(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 August 2019 (15.08.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/155427 A1

(51) International Patent Classification:
A61K 39/00 (2006.01) *A61P 17/04* (2006.01)

(21) International Application Number:
PCT/IB2019/051051

(22) International Filing Date:
08 February 2019 (08.02.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/628,714 09 February 2018 (09.02.2018) US

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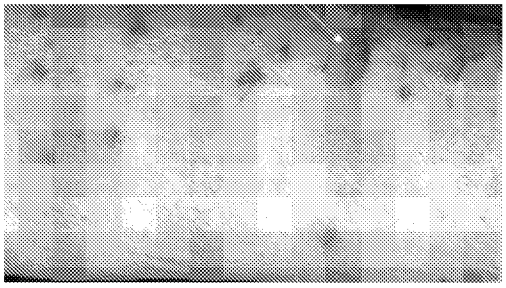
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: NEMOLIZUMAB IN THE TREATMENT OF ATOPIC DERMATITIS WITH MODERATE TO SEVERE EXCORIATION

FIG. 1C



Severe (score = 3)

(57) Abstract: Disclosed herein are methods for selectively treating atopic dermatitis (AD) in a subject having skin excoriations, pharmaceutical compositions for use in the treatment of atopic dermatitis in a subject having skin excoriations, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having skin excoriations, and methods of identifying a subject having atopic dermatitis that is likely to respond to nemolizumab treatment or an equivalent thereof.

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NEMOLIZUMAB IN THE TREATMENT OF ATOPIC DERMATITIS WITH MODERATE TO SEVERE EXCORIATION

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 62/628,714 filed February 9, 2018, the entire contents of which are incorporated herein by reference.

FIELD

[0002] Described herein are methods for selectively treating atopic dermatitis (AD) in a subject having skin excoriations, pharmaceutical compositions for use in the treatment of atopic dermatitis in a subject having skin excoriations, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having skin excoriations, and methods of identifying a subject having atopic dermatitis that is likely to respond to nemolizumab treatment or an equivalent thereof.

BACKGROUND

[0003] The following discussion is provided to aid the reader in understanding the disclosure and is not admitted to describe or constitute prior art thereto.

[0004] Atopic dermatitis ("AD," also known as atopic eczema) is a chronic inflammation of the skin that can result in itchy (pruritic), swollen, red, and/or cracked skin. AD can be triggered by an immune response to antigens, irritants, or mechanical irritation. AD patients with pruritus may exhibit behaviors such as skin scratching or skin massage. In some cases, AD patients with pruritus may abstain from massaging or scratching. Persistent skin scratching can lead to exacerbation of AD, interruption of sleep, and a negative effect on a patient's psychosocial well-being. Some AD patients have pruritus even if other symptoms are effectively managed through treatment.

[0005] Approved treatments for pruritus include topical glucocorticoids and antihistamines, but their effects in AD patients are limited and/or associated with significant side effects. Approved treatments for AD include calcineurin inhibitors, emollients, and topical glucocorticoids. However, these treatments have limited efficacy among AD patients with moderate-to-severe AD. Although oral antihistamines are frequently prescribed for atopic dermatitis, such drugs have little to no effect in relieving pruritus. Nemolizumab (CIM331) is a humanized monoclonal antibody that binds to interleukin-31 receptor A (IL-31RA) on cells, including neurons, to inhibit interleukin-31 signaling. Interleukin-31 is thought to play a role in the pathogenesis of AD and therefore may be effective in treating AD. However, there remains a need to develop novel therapeutic regimes to treat patients with AD, particularly those suffering from excoriations or difficulty sleeping, and for identify patients that are likely to respond to AD treatment.

SUMMARY

[0006] Provided herein are methods for selectively treating atopic dermatitis (AD) in a subject having skin excoriations, pharmaceutical compositions for use in the treatment of atopic dermatitis in a subject having one or more skin excoriations, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having skin excoriations, and methods of identifying a subject having atopic dermatitis that is likely to respond to nemolizumab treatment or an equivalent thereof.

[0007] In accordance with some embodiments, there are provided methods of selectively treating atopic dermatitis in a subject having skin excoriations, the method comprising, consisting of, or consisting essentially of administering an effective amount of nemolizumab or an equivalent thereof to the subject.

[0008] In some embodiments of the methods, the skin excoriations are moderate to severe. In some embodiments of the methods, the effective amount of nemolizumab or the equivalent thereof ranges from about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to

about 10 mg/kg. In particular embodiments, the effective amount of nemolizumab or the equivalent thereof is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, or about 2.5 mg/kg. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered by a topical or parenteral route. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered subcutaneously. In some embodiments, the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

[0009] In accordance with some embodiments, there are provided pharmaceutical compositions for use in the treatment of atopic dermatitis in a subject, wherein the subject has been determined to have one or more skin excoriations, the composition comprising, consisting of, or consisting essentially of nemolizumab or an equivalent thereof.

[0010] In some embodiments of the pharmaceutical compositions, the skin excoriations are moderate to severe. In some embodiments, the pharmaceutical composition further comprises a carrier. In some embodiments, the carrier is a pharmaceutically acceptable carrier.

[0011] In accordance with some embodiments, there are provided uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having one or more skin excoriations. In some embodiments, the skin excoriations are moderate to severe.

[0012] In accordance with some embodiments, there are provided methods of identifying a subject having atopic dermatitis that is likely to respond to nemolizumab treatment or an equivalent thereof, the method comprising, consisting of, or consisting essentially of detecting one or more excoriations of the subject's skin.

[0013] In some embodiments, the methods further comprise scoring the excoriations as mild, moderate, or severe.

[0014] In some embodiments, the methods further comprise identifying the subject as likely to respond to nemolizumab treatment or the equivalent thereof if one or more excoriations are detected that are moderate to severe.

[0015] In accordance with some embodiments, there are provided methods of treating a patient having atopic dermatitis, the method comprising, consisting of, or consisting essentially of: (a) screening the patient having atopic dermatitis for one or more skin excoriations; and (b) treating the patient screened in step (a) by administering an effective amount of nemolizumab or an equivalent thereof.

[0016] In some embodiments of the methods, the skin excoriations are moderate to severe. In some embodiments of the methods, the effective amount of nemolizumab or the equivalent thereof ranges from about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg. In particular embodiments, the effective amount of nemolizumab or the equivalent thereof is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, or about 2.5 mg/kg. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered by a topical or parenteral route. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered subcutaneously. In some embodiments, the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

[0017] In accordance with some embodiments, there are provided methods of improving sleep quality in a subject suffering from atopic dermatitis and having one or more skin excoriations, the method comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject. In some embodiments, an improvement of sleep quality is determined by detecting an improvement in one or more of: time of sleep onset latency, total sleep time, sleep efficiency, or time of waking after sleep onset.

[0018] In some embodiments of the methods, the skin excoriations are moderate to severe. In some embodiments of the methods, the effective amount of nemolizumab or the equivalent thereof ranges from about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg. In particular embodiments, the effective amount of nemolizumab or the equivalent thereof is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, or about 2.5 mg/kg. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered by a topical or parenteral route. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered subcutaneously. In some embodiments, the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] **FIGS. 1A-1C**. An atlas of representative images of excoriations and their corresponding Scoring Atopic Dermatitis Index (SCORAD) scores are provided. Images are from the Consensus Report of the European Task Force on Atopic Dermatitis entitled "Severity Scoring of Atopic Dermatitis: The SCORAD Index," (Stalder, J.F. *et al.*, Dermatology (1993), 186: 23-31). **FIG. 1A** depicts mild excoriations with a score of 1. **FIG. 1B** depicts moderate excoriations with a score of 2. **FIG. 1C** depicts severe excoriations with a score of 3. White arrows denote exemplary excoriation.

[0020] **FIGS. 2A-2D**. Representative drawings of excoriations on a subject's wrist. The excoriations are scored according to the SCORAD method as indicated: **FIG. 2A** depicts none (i.e. excoriations are absent) with a score of 0. **FIG. 2B** depicts mild excoriations with a score of 1. **FIG. 2C** depicts moderate excoriations with a score of 2. **FIG. 2D** depicts severe excoriations with a score of 3.

[0021] **FIGS. 3A-3D**. An atlas of representative images of excoriations and their corresponding Eczema Area and Severity Index (EASI) scores are provided. The excoriations

are scored according to the EASI method as indicated: **FIG. 3A** depicts none (i.e. excoriations are absent) with a score of 0. **FIG. 3B** depicts mild excoriations with a score of 1. **FIG. 3C** depicts moderate excoriations with a score of 2. **FIG. 3D** depicts severe excoriations with a score of 3.

[0022] **FIG. 4**. Graphical depiction of the 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.

[0023] **FIG. 5**. Graphical depiction of the results from part A and part B of the phase II study.

[0024] **FIG. 6**. Depicts pruritus visual analog scale (VAS) scores. **FIG. 6A** depicts the percentage change from baseline in pruritus VAS score. Data are presented as means (SEs). **FIG. 6B** depicts the proportion of patients with a pruritus VAS score of less than 30 mm (post hoc analysis).

[0025] **FIG. 7**. Graphical depiction of change from baseline in key secondary and exploratory end points for the intent-to-treat (ITT) population who received nemolizumab in part A (includes data after rescue therapy). **FIG. 7A** depicts percentage change in EASI score (mean ± SE). **FIG. 7B** depicts proportion of patients with an sIGA score of 0 or 1 (percentage). **FIG. 7C** depicts percentage change from baseline in sleep disturbance visual analog scale (VAS) (mean ± SE). **FIG. 7D** depicts proportion of patients with a 4-point or greater decrease in DLQI (percentage; post hoc analysis).

DETAILED DESCRIPTION

[0026] Embodiments according to the present disclosure will be described more fully hereinafter. Aspects of the disclosure may, however, be embodied in different forms and should

not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. The terminology used in the description herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0027] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the present application and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. While not explicitly defined below, such terms should be interpreted according to their common meaning.

[0028] The terminology used in the description herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

[0029] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the disclosure also contemplates that in some embodiments, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

[0030] Unless explicitly indicated otherwise, all specified embodiments, features, and terms intend to include both the recited embodiment, feature, or term and biological equivalents thereof.

Definitions

[0031] As used herein, the singular forms “a,” “an,” and “the” designate both the singular and the plural, unless expressly stated to designate the singular only.

[0032] It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term "about." The term "about" means that the number comprehended includes but is not limited to the exact number set forth herein, and is intended to refer to the recited number as well as numbers substantially around the recited number while not departing from the scope of the invention. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 15%, 10%, 5%, 1%, or 0.1% of the particular term.

[0033] Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0034] The terms "administer," "administration," or "administering" as used herein refer to (1) providing, giving, dosing and/or prescribing, such as by either a health professional or his or her authorized agent or under his direction, and (2) putting into, taking or consuming, such as by a health professional or the subject. Administration shall include without limitation, administration by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray nasal, vaginal, rectal, sublingual, urethral (e.g., urethral suppository) or topical routes of administration (e.g., gel, ointment, cream, aerosol, etc.) and can be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, excipients, and vehicles appropriate for each route of administration. The invention is not limited by the route of administration, the formulation or dosing schedule.

[0035] The terms "treat", "treating" or "treatment", as used herein, include alleviating, abating or ameliorating AD, pruritus, or one or more symptoms thereof, whether or not AD and/or pruritus is considered to be "cured" or "healed" and whether or not all symptoms are resolved. The terms also include reducing or preventing progression of AD and/or pruritus or

one or more symptoms thereof, impeding or preventing an underlying mechanism of AD and/or pruritus or one or more symptoms thereof, and achieving any therapeutic and/or prophylactic benefit.

[0036] Interleukin 31 receptor subunit alpha ("IL-31RA," also known as NR10, glm-r, and GPL) is a protein that forms a heterodimer with oncostatin M receptor (OSMR) and functions as an IL-31 receptor. There are multiple known splicing variants of human-derived IL-31RA (WO 00/075314): NR10.1 consists of 662 amino acids and contains a transmembrane domain. NR10.2 is a soluble receptor-like protein consisting of 252 amino acids without the transmembrane domain. Meanwhile, known IL-31RA splicing variants that function as transmembrane receptor proteins include NR10.3 and IL-31RAv3. Preferred IL-31RA variants include NR10.3 (also referred to as ILRAv4 (Nat Immunol 5, 752-60, 2004) and IL-31RAv3. NR 10.3 (IL31RAv4) consists of 662 amino acids (WO 00/075314; Nat Immunol 5, 752-60, 2004) and IL31RAv3 consists of 732 amino acids (GenBank Accession No: NM—139017).

