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(54) Titre : TRAITEMENT DE LESIONS CUTANEES ET DU PRURIT CHEZ DES PATIENTS-ES AFFECTES-ES DE PRURIGO NODULARIS

(54) Title: TREATMENT OF SKIN LESIONS AND PRURITUS IN PRURIGO NODULARIS PATIENTS

(57) Abrégé/Abstract:
Disclosed herein are methods for selectively treating pruritus in a subject having chronic prurigo (CP), including prurigo nodularis (PN), pharmaceutical compositions for use in the treatment of pruritus in a subject having CP or PN, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of pruritus in a subject having CP or PN.

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(54) Title: TREATMENT OF SKIN LESIONS AND PRURITUS IN PRURIGO NODULARIS PATIENTS

(57) Abstract: Disclosed herein are methods for selectively treating pruritus in a subject having chronic prurigo (CP), including prurigo nodularis (PN), pharmaceutical compositions for use in the treatment of pruritus in a subject having CP or PN, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of pruritus in a subject having CP or PN.

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TREATMENT OF SKIN LESIONS AND PRURITUS IN PRURIGO NODULARIS PATIENTS

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/797,803 filed January 28, 2019, and U.S. Provisional Application No. 62/809,404 filed February 22, 2019, the entire contents of which are incorporated herein by reference.

FIELD

[0002] Described herein are methods for treating skin lesions and pruritus of a subject having chronic prurigo (CP), including prurigo nodularis (PN), pharmaceutical compositions for use in the treatment of skin lesions and pruritus in a subject having CP, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of skin lesions and pruritus in a subject having CP.

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] Chronic prurigo (CP) is a skin disease due to neuronal sensitization to itch and development of an itch-scratch cycle. Prurigo nodularis (PN), a subtype of CP, and is a skin disease that causes hard, itchy lumps (nodules) to form on the skin. The itching (pruritus) can be intense, causing people to scratch themselves to the point of bleeding or pain. Scratching can cause more skin lesions to appear. The itching is worsened by heat, sweating, or irritation from clothing. In some cases, people with PN have a history of other diseases including eczema (atopic dermatitis), diabetes, lymphoma, HIV infection, severe anemia, or kidney disease.

[0005] The exact cause of CP or PN is unknown. Although scratching is known to cause more nodules to appear, it is unclear what causes the itching to develop in the first place.

Diagnosis of the disease is based on observing signs such as extremely itchy skin with the formation of nodules. In some cases, a skin biopsy is used to confirm the diagnosis. Currently treatment may include corticosteroid creams, oral medications, cryotherapy, or photochemotherapy.

[0006] There remains a need to develop novel therapeutic regimes to treat patients with PN, particularly those suffering from chronic pruritus.

SUMMARY

[0007] Provided herein are methods for treating skin lesions and pruritus in a subject having chronic prurigo (CP) including prurigo nodularis (PN), pharmaceutical compositions for use in the treatment of skin lesions and pruritus in a subject having CP including PN, uses of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of skin lesions and pruritus in a subject having CP including PN.

[0008] In accordance with some embodiments, there are provided methods of treating skin lesions and pruritus in a subject having CP, the method comprising, consisting of, or consisting essentially of administering an effective amount of nemolizumab or an equivalent thereof to the subject.

[0009] In some embodiments of the methods, the subject has prurigo nodularis (PN). In some embodiments of the methods, the subject has been diagnosed of PN for at least about 6 months. In particular embodiments of the methods, the subject has at least about 20 nodules on his/her body with a bilateral distribution. In particular embodiments of the methods, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments of the methods, the pruritus has been assigned a score of at least 4, while in some embodiments the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments of the methods, the mean of the worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments of the methods, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0010] In some embodiments of the methods, the subject does not have atopic dermatitis. In some embodiments of the methods, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments of the methods, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0011] 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 particular embodiments, the effective amount of nemolizumab or the equivalent thereof is a 40 mg flat dose. In other particular embodiments, the effective amount of nemolizumab or equivalent thereof is 30 mg with a 60 mg loading dose. In other particular embodiments, the effective amount of nemolizumab or the equivalent thereof is 6 60 mg flat dose, administered once every 4 weeks. 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. In certain embodiments, the numolizumab is administered over a period of at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 5 months, 6 months or longer.

[0012] In accordance with some embodiments, there are provided pharmaceutical compositions for use in the treatment of skin lesion and pruritus in a subject having chronic prurigo (CP), the composition comprising, consisting of, or consisting essentially of nemolizumab or an equivalent thereof.

[0013] In some embodiments of the pharmaceutical compositions, the subject has prurigo nodularis (PN). In some embodiments of the compositions, the subject has been diagnosed of PN for at least about 6 months. In particular embodiments of the compositions, the subject has at least about 20 nodules on his/her body with a bilateral distribution. In particular embodiments of the compositions, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments of the compositions, the pruritus has been assigned a score of at least 4, while in some embodiments the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments of the compositions, the mean of the worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments of the compositions, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0014] In some embodiments of the pharmaceutical compositions, the subject does not have atopic dermatitis. In some embodiments of the compositions, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments of the compositions, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0015] In some embodiments, the pharmaceutical composition further comprises a carrier. In some embodiments, the carrier is a pharmaceutically acceptable carrier.

[0016] In some embodiments of the pharmaceutical compositions, the nemolizumab or equivalent thereof is administered according to a flat dosing regimen, while in some embodiments the nemolizumab or equivalent thereof is administered according to a loading dose regimen, in which the loading dose may be higher than the subsequent serial doses (*e.g.*, a 60 mg loading dose followed by 30 mg serial doses).

[0017] In some embodiments of the pharmaceutical compositions, the nemolizumab or equivalent thereof is administered at a dose of 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. while in some embodiments, the nemolizumab or equivalent thereof is administered at a dose of 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg of nemolizumab or the equivalent thereof.

[0018] 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 pruritus in a subject having PN.

[0019] In some embodiments of the uses, the pruritus is moderate to severe. In some embodiments of the uses, the subject has been diagnosed of PN for at least 6 months. In particular embodiments of the uses, the subject has at least 20 nodules on his/her body with a bilateral distribution. In particular embodiments of the uses, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments of the uses, pruritus has been assigned a score of at least 4, while in some embodiments the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments of the uses, the mean of the worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments of the uses, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0020] In some embodiments of the uses, the subject does not have atopic dermatitis. In some embodiments of the uses, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments of the uses, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0021] In some embodiments of the uses, the nemolizumab or equivalent thereof is administered according to a flat dosing regimen, while in some embodiments the nemolizumab or equivalent thereof is administered according to a loading dose regimen, in

which the loading dose may be higher than the subsequent serial doses (*e.g.*, a 60 mg loading dose followed by 30 mg serial doses).

[0022] In some embodiments of the uses, the nemolizumab or equivalent thereof is administered at a dose of 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. while in some embodiments, the nemolizumab or equivalent thereof is administered at a dose of 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg of nemolizumab or the equivalent thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1** Overview of the clinical study of treating pruritus in patient having prurigo nodularis (PN) with nemolizumab. A multi-center (20 sites in EU & US), randomized, double-blinded, placebo-controlled, parallel group study was conducted with approximately 70 randomized patients in 2 arms (35 per arm) were conducted, and stratified on background of atopy. Enrolled patients received nemolizumab or placebo at a dose of 0.5 mg/kg every 4 weeks from baseline to Week 8.

[0024] **FIG. 2** illustrates percentage change from baseline in weekly average peak pruritus numerical rating score (NRS) at Week 4.

[0025] **FIG. 3** illustrates percentage change from baseline in weekly average peak pruritus NRS over 18 weeks.

[0026] **FIG. 4** illustrates absolute change from baseline in weekly average peak pruritus NRS over 18 weeks.

[0027] **FIG. 5** illustrates absolute change from baseline in weekly average peak pruritus NRS over 18 weeks in patients with no atopy.

[0028] **FIG. 6** illustrates absolute change from baseline in weekly average peak pruritus NRS over 18 weeks in patients with atopy.

[0029] **FIG. 7** illustrates proportion of subjects achieving Investigators' Global Assessment (IGA) success (0/1). Investigators' Global Assessment (IGA) scores range from 0 (clear) to 4 (severe disease) and are presented as a percentage of patients in the indicated population.

[0030] **FIG. 8** illustrates IGA distribution in patients over 18 weeks treatment.

[0031] **FIG. 9** illustrates percentage change in verbal rating scale (VRS) over 18 week treatment. The verbal rating scale (VRS) is a monodimensional scale that allows patients to describe their itch intensity by means of gradually rising adjectives.

[0032] **FIG. 10** illustrates dermatology life quality index (DLQI) Responders (≥ 4) at Week 4 and Week 12. Dermatology Life Quality Index (DLQI) scores range from 0 to 30, with higher scores indicating a lower quality of life.

[0033] **FIG. 11** illustrates change from baseline in DLQI at Week 4 and Week 12.

[0034] **FIG. 12** compares full body image of patients before nemolizumab treatment (A and C) and after treatment for 16 weeks (B and D).

[0035] **FIG. 13** compares full body image of patients before nemolizumab treatment (A and C) and after treatment for 16 weeks (B and D).

