLE I. Percentage change from baseline in secondary and exploratory end points at week 12 and week 64 (ITT population who received nemolizumab in part A, includes data after rescue therapy)

	Nemolizumab			
End point	**0.1 mg/kg Q4W (n = 53)**	**0.5 mg/kg Q4W (n = 54)**	**2.0 mg/kg Q4W (n = 52)**	**2.0 mg/kg Q8W (n = 52)**
Percentage change in pruritus VAS score, mean ± SD				
Week 12	(n = 45)	(n = 45)	(n = 46)	(n = 39)
	−48.6 ± 28.3	−66.3 ± 33.7	−66.3 ± 29.0	−64.1 ± 31.6
Week 64	(n = 29)	(n = 26)	(n = 28)	(n = 18)
	−73.0 ± 28.4	−89.6 ± 11.2	−74.7 ± 28.4	−79.1 ± 24.2
Patients with pruritus VAS score <30 mm,* no. (%)				
Week 12	(n = 45)	(n = 45)	(n = 47)	(n = 39)
	14 (31)	30 (67)	29 (62)	23 (59)
Week 64	(n = 29)	(n = 26)	(n = 28)	(n = 18)
	22 (76)	25 (96)	21 (75)	14 (78)
Percentage change in EASI score, mean ± SD				
Week 12	(n = 45)	(n = 46)	(n = 46)	(n = 37)
	−35.1 ± 47.9	−47.8 ± 45.4	−46.8 ± 35.2	−42.1 ± 40.8
Week 64	(n = 31)	(n = 28)	(n = 29)	(n = 19)
	−68.5 ± 41.6	−75.8 ± 25.4	−78.9 ± 24.3	−69.3 ± 44.0
Percentage change in SCORAD score, mean ± SD				
Week 12	(n = 39)	(n = 40)	(n = 41)	(n = 32)
	−36.4 ± 22.2	−42.2 ± 30.7	−42.6 ± 27.1	−41.9 ± 20.8
Week 64	(n = 28)	(n = 23)	(n = 26)	(n = 18)
	−56.6 ± 28.3	−64.0 ± 27.7	−66.6 ± 19.9	−63.1 ± 28.0
Patients with ≥2-point improvement in sIGA score, no. (%)				
Week 12	(n = 45)	(n = 46)	(n = 46)	(n = 37)
	12 (27)	16 (35)	11 (24)	7 (19)
Week 64	(n = 31)	(n = 28)	(n = 29)	(n = 19)
	18 (58)	18 (64)	19 (66)	9 (47)
Patients with sIGA score of 0 or 1, no. (%)				
Week 12	(n = 45)	(n = 46)	(n = 46)	(n = 37)
	3 (7)	9 (20)	8 (17)	3 (8)
Week 64	(n = 31)	(n = 28)	(n = 29)	(n = 19)
	11 (35)	9 (32)	11 (38)	6 (32)
Percentage change in BSA affected by AD, mean ± SD				
Week 12	(n = 45)	(n = 46)	(n = 46)	(n = 37)
	−24.5 ± 49.8	−25.3 ± 63.4	−25.9 ± 44.4	−18.6 ± 52.3
Week 64	(n = 31)	(n = 28)	(n = 29)	(n = 19)
	−62.5 ± 40.9	−66.0 ± 36.4	−63.4 ± 40.4	−60.5 ± 56.0
Patients with ≥2-point improvement in pruritus VRS score, no. (%)				
Week 12	(n = 45)	(n = 44)	(n = 46)	(n = 39)
	10 (22)	24 (55)	17 (37)	21 (54)
Week 64	(n = 29)	(n = 26)	(n = 28)	(n = 18)
	17 (59)	20 (77)	17 (61)	13 (72)
Percentage change in sleep disturbance VAS score, mean ± SD				
Week 12	(n = 45)	(n = 44)	(n = 46)	(n = 39)
	−56.9 ± 34.4	−67.8 ± 42.5	−62.0 ± 52.2	−66.9 ± 34.4
Week 64	(n = 29)	(n = 26)	(n = 28)	(n = 18)
	−81.5 ± 31.9	−92.2 ± 11.9	−72.5 ± 38.1	−79.5 ± 32.2
Patients with ≥4-point decrease in DLQI score,* no. (%)				
Week 12	(n = 43)	(n = 44)	(n = 44)	(n = 37)
	31 (72)	27 (61)	34 (77)	25 (68)
Week 64	(n = 30)	(n = 27)	(n = 28)	(n = 18)
	28 (93)	22 (81)	25 (89)	15 (83)

ITT, Intent-to-treat.
**Post hoc* analysis.

therapy, and the number of evaluable patients within the total number of patients receiving glucocorticosteroid therapy was limited (18/30, 17/24, and 20/27 in the 0.1-, 0.5-, and 2.0-mg/kg Q4W groups, respectively, and 11/24 in the 2.0-mg/kg Q8W group). The proportion of patients receiving "very potent" topical glucocorticosteroids was similar among groups, whereas the proportion of patients receiving "potent" agents was greatest in the lowest nemolizumab Q4W group (63% [19/30] in the 0.1-mg/kg group, 42% [10/24] in the 0.5-mg/kg group, and 56% [15/27] in the 2.0-mg/kg group). Duration