[0037] The amino acid sequence of IL31RAv4 is:

MKLSPQPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENISCVYYYRKNLTCTWSPGKETSY
TQYTVKRTYAFGEKHDNCTTNSSTSENRASCSFFLPRITIPDNYTIEVEAENGDGVIKSHMTY
WRLENIAKTEPPKIFRVKPVLGIKRMIQIEWIKPELAPVSSDLKYTLRFRTVNSTSWMEVNFA
KNRKDKNQTYNLTGLQPFTEYVIALRCAVKESKFWSDWSQEKMGMTEEEAPCGLELWRVLKPA
EADGRRPVRLLWKKARGAPVLEKTLGYNIWYYPESNTNLTETMNTTNQQLELHLGGESFWVSM
ISYNSLGKSPVATLRIPAIQEKSFQCIEVMQACVAEDQLVVKWQSSALDVNTWMIEWFPDVDS
EPTTLSWESVSQATNWTIQQDKLKPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETK
VENIGVKTVTITWKEIPKSERKGIICNYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYI
VQVMASTSAGGTNGTSINFKTLSFSVFEIILITSLIGGGLLILIILTVAYGLKKPNKLTHLCW
PTVPNPAESSIATWHGDDFKDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKLVVNFGNVLQ
EIFTDEARTGQENNLGGEKNGTRILSSCPTSI

The amino acid sequence of IL31RAv3 is:

MMWTWALWMLPSLCKFSLAALPAKPENISCVYYYRKNLTCTWSPGKETSYTQYTVKRTYAFGE
KHDNCTTNSSTSENRASCSFFLPRITIPDNYTIEVEAENGDGVIKSHMTYWRLENIAKTEPPK
IFRVKPVLGIKRMIQIEWIKPELAPVSSDLKYTLRFRTVNSTSWMEVNFAKNRKDKNQTYNLT
GLQPFTEYVIALRCAVKESKFWSDWSQEKMGMTEEEAPCGLELWRVLKPAEADGRRPVRLLWK
KARGAPVLEKTLGYNIWYYPESNTNLTETMNTTNQQLELHLGGESFWVSMISYNSLGKSPVAT
LRIPAIQEKSFQCIEVMQACVAEDQLVVKWQSSALDVNTWMIEWFPDVDSEPTTLSWESVSQA
TNWTIQQDKLKPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKTVTITW
KEIPKSERKGIICNYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYIVQVMASTSAGGTN
GTSINFKTLSFSVFEIILITSLIGGGLLILIIILTVAYGLKKPNKLTHLCWPTVPNPAESSIAT
WHGDDFKDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKLVVNFGNVLQEIFTDEARTGQEN
NLGGEKNGYVTCPFRPDCPLGKSFEELPVSPEIPPRKSQYLRSRMPEGTRPEAKEQLLFSGQS
LVPDHLCEEGAPNPYLKNSVTAREFLVSEKLPEHTKGEV

Mouse-derived IL-31RA includes proteins comprising the amino acid sequence:

MWTLALWAFSFLCKFSLAVLPTKPENISCVFYFDRNLTCTWRPEKETNDTSYIVTLTYSYGKS
NYSDNATEASYSFPRSCAMPPDICSVEVQAQNGDGKVKSDITYWHLISIAKTEPPIILSVNPI
CNRMFQIQWKPREKTRGFPLVCMLRFRTVNSSRWTEVNFENCKQVCNLTGLQAFTEYVLALRF
RFNDSRYWSKWSKEETRVTMEEVPHVLDLWRILEPADMNGDRKVRLLWKKARGAPVLEKTFGY
HIQYFAENSTNLTEINNITTQQYELLLMSQAHSVSVTSFNSLGKSQEAILRIPDVHEKTFQYI
KSMKAYIAEPLLVVNWQSSIPAVDTWIVEWLPEAAMSKFPALSWESVSQVTNWTIEQDKLKPF
TCYNISVYPVLGHRVGEPYSIQAYAKEGTPLKGPETRVENIGLRTATITWKEIPKSARNGFIN
NYTVFYQAEGGKELSKTVNSHALQCDLESLTRRTSYTVWVMASTRAGGTNGVRINFKTLSISV
FEIVLLTSLVGGGLLLLSIKTVTFGLRKPNRLTPLCCPDVPNPAESSLATWLGDGFKKSNMKE
TGNSGDTEDVVLKPCPVPADLIDKLVVNFENFLEVVLTEEAGKGQASILGGEANEYVTSPSRP
DGPPGKSFKEPSVLTEVASEDSHSTCSRMADEAYSELARQPSSSCQSPGLSPPREDQAQNPYL
KNSVTTREFLVHENIPEHSKGEV

Cynomolgus monkey-derived IL-31RA includes proteins comprising the amino acid sequence:

MMWTWALWMFPLLCKFGLAALPAKPENISCVYYYRKNLTCTWSPGKETSYTQYTAKRTYAFGK
KHDNCTTSSSTSENRASCSFFLPRITIPDNYTIEVEAENGDGVIKSDMTCWRLEDIAKTEPPE
IFSVKPVLGIKRMIRIEWIKPELAPVSSDLKYALRFRTVNSTSWMEVNFAKNRKDTNQTYNLM
GLQAFTEYVVALRCAVKESKFWSDWSQEKMGMTEEEAPCGLELWRVLKPTEVDGRRPVRLLWK
KARGAPVLEKTLGYNIWYFPENNTNLTETVNTTNQQLELHLGGESYWVSMISYNSLGKSPVTT
LRIPAIQEKSFRCIEVMQACLAEDQLVVKWQSSALDVNTWMIEWFPDMDSEHPTLSWESVSQA
TNWTIQQDKLKPFWCYNISVYPMLHDKVGEPYSIQAYAKEGIPSKGPETKVENIGVKTVTITW
KEIPKSERKGIICNYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYTVRVMASTSAGGIN
GTSINFKTLSFSVFEIILITSLIGGGLLILIIILTVAYGLKKPNKLTHLCWPSVPNPAESSIAT
WRGDDFKDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKSVVNFGNVLQEMFTDEARTGQEN
NLGGEKNEYVTHPFRADCPLGKSFEELPVSPEIPPRKSQYLRSRMPEGTCLEAEEQLLVSGQS
LESLAPDHVREAAAPNPYLKNSVTTREFLVSQKLPEHTKGEV

[0038] As used herein, the term "subject" is used interchangeably with "patient," and indicates a mammal, in particular a human, equine, bovine, porcine, feline, canine, murine, rat, or non-human primate. In preferred embodiments, the subject is a human. The subject may or may not be in need of an assessment of skin scratching and/or skin excoriations. In some embodiments, the subject is assessed for skin scratching and/or skin excoriations prior to the administration of nemolizumab treatment. In some embodiments, the subject is a child, less than 13 years old, less than 8 years old, less than 5 years old, less than 3 years old, less than 2 years old, or less than 1-year-old. In other embodiments, the subject is an adult.

[0039] The term "atopic dermatitis" (i.e., "AD") is used herein as it is in the art and means chronic inflammation of the skin. The cause of AD is unknown but may involve genetics, immune system dysfunction, environmental exposures, and/or difficulties with the permeability of the skin. Symptoms of AD include but are not limited to pruritus, dry skin, itching, which may be severe especially at night, red to brownish-gray patches of skin especially on the hands, feet, ankles, wrists, neck, upper chest, eyelids, inside the bend of the elbows and knees, and in infants, the face and scalp, small, raised bumps which may leak fluid and crust over when scratched, thickened skin, cracked skin, scaly skin, raw skin, skin sensitivity, swollen skin, and

interruption and/or loss of sleep. AD most often begins before age 5 and may persist into adolescence and adulthood. In some patients, AD flares up periodically followed by periods of clearance that may last several years.

[0040] The term "pruritus" is used herein as it is in the art and refers to itchy skin and/or an itch sensation. Pruritus may be caused by AD or other diseases or conditions such as dry skin. In some cases, pruritus involves generalized itchy skin over the whole body. In some cases, pruritus is localized to specific regions of the body such as on an arm or leg. Pruritus can be chronic or acute. Symptoms of pruritus include but are not limited to skin excoriations, redness, bumps, spots, blisters, dry skin, cracked skin, and leathery or scaly texture to the skin. In some cases, pruritus does not result in detectable changes to the skin. Behavioral responses to pruritus include but are not limited to skin scratching and/or skin massage. In some cases, skin scratching can result in excoriations that range from mild to severe. In some cases, patients with pruritus abstain from scratching and/or massaging the skin. Traditional treatments for pruritus include but are not limited to skin moisturizers, topical emollients, antihistamines such as diphenhydramine, corticosteroids such as hydrocortisone topical cream, counterirritants such as mint oil, menthol, or camphor, crotamiton, an antipruritic agent often used to treat scabies, local anesthetics such as benzocaine topical cream, and phototherapy. The common type of light used is for phototherapy is UVB.

[0041] As used herein, the term "antibody" collectively refers to immunoglobulins or immunoglobulin-like molecules including by way of example and without limitation, IgA, IgD, IgE, IgG and IgM, combinations thereof or fragments thereof. Fragments of antibodies including, by way of example and without limitation, Fab fragments and single chain variable fragments (scFv), and similar molecules produced during an immune response in any vertebrate, for example, in mammals such as humans, goats, rabbits and mice, as well as non-mammalian species, such as shark immunoglobulins.

[0042] In terms of antibody structure, an immunoglobulin generally has heavy (H) chains and light (L) chains interconnected by disulfide bonds. There are two types of light chain, lambda (λ) and kappa (κ). There are five main heavy chain classes (or isotypes) which determine the

functional activity of an antibody molecule: IgM, IgD, IgG, IgA and IgE. Each heavy and light chain contains a constant region and a variable region, (the regions are also known as "domains"). In combination, the heavy and the light chain variable regions, also called the "Fab region," specifically bind the antigen. Light and heavy chain variable regions contain a "framework" region interrupted by three hypervariable regions, also called "complementarity-determining regions" or "CDRs". The extent of the framework region and CDRs has been defined (see, Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1991, which is hereby incorporated by reference). The Kabat database is now maintained online. The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, largely adopts a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions.

[0043] The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found. An antibody that binds IL-31RA will have a specific V_H region and the V_L region sequence, and thus specific CDR sequences. Antibodies with different specificities (*i.e.* different combining sites for different antigens) have different CDRs. Although it is the CDRs that vary from antibody to antibody, only a limited number of amino acid positions within the CDRs are directly involved in antigen binding. These positions within the CDRs are called specificity determining residues (SDRs). The base of the antibody plays a role in modulating immune cell activity. This region is called the Fc fragment region (Fc) and is composed of two heavy chains that contribute two or three constant domains depending on the class of the antibody. The Fc region functions to guarantee

that each antibody generates an appropriate immune response for a given antigen, by binding to a specific class of proteins found on certain cells, such as B lymphocytes, follicular dendritic cells, natural killer cells, macrophages, neutrophils, etc. and are call "Fc receptors." Because the constant domains of the heavy chains make up the Fc region of an antibody, the classes of heavy chain in antibodies determine their class effects. The heavy chains in antibodies include alpha, gamma, delta, epsilon, and mu, and correlate to the antibody's isotypes IgA, G, D, E, and M, respectively. This infers different isotypes of antibodies have different class effects due to their different Fc regions binding and activating different types of receptors.

[0044] There are four subclasses of IgG, which is the most abundant antibody isotype found in human serum. The four subclasses, IgG1, IgG2, IgG3, and IgG4, which are highly conserved. See generally, world wide web: ncbi.nlm.nih.gov/pmc/articles/PMC4202688/**.** The amino acid sequence of the constant regions of these peptides are known in the art, e.g., see Rutishauser, U. et al. (1968) "Amino acid sequence of the Fc region of a human gamma G-immunoglobulin" PNAS 61(4):1414-1421; Shinoda et al. (1981) "Complete amino acid sequence of the Fc region of a human delta chain" PNAS 78(2):785-789; and Robinson et al. (1980) "Complete amino acid sequence of a mouse immunoglobulin alpha chain (MOPC 511)" PNAS 77(8):4909-4913.

Therapeutic Antibodies

[0045] "Nemolizumab" is a humanized monoclonal antibody that binds to IL-31RA. Nemolizumab is annotated as follows: immunoglobulin G2-kappa, anti-[Homo sapiens IL31RA (interleukin 31 receptor subunit alpha)], humanized monoclonal antibody; gamma2 heavy chain (1-445) [humanized VH (Homo sapiens IGHV1-2*02 (83.70%) -(IGHD)-IGHJ5*01) [8.8.14] (1-121) -Homo sapiens IGHG2*01 (CH1 C10>S (135), R12>K (137), E16>G (141), S17>G (142) (122-219), hinge C4>S (223) (220-231), CH2 H30>Q (268) (232-340), CH3 R11>Q (355), Q98>E (419) (341-445)) (122-445)], (224- 214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (Homo sapiens IGKV1-39*01 (82.10%) - IGKJ4*01) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (108'- 214')]; dimer (227-227":230-230")-bisdisulfide. Nemolizumab has disulfide bridges at the following locations: Intra-H (C23-C104) 22-96 148-

204 261-321 367-425 22"-96" 148"-204" 261"-321" 367"-425"; Intra-L (C23-C104) 23'-88' 134'-194' 23'"-88'" 134'"-194'"; Inter-H-L (h 5-CL 126) 224-214' 224"-214'"; Inter-H-H (h 8, h 11) 227-227" 230-230". Nemolizumab has N-glycosylation sites at the following locations: H CH2 N84.4: 297, 297". Nemolizumab lacks H Chain C-terminal glycine and lysine (CHS G1>del, K2>del).

[0046] Nemolizumab heavy chain amino acid sequence:

QVQLVQSGAE VKKPGASVKV SCKASGYTFT GYIMNWVRQA PGQGLEWMGL INPYNGGTDY NPQFQDRVTI TADKSTSTAY MELSSLRSED TAVYYCARDG YDDGPYTLET WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ TYTCNVDHKP SNTKVDKTVE RKSCVECPPC PAPPVAGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTF RVVSVLTVVH QDWLNGKEYK CKVSNKGLPA PIEKTISKTK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPMLDS DGSFFLYSKL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSP

[0047] Nemolizumab light chain amino acid sequence:

DIQMTQSPSS LSASVGDRVT ITCQASEDIY SFVAWYQQKP GKAPKLLIYN AQTEAQGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQH HYDSPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

[0048] The variable domains of the heavy and light chain sequences are shown in bold above, and the CDR sequences are underlined.

[0049] Equivalent antibodies to nemolizumab include but are not limited to: (i) antibodies with heavy chains comprising at least 55%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% amino acid sequence identity to nemolizumab's heavy chain sequence, (ii) antibodies with light

chains comprising at least 55%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% amino acid sequence identity to nemolizumab's light chain sequence, (iii) antibodies with variable regions comprising at least 55%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% amino acid sequence identity to nemolizumab's variable region sequences, (iv) antibodies with CDRs comprising at least 55%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% amino acid sequence identity to nemolizumab's CDR sequences, (v) antibodies that bind to the same isoform of IL-31RA as nemolizumab (e.g., IL31-RAv3), optionally the same epitope of IL-31RA, (vi) antibodies that block or neutralize IL-31RA, (vii) antibodies that bind to oncostatin M receptor (OSMR), and (viii) combinations thereof. For example, suitable equivalents include immunoglobulins or immunoglobulin-like molecules with the same or substantially similar heavy and light chain amino acid sequences as nemolizumab. Additional exemplary nemolizumab equivalents are described, for example, in WO 2010/064697.