[0036] **FIG. 14** compares full body image of patients before nemolizumab treatment (A and C) and after treatment for 16 weeks (B and D).

[0037] **FIG. 15** illustrates percentage change in average pruritus Numerical Rating Scale (NRS) over 18 week treatment.

[0038] **FIG. 16** illustrates proportion of subjects with Prurigo Activity Score (PAS) 75% healed over 18 week treatment.

[0039] **FIG. 17** illustrates proportion of subjects with Prurigo Activity Score (PAS) 50% healed over 18 week treatment.

[0040] **FIG. 18** illustrates proportion of subjects with Prurigo Activity Score (PAS) 0-24% healed over 18 week treatment.

[0041] **FIG. 19** illustrates percentage change from baseline in sleep disturbance NRS at week 4.

[0042] **FIG. 20** illustrates percentage change in sleep disturbance NRS at week 4.

DETAILED DESCRIPTION

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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

[0048] 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.

[0049] 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 is not limited to the exact number set forth herein, and is intended to refer to 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.

[0050] 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").

[0051] 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.

[0052] The terms “treat”, “treating” or “treatment”, as used herein, include alleviating, abating or ameliorating PN, pruritus, or one or more symptoms thereof, whether or not PN 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 PN and/or pruritus or one or more symptoms thereof, impeding or preventing an underlying mechanism of PN and/or pruritus or one or more symptoms thereof, and achieving any therapeutic and/or prophylactic benefit.

[0053] 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).

[0054] The amino acid sequence of IL31RAv4 is:

MKLSPQPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENISCVYYYRKNLTCTW
SPGKETSYTQYTVKRTYAFGEKHDNCTTNSSTSENRASCSFFLPRITIPDNYTIEVEAE
NGDGVIKSHMTYWRLENIAKTEPPKIFRVKPVLGIKRMIQIEWIKPELAPVSSDLKYT
LRFRTVNSTSWMEVNFAKNRKDKNQTYNLTGLQPFTEYVIALRCAVKESKFWSDW
SQEKMGMTEEEAPCGLELWRVLKPAEADGRRPVRLLWKKARGAPVLEKTLGYNIW

YYPESNTNLTETMNTTNQQLELHLGGESFWVSMISYNSLGKSPVATLRIPAIQEKSFQ
CIEVMQACVAEDQLVVKWQSSALDVNTWMIEWFPDVDSEPTTLSWESVSQATNWT
IQQDKLKPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKTVTIT
WKEIPKSERKGIICNYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYIVQVMASTS
AGGTNGTSINFKTLSFSVFEIILITSLIGGGLLILIILTVAYGLKKPNKLTHLCWPTVPNP
AESSIATWHGDDFKDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKLVVNFGNVLQ
EIFTDEARTGQENNLGGEKNGTRILSSCPTSI (SEQ ID NO: 1)

[0055] The amino acid sequence of IL31RAv3 is:

MMWTWALWMLPSLCKFSLAALPAKPENISCVYYYRKNLTCTWSPGKETSYTQYTV
KRTYAFGEKHDNCTTNSSTSENRASCSFFLPRITIPDNYTIEVEAENGDGVIKSHMTY
WRLENIAKTEPPKIFRVKPVLGIKRMIQIEWIKPELAPVSSDLKYTLRFRTVNSTSWM
EVNFAKNRKDKNQTYNLTGLQPFTEYVIALRCAVKESKFWSDWSQEKMGMTEEEA
PCGLELWRVLKPAEADGRRPVRLLWKKARGAPVLEKTLGYNIWYYPESNTNLTET
MNTTNQQLELHLGGESFWVSMISYNSLGKSPVATLRIPAIQEKSFQCIEVMQACVAE
DQLVVKWQSSALDVNTWMIEWFPDVDSEPTTLSWESVSQATNWTIQQDKLKPFWC
YNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKTVTITWKEIPKSERKG
IICNYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYIVQVMASTSAGGTNGTSINF
KTLSFSVFEIILITSLIGGGLLILIILTVAYGLKKPNKLTHLCWPTVPNPAESSIATWHGD
DFKDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKLVVNFGNVLQEIFTDEARTGQE
NNLGGEKNGYVTCPFRPDCPLGKSFEELPVSPEIPPRKSQYLRSRMPEGTRPEAKEQL
LFSGQSLVPDHLCEEGAPNPYLKNSVTAREFLVSEKLPEHTKGEV (SEQ ID NO: 2)

[0056] Mouse-derived IL-31RA includes proteins comprising the amino acid sequence:

MWTLALWAFSFLCKFSLAVLPTKPENISCVFYFDRNLTCTWRPEKETNDTSYIVTLT
YSYGKSNYSDNATEASYSFPRSCAMPPDICSVEVQAQNGDGKVKSDITYWHLISIAK
TEPPIILSVNPICNRMFQIQWKPREKTRGFPLVCMLRFRTVNSSRWTEVNFENCKQVC
NLTGLQAFTEYVLALRFRFNDSRYWSKWSKEETRVTMEEVPHVLDLWRILEPADMN
GDRKVRLLWKKARGAPVLEKTFGYHIQYFAENSTNLTEINNITTQQYELLLMSQAHS
VSVTSFNSLGKSQEAILRIPDVHEKTFQYIKSMKAYIAEPLLVVNWQSSIPAVDTWIV
EWLPEAAMSKFPALSWESVSQVTNWTIEQDKLKPFTCYNISVYPVLGHRVGEPYSIQ

AYAKEGTPLKGPETRVENIGLRTATITWKEIPKSARNGFINNYTVFYQAEGGKELSKT
VNSHALQCDLESLTRRTSYTVWVMASTRAGGTNGVRINFKTLSISVFEIVLLTSLVGG
GLLLLSIKTVTFGLRKPNRLTPLCCPDVPNPAESSLATWLGDGFKKSNMKETGNSGD
TEDVVLKPCPVPADLIDKLVVNFENFLEVVLTEEAGKGQASILGGEANEYVTSPSRPD
GPPGKSFKEPSVLTEVASEDSHSTCSRMADEAYSELARQPSSSCQSPGLSPPREDQAQ
NPYLKNSVTTREFLVHENIPEHSKGEV (SEQ ID NO: 3)

[0057] Cynomolgus monkey-derived IL-31RA includes proteins comprising the amino acid sequence:

MMWTWALWMFPLLCKFGLAALPAKPENISCVYYYRKNLTCTWSPGKETSYTQYTA
KRTYAFGKKHDNCTTSSSTSENRASCSFFLPRITIPDNYTIEVEAENGDGVIKSDMTC
WRLEDIAKTEPPEIFSVKPVLGIKRMIRIEWIKPELAPVSSDLKYALRFRTVNSTSWME
VNFAKNRKDTNQTYNLMGLQAFTEYVVALRCAVKESKFWSDWSQEKMGMTEEEA
PCGLELWRVLKPTEVDGRRPVRLLWKKARGAPVLEKTLGYNIWYFPENNTNLTETV
NTTNQQLELHLGGESYWVSMISYNSLGKSPVTTLRIPAIQEKSFRCIEVMQACLAEDQ
LVVKWQSSALDVNTWMIEWFPDMDSEHPTLSWESVSQATNWTIQQDKLKPFWCYN
ISVYPMLHDKVGEPYSIQAYAKEGIPSKGPETKVENIGVKTVTITWKEIPKSERKGIIC
NYTIFYQAEGGKGFSKTVNSSILQYGLESLKRKTSYTVRVMASTSAGGINGTSINFKT
LSFSVFEIILITSLIGGGLLILIILTVAYGLKKPNKLTHLCWPSVPNPAESSIATWRGDDF
KDKLNLKESDDSVNTEDRILKPCSTPSDKLVIDKSVVNFGNVLQEMFTDEARTGQEN
NLGGEKNEYVTHPFRADCPLGKSFEELPVSPEIPPRKSQYLRSRMPEGTCLEAEEQLL
VSGQSLESLAPDHVREAAAPNPYLKNSVTTREFLVSQKLPEHTKGEV (SEQ ID NO: 4)

[0058] 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. In some embodiments, the subject has been diagnosed of PN for at least 6 months. In particular embodiments, the subject has at least 20 nodules on his/her body with a bilateral distribution. In particular embodiments, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments, the subject has pruritus that has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments, the mean of the worst daily intensity of the NRS score is at least 7 over the

previous 3 days. In other particular embodiments, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0059] In some embodiments, the subject does not have atopic dermatitis. In some embodiments, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0060] The term “chronic prurigo” or (“CP”) is used herein as it is in the art and means a distinct disease defined by the presence of chronic pruritus and multiple localized or generalized pruriginous lesions. Chronic pruritic condition is characterized by excoriated, scaled or crusted plaques and/or papules and/or nodules, often with a whitish or pink center and hyperpigmented border and scars. There are four subtypes of chronic pruritus: nodular type (prurigo nodularits or PN), popular type (papular prurigo), plaque type, and umbilicated type (Kyrle type). CP occurs due to a neuronal sensitization to itch and the development of an itch-scratch cycle. CP can be of dermatological, systemic, neurologic, psychiatric/psychosomatic, multifactorial or undetermined origin. The term CP includes all stages and manefestations of chronic prurigo. The best known subtype of CP is prurigo nodularis (PN). *See* Pereira et al., *Journal of European Academy of Dermatology and Venereology* (2018) 32:1059-1065.