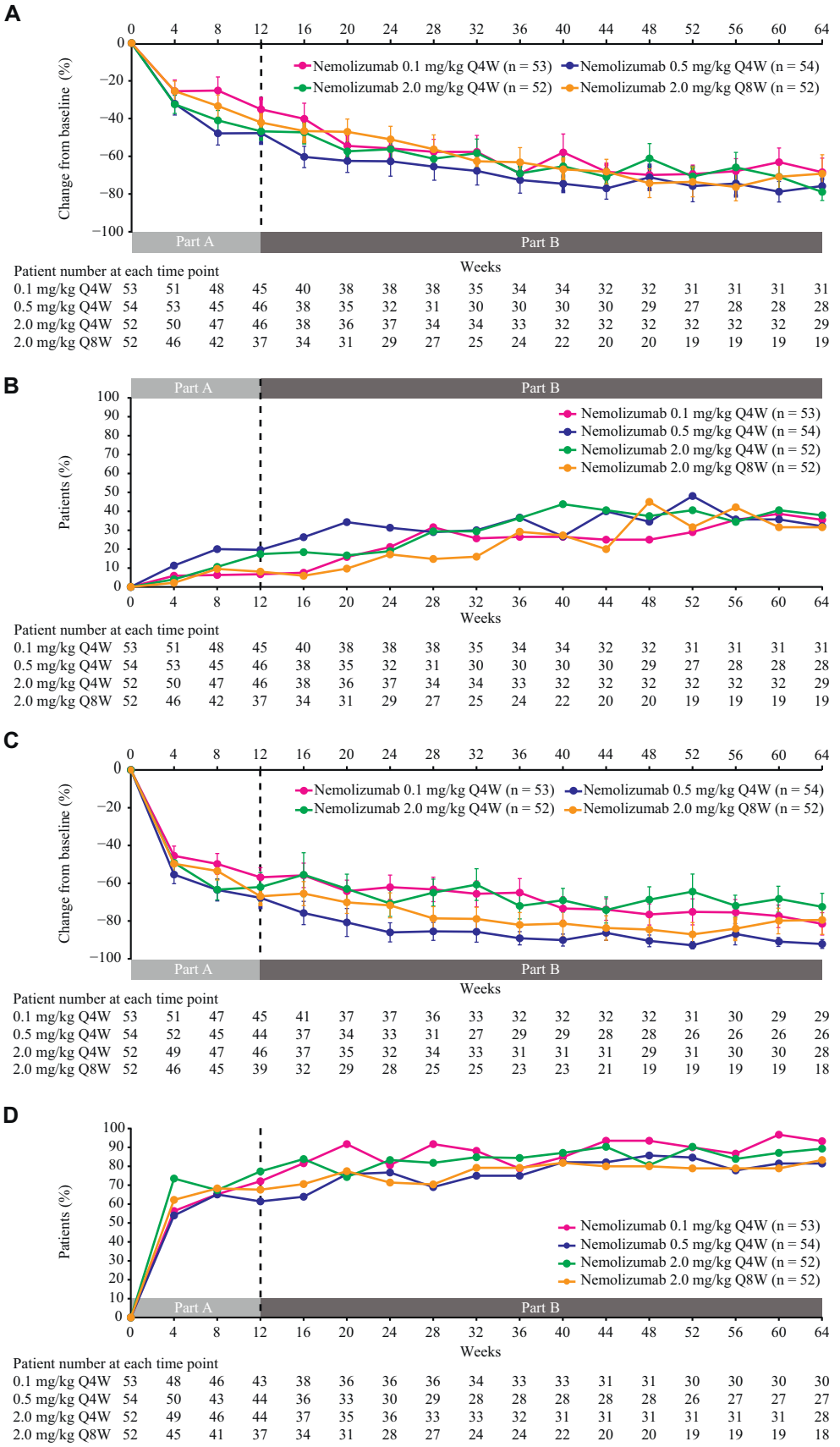

FIG 3. Change from baseline in key secondary and exploratory end points (ITT population who received nemolizumab in part A, includes data after rescue therapy). **A,** Percentage change in EASI score (mean ± SE). **B,** Proportion of patients with an sIGA score of 0 or 1 (percentage). **C,** Percentage change from baseline in sleep disturbance VAS (mean ± SE). **D,** Proportion of patients with a 4-point or greater decrease in DLQI (percentage; *post hoc* analysis). *ITT*, Intent-to-treat.

