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;■■■:■■■-■■■.)

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 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

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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

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 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