[0061] The term “prurigo nodularis” (or “PN”) is used herein as it is in the art and means a skin disease that causes hard, itchy lumps (nodules) to form on the skin. The itching (pruritus) can be intense, causing people to scratch themselves to the point of bleeding or pain. Scratching can cause more skin lesions to appear. The itching is worsened by heat, sweating, or irritation from clothing. In some cases, people with PN have a history of other diseases including eczema (atopic dermatitis), diabetes, lymphoma, HIV infection, severe anemia, or kidney disease. The exact cause of PN is not well-understood. It is thought that nodules are more likely to form when skin has been scratched or irritated in some way. Therefore, the act of a person scratching skin can cause the nodules to form. However, the

cause of the skin to originally become intensely itchy is unclear. Many people with PN have a history of eczema (atopic dermatitis), other skin conditions, or allergies. The main symptom of prurigo nodularis (PN) is the formation of hard, very itchy lumps (nodules) on the skin. The nodules can range in size from very small to about half an inch in diameter. The nodules often have a rough, dry top and can range in number from a few to hundreds. Nodules most commonly form on the outer arms, shoulders, and legs. Nodules can also form on the neck and trunk, and they rarely form on the face and palms. They may be lighter or darker in color than the surrounding skin. Scarring may occur after nodules begin to heal. The symptoms of PN can begin at any age but are most common in adults between 20-60 years. People who have PN may become very concerned about the appearance of the nodules, and the intensely itchy skin may interfere with sleep or with everyday activities. This can cause people with PN to develop stress and depression.

[0062] 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 PN 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 for phototherapy is UVB.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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

[0067] "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).

[0068] Nemolizumab heavy chain amino acid sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFT*GYIMN*WVRQAPGQGLEWMG*LIN PYNGGTDYNPQFQD*RVTITADKSTSTAYMELSSLRSEDTAVYYCAR*DGYDDGPYT LET*WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE RKSCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEK TISKTKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPMLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSP (SEQ ID NO: 5)

[0069] Nemolizumab light chain amino acid sequence:

DIQMTQSPSSLSASVGDRVTITC*QASEDIYSFVA*WYQQKPGKAPKLLIY*NAQTEA Q*GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC*QHHYDSPLT*FGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 6)

[0070] The variable domains of the heavy and light chain sequences are shown in bold above, and the CDR sequences are underlined/italicized.

[0071] 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 (viiii) 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.

[0072] 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).

[0073] 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.

[0074] 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.

[0075] The inventors have hypothesized that an anti-pruritic drug could have a greater impact on PN in patients that suffer from moderate to severe pruritus.

[0076] In some embodiments, pruritus 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.

[0077] In some embodiments, pruritus is characterized according to one or more of the following methods known by those skilled in the art. For example, the intensity can be quickly measured with monodimensional scales that are routinely used in clinical care. See Pereira et al., Allergology International (2017) 66:3-78, incorporated herein by reference. For example, patients can be asked to rate their itch intensity from 0 ("no itch") to 10 ("worst imaginable itch") with the numerical rating scale (NRS). Another monodimensional scale, the visual analogue scale (VAS), provides patients with the opportunity to indicate the intensity of their itch by marking on a 10 cm long, ruler-shaped scale. Both endpoints are marked with a number corresponding to the intensity, with 0 representing "no itch" and 10 the "worst imaginable itch." Scores below 3.0 VAS/NRS points are generally associated with mild itch, whereas scores higher than 6.9 illustrate severe itch. Scores above 9.0 represent a very severe itch. The verbal rating scale (VRS) is a further monodimensional scale that allows patients to describe their itch intensity by means of gradually rising adjectives (0 – no itch, 4 – worst imaginable itch). The NRS, VAS and VRS have been validated in large-scale studies consisting of chronic pruritus patients with pruritic dermatoses or pruritus of various origins. These instruments have high reproducibility and there was a high correlation between scales 6, 7, 8. Chronic pruritus can greatly reduce patient quality of life. For this reason, Dermatology Life Quality Index (DLQI) is widely used and has been validated. DLQI scores range from 0 to 30, with higher scores indicating a lower quality of life. 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. In the present study, IGA scores range from 0 to 4.

Pharmaceutical Compositions

[0078] Provided herein are pharmaceutical compositions for use in the treatment of skin lesions and pruritus in in a subject having chronic prurigo (CP), the composition comprising, consisting of, or consisting essentially of nemolizumab or an equivalent thereof. Moreover, the present disclosure provides therapeutic agents for CP which comprise nemolizumab or an equivalent thereof as an active ingredient.

[0079] In some embodiments, the subject has prurigo nodularis (PN). In some embodiments, the subject has been diagnosed of PN for at least about 6 months. In particular embodiments, the subject has at least about 20 nodules on his/her body with a bilateral distribution. In particular embodiments, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments, the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments, the mean of the worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0080] In some embodiments, the subject does not have atopic dermatitis. In some embodiments, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0081] 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 PN in the present disclosure may also comprise, in combination with nemolizumab or an equivalent thereof, other ingredients that enhance the treatment of PN. For example, the composition may comprise one or moretopical corticosteroid creams or

injections, ointments with menthol or phenol to cool and soothe itchy skin, capsaicin cream, oral corticoseroids, selective serotonin reuptake inhibitors (SSRIs), and oral antihistamines.

[0082] 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.

[0083] 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.

[0084] 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).

[0085] 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.

[0086] 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.

Methods of Treatment

[0087] In accordance with some embodiments, there are provided methods of treating pruritus in in a subject having prurigo nodularis (PN), the method comprising, consisting of, or consisting essentially of administering an effective amount of nemolizumab or an equivalent thereof to the subject.

[0088] In some embodiments, the pruritus is moderate to severe. In some embodiments of the methods, the subject has been diagnosed of PN for at least 6 months. In particular embodiments of the methods, the subject has at least 20 nodules on his/her body with a bilateral distribution. In particular embodiments of the methods, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments of the methods, the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments of the methods, the mean of the

worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments of the methods, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0089] In some embodiments of the methods, the subject does not have atopic dermatitis. In some embodiments of the methods, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments of the methods, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

[0090] An “effective amount” is an amount sufficient to effect beneficial or desired results such as alleviating at least one or more symptom of PN 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 PN and/or pruritus symptom (for example sleep efficiency), or reverse a symptom of PN 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.

[0091] 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.

[0092] Dosage regimens for treating CP and PN may comprise flat dosing (*i.e.*, administering the same dose repeatedly at pre-determined intervals) or comprise a loading dose (*i.e.*, administrating an initial dose that is higher or different than subsequent, serial doses). For the purposes of either type of dosing regimen an effective dose may be administered topically, parenterally, subcutaneously, subdermally, intradermally, or intramuscularly.

[0093] In some embodiments, a loading dose and the subsequent serial doses may be administered via the same route (*e.g.*, subcutaneously), while in some embodiments, a loading dose and the subsequent serial doses may be administered via different routes (*e.g.*, parenterally and subcutaneously, respectively). In some embodiments, the loading dose may be 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, or higher. In some embodiments, the loading dose may be 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, or higher. In some embodiments, the loading dose may be 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 some embodiments, the loading dose may be 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 500 mg/kg, or 1,000 mg/kg. In some embodiments, the loading dose is administered as a single injection. In some embodiments, the loading dose is administered as multiple injections, which may be administered at the same time or spaced apart at defined intervals.

[0094] The subsequent serial doses of a loading dose regimen are generally lower than the loading dose. For examples, in some embodiments, the dosing regimen may comprise a loading dose of 60 mg and a serial dose of 30 mg, which may be administered a defined intervals of, for example, every 4 weeks. In some embodiments, the serial dose of a dosing regimen may be 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, or higher. In some embodiments, the serial dose may be 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, or higher. In some embodiments, the serial dose may be 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 some embodiments, the serial dose may be 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 500 mg/kg, or 1,000 mg/kg.

[0095] For the purposes of a loading dose regimen, the first serial dose may be administered 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, or 10 weeks after the initial loading dose. In some embodiments, the first serial dose is administered 4 weeks after the initial loading dose. In some embodiments, the subsequent serial doses are administered once every 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, or 10 weeks. In some embodiments, the serial doses are spaced 4 weeks apart (*i.e.*, nemolizumab or an equivalent thereof is administered once every 4 weeks).

[0096] 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.

[0097] In some embodiments, the dose of nemolizumab or an equivalent thereof administered to the subject is within the range of 1 to 100 mg, 25 to 75 mg, 30 to 60 mg, 40 to 80 mg, 20 to 80 mg, 1 to 25 mg, 1 to 50 mg, 10 to 90 mg, 15 to 85 mg, or ranges there betwee. In some embodiments, the dose may be 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, or higher. In some embodiments, the dose may be 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, or higher.

[0098] In particular embodiments, a loading dose of about 60 mg of nemolizumab or an equivalent thereof may be administered to a subject in need thereof, followed by subsequent serial doses of nemolizumab of an equivalent thereof at about 30 mg once every 4 weeks.

[0099] 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 nodules.

[0100] 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 (*e.g.*, CP or PN). In preferred embodiments, nemolizumab or the equivalent thereof is administered every four weeks or every eight weeks.