TABLE II. Patients with a 25%, 50%, and 75% improvement from baseline in pruritus VAS and EASI scores at week 12 and week 64 (ITT population who received nemolizumab in part A, includes data after rescue therapy)

	Nemolizumab							
	0.1 mg/kg Q4W (n = 53)		0.5 mg/kg Q4W (n = 54)		2.0 mg/kg Q4W (n = 52)		2.0 mg/kg Q8W (n = 52)	
End point	Week 12	Week 64	Week 12	Week 64	Week 12	Week 64	Week 12	Week 64
Pruritus VAS	(n = 45)	(n = 29)	(n = 45)	(n = 26)	(n = 46)	(n = 28)	(n = 39)	(n = 18)
25%	35 (78)	26 (90)	38 (84)	26 (100)	42 (91)	26 (93)	33 (85)	17 (94)
50%	22 (49)	23 (79)	32 (71)	26 (100)	31 (67)	22 (79)	29 (74)	16 (89)
75%	8 (18)	19 (66)	24 (53)	24 (92)	21 (46)	19 (68)	18 (46)	14 (78)
EASI	(n = 45)	(n = 31)	(n = 46)	(n = 28)	(n = 46)	(n = 29)	(n = 37)	(n = 19)
25%	27 (60)	27 (87)	32 (70)	28 (100)	34 (74)	27 (93)	27 (73)	17 (89)
50%	21 (47)	23 (74)	25 (54)	20 (71)	22 (48)	26 (90)	16 (43)	15 (79)
75%	13 (29)	21 (68)	18 (39)	19 (68)	11 (24)	19 (66)	8 (22)	14 (74)

Data are shown as numbers (percentages).
ITT, Intent-to-treat.

of use and cumulative dose of topical glucocorticosteroids in evaluable patients tended to be lower with increasing dose for patients receiving "potent," "moderately potent," and "weak" agents (see Table E3); available data were limited for "very potent" agents.

QoL

DLQI total score decreased progressively throughout the study in patients randomized to nemolizumab Q4W and Q8W throughout the 64-week period, with a greater proportion of patients demonstrating a 4-point or greater decrease in total score at week 64 versus week 12 (Fig 3, *D*, and Table I). A similar trend was observed in patients who had received placebo in part A (see Table E2).

Safety

Overall, no new safety concerns were identified after long-term use of nemolizumab. In patients randomized to receive nemolizumab throughout the study period (64 weeks), a similar proportion had at least 1 AE (83% to 89% of patients) or at least 1 treatment-related AE (37% to 48%) over the course of the study (Table III). The most common AEs in these patients (≥5% of patients randomized to nemolizumab throughout the study period) were nasopharyngitis (27%), exacerbation of AD (25%), increased blood creatine phosphokinase (11%), upper respiratory tract infection (9%), headache (8%), peripheral edema (6%), and impetigo (6%). The most common treatment-related AEs (≥2% patients randomized to nemolizumab throughout the study period) were exacerbation of AD (8%), upper respiratory tract infection (4%), nasopharyngitis (4%), peripheral edema (3%), increased blood creatine phosphokinase level (3%), and injection-site reaction (2%). All treatment-related AEs, except nasopharyngitis and injection-site reactions, occurred at a slightly higher incidence in the 2.0-mg/kg Q4W group than in the other study groups. The proportion of patients randomized to receive nemolizumab throughout the 64-week study period who experienced new-onset AEs decreased over time, with the majority of AEs reported in the first 12 weeks of the study (see Table E4 in this article's Online Repository at www.jacionline.org). The majority of AEs during the study were mild or moderate in intensity. SAEs occurred in 9 (17%) patients receiving 2.0 mg/kg nemolizumab Q8W versus 3 to 4 (6% to 8%) patients across the Q4W treatment groups (Table III). Six SAEs reported in 5 patients were considered related to study therapy. Five patients (1 in the 0.5-mg/kg Q4W group, 2 in the 2.0-mg/kg Q4W group, and 2 in the 2.0-mg/kg Q8W group) had 1 SAE of exacerbation of AD, which was considered treatment related in 1 patient. The proportion of patients experiencing new-onset SAEs was distributed evenly over the study duration (see Table E4). After adjustment for drug exposure, rates of AEs and SAEs in patients randomized to nemolizumab for the 64-week study period were higher in the 2.0-mg/kg Q8W group than the 0.1-, 0.5-, and 2.0-mg/kg Q4W groups (Table IV); however, no increase in specific AEs was observed. Discontinuation of study therapy because of AEs in patients randomized to receive nemolizumab throughout the 64-week study period occurred in 7 (13%), 3 (6%), 5 (10%), and 6 (12%) patients in the nemolizumab 0.1-, 0.5-, and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively (see Table E5 in this article's Online Repository at www.jacionline.org). Ten patients discontinued the study prematurely because of exacerbation of AD, all in part A.

In patients rerandomized from placebo to nemolizumab in part B, AEs were reported in 67% to 92% of patients across treatment groups (see Table E6 in this article's Online Repository at www.jacionline.org). The most frequent AEs were similar to those seen during the study as a whole (see Table E6). One SAE was reported in 1 patient who had received placebo during part A. Two patients who received placebo during part A discontinued treatment because of AEs after randomization to nemolizumab in part B.

The majority of injection-related reactions (IRRs) occurred during part A of the study, with no trend of a dose-related effect (12 patients had 13 events in part A and 4 patients had 5 events in part B). Almost all IRRs were local reactions, predominantly mild in severity, and were mostly considered treatment related. One IRR resulted in discontinuation of study treatment (dermatitis exfoliative).