[0050] Equivalents of nemolizumab may be monoclonal or polyclonal antibodies. Such monoclonal antibodies having IL31-RA -binding and/or neutralizing activity can be obtained, for example, by the following procedure: anti-IL31-RA monoclonal antibodies are prepared by using as an antigen IL31-RA or a fragment thereof that is derived from a mammal such as human or mouse by known methods, and then antibodies having IL31-RA-binding and/or neutralizing activity are selected from the thus obtained anti-IL31-RA monoclonal antibodies. Specifically, a desired antigen or cells expressing the desired antigen are used as a sensitizing antigen for immunization according to conventional immunization methods. Anti-IL31-RA monoclonal antibodies can be prepared by fusing the obtained immune cells with known parental cells using conventional cell fusion methods, and screening them for monoclonal antibody-producing cells (hybridomas) by conventional screening methods. Animals to be immunized include, for example, mammals such as mice, rats, rabbits, sheep, monkeys, goats, donkeys, cows, horses, and pigs. The antigen can be prepared using the known IL31-RA gene

sequence according to known methods, for example, by methods using baculovirus (for example, WO 98/46777).

[0051] Hybridomas can be prepared, for example, according to the method of Milstein et al. (Kohler, G. and Milstein, C., Methods Enzymol. (1981) 73: 3-46). When the immunogenicity of an antigen is low, immunization may be performed after linking the antigen with a macromolecule having immunogenicity, such as albumin. Antigens used to prepare monoclonal antibodies that have a binding and/or neutralizing activity against human IL31-RA are not particularly limited, as long as they enable preparation of antibodies that have a binding and/or neutralizing activity against human IL31-RA. For example, it is known that there are a number of variants of human IL31-RA, and any variant may be used as an immunogen as long as it enables preparation of antibodies that have a binding and/or neutralizing activity against human IL31-RA. Alternatively, under the same condition, a peptide fragment of IL31-RA or a protein in which artificial mutations have been introduced into the natural IL31-RA sequence may be used as an immunogen. Human IL31-RA.3 is one of preferred immunogens in preparing antibodies that have an activity of binding and/or neutralizing IL31-RA in the present disclosure.

[0052] The IL31-RA-binding activity of the equivalent antibodies can be determined by methods known to those skilled in the art. Methods for determining the antigen-binding activity of an antibody include, for example, ELISA (enzyme-linked immunosorbent assay), EIA (enzyme immunoassay), RIA (radioimmunoassay), and fluorescent antibody method. For example, when enzyme immunoassay is used, antibody-containing samples, such as purified antibodies and culture supernatants of antibody-producing cells, are added to antigen-coated plates. A secondary antibody labeled with an enzyme, such as alkaline phosphatase, is added and the plates are incubated. After washing, an enzyme substrate, such as p-nitrophenyl phosphate, is added, and the absorbance is measured to evaluate the antigen-binding activity. The binding and/or neutralizing activity of an equivalent antibody against IL31-RA can be measured, for example, by observing the effect of suppressing the growth of the IL-31-dependent cell line. For example, the activity of a purified mouse IL-31antibody can be assayed

by assessing the IL-31-dependent growth of Ba/F3 cells transfected with mouse IL-31 receptor α and mouse OSMR genes.

Excoriations as a Biomarker for Response to Nemolizumab Treatment

[0053] The inventors have hypothesized that an anti-pruritic drug could have a greater impact on AD in patients that suffer from skin scratching due to pruritus than on patient that do not scratch. Without being bound by theory, it is believed that the itch-scratch cycle is not only a symptom of AD, but an aggravating factor of AD in a subset of AD patients that scratch their skin in response to pruritis. In the itch–scratch cycle, the strong actions of scratching facilitate susceptibility to increased itching and the exacerbation of skin lesions, called excoriations.

[0054] An objective way to identify subjects that suffer from skin scratching due to pruritus is to identify subjects with excoriations caused by scratching. Excoriations refer to an injury to the skin caused by trauma such as scratching or abrasion. In some embodiments of the methods described herein, excoriations can be identified by the presence, number, and/or intensity of lesions with one or more of the following characteristics: linearity, fissure or break in the skin surface, scabbing, serous crust, blood, redness, skin abrasion, or tearing of the skin. Fissured excoriations are excoriations with a linear split through the epidermis into the underlying dermis.

[0055] In some embodiments, excoriations are scored as none, mild, moderate, or severe. "None," "mild," "moderate," and "severe" are terms of art in describing the presence, extent, and/or intensity of excoriations. Those of skill in the art know the metes and bounds of these terms. For example, methods of assessing atopic dermatitis used by health care professionals and comprising scoring excoriations as none, mild, moderate, and severe include but are not limited to: Atopic Dermatitis Assessment Measure (ADAM), Eczema Area and Severity Index (EASI), self-administered EASI (SA-EASI), SCORing Atopic Dermatitis (SCORAD), Six Area Six Sign Atopic Dermatitis Index (SASSAD), Simple Scoring System (SSS), and Three Item Severity Score (TIS). In some embodiments, a score of none is denoted with the number zero, a

mild score is denoted with the number one, a moderate score is denoted with the number two, and a severe score is denoted with the number three.

[0056] As used herein, the term "none to mild" refers to skin excoriation(s) scored as none, mild, or there between. In some embodiments, "none to mild" refers to skin excoriation(s) scored as 0, 1, 1.5, 0 to 1, ≤ 1, or < 2. In some embodiments, "none to mild" refers to a range of skin excoriation scores from about 0 to about 1. As used herein, the term "moderate to severe" refers to skin excoriation(s) scored as moderate, severe, or there between. In some embodiments, "moderate to severe" refers to skin excoriations scored as 2, 2.5, 3, 2 to 3, or ≥ 2. In some embodiments, "moderate to severe" refers to a range of skin excoriation scores from about 2 to about 3.

[0057] In some embodiments, excoriations are scored according to one or more of the following methods: SCORAD (disclosed in Stalder, J.F. *et al.*, Dermatol (1993), 186: 23-31, the entire disclosure of which is incorporated herein by reference), Patient-Oriented SCORAD (disclosed in Vourc'h-Jourdain, M. *et al.*, Dermatology (2009) 218: 246-51, the entire disclosure of which is incorporated herein by reference), ADAM (disclosed in Charman, D. *et al.*, J. Outcome Meas. (1999) 3: 21-34, the entire disclosure of which is incorporated herein by reference), EASI (disclosed in Tofte, S.J. *et al.*, J Eur Acad Dermatol Venereol (1998) 11: S197, the entire disclosure of which is incorporated herein by reference), SA-EASI (disclosed in Housman T.S. *et al.*, Br J Dermatol (2002) 147:1192-8, the entire disclosure of which is incorporated herein by reference), SASSAD (disclosed in Berth-Jones, J., Br J Dermatol (1996) 135: 25-30, the entire disclosure of which is incorporated herein by reference), SSS (disclosed in Costa, C. *et al.*, Acta Derm Venereol (1989) 69: 42-5, the entire disclosure of which is incorporated herein by reference), and TIS (disclosed in Wolkerstorfer, A. *et al.*, Acta Derm. Venereol. (1999) 79: 356-59, the entire disclosure of which is incorporated herein by reference). In preferred embodiments, excoriations are scored according to a SCORAD and/or PO-SCORAD method.

[0058] The SCORAD methods (SCORAD and PO-SCORAD) are methods of determining the severity of AD comprising scoring excoriations as none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) on the basis of the presence and intensity of excoriations at a representative excoriation site. A representative excoriation site is a site comprising excoriation(s) of average intensity for the subject. Excoriation scoring performed according to a SCORAD method does not comprise fraction-based scoring (e.g., half-point scoring such as 0.5, 1.5, or 2.5). Exemplary images of excoriations scored according to the SCORAD excoriation method are provided in FIG. 1A-1C, FIG. 2A-2D, Stalder *et al.* (1993), and Oranje, A.P. *et al.* (Pediatr. Allergy Immunol. (1997) 8: 28-34, the entire disclosure of which is incorporated herein by reference).

[0059] The EASI methods (EASI and SA-EASI) are methods of determining the severity of eczema comprising scoring excoriations as none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) on the basis of the average excoriation intensity in each of four body regions: head and neck, trunk, upper limbs, and lower limbs. Body regions with excoriations that are absent are scored as none (score = 0), excoriations that are just perceptible, scant, and/or superficial are scored as mild (score = 1), excoriations comprising many superficial and/or some deep excoriations are scored as moderate (score = 2), and diffuse, extensive superficial excoriations and/or many deep excoriations are scored as severe (score =3). Half scores (e.g. 2.5) are permissible in the EASI method. However, a score of 0.5 is not permitted because the minimum score for present excoriations under the EASI method is mild (score = 1). An atlas of representative images of excoriations scored by the EASI method is provided in FIG. 3A-3D.

[0060] The ADAM method is a method of determining the severity of AD comprising scoring excoriations on the basis of the total number of excoriations present on the subject's skin. Fewer than 5 excoriations is scored as a 0, 5 to 20 excoriations is scored as a 1, greater than 20 excoriations is scored as a 2, and fissured excoriations are scored as a 3.

[0061] The SASSAD method is a method of determining the severity of AD comprising scoring excoriations as absent (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) on the basis of prominence of excoriations at the worst affected excoriation site within each of six areas of the subject: hands, arms, feet, legs, head/neck, and trunk. The SASSAD method defines excoriations as any damage to the skin caused by scratching, but not caused by erythema or urtication. Under the SASSAD method, absent excoriations cannot be detected with certainty even after careful inspection, mild excoriations are present excoriations that require careful inspection in order to be observed, moderate excoriations are present excoriations that are immediately apparent, and severe excoriations are present excoriations that are very prominent.

[0062] The SSS method is a method of determining the severity of AD comprising scoring excoriations and cracking as none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) on the basis of severity at each of 20 sites of the subject: scalp, ears, peribuccal, periocular, face, neck, chest, tummy, back, elbows, arms, axillae, hands and dorsal wrists, balms and wrists, buttocks and groin, popliteal space, thighs, legs, arches, and soles.

[0063] Like SCORAD, the TIS method is a method of determining the severity of AD comprising scoring excoriations on a scale from none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) on the basis of the presence and intensity of excoriations at the most representative excoriation site. A representative excoriation site is a site comprising excoriation(s) of average intensity for the subject. Excoriation scoring performed according to a TIS method does not comprise fraction-based scoring (e.g., half-point scoring such as 0.5, 1.5, or 2.5).

[0064] To test the hypothesis that AD patients that suffer from skin scratching due to pruritis are a sub-population of responders to nemolizumab treatment, published data from a study of adults with moderate-to-severe AD treated with subcutaneous nemolizumab (Ruzicka, T. *et al.* N. Engl. J. Med. (2017), 376: 826-35, the entire disclosure of which is incorporated herein by reference) were analyzed to determine the effect of treatment in patients with evidence of

scratching. AD patients from the Ruzicka *et al.* nemolizumab study were separated into two groups on the basis of skin excoriations: (i) AD patients with none to mild excoriations at baseline; and (ii) AD patients with moderate to severe excoriations at baseline. Excoriations were scored according to the SCORAD method. The study parameters were then re-analyzed, comparing the relative treatment effect in each population as compared to placebo.

[0065] The Ruzicka *et al.* nemolizumab study was a phase 2, randomized, double-blind, placebo-controlled trial lasting 12 weeks and comprising 264 patients (Clinical Trial No. NCT01986933). Eligible patients were adults with moderate to severe atopic dermatitis that is not adequately controlled by topical treatments. Patients were not eligible for the study if they had active dermatologic diseases concomitant with AD. Enrolled patients received subcutaneous nemolizumab or placebo at a dose of 0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg every 4 weeks. Some patients alternatively received a dose of 2.0 mg/kg every 8 weeks. The primary end point of the study was an improvement in the pruritus visual-analog scale (VAS) score. Additional end points included improvements in body-surface area of atopic dermatitis and the Eczema Area and Severity Index (EASI). At the conclusion of the study, the largest percentage change in the EASI score at 12 weeks, -42.3%, occurred in the group receiving 0.5 mg/kg nemolizumab every 4 weeks. This dose also presented the best benefit-risk profile. However, improvements in EASI scores were also observed in the other dosage groups (-23.0% in the 0.1 mg group and -40.9% in the 2.0 mg group). Improvements were also observed in VAS score for each dose.

[0066] The results of inventors' analysis of the Ruzicka *et al.* nemolizumab study are presented in Table 1 and Table 2 below. Pruritus VAS scores range from 0 (no itch) to 100 (worst imaginable itch) and were recorded daily by patients using an electronic reporting tool. Negative changes in VAS score indicate improvement. EASI scores range from 0 to 72, with higher scores indicating worse disease severity. Investigators' Global Assessment (IGA) scores range from 0 (clear) to 5 (very severe disease) and are presented as a percentage of patients in the indicated population. Sleep refers to sleep measurements which were recorded by means of actigraphy, which documents whole-body movement and is a validated motion-detection

method for recording sleep measurements including sleep efficiency. Sleep efficiency is the total sleeping time divided by the total time in bed. Dermatology Life Quality Index (DLQI) scores range from 0 to 30, with higher scores indicating a lower quality of life. To be eligible for the Ruzicka *et al.* study, patients were required to have a baseline EASI score of at least 10, a baseline pruritus VAS score of at least 50 mm, and a baseline IGA score of at least 3.