[0101] 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 or pruritus (*e.g.*, CP or PN). 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.

[0102] 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 pruritus s in a subject having prurigo nodularis (PN).

[0103] In some embodiments of the uses, the pruritus is moderate to severe. In some embodiments of the uses, the subject has been diagnosed of PN for at least 6 months. In particular embodiments of the uses, the subject has at least 20 nodules on his/her body with a bilateral distribution. In particular embodiments of the uses, the subject has prurigo lesions on upper limbs, with or without lesions on the trunk or lower limbs. In particular embodiments of the methods, the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS). In particular embodiments of the uses, the mean of the worst daily intensity of the NRS score is at least 7 over the previous 3 days. In other particular embodiments of the uses, the mean of the worst daily intensity of the NRS score is at least 7 over the previous week.

[0104] In some embodiments of the uses, the subject does not have atopic dermatitis. In some embodiments of the uses, the subject does not have chronic pruritus resulting from a condition other than PN, such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. In some embodiments of the uses, the subject does not have neuropathic or psychogenic pruritus, such as notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia.

EXAMPLES

Example 1 Determine efficacy of nemolizumab in the treatment of pruritus of PN patients.

[0105] A multi-center (20 sites in EU & US), randomized, double-blinded, placebo-controlled, parallel group study was conducted comprising approximately 70 randomized patients in 2 arms (35 per arm) stratified on background of atopy. Enrolled patients received subcutaneous nemolizumab or placebo at a dose of 0.5 mg/kg every 4 weeks. The patients were selected based on the following criteria.

[0106] Inclusion criteria:

[0107] 1. Male or female of at least 18 years at screening.

[0108] 2. Clinical diagnosis of PN for at least 6 months with: (a) Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs, and (b) at least 20 nodules on the entire body with a bilateral distribution

[0109] 3. Severe pruritus on a Numerical Rating Scale (NRS). NRS is determined both by screening visit and baseline visit. Screening visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous 3 days. Baseline visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous week.

[0110] 4. Female subjects must fulfill one of the criteria: (a) Female subjects of non-childbearing potential (postmenopausal, i.e. absence of menstrual bleeding for 1 year prior to screening, without any other medical reason, hysterectomy or bilateral oophorectomy); (b) Female subjects of childbearing potential who agree to a true abstinence (when in line with the preferred and usual lifestyle of the subject), or to use an effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration.

[0111] Patients with the following conditions are excluded.

[0112] Exclusion criteria:

[0113] 1. Chronic pruritus resulting from another condition than PN such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease.

[0114] 2. Unilateral lesions of prurigo (e.g only one arm affected).

[0115] 3. Cutaneous bacterial or viral infection within 1 week before the baseline visit.

[0116] 4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit, or during the screening period, unless completely resolved at the screening/ baseline visits respectively.

[0117] 5. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results and/or put the subject at significant risk according to Investigator's judgment (e.g. solid cancer, AIDS, serious or uncontrolled cardiac disease) at Screening or Baseline.

[0118] Any active dermatoses that would need immediate therapy.

[0119] 7. Active atopic dermatitis or known with recurrent flares of atopic dermatitis

[0120] 8. Neuropathic and psychogenic pruritus (notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia).

[0121] 9. Positive serology results hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), hepatitis C antibody or Human Immunodeficiency virus (HIV) antibody) at the screening visit.

[0122] 10. Abnormal lab criteria listed below, at the screening visit: Elevated ALT / AST ≥ 3 ULN , Elevated CPK > 1.5 ULN, Neutrophil count < 1.5 x 10^3/µl , Creatinine clearance <60ml/min/1.73m²;

[0123] 11. Medical history of asthma that fulfill any or more of the conditions:(i) had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit; (ii)Whose asthma has not been well-controlled (i.e. symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit; PEF <80% of the predicted value at screening or baseline visit.

[0124] 12. Latent or active TB, as determined by a positive Quantiferon-based TB test result at screening visit.

[0125] 13. Having received any of forbidden treatments within the specified time frame prior to the baseline visit:

Table 1. Forbidden Therapies

Topical treatments	Wash-out periods
Calcineurin inhibitors (tacrolimus, pimecrolimus), TCS, vitamin D analogs , PDE-4 inhibitors	2 weeks
Any topical treatment other than moisturizer (e.g capsaicin, cryotherapy)	2 weeks
Emollients or moisturizer with menthol, capsaicine, polidocanol or other having “anti-itch” claim	1 week
Systemic treatments	Wash-out periods
Corticosteroids oral, injectable	4 weeks
immunosuppressive or immunomodulatory drugs (e.g, azathioprine, methotrexate, thalidomide, cyclosporine	8 weeks or 5 half-lives (whichever is longer)
Antihistamines	1 week
Phototherapy	4 weeks
Roxitromycin, erythromycin	1 week

Opiods (naltrexone, naloxone, nalbuphine etc), NK1 receptor antagonists (aprepitant), antiepileptics (gabapentin, pregabalin)	4 weeks or 5 half-lives (whichever is longer)
Biologics, Retinoids	8 weeks or 5 half-lives (whichever is longer)
Live vaccine	4 weeks
Drugs with sedative effect such as benzodiazepines, imidazopyridines, hydroxizine barbiturates, or sedative anti-depressants such as amitryptiline, paroxetine, except if these treatments were taken at a stable dose for at least 3 months before screening	3 months

[0126] If deemed to be medically necessary by the Investigator, rescue treatments for pruritus could be associated to the study drug from Day 29. All efficacy and safety assessments should be completed before starting the rescue treatments.

[0127] **Table 2. Rescue Therapies**

Rescue therapies	**Action to be taken**
Antihistamines, association of antihistamines and TCS of mid-potency	Continue the study drug
cyclosporine, thalidomide, gabapentin, phototherapy, etc..	Discontinue the study drug

[0128] Endpoints :

[0129] The primary endpoint of the study was a percent reduction from baseline (BL) in pruritus NRS at week 4.

[0130] The secondary endpoints of the study was a reduction at every visit up to 18 weeks, characterized by NRS, VRS, or DPS. Safety evaluations were also conducted at the secondary endpoint. Prurigo remission was characterized by prurigo activity score (PAS) and IGA.

Pharmacokinetic (PK) profile of PN patients was measured. Pharmacodynamic (PD) profile of PN patients was measured in patients' blood, biopsies, and D-squames samples. Quality of life of PN patients was measured by DLQI. Actigraphy was applied to assess sleep improvement and scratching (by Actiwatch). Photographs of PN patients were taken by fotofinder in selected centers.

[0131] The results of the clinical study are presented in the tables below.

Table 3. Demographics and baseline characteristics

	Placebo (N=36)	Nemolizumab 0.5 mg /kg (N=34)	Total (N=70)

Gender			
Male	14 (38.9%)	15 (44.1%)	29 (41.4%)
Female	22 (61.1%)	19 (55.9%)	41 (58.6%)
Race			
White	35 (97.2%)	33 (97.1%)	68 (97.1%)
Black/African American	1 (2.8%)	1 (2.9%)	2 (2.9%)
Asian	0	0	0
Other	0	0	0
Age (years)			
Mean (SD)	52.4 (17.47)	59.7 (13.16)	56.0 (15.85)
Range	20-77	26-85	20-85
Weight Mean (SD) (kg)	36 80.30 (20.716)	34 81.61 (21.766)	70 80.94 (21.088)

Note: Percentages are based on the number of subjects having a non-missing value in the respective treatment arm.

[0132] As shown in Table 3, the placebo group and the nemolizumab treated group in the study presented comparable composition in gender, race, age, and weight.

Table 4. Baseline clinical disease characteristics

	Placebo (N=36)	Nemolizumab 0.5 mg/kg (N=34)	Total (N=70)
Mean Prurigo baseline assessment (PAS) (SD)	22.4 (17.50)	17.1 (13.39)	19.8 (15.76)
Background of atopy			
Presence	6 (16.7%)	5 (14.7%)	1
Absence	30 (83.3%)	29 (85.3%)	1 (15.7%)
Number of nodules on the entire body n (%)			59 (84.3%)
20-100	21 (58.3)	21 (61.8)	
>100	15 (41.7)	13 (38.2)	42 (60.0)
Weekly peak pruritus NRS			28 (40.0)
Mean ± SD	8.4 (1.18)	8.4 (1.19)	
Range	(7-9)	(8-9)	8.4 (1.17)
Weekly avg pruritus NRS	34	33	(8-9)
Mean (SD)	7.9 (1.28)	7.8 (1.66)	67
Investigator Global Assessment (IGA) n (%)			7.9 (1.47)
Moderate	22 (61.1)	16 (47.1)	
Severe	14 (38.9)	18 (52.9)	38 (54.3)
			32 (45.7)
DLQI baseline score (range 0-30)			

Mean ± SD	15.8 ± 6.0	16.9 ± 7.5	

[0133] As shown in Table 4, the placebo group and the nemolizumab treated group in the study presented comparable baseline level of pruritus, measured by number of nodules on the entire body, weekly peak pruritus numerical rating scale (NRS) score, weekly average pruritus NRS score, and Investigator's global assessment (IGA) score.