DISCUSSION

We describe a double-blind, randomized, long-term extension study that evaluated the efficacy and tolerability of nemolizumab, an anti–IL-31 receptor A mAb, for the treatment of patients with AD inadequately controlled by using topical therapy. The study demonstrated that improvements in pruritus, dermatitis, and sleep measures versus placebo in the 12-week placebo-controlled portion of the study (part A)[16] were

TABLE III. AEs over the total 64-week study period in patients randomized to nemolizumab throughout the study period (safety population, events reported during overall treatment period [baseline to 12 weeks after the last dose])

Event	Nemolizumab			
	0.1 mg/kg Q4W (n = 53)	0.5 mg/kg Q4W (n = 54)	2.0 mg/kg Q4W (n = 52)	2.0 mg/kg Q8W (n = 52)
Total no. of AEs	226	202	219	186
Patients with ≥1 AE, no. (%)	47 (89)	46 (85)	45 (87)	43 (83)
Related to study treatment, no. (%)	20 (38)	20 (37)	25 (48)	19 (37)
Patients with ≥1 SAE,* no. (%)	3 (6)	3 (6)	4 (8)	9 (17)
Related to study treatment, no. (%)	0	0	2 (4)	3 (6)
Patients with AEs leading to withdrawal from treatment, no. (%)	7 (13)	3 (6)	5 (10)	6 (12)†
Related to study treatment, no. (%)	3 (6)	3 (6)	3 (6)	2 (4)
AEs in ≥5% of patients, no. (%)				
Nasopharyngitis	15 (28)	14 (26)	15 (29)	12 (23)
Exacerbation of AD	15 (28)	13 (24)	14 (27)	11 (21)
Increased blood creatine phosphokinase	5 (9)	3 (6)	9 (17)	6 (12)
Upper RTI	6 (11)	3 (6)	5 (10)	5 (10)
Headache	3 (6)	6 (11)	5 (10)	2 (4)
Peripheral edema‡	2 (4)	3 (6)	6 (12)	2 (4)
Impetigo	6 (11)	3 (6)	0	3 (6)
Influenza	5 (9)	1 (2)	2 (4)	0
Pharyngitis	1 (2)	3 (6)	3 (6)	1 (2)
Bronchitis	3 (6)	2 (4)	2 (4)	0
Cough	2 (4)	3 (6)	1 (2)	1 (2)
Arthralgia	1 (2)	2 (4)	3 (6)	2 (4)
Lymphadenopathy	3 (6)	1 (2)	1 (2)	2 (4)
Cystitis	1 (2)	3 (6)	1 (2)	1 (2)
Sinusitis	1 (2)	3 (6)	1 (2)	1 (2)
Urticaria	1 (2)	3 (6)	1 (2)	1 (2)
Folliculitis	1 (2)	0	1 (2)	3 (6)
Dizziness	3 (6)	0	0	2 (4)
Asthma	3 (6)	0	1 (2)	0

RTI, Respiratory tract infection.

*SAEs (number of events): exacerbation of AD (n = 5), dermatitis exfoliative (n = 1), rash (n = 1), urticaria (n = 1), infection (n = 2), herpes simplex (n = 1), herpes zoster (n = 1), pyelonephritis (n = 1), pyoderma (n = 1), skin infection (n = 1), atrial fibrillation (n = 1), coronary artery stenosis (n = 1), grand mal convulsion (n = 1), Parkinson disease (n = 1), lymphadenopathy (n = 1), cataract (n = 1), nonalcoholic steatohepatitis (n = 1), joint dislocation (n = 1), and upper limb fracture (n = 1).

†One patient withdrew from the study because of an AE after the last study drug injection and is not listed.

‡Peripheral edema was reported predominantly in the lower extremities and varied in duration (3-176 days). Severe peripheral edema was reported for 1 patient in the 0.1-mg/kg Q4W group (edema of bilateral lower extremities) and 2 patients in the 2.0-mg/kg Q4W group (edema of legs and edema of bilateral upper extremities). Treatment was required for 6 patients overall across all treatment groups. No patients withdrew from the study owing to peripheral edema. No abnormalities related to the presentation of peripheral edema (eg, renal or cardiac function) were reported.

maintained or progressively increased with long-term treatment for up to 64 weeks (extension phase: part B). In keeping with results from part A, although the study was not designed to compare formally the different dose groups, there was no evidence that 2.0 mg/kg nemolizumab administered Q4W or Q8W was more effective than the 0.5-mg/kg dose. In part B patients were allowed to use mild topical glucocorticosteroids, with potent or very potent topical glucocorticosteroids permitted as rescue therapy. Over the course of the study, the duration and cumulative dose of concomitant topical glucocorticosteroid therapy was lower in patients receiving higher (≥0.5 mg/kg) doses of nemolizumab; however, limited patient numbers preclude any conclusions. These findings propose that the absence of a dose-dependent response, which would have resulted in increased efficacy with higher doses of nemolizumab, might have been affected by the greater use of topical glucocorticosteroid therapy in patients in the 0.1-mg/kg group. Therefore concomitant use of topical glucocorticosteroids might strengthen the antidermatitis effect of nemolizumab and will be assessed in ongoing trials.[20,21]

AD and the accompanying pruritus impairs QoL in patients with the disease.[5,6,22] The reduction in DLQI scores observed during part A of the study[16] was maintained throughout the long-term extension, suggesting prolonged alleviation of the effect of symptoms on daily life. Although improvements in efficacy end points were observed from week 16 in patients who switched from placebo to nemolizumab at week 12, the small number of patients in each dose group and the high attrition rate and high degree of variability at each visit preclude drawing conclusions. However, these findings are consistent with the early improvement in pruritus observed within week 1 of nemolizumab treatment in part A of the study.[16]

Overall, nemolizumab was well tolerated over 64 weeks. The safety profile was comparable with that seen in part A, with no new AEs observed in the extension study. The incidence of IRRs was lower in part B, suggesting that tolerability to nemolizumab injections improved over time.