[0067] As shown in Table 1, the two groups of AD patients in the study presented comparable level of pruritus, DLQI, and sleep efficiency. While the EASI and IGA were not balanced between the two groups, this is expected because these two parameters are influenced by the presence or absence of excoriations.

Table 1: Baseline Clinical Characteristics

BASELINE		**Excoriation None to Mild**	**Excoriation Moderate to Severe**
		(n=44)	**(n=220)**
Pruritus VAS	Mean mm	78.9	78.8
	Very Severe (%)	29.5	27.3
DLQI	Mean	13.3	15.1
Sleep efficiency	Mean (%)	67.3	66.7
EASI	Mean	20.2	31.3
	Moderate(%)	68.2	26.8
	Severe(%)	31.8	61.8
	Very Severe(%)	0	11.4
IGA	Moderate(%)	65.9	42.3
	Severe(%)	34.1	44.1
	Very Severe(%)	0	13.6

[0068] As shown in Table 2, the presence of excoriations influenced the efficacy of nemolizumab treatment in AD patients. Treatment outcome at 12 weeks was improved for all parameters in the population of patients with moderate to severe excoriations. These results were generated by comparing the net effect (nemolizumab effect – placebo effect) between the two groups. For example, upon treatment with nemolizumab, patients with none to mild excoriations exhibited a 13% improvement in sleep efficiency. In contrast, patients with

moderate to severe excoriations exhibited a 39% improvement in sleep efficiency, a three-fold better response than the none to mild excoriation population.

Table 2: Treatment Outcome

WEEK 12		Excoriation None to Mild			Excoriation Moderate to Severe		
		Placebo (n=8)	Nemo-lizumab 0.5 mg/kg (n=9)	Net effect	Net effect	Placebo (n=35)	Nemo-lizumab 0.5 mg/kg (n=36)
Pruritus VAS	Mean Change	-25	-50.8	-25.8	**-35.7**	-20.4	-56.1
	Mean Reduction	32	62.6	30.6	**42.1**	26.5	68.6
DLQI	Mean Change	-3.9	-5.8	-1.9	**-2.6**	-3.9	-6.5
Sleep	Mean Change	-27.3	-40.8	-13.5	**-39.9**	-15.2	-55.1
EASI	Mean Change	-9.6	-10	-0.4	**-2.1**	-10.4	-12.5
	Mean Reduction	51.3	57	5.7	**14.9**	31.8	46.7
IGA	% success	12.5	22.2	9.7	**16.6**	2.9	19.5

[0069] The data presented in Table 2 demonstrates that the presence of moderate to severe excoriations is a biomarker for predicting the efficacy of nemolizumab treatment in AD patients.

[0070] Accordingly, provided herein are methods of identifying a subject having atopic dermatitis that is likely to respond to nemolizumab treatment or treatment with an equivalent thereof, the method comprising, consisting of, or consisting essentially of detecting one or more excoriations of the subject's skin. In some embodiments, provided herein are methods of determining whether a subject having atopic dermatitis is likely to respond to nemolizumab treatment or treatment with an equivalent thereof comprising, consisting of, or consisting essentially of detecting one or more excoriations of the subject's skin. In some embodiments, provided herein are methods of predicting whether a subject having atopic dermatitis is likely to respond to nemolizumab treatment or treatment with an equivalent thereof comprising,

consisting of, or consisting essentially of detecting one or more excoriations of the subject's skin. In some embodiments, the skin excoriations were caused by pruritis.

[0071] In some embodiments, the methods comprise detecting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations. In some embodiments, the extent of skin excoriations is detected by detecting the total skin surface area affected, the number and/or size of regions affected, or the percent of body surface area affected. In some embodiments, excoriations are detected at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's average intensity of excoriations. In some embodiments, excoriations are detected at a specific region or site of the subject's skin that comprises excoriations that are representative of the worst (i.e. most severe) intensity of excoriations. In some embodiments, the average intensity or worst intensity of excoriations is detected at one or more of the following sites of the subject: hands, arms, feet, legs, head, neck, head and neck, trunk, upper limbs, lower limbs, scalp, ears, peribuccal, periocular, face, neck, chest, tummy, back, elbows, arms, axillae, hands and dorsal wrists, balms and wrists, buttocks and groin, popliteal space, thighs, legs, arches, and soles. In some embodiments, the excoriations are detected by a healthcare professional. In some embodiments, the excoriations are detected by the subject or the subject's adult guardian.

[0072] In some embodiments, the methods further comprise scoring the excoriations as mild, moderate, or severe according to the standards described herein. In some embodiments, the excoriations are scored as none (scored as 0), mild (scored as 1), moderate (scored as 2), or severe (scored as 3) according to the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS method. In preferred embodiments, the excoriations are scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored by a healthcare professional. In some embodiments, the excoriations are scored by the subject or the subject's adult guardian.

[0073] In some embodiments, the methods further comprise identifying the subject as likely to respond to nemolizumab treatment or the equivalent thereof if excoriations are detected that

are scored as moderate to severe. In some embodiments, the methods further comprise determining that the subject having atopic dermatitis is likely to respond to nemolizumab treatment or treatment with an equivalent thereof if excoriations are detected that are scored as moderate to severe. In some embodiments, the methods further comprise predicting that a subject having atopic dermatitis is likely to respond to nemolizumab treatment or treatment with an equivalent thereof comprising if excoriations are detected that are scored as moderate to severe.

[0074] In some embodiments, the methods further comprise identifying the subject as not likely to respond to nemolizumab treatment or the equivalent thereof if no excoriations scored as none to mild are detected. In some embodiments, the methods further comprise determining that the subject having atopic dermatitis is not likely to respond to nemolizumab treatment or treatment with an equivalent thereof if no excoriations scored as none to mild are detected. In some embodiments, the methods further comprise predicting that a subject having atopic dermatitis is not likely to respond to nemolizumab treatment or treatment with an equivalent thereof comprising if no excoriations scored as none to mild are detected.

Pharmaceutical Compositions

[0075] Provided herein are pharmaceutical compositions for use in the treatment of atopic dermatitis in a subject determined to have one or more skin excoriations, the composition comprising, consisting of, or consisting essentially of nemolizumab or an equivalent thereof. Moreover, the present disclosure provides therapeutic agents for AD which comprise nemolizumab or an equivalent thereof as an active ingredient.

[0076] In some embodiments, the excoriations were previously detected and/or scored by a healthcare professional, by the subject, or by the subject's adult guardian. In some embodiments, the excoriations were scored according to one or more of the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS method. In a preferred embodiment, the excoriations were scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored as moderate to severe. In some

embodiments, the excoriations have a score of 2 to 3. In some embodiments, the subject does not have skin excoriations that are scored as none to mild. In some embodiments, the excoriations do not have a score of 0 to 1. In some embodiments, the skin excoriations are not mild. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's average intensity of excoriations. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's worst intensity of excoriations. In some embodiments, the skin excoriations were caused by pruritis. In some embodiments, the subject has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations that are moderate to severe.

[0077] The phrase "comprise(s) nemolizumab or an equivalent thereof as an active ingredient" means comprising nemolizumab or an equivalent thereof as at least one of the active ingredients, and does not limit the proportion of the antibody. In addition, the therapeutic agents for AD in the present disclosure may also comprise, in combination with nemolizumab or an equivalent thereof, other ingredients that enhance the treatment of AD. For example, the composition may comprise one or more calcineurin inhibitors (e.g., a topical calcineurin inhibitor), emollients, topical steroids such as topical glucocorticoids, and oral antihistamines.

[0078] Pharmaceutical compositions of nemolizumab or an equivalent thereof of the present disclosure can be prepared as formulations according to standard methods (see, for example, Remington's Pharmaceutical Science, Mark Publishing Company, Easton, USA). In some embodiments, the pharmaceutical compositions comprise a carrier and/or additive. In some embodiments, the carrier is a pharmaceutically acceptable carrier. For example, in some embodiments, the pharmaceutical composition comprises one or more surfactants (for example, PEG and Tween), excipients, antioxidants (for example, ascorbic acid), coloring agents, flavoring agents, preservatives, stabilizers, buffering agents (for example, phosphoric acid, citric acid, and other organic acids), chelating agents (for example, EDTA), suspending agents, isotonizing agents, binders, disintegrators, lubricants, fluidity promoters, corrigents, light anhydrous silicic acid, lactose, crystalline cellulose, mannitol, starch, carmelose calcium,

carmelose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylacetaldiethylaminoacetate, polyvinylpyrrolidone, gelatin, medium chain fatty acid triglyceride, polyoxyethylene hydrogenated castor oil 60, sucrose, carboxymethylcellulose, corn starch, and inorganic salt. In some embodiments, the pharmaceutical composition comprises one or more other low-molecular-weight polypeptides, proteins such as serum albumin, gelatin, and immunoglobulin, and amino acids such as glycine, glutamine, asparagine, arginine, and lysine.

[0079] When nemolizumab or an equivalent thereof is prepared as an aqueous solution for injection, nemolizumab or an equivalent thereof may be dissolved in an isotonic solution containing, for example, physiological saline, dextrose, or other adjuvants. The adjuvants may include, for example, D-sorbitol, D-mannose, D-mannitol, and sodium chloride. In addition, appropriate solubilizing agents, for example, alcohols (for example, ethanol), polyalcohols (for example, propylene glycols and PEGs), and non-ionic detergents (polysorbate 80 and HCO-50) may be used concomitantly.

[0080] If necessary, nemolizumab or an equivalent thereof may be encapsulated in microcapsules (microcapsules made of hydroxymethylcellulose, gelatin, polymethylmethacrylate, and the like), and made into components of colloidal drug delivery systems (liposomes, albumin microspheres, microemulsions, nano-particles, and nano-capsules) (for example, see "Remington's Pharmaceutical Science 16th edition" &, Oslo Ed. (1980)). Moreover, methods for making sustained-release drugs are known, and these can be applied for nemolizumab or an equivalent thereof (Langer et al., J. Biomed. Mater. Res. (1981) 15, 167-277; Langer, Chem. Tech. (1982) 12, 98-105; U.S. Pat. No. 3,773,919; European Patent Application (EP) No. 58,481; Sidman et al., Biopolymers (1983) 22, 547-56; EP 133,988).

[0081] The pharmaceutical compositions of the present disclosure can be administered either orally or parenterally, but are preferably administered parenterally. Specifically, the pharmaceutical compositions are administered to patients by injection or percutaneous

administration. Injections include, for example, intravenous injections, intramuscular injections, and subcutaneous injections, for systemic or local administration. The pharmaceutical compositions may be given to sites where inflammation is to be suppressed, or areas surrounding the sites by local infusion or intramuscular injection. In some embodiments, the pharmaceutical compositions are administered at the site of one or more skin excoriations, or proximal to the site of one or more skin excoriations.

[0082] The administration methods can be properly selected according to the patient's age and condition. The single-administration dose can be selected, for example, from within the range of 0.0001 to 100 mg of the active ingredient per kg body weight. Alternatively, for example, when the agents are administered to human patients, the dose of the active ingredient can be selected from within the range of 0.001 to 1,000 mg/kg body weight. In some embodiments, the composition is formulated to administer a dose containing, for example, about 0.01 to 50 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, about 0.05 mg/kg to 0.15 mg/kg, about 0.1 mg/kg to about 0.6 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 0.25 mg/kg to about 0.75 mg/kg, about 0.4 mg/kg to about 0.8 mg/kg, about 0.4 mg/kg to about 1.8 mg/kg, about 0.5 to about 2.5 mg/kg, about 0.8 mg/kg to about 2.2 mg/kg, about 1 mg/kg to about 2.5 mg/kg, about 1 mg/kg to about 3.5 mg/kg, about 1 mg/kg to about 5 mg/kg, about 2 mg/kg to about 4 mg/kg, about 2.5 mg/kg to about 10 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 40 mg/kg, about 20 mg/kg to about 50 mg/kg, about 25 mg/kg to about 75 mg/kg, about 50 mg/kg to about 100 mg/kg, or about 100 mg/kg to about 500 mg/kg, or about 100 mg/kg to about 1000 mg/kg body weight of nemolizumab or an equivalent thereof. In preferred embodiments, the dose ranges from about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg. In some embodiments, the dose is about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg,

about 1.8 mg/kg, about 1.9 mg/kg, about 2 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 15 mg/kg, about 25 mg/kg, about 50 mg/kg, about 75 mg/kg, about 100 mg/kg, about 500 mg/kg, or about 1,000 mg/kg. In particular embodiments, the effective amount of nemolizumab or the equivalent thereof is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, or about 2.5 mg/kg. In a preferred embodiment, the dose is about 0.5 mg/kg.

[0083] In some embodiments, a single-administration dose can be selected, for example, from within the range of 1 to 100 mg of the active ingredient (i.e., nemolizumab or the equivalent thereof), or more specifically about 10 to about 90 mg, about 20 to about 80 mg, about 25 to about 70 mg, or about 30 to about 60 mg. For example, in some embodiments, a single-administration dose may be about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 about, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95mg, or about 100 mg.

[0084] In some embodiments, the single-administration dose may vary over time. For example, a subject may receive an initial "loading dose(s)" that is higher that the "maintenance dose(s)" administrated thereafter. In some embodiments, a subject may be administered one or more initial loading doses of 60 mg of nemolizumab (or an equivalent thereof) followed by subsequent maintenance doses of 30 mg. In other embodiments, the initial dose and subsequent doses may be the same. For example, the initial dose and subsequent doses may be 60 mg. In any of these embodiments, the antibody (nemolizumab or the equivalent thereof) may be administered to the subject with or without a second active agent, such as a topical steroid or topical calcineurin inhibitor.

Methods of Treatment

[0085] In accordance with some embodiments, there are provided methods of selectively treating atopic dermatitis in a subject having one or more skin excoriations, the method comprising, consisting of, or consisting essentially of administering an effective amount of nemolizumab or an equivalent thereof to the subject.