Table 5. Incidence of Rescue Medication

	Placebo (N=36)	**Nemolizumab 0.5 mg/kg (N=34)**	**Total (N=70)**
Subject with ≥ 1 rescue medications during treatment period	4 (11.1%)	2 (5.9%)	6 (8.6%)
Type of rescue during treatment period: Topical rescue medication (n) Systemic rescue medication (n)	 4 (11.1%) 3 (8.3%)	 0 2 (5.9%)	 4 (5.7%) 5 (7.1%)

[0134] As shown in Table 5, the placebo group has more incidence of topical rescue medication and systemic rescue medication.

[0135] The efficacy results are shown by Figures 2-15. In particular, at primary endpoint, the nemolizumab treatment significantly reduced pruritus at week 4, as illustrated by the percentage change from baseline in weekly average peak pruritus NRS (FIG. 2). Thus, nemolizumab treatment at the dosage of 0.5mg/kg is superior to placebo (-38%, 95%CI=[-51%,-25%] and statistically significant ($p < 0.001$) at Week 4.

[0136] At secondary endpoints, the nemolizumab treatment group consistently shows more reduced pruritus throughout the 18 weeks study, as evidenced by both the percentage change (FIG. 3) and the absolute change (FIG. 4) in peak pruritus NRS, and the results are statistically significant ($p < 0.001$). The same results were also observed both in patients without or with atopic dermatitis (FIGs. 5 and 6).

[0137] Investigators' Global Assessment (IGA) scores range from 0 (clear) to 4 (severe disease) and are presented as a percentage of patients in the indicated population. A much higher percentage of patients treated with nemolizumab compared to the placebo group achieved IGA success (IGA 0/1) (FIG. 7). In addition, IGA distribution shows that the nemolizumab treatment group has consistently higher percentage of patients with lower IGA than the placebo group (FIG. 8). The findings are statistically significant ($p<0.05$) at Week 12 and Week 18.

[0138] Verbal rating scale (VRS) is a monodimensional scale that allows patients to describe their itch intensity by means of gradually rising adjectives (1=no itch, and 4=very severe itch). In other words, the nemolizumab treatment group shows consistently higher percentage change in negative value, which translates into more reduced itchiness throughout the 18 weeks study compared to the placebo group (FIG. 9). The results are statistically significant ($p < 0.001$).

[0139] Dermatology Life Quality Index (DLQI) scores range from 0 to 30, with higher scores indicating a lower quality of life. As shown in FIG. 10, the nemolizumab treatment group has a higher percentage of responders rating DLQI ≥ 4 compared to the placebo group both at week 4 and week 12. As shown in FIG. 11, change from baseline in DLQI is statistically significant ($p<0.01$) in favor of nemolizumab at week 4 but not at week 12.

[0140] Fully body images were taken of representative patients. As shown by FIGs. 12-14, nemolizumab treatment significantly reduced the number of nodules on patient's body after 16 weeks.

[0141] Preliminary Safety Results

[0142] As shown in Tables 6 and 7, the nemolizumab treatment group and the placebo group shows comparable numbers of treatment emergent adverse events (TEAEs) of all causes, and comparable incidence of TEAEs by system organ class (SOC) of all causes. Overall nemolizumab was well tolerated.

Table 6. Safety-overall summary of treatment emergent adverse events (TEAEs) of all causes

	Placebo (N=36)	Nemolizumab 0.5 mg/kg (N=34)	Total (N=70)
Number of TEAEs	69	77	146
Subjects with at least one TEAE	24 (66.7%)	23 (67.6%)	47 (67.1%)
Serious TEAE	3 (8.3%)	4 (11.8%)	7 (10.0%)
Severe TEAE	1 (2.8%)	5 (14.7%)	6 (8.6%)
Fatal TEAE	0	0	0
TEAE leading to temporary drug discontinuation	1 (2.8%)	0	1 (1.4%)
TEAE leading to permanent drug discontinuation	1 (2.8%)	2 (5.9%)	3 (4.3%)
TEAE leading to withdrawal	2 (5.6%)	2 (5.9%)	4 (5.7%)

Table 7. Incidence of TEAEs by System Organ Class (SOC) (>5%), all causes

	Placebo (N=36)	Nemolizumab 0.5 mg/kg (N=34)	Total (N=70)

Infections and infestation	12 (33.3%)	10 (29.4%)	22 (31.4%)
Skin and subcutaneous tissue disorders	12 (33.3%)	10 (29.4%)	22 (31.4%)
Gastrointestinal disorders	5 (13.9%)	7 (20.6%)	12 (17.1%)
Musculoskeletical and connective tissue disorders	5 (13.9%)	6 (17.6%)	11 (15.7%)
General disorders and administration site conditions	4 (11.1%)	5 (14.7%)	9 (12.9%)
Injury, poisoning and procedural complication	2 (5.6%)	4 (11.8%)	6 (8.6%)
Renal and urinary disorders	2 (5.6%)	2 (5.9%)	4 (5.7%)
Nervous system disorders	1 (2.8%)	2 (5.9%)	3 (4.3%)
Respiratory, thoracic and mediastatial disorders	3 (8.3%)	0	3 (4.3%)
Blood and lymphatic system disorders	2 (5.6%)	0	2 (2.9%)
Metabolism and nutrition disorders	0	2 (5.9%)	2 (2.9%)
Psychiatric disorders	2 (5.6%)	0	2 (2.9%)
Vascular disorders	2 (5.6%)	0	2 (2.9%)

WHAT IS CLAIMED IS:

1. A method of treating skin lesions and pruritus in a subject having chronic prurigo (CP), the method comprising administering an effective amount of nemolizumab or an equivalent thereof to the subject.

2. The method of claim 1, wherein the subject has prurigo nodularis (PN).

3. The method of claim 2, wherein the subject has been diagnosed of PN for at least about 6 months.

4. The method of any one of the proceeding claims, wherein the subject has at least about 20 nodules on his/her body with a bilateral distribution.

5. The method of any one of the proceeding claims, wherein the subject has prurigo lesions on upper limbs.

6. The method of any one of the proceeding claims, wherein the pruritus has been assigned a score of at least 4 on the Numerical Rating Scale (NRS).

7. The method of any one of the proceeding claims, wherein the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS).

8. The method of any one of the proceeding claims, wherein the subject does not have atopic dermatitis.

9. The method of any one of the proceeding 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.

10. The method of any one of the proceeding claims, wherein the effective amount of nemolizumab or the equivalent thereof is 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg.

11. The method of any one of the proceeding claims, wherein the nemolizumab or equivalent thereof is administered according to a flat dosing regimen.

12. The method of any one of the proceeding claims, wherein the nemolizumab or equivalent thereof is administered according to a loading dose regimen.

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

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

15. 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.

16. A pharmaceutical composition for use in the treatment of skin lesions and pruritus in a subject having chronic prurigo (CP), the composition comprising nemolizumab or an equivalent thereof.

17. The pharmaceutical composition of claim 16, wherein the subject has prurigo nodularis (PN).

18. The pharmaceutical composition of claim 17, wherein the subject has been diagnosed of PN for at least about 6 months.

19. The pharmaceutical composition of any one of claims 16-18, wherein the subject has at least about 20 nodules on his/her body with a bilateral distribution.

20. The pharmaceutical composition of any one of claims 16-19, wherein the subject has prurigo lesions on upper limbs.

21. The pharmaceutical composition of any one of claims 16-20, wherein the pruritus has been assigned a score of at least 4 on the Numerical Rating Scale (NRS).

22. The pharmaceutical composition of any one of claims 16-21, wherein the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS).

23. The pharmaceutical composition of any one of claims 16-22, wherein the subject does not have atopic dermatitis.

24. The pharmaceutical composition of any one of claims 16-23, further comprising a carrier.

25. The pharmaceutical composition of claim 24, wherein the carrier is a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of any one of claims 16-25, wherein the nemolizumab or equivalent thereof is administered according to a flat dosing regimen.

27. The pharmaceutical composition of any one of claims 16-25, wherein the nemolizumab or equivalent thereof is administered according to a loading dose regimen.

28. The pharmaceutical composition of any one of claims 16-27, wherein the composition comprises 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 of nemolizumab or the equivalent thereof.

29. The pharmaceutical composition of any one of claims 16-27, wherein the composition comprises 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg of nemolizumab or the equivalent thereof.

30. Use of nemolizumab or an equivalent thereof in the manufacture of a medicament for the treatment of skin lesions and pruritus in a subject having chronic prurigo (CP).

31. The use of claim 30, wherein the subject has prurigo nuodularis (PN).

32. The use of claim 31, wherein the subject has been diagnosed of PN for at least about 6 months.

33. The use of any one of claims 30-32, wherein the subject has at least about 20 nodules on his/her body with a bilateral distribution.

34. The use of any one of claims 30-33, wherein the subject has prurigo lesions on upper limbs.

35. The use of any one of claims 30-34, wherein the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS).

36. The use of any one of claims 30-35, wherein the pruritus has been assigned a score of at least 7 on the Numerical Rating Scale (NRS).

37. The use of any one of claims 30-36, wherein the subject does not have atopic dermatitis.

38. The use of any one of claims 30-37, wherein the nemolizumab or equivalent thereof is administered according to a flat dosing regimen.

39. The use of any one of claims 30-37, wherein the nemolizumab or equivalent thereof is administered according to a loading dose regimen.