AD is a T cell–mediated disease: T_H2 cells are the predominant source of the proinflammatory cytokine IL-31 in patients with AD and trigger cytokine-induced itching through binding of IL-31 to IL-31 receptor A on sensory neurons in the skin.[10,12,13] In addition to a role in pruritus, IL-31 might be involved in the recruitment of inflammatory cells to affected skin areas, perpetuating the

TABLE IV. Exposure-adjusted AEs (safety population, events reported during exposure period [baseline to 4 weeks after last dose])

		Nemolizumab*			
	Placebo† (n = 53)	0.1 mg/kg Q4W (n = 53)	0.5 mg/kg Q4W (n = 54)	2.0 mg/kg Q4W (n = 52)	2.0 mg/kg Q8W (n = 52)
Total exposure period (patient-years)	11.4	45.6	42.4	45.1	35.0
AEs					
Patients with ≥1 AE, no.	36	47	45	45	42
Total no. of AEs, no.	105	208	193	211	172
Event/100 patient-years	924.1	455.9	455.1	468.3	491.3
Nasopharyngitis	70	70	68	49	60
Exacerbation of AD	70	42	35	36	34
Increased blood creatine phosphokinase	26	11	14	31	11
Upper RTI	62	18	19	20	14
Headache	—	13	21	11	9
Peripheral edema	—	7	7	18	9
Impetigo	—	13	7	—	9
SAEs					
Patients with ≥1 SAE, no.	1	2	2	4	8
Total no. of SAEs	1	2	2	6	10
Event/100 patient-years	8.8	4.4	4.7	13.3	28.6

Event rates of AEs are presented as the number of events per 100 patient-years based on the ratio of observed number of events to total number of patient-years of exposure.
RTI, Respiratory tract infection.
*Patients who received nemolizumab during part A and part B.
†Patients who received placebo during part A.

inflammatory response and contributing to ongoing disease.[12] The role of the IL-31 signaling pathway in immune regulation remains to be fully elucidated and might be tissue specific.[23-26] IL-31 also dysregulates the physical and functional properties of the skin barrier, whereas low levels stimulate expression of antimicrobial peptides.[14] Therefore blocking IL-31–mediated signaling can attenuate multiple pathogenic mechanisms in patients with AD, although complete inhibition might be undesirable.[14]

Treatment options are limited for patients with moderate-to-severe AD that is inadequately controlled by topical treatments. The systemic immunosuppressive therapy cyclosporine is used for such patients but is associated with notable side effects,[9,27] mostly on prolonged use. Therefore new agents with novel mechanisms of action are required. The anti–IL-4 receptor α mAb dupilumab demonstrated improvements in disease severity and pruritus in patients with inadequately controlled AD[28,29] and was recently approved in the United States and Europe.[30,31] Although cross-trial comparisons should be considered with caution because of different patient populations and study designs, both dupilumab and nemolizumab might be new treatment options for this difficult-to-treat patient population. Nemolizumab therapy is under investigation in pediatric AD in phase I and phase III studies[21,32] supported by findings that IL-31 mRNA expression is increased in skin biopsy specimens from children with AD compared with adults with AD, including in nonlesional skin.[33]

The limitations of the current study should be considered when reviewing the findings. The study had a relatively small sample size and a high attrition rate, with discontinuations predominantly caused by patient withdrawal from the study. There was also no placebo arm in part B of the study, which might have introduced bias because of administration of only the active drug, and the study might have been affected by intersite and interinvestigator variability.

In summary, nemolizumab was efficacious and overall well tolerated when administered for up to 64 weeks in patients with moderate-to-severe AD that is inadequately controlled by previous topical therapy. Treatment with nemolizumab resulted in clinically meaningful reductions in pruritus and dermatitis. No new safety concerns were identified with long-term nemolizumab use. Our findings support previous observations for use of nemolizumab in patients with moderate-to-severe AD[15,16] and encourage additional clinical trials to further evaluate the use of nemolizumab in this setting.

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Clinical implications: Long-term phase II study data (up to 64 weeks) suggest that nemolizumab might be a new treatment option in adults with moderate-to-severe AD that is controlled inadequately by topical therapy.