[0086] In some embodiments, the excoriations were previously detected and/or scored by a healthcare professional, by the subject, or by the subject's adult guardian. In some embodiments, the excoriations were scored according to one or more of the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS methods. In a preferred embodiment, the excoriations were scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored as moderate to severe. In some embodiments, the excoriations have a score of 2 to 3. In some embodiments, the subject does not have skin excoriations that are scored as none to mild. In some embodiments, the excoriations do not have a score of 0 to 1. In some embodiments, the skin excoriations are not mild. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's average intensity of excoriations. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's worst intensity of excoriations. In some embodiments, the skin excoriations were caused by pruritis. In some embodiments, the subject has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations that are moderate to severe.

[0087] An "effective amount" is an amount sufficient to effect beneficial or desired results such as alleviating at least one or more symptom of AD and/or pruritus. An effective amount as used herein would also include an amount sufficient to delay the development of AD and/or pruritus, alter the course of an AD and/or pruritus symptom (for example sleep efficiency), or reverse a symptom of AD and/or pruritus. Thus, it is not possible to specify the exact "effective amount." However, for any given case, an appropriate "effective amount" can be determined by one of ordinary skill in the art using only routine experimentation.

[0088] An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents of the present disclosure for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disorder being treated and form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. The dosage can be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment. Typically, dosage-effect relationships from *in vitro* and/or *in vivo* tests initially can provide useful guidance on the proper doses for patient administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[0089] In some embodiments, the dose of nemolizumab or an equivalent thereof administered to the subject is within the range of 0.001 to 1,000 mg/kg body weight of the subject. In some embodiments, the dose ranges from about 0.01 to 50 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, about 0.05 mg/kg to 0.15 mg/kg, about 0.1 mg/kg to about 0.6 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 0.25 mg/kg to about 0.75 mg/kg, about 0.4 mg/kg to about 0.8 mg/kg, about 0.4 mg/kg to about 1.8 mg/kg, about 0.5 to about 2.5 mg/kg, about 0.8 mg/kg to about 2.2 mg/kg, about 1 mg/kg to about 2.5 mg/kg, about 1 mg/kg to about 3.5 mg/kg, about 1 mg/kg to about 5 mg/kg, about 2 mg/kg to about 4 mg/kg, about 2.5 mg/kg to about 10 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 40 mg/kg, about 20 mg/kg to about 50 mg/kg, about 25 mg/kg to about 75 mg/kg, about 50 mg/kg to about 100 mg/kg, or about 100 mg/kg to about 500 mg/kg, or about 100 mg/kg to about 1000 mg/kg body weight of nemolizumab or an equivalent thereof. In preferred embodiments, the

dose ranges from about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg. In some embodiments, the dose is about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 15 mg/kg, about 25 mg/kg, about 50 mg/kg, about 75 mg/kg, about 100 mg/kg, about 500 mg/kg, or about 1,000 mg/kg. In particular embodiments, the effective amount of nemolizumab or the equivalent thereof is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, or about 2.5 mg/kg. In a preferred embodiment, the dose is about 0.5 mg/kg.

[0090] In some embodiments, a single-administration dose can be selected, for example, from within the range of 1 to 100 mg of the active ingredient (i.e., nemolizumab or the equivalent thereof), or more specifically about 10 to about 90 mg, about 20 to about 80 mg, about 25 to about 70 mg, or about 30 to about 60 mg. For example, in some embodiments, a single-administration dose may be about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 about, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95mg, or about 100 mg.

[0091] In some embodiments, the single-administration dose may vary over time. For example, a subject may receive an initial "loading dose(s)" that is higher that the "maintenance dose(s)" administrated thereafter. In some embodiments, a subject may be administered one or more initial loading doses of 60 mg of nemolizumab (or an equivalent thereof) followed by

subsequent maintenance doses of 30 mg. In other embodiments, the initial dose and subsequent doses may be the same. For example, the initial dose and subsequent doses may be 60 mg. In any of these embodiments, the antibody (nemolizumab or the equivalent thereof) may be administered to the subject with or without a second active agent, such as a topical steroid or topical calcineurin inhibitor.

[0092] In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered by a topical or parenteral route. In some embodiments of the methods, the nemolizumab or the equivalent thereof is administered subcutaneously. In some embodiments, the dose is administered subcutaneously at or proximal to a site of one or more excoriations.

[0093] In some embodiments, nemolizumab or the equivalent thereof is administered daily, every other day, twice per week, three times per week, four times per week, five times per week, six times per week, once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, twice per year, once per year, and/or as needed based on the appearance of symptoms of atopic dermatitis or pruritus. In preferred embodiments, nemolizumab or the equivalent thereof is administered every four weeks or every eight weeks.

[0094] In particular embodiments, both the dose and dosing schedule may be determined before commencing the method of treatment. For example, a subject may be administered about 30 to about 60 mg of nemolizumab or an equivalent thereof once every two weeks (Q2W), once every three weeks (Q3W), once every four weeks (Q4W), once every five weeks (Q5W), once every six weeks (Q6W), once every seven weeks (Q7W), or once every eight weeks (Q8W), either alone or in combination with a second active agent (e.g., a topical steroid or topical calcineurin inhibitor). In some embodiments, a subject may be administered an initial loading dose of 60 mg of nemolizumab or an equivalent thereof and thereafter receive maintenance doses of 30 mg of nemolizumab or an equivalent thereof once every four weeks (Q4W). In some embodiments, the maintenance doses may be administered as infrequently as

once every eight weeks (Q8W). Such a treatment regimen may be administered with or without concurrent use of a topical steroid or topical calcineurin inhibitor. In another embodiment, a subject may be administered a dose of 60 mg of nemolizumab or an equivalent thereof once every four weeks (Q4W) without a decrease in the dose over time. In some embodiments, the doses may be administered as infrequently as once every eight weeks (Q8W). Such a treatment regimen may be administered with or without concurrent use of a topical steroid or topical calcineurin inhibitor.

[0095] Alternatively, doses for a particular regimen may be administered according to the weight of the subject (e.g., mg/kg), rather than a pre-set dose. For example, a subject may be administered about 0.1 to about 2.0 mg/kg of nemolizumab or an equivalent thereof once every two weeks (Q2W), once every three weeks (Q3W), once every four weeks (Q4W), once every five weeks (Q5W), once every six weeks (Q6W), once every seven weeks (Q7W), or once every eight weeks (Q8W), either alone or in combination with a second active agent (e.g., a topical steroid or topical calcineurin inhibitor). In some embodiments, a subject may be administered an initial loading dose of 0.1, 0.5, or 2.0 mg/kg of nemolizumab or an equivalent thereof and thereafter receive maintenance doses of nemolizumab or an equivalent thereof once every four weeks (Q4W) that is less than the initial loading dose. In some embodiments, the maintenance doses may be administered as infrequently as once every eight weeks (Q8W). Such a treatment regimen may be administered with or without concurrent use of a topical steroid or topical calcineurin inhibitor. In another embodiment, a subject may be administered a dose of 0.1, 0.5, or 2.0 mg/kg of nemolizumab or an equivalent thereof once every four weeks (Q4W) without a decrease in the dose over time. In some embodiments, the doses may be administered as infrequently as once every eight weeks (Q8W). Such a treatment regimen may be administered with or without concurrent use of a topical steroid or topical calcineurin inhibitor.

[0096] In some embodiments, the duration of treatment is about one day, about one week, about two weeks, about three weeks, about four weeks, about five weeks, about six weeks, about seven weeks, about eight weeks, about nine weeks, about 10 weeks, about 11 weeks,

about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 24 weeks, about 30 weeks, about 36 weeks, about 40 weeks, about 48 weeks, about 50 weeks, about one year, about two years, about three years, about four years, about five years, or as needed based on the appearance of symptoms of atopic dermatitis. In preferred embodiments, duration of treatment is about 12 weeks to about 24 weeks, about 12 to about 36 weeks, about 12 to about 48 weeks, or about 24 to about 36 weeks.

[0097] In accordance with some embodiments, there are provided uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having one or more skin excoriations. In some embodiments, the excoriations were previously detected and/or scored by a healthcare professional, by the subject, or by the subject's adult guardian. In some embodiments, the excoriations were scored according to one or more of the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS methods. In a preferred embodiment, the excoriations were scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored as moderate to severe. In some embodiments, the excoriations have a score of 2 to 3. In some embodiments, the subject does not have skin excoriations that are scored as none to mild. In some embodiments, the excoriations do not have a score of 0 to 1. In some embodiments, the skin excoriations are not mild. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's average intensity of excoriations. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's worst intensity of excoriations. In some embodiments, the skin excoriations were caused by pruritis. In some embodiments, the subject has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations that are moderate to severe.

[0098] In accordance with some embodiments, there are provided methods of treating a patient having atopic dermatitis, the method comprising, consisting of, or consisting essentially of: (a) screening the patient having atopic dermatitis for skin excoriations; and (b) treating the

patient screened in step (a) by administering an effective amount of nemolizumab or an equivalent thereof. In some embodiments, the patient screened in step (a) has skin excoriations. In some embodiments, screening comprising detecting and/or scoring excoriations. In some embodiments, excoriations are scored according to one or more of the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS methods. In a preferred embodiment, the excoriations are scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored as moderate to severe. In some embodiments, the excoriations have a score of 2 to 3. In some embodiments, the patient does not have skin excoriations that are scored as none to mild. In some embodiments, the excoriations do not have a score of 0 to 1. In some embodiments, the skin excoriations are not mild. In some embodiments, the excoriations are screened at a specific region or site of the patient's skin that comprises excoriations that are representative of the patient's average intensity of excoriations. In some embodiments, the excoriations are screened at a specific region or site of the patient's skin that comprises excoriations that are representative of the patient's worst intensity of excoriations. In some embodiments, the skin excoriations were caused by pruritis. In some embodiments, the patient has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations that are moderate to severe.

[0099] In accordance with some embodiments, there are provided methods of improving sleep quality in a subject suffering from atopic dermatitis and having one or more skin excoriations, the method comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject. In some embodiments, an improvement of sleep quality is determined by detecting an improvement in one or more of: time of sleep onset latency, total sleep time, sleep efficiency, or time of waking after sleep onset. As described above, sleep efficiency is defined as the total amount of sleeping time divided by the total time in bed. In some embodiments, sleep quality is recorded or detected by one or more of actigraphy, motion sensing, video monitoring, and/or self-reporting. In some embodiments, the excoriations were previously detected and/or scored by a healthcare professional, by the subject, or by the subject's adult guardian. In some embodiments, the excoriations were scored according to one or more of the SCORAD, PO-SCORAD, ADAM, EASI, SA-EASI, SASSAD, SSS, and/or TIS

method. In a preferred embodiment, the excoriations were scored according to the SCORAD or PO-SCORAD method. In some embodiments, the excoriations are scored as moderate to severe. In some embodiments, the excoriations have a score of 2 to 3. In some embodiments, the subject does not have skin excoriations that are scored as none to mild. In some embodiments, the excoriations do not have a score of 0 to 1. In some embodiments, the skin excoriations are not mild. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's average intensity of excoriations. In some embodiments, the scored excoriations are at a specific region or site of the subject's skin that comprises excoriations that are representative of the subject's worst intensity of excoriations. In some embodiments, the skin excoriations were caused by pruritis. In some embodiments, the subject has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,18, 19, 20, 30, 40, or 50 or more skin excoriations that are moderate to severe.

[0100] Success of treatment with nemolizumab or an equivalent thereof can be determined or assessed by detecting improvement, alleviation, ablation, or amelioration of AD, pruritus, or one or more symptoms of each thereof. For example, success can be determined by detecting an improvement in one or more of: number of skin excoriations, intensity of skin excoriations, excoriation score, the subject's pruritus VAS score, the subject's DLQI score, sleep efficiency, sleep onset latency, total sleep time, waking after sleep onset, percent body surface area affected, the subject's EASI score, the subject's IGA score, degree or amount of dry skin, frequency or presence of itching, severity of itching, redness of skin, frequency of raised bumps, degree or amount of thickened skin, degree or amount of cracked skin, degree or amount of scaly skin, degree or amount of raw skin, degree or amount of skin sensitivity, and/or degree or amount of swollen skin. In some embodiments, success does not depend on whether or not AD and/or pruritus is considered to be "cured" or "healed" and whether or not all symptoms are resolved.

EXAMPLE

[0101] A randomized, double-blind, placebo-controlled, dose-finding study was performed to assess the long-term efficacy and safety of continuous subcutaneous nemolizumab when injected every four weeks (Q4W) or every 8 weeks (Q8W) in patients with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments. The study was published in Kabashima, *et al., J Allergy Clin Immunol* (2018) 142(4)1121, which publication, including the figures, is incorporated in its entirety by reference. 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.

Methods

[0102] *Study Design.* This study was performed in 2 parts (**FIG. 4**). For Part A, nemolizumab 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 re-randomized 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.

[0103] *Study Population.* Key inclusion criteria are described in **FIG. 4**. 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.

[0104] *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 (e.g., 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, 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.

[0105] *Study Assessments.* Baseline assessments for patients re-randomized 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 inter-site and inter-investigator 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.

[0106] *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 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) 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, was explored in a *post hoc* analysis. The long-term safety profile was also evaluated.

[0107] *Statistical Analysis.* 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 Parts 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 re-randomized to nemolizumab in Part B).

Results

[0108] In total, 264 patients were randomized to Part A; of these, 216 completed Part A, and 191 participated in Part B, including 38 re-randomized from the placebo group (*see* **FIG. 5**). 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 re-randomized 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.