40. The use of any one of claims 30-39, wherein the nemolizumab or the equivalent thereof is administered at a dose of 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.

41. The use of any one of claims 30-39, wherein the nemolizumab or the equivalent thereof is administered at a dose of 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 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg.

FIG. 1

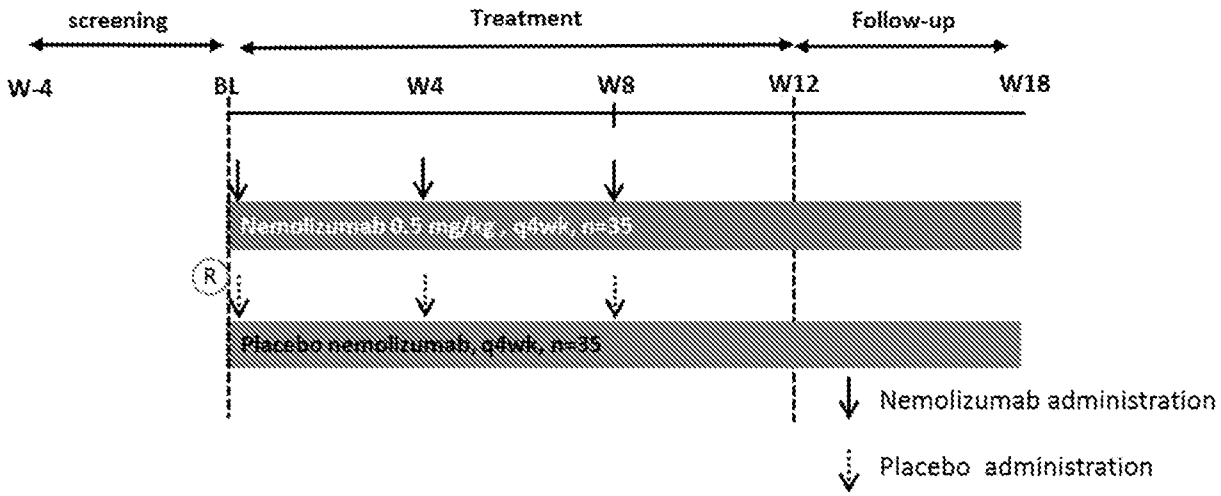

screening
Treatment
Follow-up
W-4
BL
W4
W8
W12
W18
Nemolizumab 0.5 mg/kg, q4wk, n=35
R
Placebo nemolizumab, q4wk, n=35
Nemolizumab administration
Placebo administration

FIG. 2

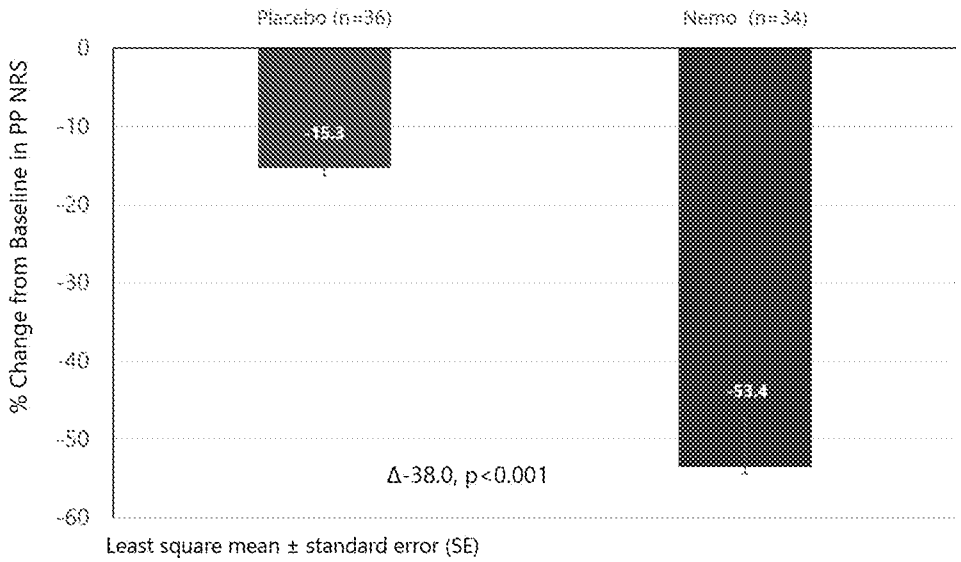

Placebo (n=36)
Nemo (n=34)
% Change from Baseline in PP NRS
0
-10
-20
-30
-40
-50
-60
-15.3
-53.4
Δ-38.0, p<0.001
Least square mean ± standard error (SE)

FIG. 3

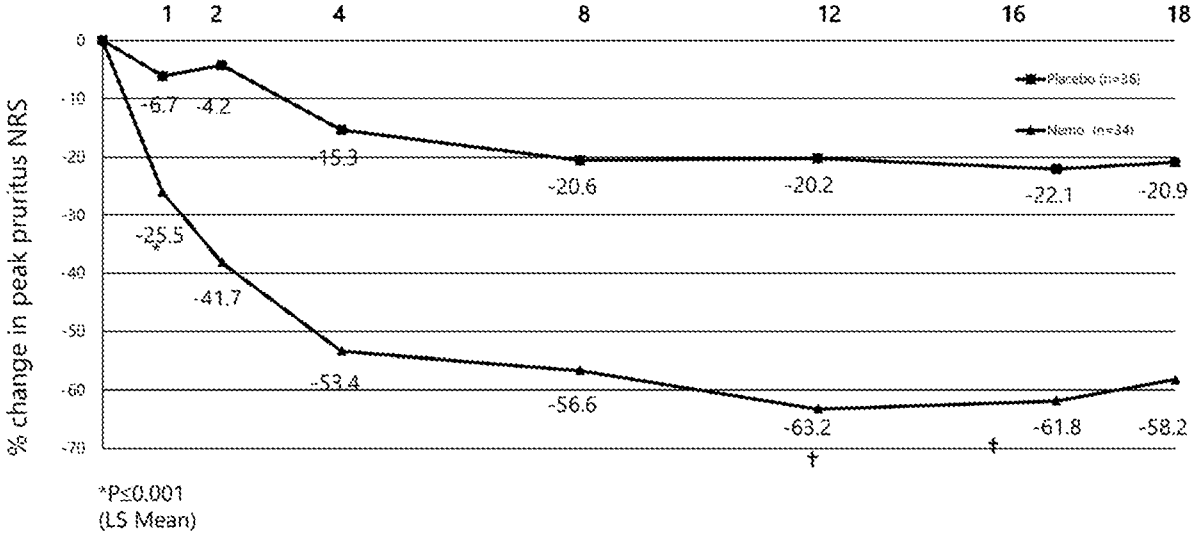

1
2
4
8
12
16
18
0
-10
-20
-30
-40
-50
-60
-70
% change in peak pruritus NRS
Placebo (n=36)
Nemo (n=34)
-6.7
-4.2
-15.3
-20.6
-20.2
-22.1
-20.9
-25.5
-41.7
-53.4
-56.6
-63.2
-61.8
-58.2
*P≤0.001
(LS Mean)