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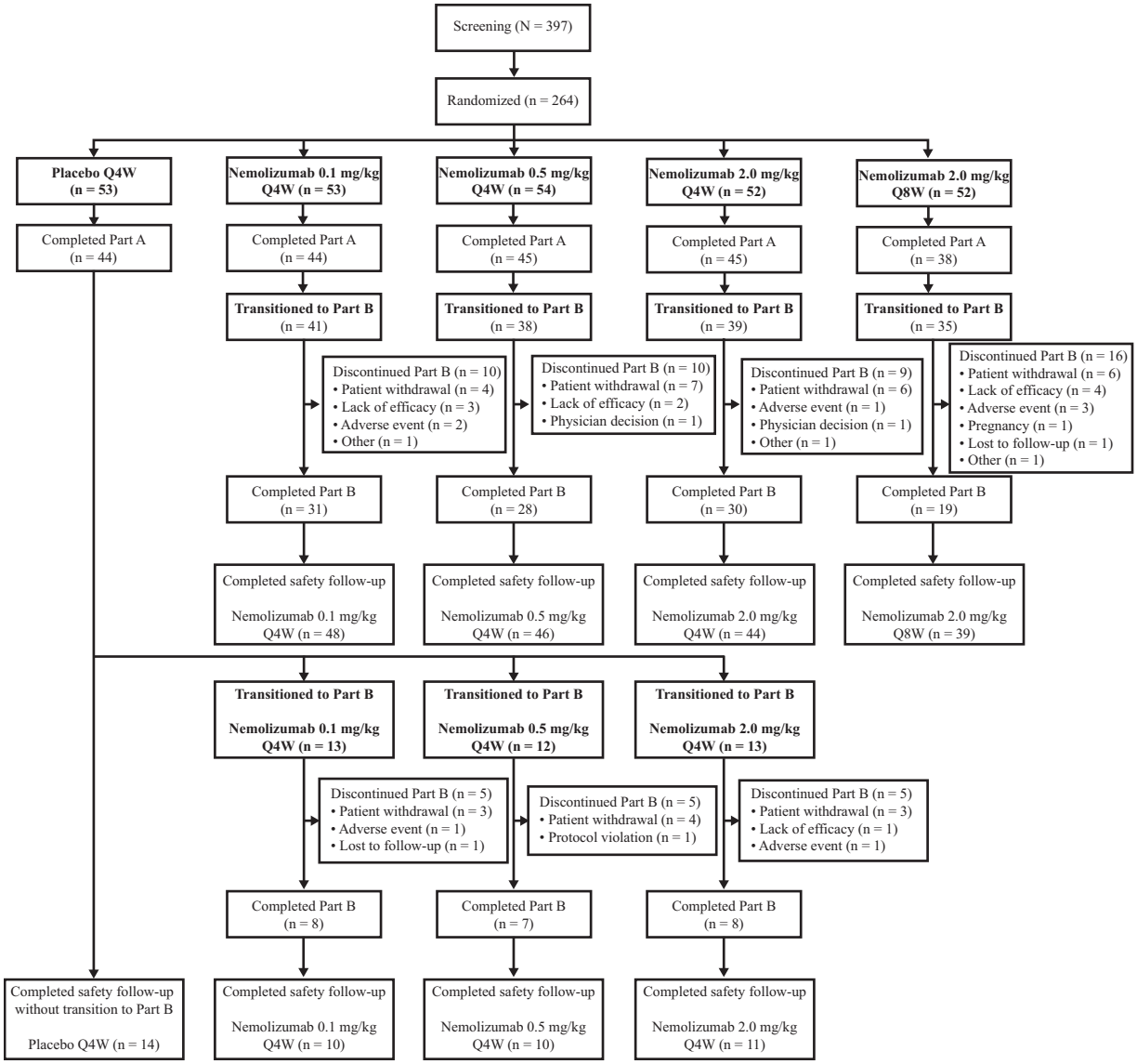

FIG E1. Patient disposition. Completion of safety follow-up for patients who received nemolizumab in part A is the sum of patients who completed part A and a safety follow-up visit but who did not transition to part B plus patients who completed part B and a safety follow-up visit.

TABLE E1. Baseline total serum IgE levels (ITT population)

		Nemolizumab			
	Placebo (n = 53)*	**0.1 mg/kg Q4W (n = 53)**	**0.5 mg/kg Q4W (n = 54)**	**2.0 mg/kg Q4W (n = 52)**	**2.0 mg/kg Q8W (n = 52)**
Total serum IgE levels (kU/L)					
	(n = 53)	(n = 53)	(n = 54)	(n = 51)	(n = 52)
Mean	6,338	10,599	5,496	6,247	8,997
SD	11,389	15,919	9,074	17,182	20,433

ITT, Intent-to-treat.

*Patients who received placebo during part A.