[0109] Patients had intense itch at baseline according to the pruritus visual analog scale (VAS) score and moderate-to-severe disease according to the static investigator's global assessment (sIGA), body surface area (BSA) affected by AD, and eczema area and severity index (EASI) scores. Mean baseline total serum IgE levels are reported in Table 3. 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 re-randomized to nemolizumab Q4W in Part B were similar between groups.

Table 3. Baseline total serum IgE levels in intent to treat (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

[0110] The improvement from baseline in pruritus VAS score observed in part A was maintained or increased from week 12 to week 64 in patients randomized to receive nemolizumab throughout the 64-week study period (*see* **FIG. 6**). The greatest improvement throughout the study was observed in the 0.5-mg/kg nemolizumab group (*see* Table 4). The proportion of patients who achieved a pruritus VAS score of less than 30 mm was maintained until week 64 (**FIG. 6B, and 4**). The mean ± SD percentage change from baseline in EASI score, SCORing atopic dermatitis (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 verbal rating scores (VRS) were also maintained or increased from week 12 to week 64 in patients who had received nemolizumab in Part A (FIG. 7A-C, and Table 4 below). 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 5 below).

Table 4. Percentage change from baseline in secondary and exploratory end points at week 12 and week 64 in intent to treat (ITT) population who received nemolizumab in part A.

	Nemolizumab			
	0.1mg/kg Q4W (n=53)	**0.5mg/kg Q4W (n=54)**	**2.0mg/kg Q4W (n=52)**	**2.0mg/kg Q8W (n=52)**
Percentage change in pruritus VAS score, mean±SD				
Week 12	(n=45)−48.6±28.3	(n=45)−66.3±33.7	(n=46)−66.3±29.0	(n=39)−64.1±31.6
Week 64	(n=29)−73.0 ± 28.4	(n=26)−89.6±11.2	(n=28)−74.7±28.4	(n=18)−79.1±24.2
Patients with pruritus VAS score <30mm,* no. (%)				
Week 12	(n=45)14 (31)	(n=45)30 (67)	(n=47)29 (62)	(n=39)23 (59)
Week 64	(n=29)22 (76)	(n=26)25 (96)	(n=28)21 (75)	(n=18)14 (78)
Percentage change in EASI score, mean±SD				

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

* Post hoc analysis

Table 5. Patients with a 25%, 50%, and 75% improvement from baseline in pruritus VAS and EASI scores at week 12 and week 64 for intent to treat (ITT) population who received nemolizumab in part A (data are shown as number percentage). Includes data after rescue therapy.

End point	Nemolizumab							
	0.1mg/kg Q4W (n=53)		0.5mg/kg Q4W (n=54)		2.0mg/kg Q4W (n=52)		2.0mg/kg Q8W (n=52)	
	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)

[0111] 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 (i.e. 4 weeks after switch to active treatment) and maintained through week 64 (1 year after the switch to active treatment, *see* Table 6 below). 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 6). 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 6).

Table 6. 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 for intent to treat (ITT) population who received placebo in part A (includes data after rescue therapy).

End point	Patients rerandomized from placebo to nemolizumab in Part B		
	0.1mg/kg Q4W (n=12)	0.5mg/kg Q4W (n=12)	2.0mg/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)

* Post hoc analysis

[0112] 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 7).

Table 7. Duration of use and cumulative dose of topical glucocorticosteroids throughout the study period from baseline (*) to endo treatment overall and by potency (*) in the intent to treat population who received nemolizumab in part A (data is shown as median ranges).

Topical glucocorticosteroid use†	**Nemolizumab**			
	0.1mg/kgQ4W (n=53)	**0.5mg/kgQ4W (n=54)**	**2.0mg/kgQ4W (n=52)**	**2.0mg/kgQ8W (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)

†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.

*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.

[0113] 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 7). However, there was a high degree of variation between patients for duration and dose of topical glucocorticosteroid 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 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 7); available data were limited for "very potent" agents.

[0114] The dermatology life quality index (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. 7**, and Table 4). A similar trend was observed in patients who had received placebo in part A (*see* Table 6).

[0115] 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 (*see* Table 8 below). 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 9 below). 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 (*see* Table 8). 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.

Table 8. Adverse events (AEs) over the total 64-week study period in patients randomized to nemolizumab throughout the study period.

	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

* Patients who received placebo during part A

[0116] The proportion of patients experiencing new-onset SAEs was distributed evenly over the study duration (*see* Table 9 below). 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 10); 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 11). Ten patients, all in Part A, discontinued the study prematurely because of exacerbation of AD.

Table 9. New onset adverse events (AEs) and severe adverse events (SAEs) by time period in patients randomized to receive nemolizumab throughout the study period (safety population).

	Period						
	Any period	**0-12wk**	**>12-24wk**	**>24-36wk**	**>36-48wk**	**>48-64wk**	**Follow-up**
AEs							
Nemolizumab, 0.1mg/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, 0.5mg/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, 2.0mg/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, 2.0mg/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, 0.1mg/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, 0.5mg/kg Q4W							
No. of patients	54	54	38	34	30	30	49
Patients with any SAE, no. (%)	3 (6)	—	—	—	—	2 (7)	1 (2)
Nemolizumab, 2.0mg/kg Q4W							
No. of patients	52	52	39	36	33	32	49
Patients with any SAE, no. (%)	4 (8)	3 (6)	1 (3)	—	—	—	—
Nemolizumab, 2.0mg/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 10. Exposure-adjusted adverse events (AEs) represented as the number of events per 100 patient-years based on the ration of observed number of events to total number of patient-years of exposure.

	Nemolizumab*				
	Placebo† (n=53)	**0.1mg/kg Q4W (n=53)**	**0.5mg/kg Q4W (n=54)**	**2.0mg/kg Q4W (n=52)**	**2.0mg/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

*Patients who received nemolizumab during part A and part B. † Patients who received placebo during part A.

Table 11. Adverse events (AEs) leading to withdrawal from treatment in patients with randomized to nemolizumab throughout the study period.

Event	Nemolizumab			
	0.1mg/kg Q4W (n=53)	0.5mg/kg Q4W (n=54)	2.0mg/kg Q4W (n=52)	2.0mg/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.

[0117] In patients re-randomized from placebo to nemolizumab in part B, AEs were reported in 67% to 92% of patients across treatment groups (*see* Table 12). The most frequent AEs were similar to those seen during the study as a whole (*see* Table 12). 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).

Table 12. Adverse events (AEs) in part B patients randomized to receive placebo in part A (safety population).

Event	Patients rerandomized from placebo to nemolizumab in part B		
	0.1mg/kg Q4W (n=13)	0.5mg/kg Q4W (n=12)	2.0mg/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

Discussion

[0118] This study evaluated the efficacy and tolerability of nemolizumab, an anti–IL-31 receptor A mAb, for the treatment of patients with AD inadequately controlled by 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) were 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.

[0119] AD and the accompanying pruritus impairs quality of life (QoL) in patients with the disease. The reduction in dermatology life quality index (DLQI) scores observed during Part A of the study were maintained throughout the long-term extension, suggesting prolonged alleviation of the effect of symptoms on daily life. These findings are consistent with the early improvement in pruritus observed within week 1 of nemolizumab treatment in Part A of the study.

[0120] 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.

[0121] 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.

WHAT IS CLAIMED IS:

1. A method of selectively treating atopic dermatitis in a subject having one or more skin excoriations, the method comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject.

2. The method of claim 1, wherein the skin excoriations are moderate to severe.

3. The method of claim 1 or 2, wherein the skin excoriations have been assigned a score of at least 2 on the SCORAD scale.

4. The method of any one of the previous claims, wherein the effective amount of nemolizumab or the equivalent thereof is about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg.

5. The method of any one of the previous claims, wherein the nemolizumab or the equivalent thereof is administered by a topical or parenteral route.

6. The method of any one of the previous claims, wherein the nemolizumab or the equivalent thereof is administered subcutaneously.

7. The method of any one of the previous claims, wherein the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

8. A pharmaceutical composition for use in the treatment of atopic dermatitis in a subject determined to have one or more skin excoriations, the composition comprising nemolizumab or an equivalent thereof.

9. The pharmaceutical composition of claim 8, wherein the skin excoriations are moderate to severe.

10. The pharmaceutical composition of claim 8 or 9, wherein the skin excoriations have been assigned a score of at least 2 on the SCORAD scale.

11. The pharmaceutical composition of any one of claims 8-10, further comprising a carrier.

12. The pharmaceutical composition of claim 8, wherein the carrier is a pharmaceutically acceptable carrier.

13. Use of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of atopic dermatitis in a subject having one or more skin excoriations.

14. The use of claim 13, wherein the skin excoriations are moderate to severe.

15. The use of claim 13 or 14, wherein the skin excoriations have been assigned a score of at least 2 on the SCORAD scale.

16. A method of identifying a subject having atopic dermatitis that is likely to respond to treatment with nemolizumab or an equivalent thereof, the method comprising detecting one or more excoriations of the subject's skin.

17. The method of claim 16, further comprising scoring the excoriations as mild, moderate, or severe.

18. The method of claim 16, further comprising scoring the excoriations as 1, 2, or 3 according to the SCORAD scale.

19. The method of claim 17, further comprising identifying the subject as likely to respond to treatment with nemolizumab or an equivalent thereof if one or more excoriations are detected that are moderate to severe.

20. The method of claim 18, further comprising identifying the subject as likely to respond to treatment with nemolizumab or an equivalent thereof if one or more excoriations are scored as a 2 or a 3 according to the SCORAD scale.

21. The method of claim 19, further comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject identified as likely to respond to treatment with nemolizumab or an equivalent thereof.

22. The method of claim 21, wherein the effective amount of nemolizumab or the equivalent thereof is about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg.

23. The method of claim 21 or 22, wherein the nemolizumab or the equivalent thereof is administered by a topical or parenteral route.

24. The method of any one of claims 21-23, wherein the nemolizumab or the equivalent thereof is administered subcutaneously.

25. The method of any one of claims 21-24, wherein the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

26. A method for treating a patient having atopic dermatitis, the method comprising:

(a) screening the patient having atopic dermatitis for one or more skin excoriations; and

(b) treating the patient screened in step (a) by administering an effective amount of nemolizumab or an equivalent thereof.

27. The method of claim 26, wherein the skin excoriations are moderate to severe.

28. The method of claim 26, wherein the skin excoriations have been assigned a score of at least 2 on the SCORAD scale.

29. The method of any one of claims26-28, wherein the effective amount of nemolizumab or the equivalent thereof is about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg.

30. The method of any one of claims 26-29, wherein the effective amount of nemolizumab or the equivalent thereof is administered by a topical or parenteral route.

31. The method of any one of claims 26-30, wherein the effective amount of nemolizumab or the equivalent thereof is administered subcutaneously.

32. The method of any one of claims 26-31, wherein the effective amount of nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

33. A method of improving sleep quality in a subject suffering from atopic dermatitis and having one or more skin excoriations, the method comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject.

34. The method of claim 33, wherein the skin excoriations are moderate to severe.

35. The method of claim 33, wherein the skin excoriations have been assigned a score of at least 2 on the SCORAD scale.

36. The method of any one of claims 33 or 35, wherein the effective amount of nemolizumab or the equivalent thereof is about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 0.5 mg/kg, about 0.5 mg/kg to about 1.5 mg/kg, about 1.5 mg/kg to about 2.5 mg/kg, or about 2.5 mg/kg to about 10 mg/kg.

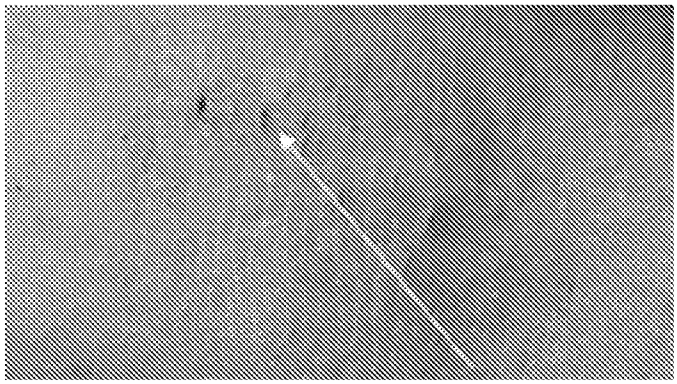
37. The method of any one of claims 33-36, wherein the nemolizumab or the equivalent thereof is administered by a topical or parenteral route.

38. The method of any one of claims 33-37, wherein the nemolizumab or the equivalent thereof is administered subcutaneously.

39. The method of any one of claims 33-38, wherein the nemolizumab or the equivalent thereof is administered once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.

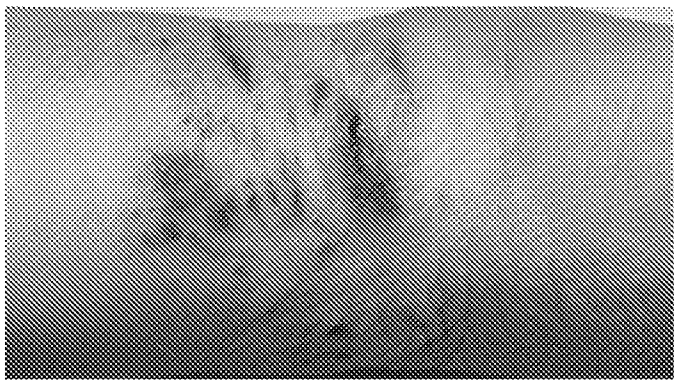
40. The method of any one of claims 33-39, wherein an improvement of sleep quality is determined by detecting an improvement in one or more of: time of sleep onset latency, total sleep time, sleep efficiency, or time of waking after sleep onset.