FIG. 4

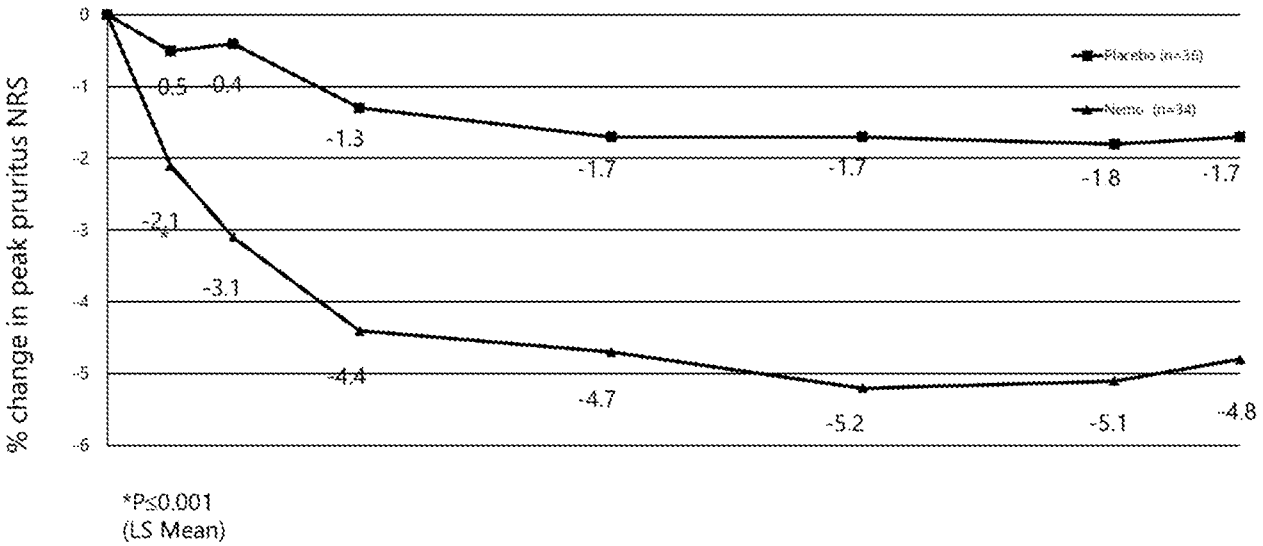
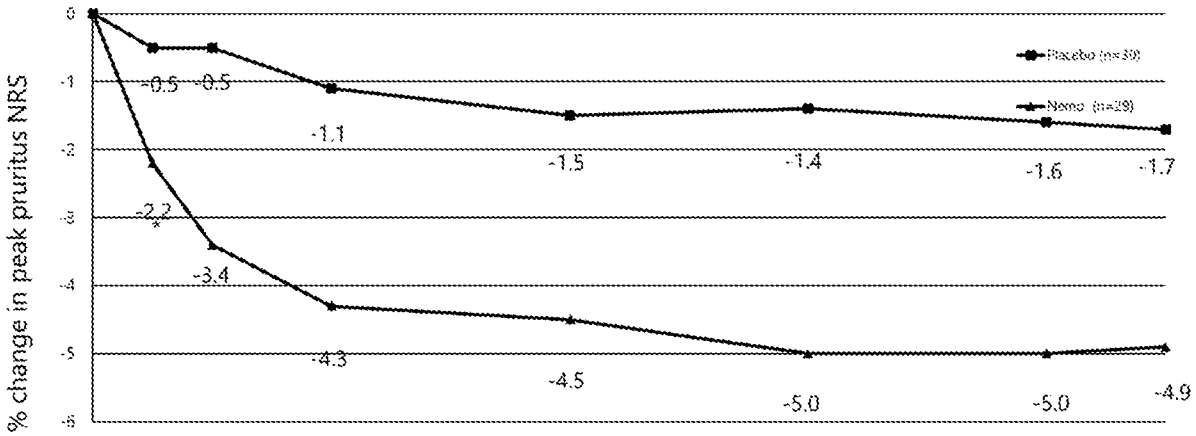
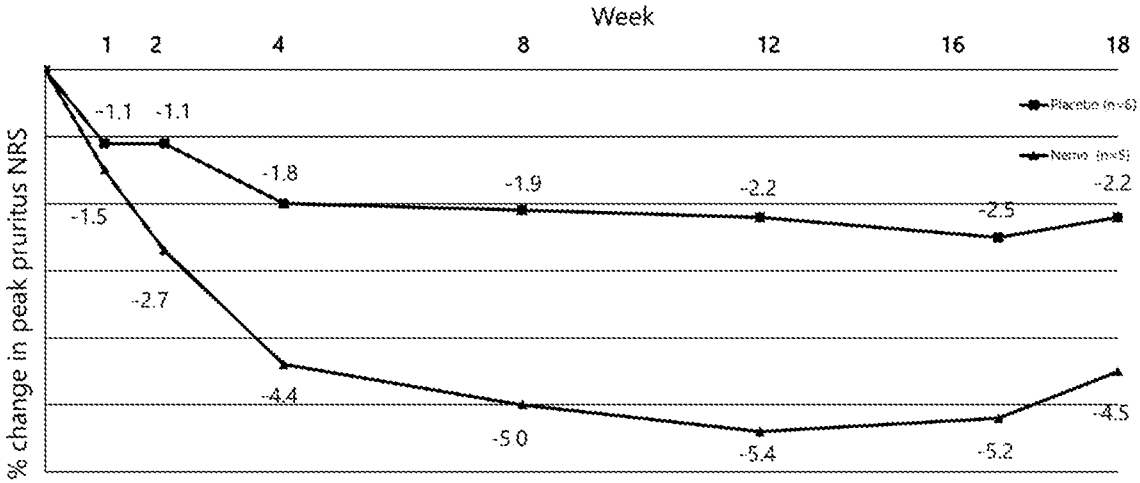

0
-1
-2
-3
-4
-5
-6
% change in peak pruritus NRS
Placebo (n=36)
Nemo (n=34)
-0.5
-0.4
-1.3
-1.7
-1.7
-1.8
-1.7
-2.1
-3.1
-4.4
-4.7
-5.2
-5.1
-4.8
*P≤0.001
(LS Mean)

FIG. 5



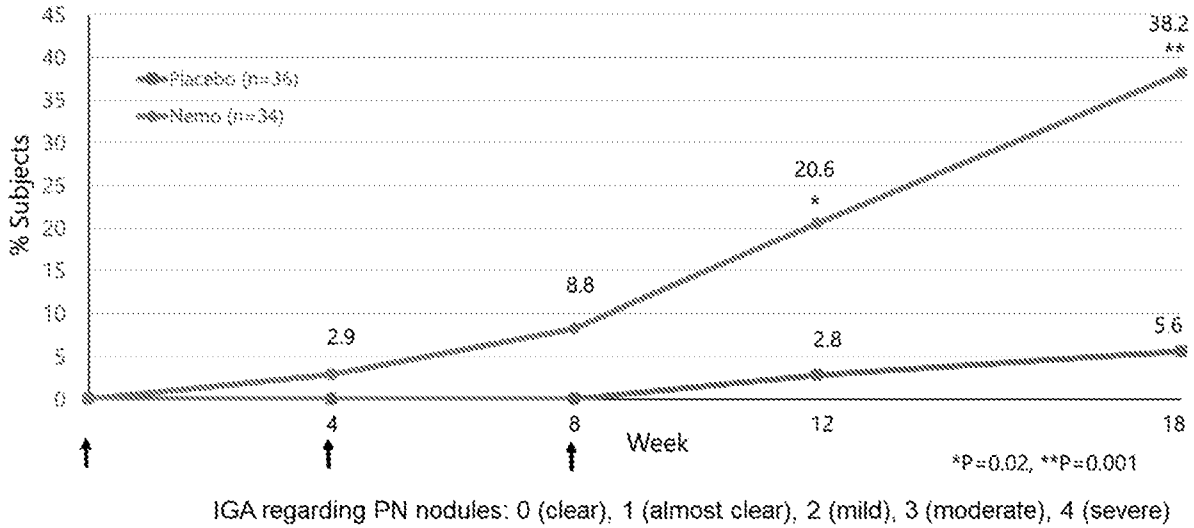
*P≤0.001
(LS Mean)

FIG. 6



(LS Mean)

FIG. 7



IGA regarding PN nodules: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe)

FIG.8

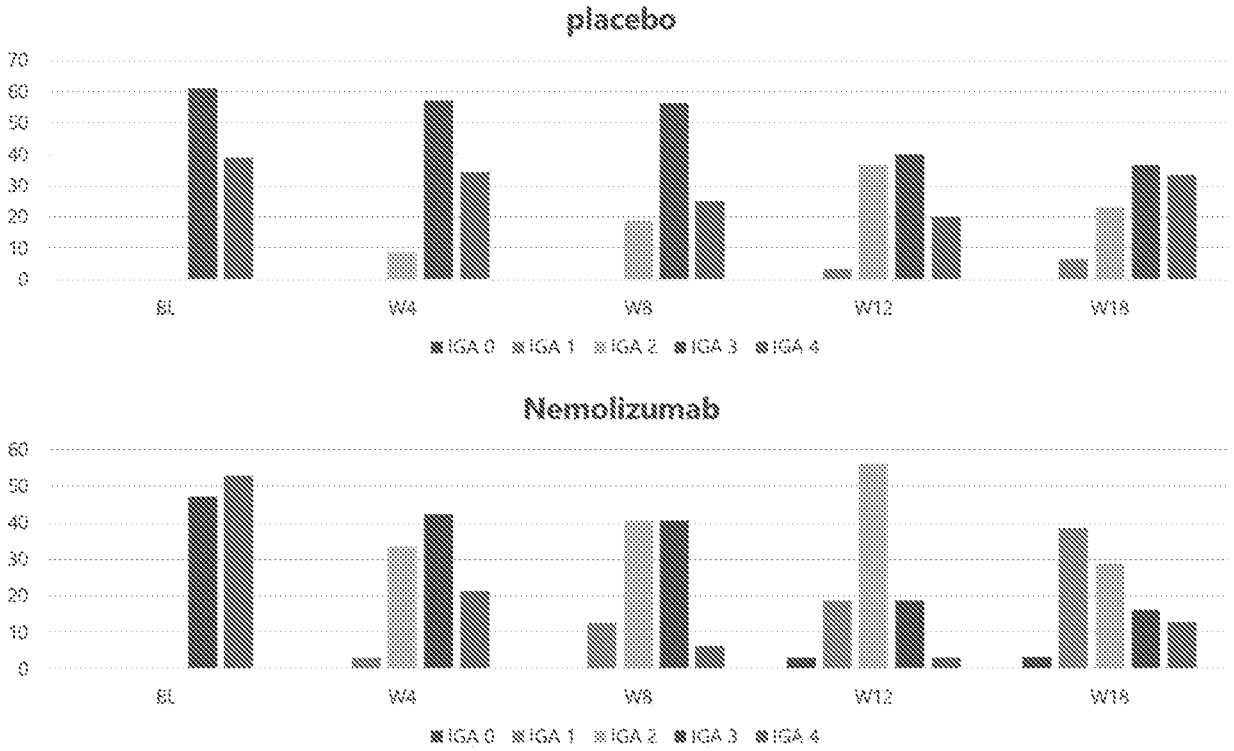

placebo
70
60
50
40
30
20
10
0
BL
W4
W8
W12
W18
IGA 0
IGA 1
IGA 2
IGA 3
IGA 4
Nemolizumab
60
50
40
30
20
10
0
BL
W4
W8
W12
W18
IGA 0
IGA 1
IGA 2
IGA 3
IGA 4