TABLE E2. Percentage change from baseline (week 12) in secondary and exploratory end points at week 16 (4 weeks after first nemolizumab dose in part B) and week 64 (ITT population who received placebo in part A, includes data after rescue therapy)

	Patients rerandomized from placebo to nemolizumab in Part B		
End point	**0.1 mg/kg Q4W (n = 12)**	**0.5 mg/kg Q4W (n = 12)**	**2.0 mg/kg Q4W (n = 13)**
Percentage change in pruritus VAS score, mean ± SD			
Week 16	(n = 12) −33.3 ± 35.4	(n = 12) −39.3 ± 33.1	(n = 13) −55.5 ± 30.3
Week 64	(n = 8) −44.7 ± 32.0	(n = 5) −41.3 ± 64.2	(n = 6) −47.5 ± 72.7
Percentage change in EASI score, mean ± SD			
Week 16	(n = 12) −5.9 ± 45.2	(n = 12) −27.8 ± 33.6	(n = 11) 30.4 ± 156.5
Week 64	(n = 8) −62.7 ± 19.4	(n = 7) 6.3 ± 171.2	(n = 7) −52.9 ± 65.2
Percentage change in SCORAD score, mean ± SD			
Week 16	(n = 10) −12.3 ± 19.2	(n = 11) −22.5 ± 25.5	(n = 11) −21.6 ± 34.4
Week 64	(n = 6) −40.6 ± 17.9	(n = 6) −9.3 ± 86.5	(n = 7) −46.2 ± 60.9
Percentage change in BSA affected by AD, mean ± SD			
Week 16	(n = 12) 30.1 ± 134.9	(n = 12) −6.2 ± 28.1	(n = 11) 21.4 ± 100.2
Week 64	(n = 8) −33.0 ± 29.6	(n = 7) −50.4 ± 59.4	(n = 7) −64.6 ± 42.0
Percentage change in sleep disturbance VAS, mean ± SD			
Week 16	(n = 12) −20.5 ± 41.0	(n = 12) −46.6 ± 40.1	(n = 13) −52.5 ± 33.9
Week 64	(n = 8) −47.2 ± 34.8	(n = 5) 9.4 ± 162.0	(n = 6) −72.5 ± 30.4
Proportion of patients with ≥4-point decrease in DLQI score,* no. (%)			
Week 16	(n = 12) 6 (50)	(n = 12) 8 (67)	(n = 12) 10 (83)
Week 64	(n = 8) 6 (75)	(n = 7) 8 (86)	(n = 8) 8 (100)

ITT, Intent-to-treat.
**Post hoc* analysis.

TABLE E3. Duration of use and cumulative dose of topical glucocorticosteroids throughout the study period from baseline* to end of treatment overall and by potency* (ITT population who received nemolizumab in part A)

	Nemolizumab			
Topical glucocorticosteroid use†	**0.1 mg/kg Q4W (n = 53)**	**0.5 mg/kg Q4W (n = 54)**	**2.0 mg/kg Q4W (n = 52)**	**2.0 mg/kg Q8W (n = 52)**
Overall	(n = 18)	(n = 17)	(n = 20)	(n = 11)
Duration of use (wk)	27.0 (1-62)	8.0 (1-57)	7.5 (1-59)	3.0 (1-48)
Cumulative amount used (g)	137.4 (2-2,245)	60.7 (2-822)	55.8 (1-1,174)	44.7 (10-250)
By potency				
Very potent	(n = 1)	(n = 2)	(n = 0)	(n = 0)
Duration of use (wk)	1.0	40.0 (40-40)	—	—
Cumulative amount used (g)	1.9	129.1 (60-198)	—	—
Potent	(n = 13)	(n = 9)	(n = 12)	(n = 7)
Duration of use (wk)	14.0 (2-62)	4.0 (1-23)	5.5 (1-24)	3.0 (1-4)
Cumulative amount used (g)	72.0 (24-1,015)	19.2 (2-38)	21.2 (1-166)	32.8 (12-200)
Moderately potent	(n = 9)	(n = 8)	(n = 6)	(n = 4)
Duration of use (wk)	24.0 (3-62)	6.0 (2-51)	6.0 (1-59)	2.5 (2-4)
Cumulative amount used (g)	70.2 (3-214)	63.2 (6-586)	50.7 (2-1,174)	7.1 (2-39)
Weak	(n = 3)	(n = 5)	(n = 4)	(n = 4)
Duration of use (wk)	28.0 (21-52)	23.0 (1-36)	9.0 (4-13)	3.5 (1-9)
Cumulative amount used (g)	581.0 (96-620)	41.5 (6-635)	108.1 (18-271)	11.6 (2-80)
Unknown	(n = 4)	(n = 5)	(n = 2)	(n = 3)
Duration of use (wk)	22.5 (3-52)	8.0 (3-52)	50.5 (49-52)	29.0 (4-48)
Cumulative amount used (g)	87.4 (33-2,218)	9.5 (2-320)	415.8 (89-743)	100.0 (45-105)

Data are shown as medians (ranges).

ITT, Intent-to-treat.

*Baseline values are unavailable (zero) because patients were not permitted to use potent or very potent topical glucocorticosteroids within 2 weeks before randomization or mild or moderately potent topical glucocorticosteroids within 1 week before randomization. Use of topical glucocorticosteroids was not permitted during part A of the study, except as a rescue therapy at or after week 4 (see Ruzicka T, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med 2017;376:826-35).

†Potency of topical glucocorticosteroids, as defined by the National Institute for Health and Care Excellence (see Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. Clinical guideline. 2007. Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0009229/pdf/PubMedHealth_PMH0009229.pdf. Accessed March 1, 2017).