FIG. 1A



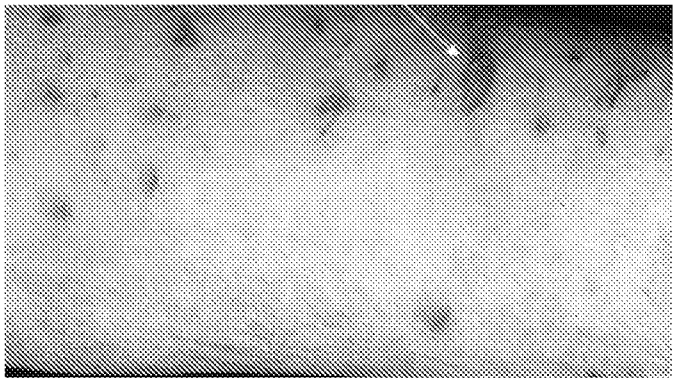
Mild (score = 1)

FIG. 1B



Moderate (score = 2)

FIG. 1C

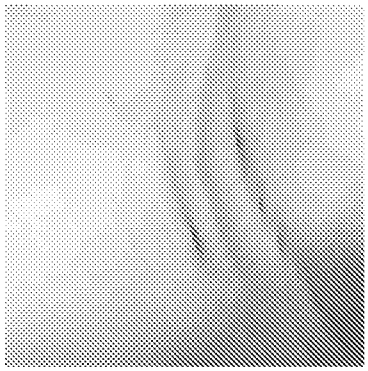


Severe (score = 3)

FIG. 2A

None (score = 0)

FIG. 2B

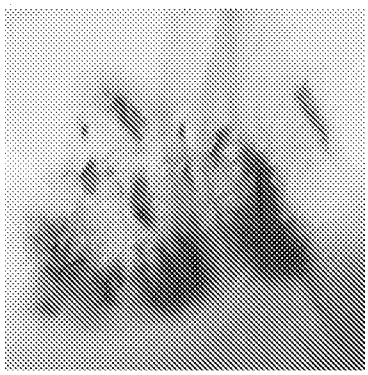


Mild (score = 1)

FIG. 2C

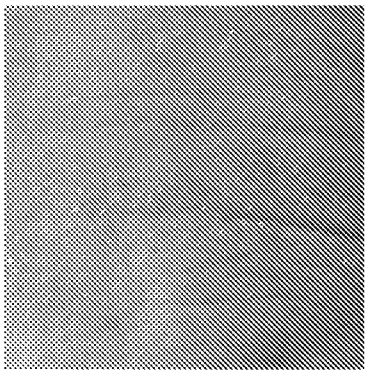
Moderate (score = 2)

FIG. 2D



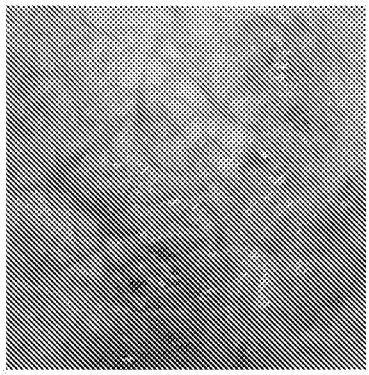
Severe (score = 3)

FIG. 3A



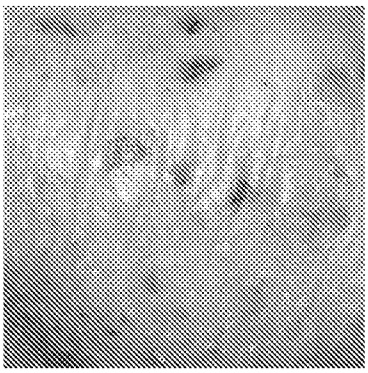
None (score = 0)

FIG. 3B



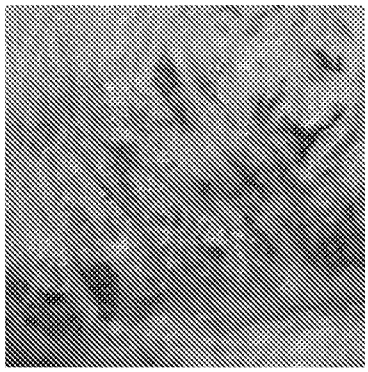
Mild (score = 1)

FIG. 3C



Moderate (score = 2)

FIG. 3D



Severe (score = 3)

FIG. 4

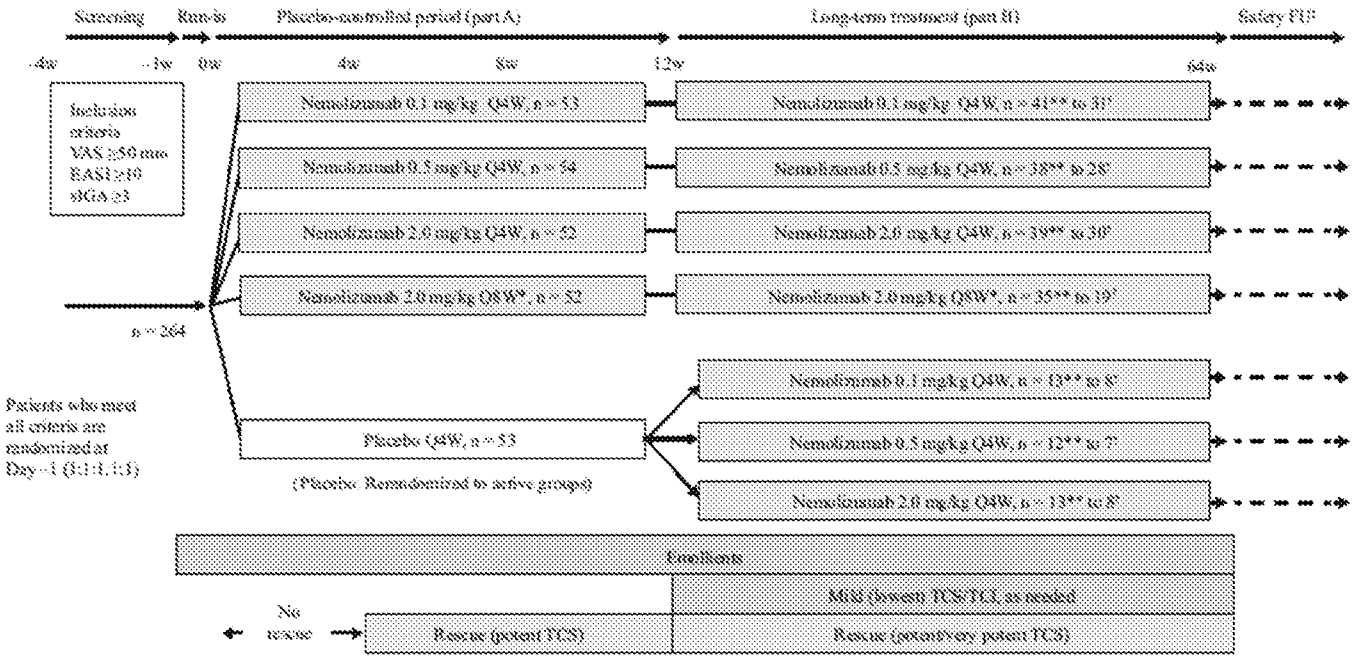

Screening
Run-in
Placebo-controlled period (part A)
Long-term treatment (part B)
Safety FU
-4w
-1w
0w
4w
8w
12w
64w
Inclusion criteria
VAS ≥50 mm
BASI ≥10
sIGA ≥3
Nemolizumab 0.1 mg/kg Q4W, n = 53
Nemolizumab 0.1 mg/kg Q4W, n = 41** to 31*
Nemolizumab 0.5 mg/kg Q4W, n = 54
Nemolizumab 0.5 mg/kg Q4W, n = 38** to 28*
Nemolizumab 2.0 mg/kg Q4W, n = 52
Nemolizumab 2.0 mg/kg Q4W, n = 39** to 30*
Nemolizumab 2.0 mg/kg Q8W*, n = 52
Nemolizumab 2.0 mg/kg Q8W*, n = 35** to 19*
n = 264
Patients who meet all criteria are randomized at Day -1 (1:1:1:1:1)
Placebo Q4W, n = 53
Nemolizumab 0.1 mg/kg Q4W, n = 18** to 8*
Nemolizumab 0.5 mg/kg Q4W, n = 12** to 7*
Nemolizumab 2.0 mg/kg Q4W, n = 13** to 8*
(Placebo: Rerandomized to active groups)
Emollients
MoU (lowest TCS/TCI, as needed
No rescue
Rescue (potent TCS)
Rescue (potent/very potent TCS)

FIG. 5

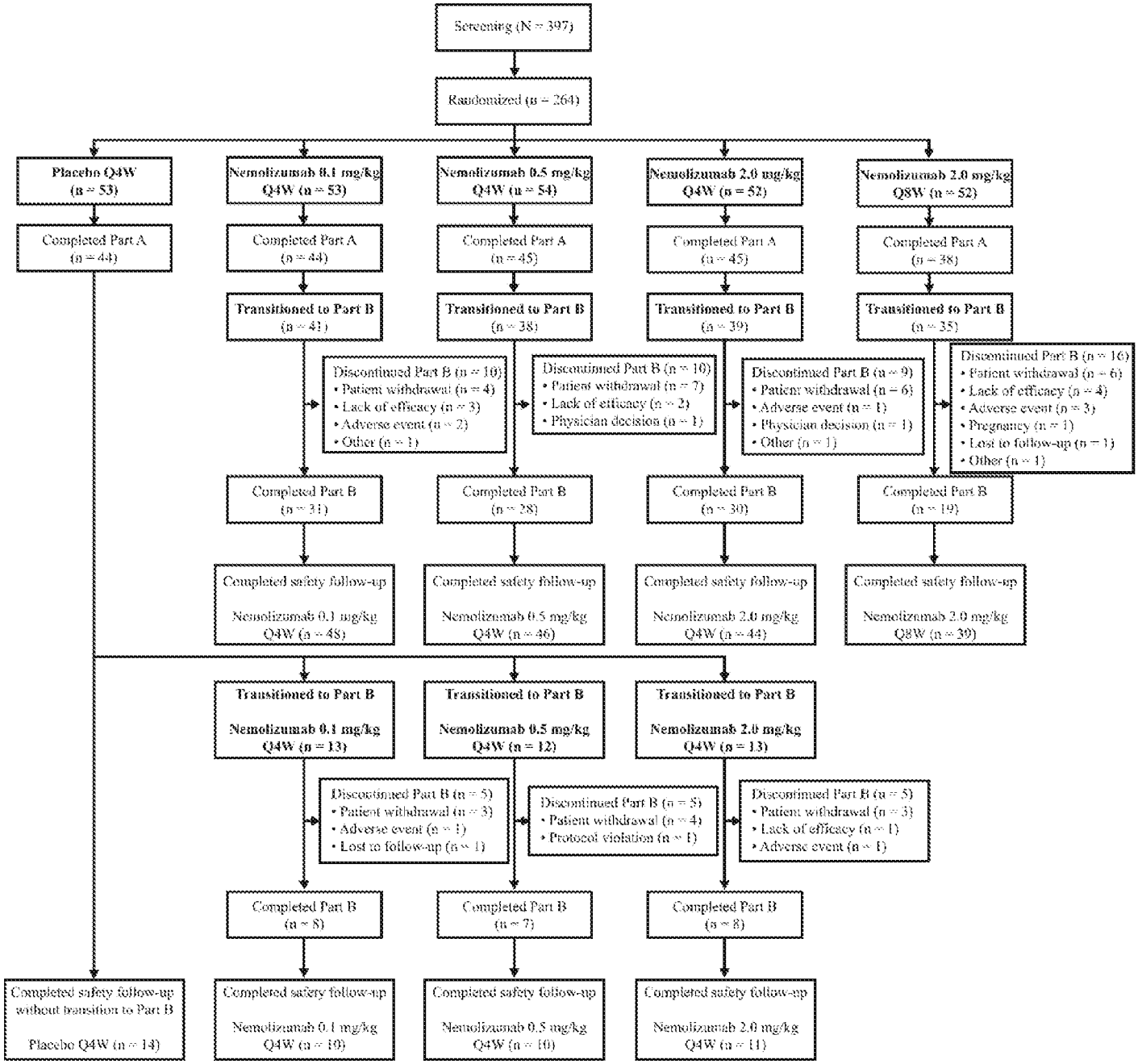

Screening (N = 397)
Randomized (n = 264)
Placebo Q4W (n = 53)
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
Completed Part A (n = 44)
Completed Part A (n = 44)
Completed Part A (n = 45)
Completed Part A (n = 45)
Completed Part A (n = 38)
Transitioned to Part B (n = 41)
Transitioned to Part B (n = 38)
Transitioned to Part B (n = 39)
Transitioned to Part B (n = 35)
Discontinued Part B (n = 10)
• Patient withdrawal (n = 4)
• Lack of efficacy (n = 3)
• Adverse event (n = 2)
• Other (n = 1)
Discontinued Part B (n = 10)
• Patient withdrawal (n = 7)
• Lack of efficacy (n = 2)
• Physician decision (n = 1)
Discontinued Part B (n = 9)
• Patient withdrawal (n = 6)
• Adverse event (n = 1)
• Physician decision (n = 1)
• Other (n = 1)
Discontinued Part B (n = 16)
• Patient withdrawal (n = 6)
• Lack of efficacy (n = 4)
• Adverse event (n = 3)
• Pregnancy (n = 1)
• Lost to follow-up (n = 1)
• Other (n = 1)
Completed Part B (n = 31)
Completed Part B (n = 28)
Completed Part B (n = 30)
Completed Part B (n = 19)
Completed safety follow-up
Nemolizumab 0.1 mg/kg Q4W (n = 48)
Completed safety follow-up
Nemolizumab 0.5 mg/kg Q4W (n = 46)
Completed safety follow-up
Nemolizumab 2.0 mg/kg Q4W (n = 44)
Completed safety follow-up
Nemolizumab 2.0 mg/kg Q8W (n = 39)
Transitioned to Part B
Nemolizumab 0.1 mg/kg Q4W (n = 13)
Transitioned to Part B
Nemolizumab 0.5 mg/kg Q4W (n = 12)
Transitioned to Part B
Nemolizumab 2.0 mg/kg Q4W (n = 13)
Discontinued Part B (n = 5)
• Patient withdrawal (n = 3)
• Adverse event (n = 1)
• Lost to follow-up (n = 1)
Discontinued Part B (n = 5)
• Patient withdrawal (n = 4)
• Protocol violation (n = 1)
Discontinued Part B (n = 5)
• Patient withdrawal (n = 3)
• Lack of efficacy (n = 1)
• Adverse event (n = 1)
Completed Part B (n = 8)
Completed Part B (n = 7)
Completed Part B (n = 8)
Completed safety follow-up without transition to Part B
Placebo Q4W (n = 14)
Completed safety follow-up
Nemolizumab 0.1 mg/kg Q4W (n = 10)
Completed safety follow-up
Nemolizumab 0.5 mg/kg Q4W (n = 10)
Completed safety follow-up
Nemolizumab 2.0 mg/kg Q4W (n = 11)