TABLE E4. New-onset AEs and SAEs by time period in patients randomized to receive nemolizumab throughout the study period (safety population)

	Period						
	Any period	**0-12 wk**	**>12-24 wk**	**>24-36 wk**	**>36-48 wk**	**>48-64 wk**	**Follow-up**
AEs							
Nemolizumab, 0.1 mg/kg Q4W							
No. of patients	53	53	41	38	33	32	51
Patients with any AE, no. (%)	47 (89)	37 (70)	6 (15)	3 (8)	1 (3)	—	—
Nemolizumab, 0.5 mg/kg Q4W							
No. of patients	54	54	38	34	30	30	49
Patients with any AE, no. (%)	46 (85)	37 (69)	5 (13)	1 (3)	—	2 (7)	1 (2)
Nemolizumab, 2.0 mg/kg Q4W							
No. of patients	52	52	39	36	33	32	49
Patients with any AE, no. (%)	45 (87)	39 (75)	2 (5)	1 (3)	2 (6)	—	—
Nemolizumab, 2.0 mg/kg Q8W							
No. of patients	52	52	35	30	25	20	43
Patients with any AE, no. (%)	43 (83)	38 (73)	1 (3)	3 (10)	—	—	1 (2)
SAEs							
Nemolizumab, 0.1 mg/kg Q4W							
No. of patients	53	53	41	38	33	32	51
Patients with any SAE, no. (%)	3 (6)	1 (2)	—	—	1 (3)	—	1 (2)
Nemolizumab, 0.5 mg/kg Q4W							
No. of patients	54	54	38	34	30	30	49
Patients with any SAE, no. (%)	3 (6)	—	—	—	—	2 (7)	1 (2)
Nemolizumab, 2.0 mg/kg Q4W							
No. of patients	52	52	39	36	33	32	49
Patients with any SAE, no. (%)	4 (8)	3 (6)	1 (3)	—	—	—	—
Nemolizumab, 2.0 mg/kg Q8W							
No. of patients	52	52	35	30	25	20	43
Patients with any SAE, no. (%)	9 (17)	4 (8)	2 (6)	1 (3)	1 (4)	1 (5)	1 (2)

TABLE E5. AEs leading to withdrawal from treatment in patients randomized to nemolizumab throughout the study period (safety population, events reported during overall treatment period [baseline to 12 weeks following last dose])

	Nemolizumab			
Event	**0.1 mg/kg Q4W (n = 53)**	**0.5 mg/kg Q4W (n = 54)**	**2.0 mg/kg Q4W (n = 52)**	**2.0 mg/kg Q8W (n = 52)**
Patients with AEs leading to withdrawal from treatment, no. (%)	7 (13)	3 (6)	5 (10)	6 (12)*
Total no. of events	7	5	8	7
Exacerbation of AD	2	3	3	2
Impetigo	1	0	0	1
Kaposi varicelliform eruption	1	0	0	1
Lymphadenopathy	1	0	1	0
Skin infection	0	1	1	0
Asthma	1	0	0	0
Atopic keratoconjunctivitis	0	0	1	0
Dermal cyst	1	0	0	0
Dermatitis exfoliative	0	0	0	1
Erysipelas	0	0	1	0
Grand mal convulsion	0	0	0	1
Palindromic rheumatism	0	0	1	0
Restlessness	0	1	0	0
Sinus tachycardia	0	0	0	1

*One patient withdrew from the study because of an AE after the last study drug injection and is not listed.

TABLE E6. AEs in part B in patients randomized to receive placebo in part A (safety population)

	Patients rerandomized from placebo to nemolizumab in part B		
Event	**0.1 mg/kg Q4W (n = 13)**	**0.5 mg/kg Q4W (n = 12)**	**2.0 mg/kg Q4W (n = 13)**
Total no. of AEs	37	27	57
Patients with ≥1 AE, no. (%)	9 (69)	8 (67)	12 (92)
Related to study treatment, no. (%)	4 (31)	1 (8)	4 (31)
Patients with ≥1 SAE, no. (%)	0	0	1 (8)*
Related to study treatment, no. (%)	0	0	1 (8)
Patients with AEs leading to withdrawal from treatment, no. (%)	1 (8)†	0	1 (8)‡
Related to study treatment, no. (%)	1 (8)	0	1 (8)
AEs in ≥2 patients, no. (%)			
Nasopharyngitis	2 (15)	3 (25)	4 (31)
Exacerbation of AD	2 (15)	3 (25)	1 (8)
Increased blood creatine phosphokinase	2 (15)	1 (8)	2 (15)
Headache	2 (15)	1 (8)	1 (8)
Abdominal pain	1 (8)	0	1 (8)
Asthma	1 (8)	1 (8)	0
Back pain	0	1 (8)	1 (8)
Contact dermatitis	1 (8)	0	1 (8)
Contusion	0	0	2 (15)
Cough	1 (8)	0	1 (8)
Eyelid edema	1 (8)	0	1 (8)
Herpes zoster	0	0	2 (15)
Impetigo	1 (8)	1 (8)	0
Otitis externa	0	2 (17)	0
Peripheral edema	0	0	2 (15)

*SAE of diverticulitis.
†Asthma.
‡Bronchial hyperreactivity.