FIG. 6

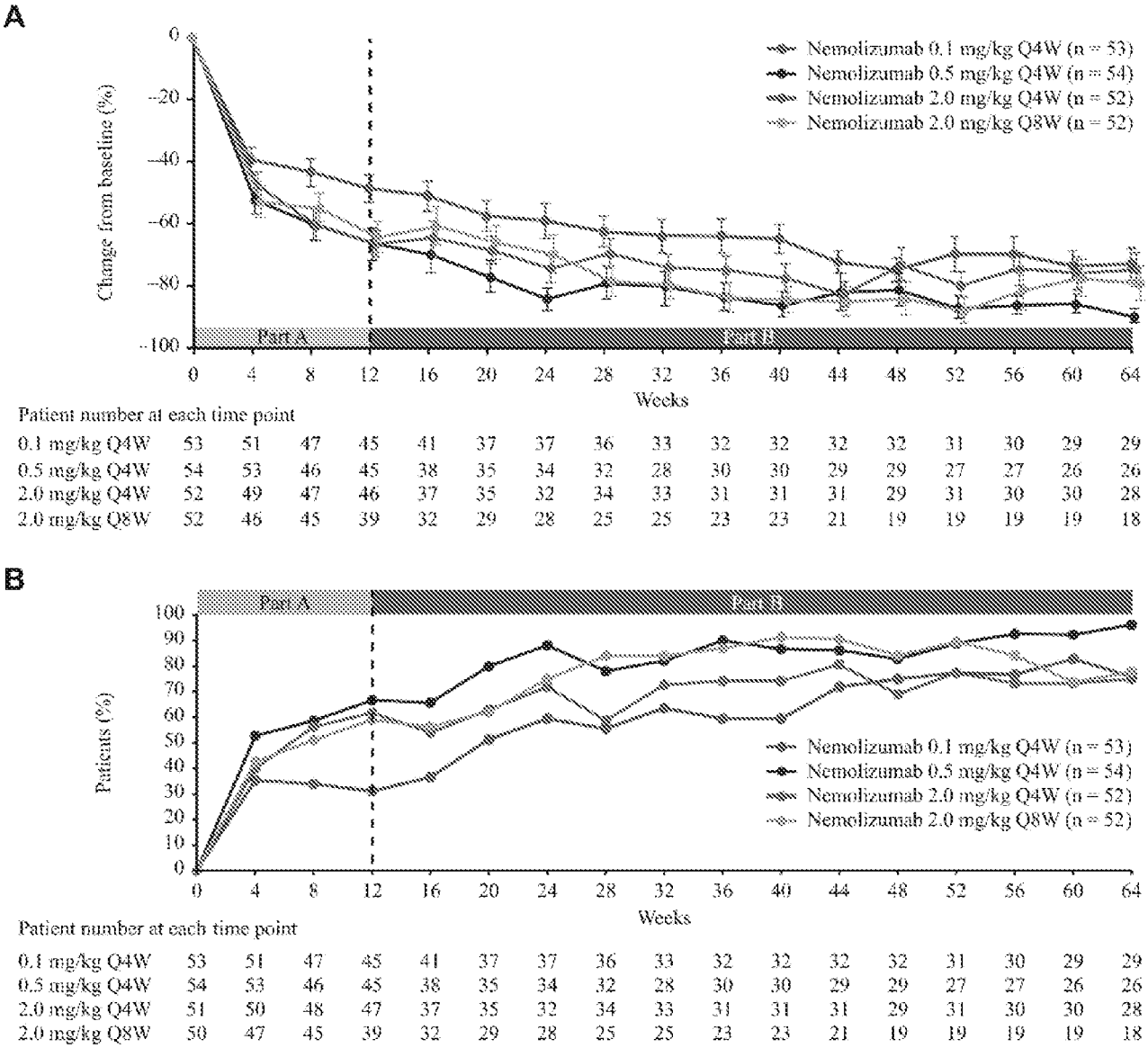
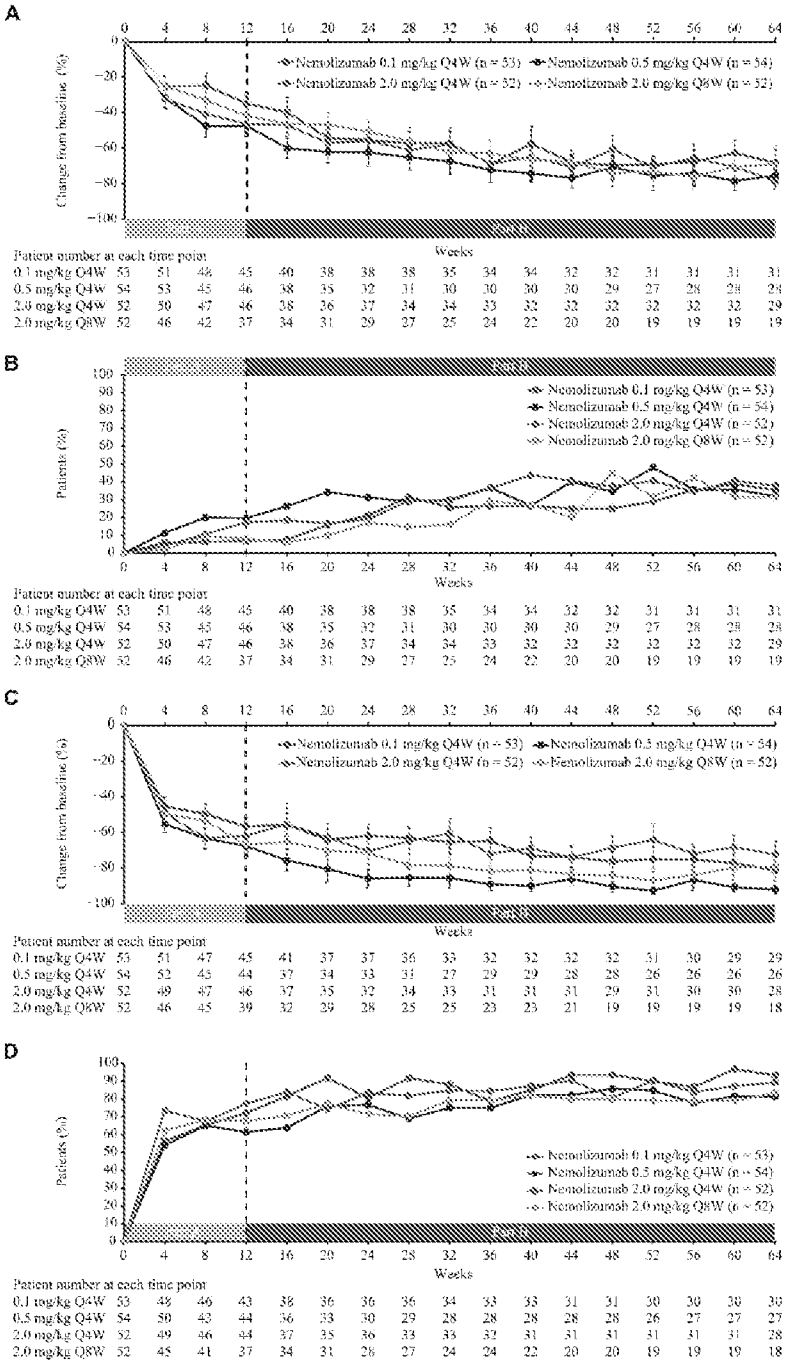

A
Change from baseline (%)
0
−20
−40
−60
−80
−100
Part A
Part B
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 51 47 45 41 37 37 36 33 32 32 32 32 31 30 29 29
0.5 mg/kg Q4W 54 53 46 45 38 35 34 32 28 30 30 29 29 27 27 26 26
2.0 mg/kg Q4W 52 49 47 46 37 35 32 34 33 31 31 31 29 31 30 30 28
2.0 mg/kg Q8W 52 46 45 39 32 29 28 25 25 23 23 21 19 19 19 19 18
B
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
Part A
Part B
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 51 47 45 41 37 37 36 33 32 32 32 32 31 30 29 29
0.5 mg/kg Q4W 54 53 46 45 38 35 34 32 28 30 30 29 29 27 27 26 26
2.0 mg/kg Q4W 51 50 48 47 37 35 32 34 33 31 31 31 29 31 30 30 28
2.0 mg/kg Q8W 50 47 45 39 32 29 28 25 25 23 23 21 19 19 19 19 18

FIG. 7


A
Change from baseline (%)
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 51 48 45 40 38 38 38 35 34 34 32 32 31 31 31 31
0.5 mg/kg Q4W 54 53 45 46 38 35 32 31 30 30 30 30 29 27 28 28 28
2.0 mg/kg Q4W 52 50 47 46 38 36 37 34 34 33 32 32 32 32 32 32 29
2.0 mg/kg Q8W 52 46 42 37 34 31 29 27 25 24 22 20 20 19 19 19 19
B
Patients (%)
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 51 48 45 40 38 38 38 35 34 34 32 32 31 31 31 31
0.5 mg/kg Q4W 54 53 45 46 38 35 32 31 30 30 30 30 29 27 28 28 28
2.0 mg/kg Q4W 52 50 47 46 38 36 37 34 34 33 32 32 32 32 32 32 29
2.0 mg/kg Q8W 52 46 42 37 34 31 29 27 25 24 22 20 20 19 19 19 19
C
Change from baseline (%)
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 51 47 45 41 37 37 36 33 32 32 32 32 31 30 29 29
0.5 mg/kg Q4W 54 52 45 44 37 34 33 31 27 29 29 28 28 26 26 26 26
2.0 mg/kg Q4W 52 49 47 46 37 35 32 34 33 31 31 31 29 31 30 30 28
2.0 mg/kg Q8W 52 46 45 39 32 29 28 25 25 23 23 21 19 19 19 19 18
D
Patients (%)
Nemolizumab 0.1 mg/kg Q4W (n = 53)
Nemolizumab 0.5 mg/kg Q4W (n = 54)
Nemolizumab 2.0 mg/kg Q4W (n = 52)
Nemolizumab 2.0 mg/kg Q8W (n = 52)
Weeks
Patient number at each time point
0.1 mg/kg Q4W 53 48 46 43 38 36 36 36 34 33 33 31 31 30 30 30 30
0.5 mg/kg Q4W 54 50 42 44 36 33 30 29 28 28 28 28 28 26 27 27 27
2.0 mg/kg Q4W 52 49 46 44 37 35 36 33 33 32 31 31 31 31 31 31 28
2.0 mg/kg Q8W 52 45 41 37 34 31 28 27 24 24 22 20 20 19 19 19 18

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051051

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/00 A61P17/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOMAS RUZICKA ET AL: "Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis", THE NEW ENGLAND JOURNAL OF MEDICINE, - NEJM -, MASSACHUSETTS MEDICAL SOCIETY, US, vol. 376, 1 March 2017 (2017-03-01), pages 826-835, XP009195193, ISSN: 0028-4793, DOI: 10.1056/NEJMOA1606490 title, abstract; p. 827, last ; p. 834, first ; ----- -/--	1-40

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2019	29/05/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOMAS RUZICKA ET AL: "Supplementary Appendix of: Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis", THE NEW ENGLAND JOURNAL OF MEDICINE, - NEJM -, vol. 376, no. 9, 2 March 2017 (2017-03-02) , pages 826-835, XP055588908, US ISSN: 0028-4793, DOI: 10.1056/NEJMoa1606490 Fig. S4, S5	1-40
Y	SOHEI OYAMA ET AL: "Cynomolgus monkey model of interleukin-31-induced scratching depicts blockade of human interleukin-31 receptor A by a humanized monoclonal antibody", EXPERIMENTAL DERMATOLOGY, vol. 27, no. 1, 10 April 2017 (2017-04-10) , pages 14-21, XP55588986, COPENHAGEN; DK ISSN: 0906-6705, DOI: 10.1111/exd.13236 title, abstract; p. 15, first	1-40
X	O. NEMOTO ET AL: "The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-co", BRITISH JOURNAL OF DERMATOLOGY, vol. 174, no. 2, 19 December 2015 (2015-12-19), pages 296-304, XP055517114, UK ISSN: 0007-0963, DOI: 10.1111/bjd.14207 title, abstract; p. 299, last to p. 300; p. 303, last of col. 1; first of discussion	1-40
X	CA 2 980 992 A1 (CHUGAL SEIYAKU KK [JP]) 20 October 2016 (2016-10-20) [0044], [0045]; [0074]; [0068]; [0070]; results on p. p. 67/68	1-40

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. FURUE ET AL: "Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis", ALLERGY, vol. 73, no. 1, 20 July 2017 (2017-07-20), pages 29-36, XP055588801, United Kingdom ISSN: 0105-4538, DOI: 10.1111/all.13239 title, abstract; first of introduction	1-40
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Y,P	title, abstract; p. 1123, last to p. 1124, col. 2	1-40

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/051051

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