FIG. 9

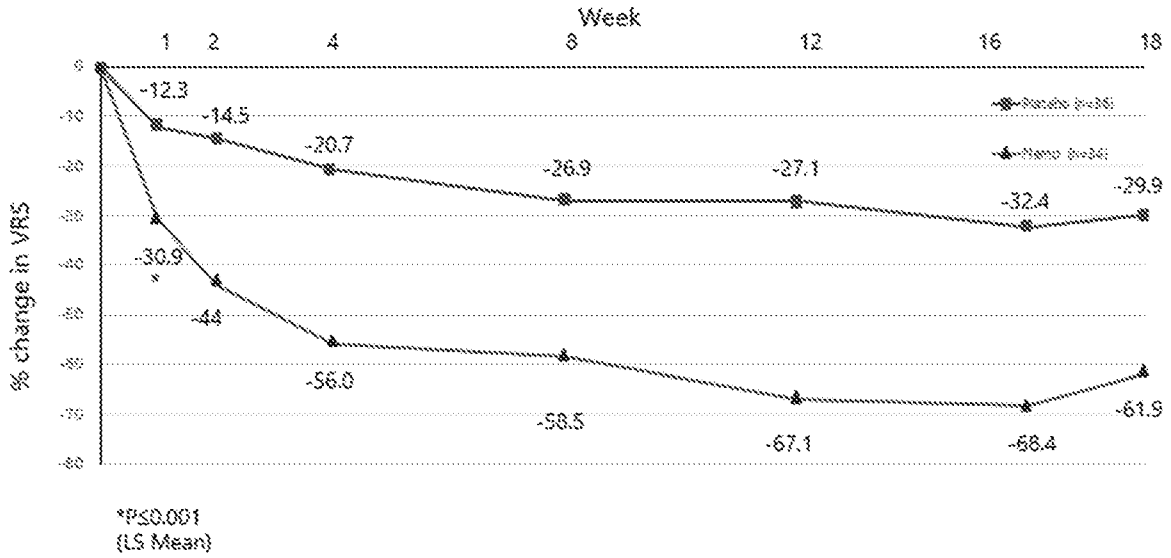

Week
1
2
4
8
12
16
18
% change in VRS
-12.3
-14.5
-20.7
-26.9
-27.1
-32.4
-29.9
-30.9
*
-44
-56.0
-58.5
-67.1
-68.4
-61.9
*P≤0.001
(LS Mean)

FIG. 10

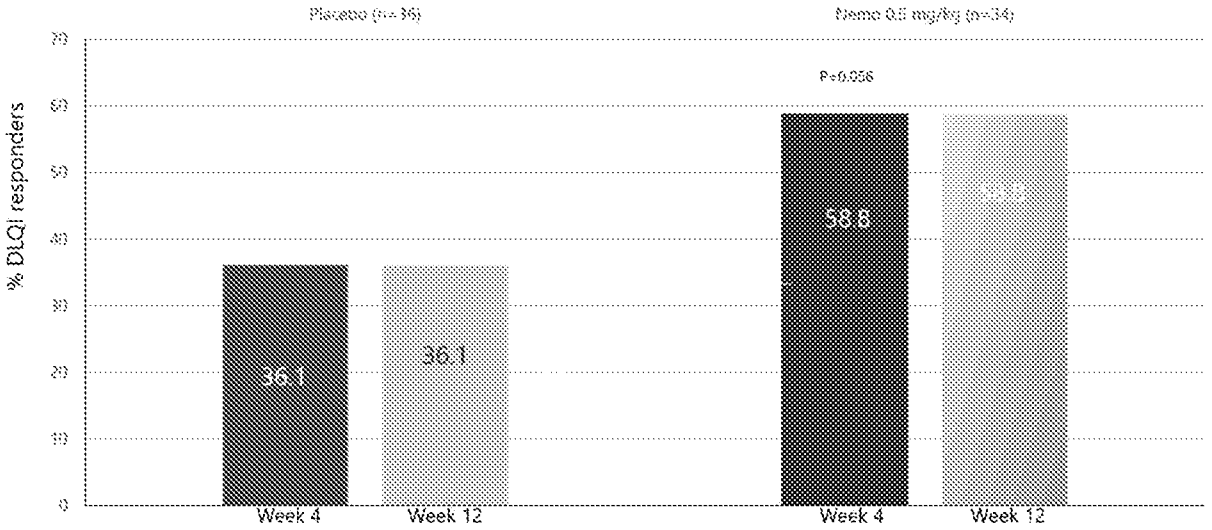

Placebo (n=36)
Demo 0.5 mg/kg (n=34)
P=0.056
% DLQI responders
36.1
36.1
58.8
Week 4
Week 12
Week 4
Week 12

FIG. 11

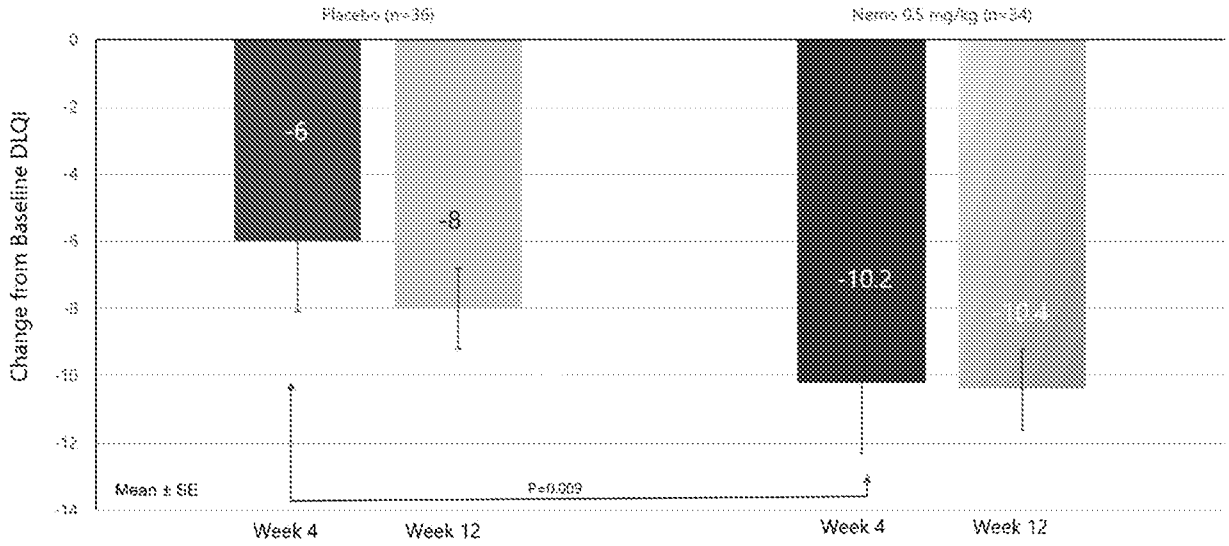

Placebo (n=36)
Nemo 0.5 mg/kg (n=34)
Change from Baseline DLQI
0
-2
-4
-6
-8
-10
-12
-14
-6
-9
-10.2
Mean ± SE
P=0.009
Week 4
Week 12
Week 4
Week 12

FIG. 12A

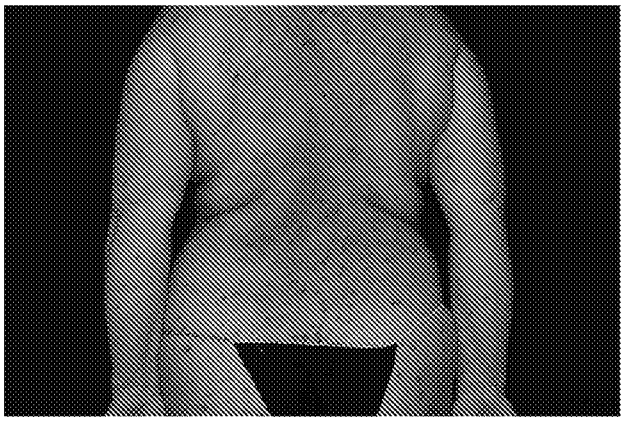


FIG. 12B

FIG. 12C

FIG. 12D

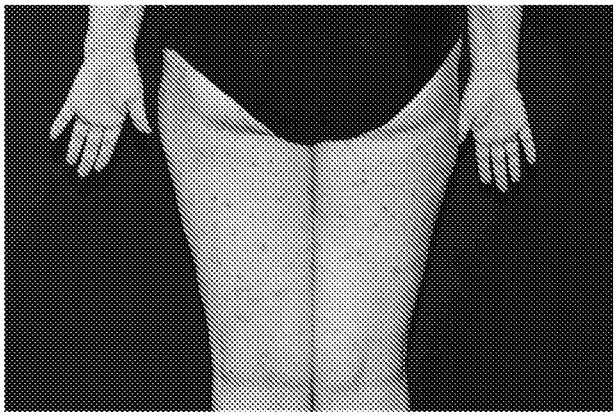


FIG. 13A

FIG. 13B

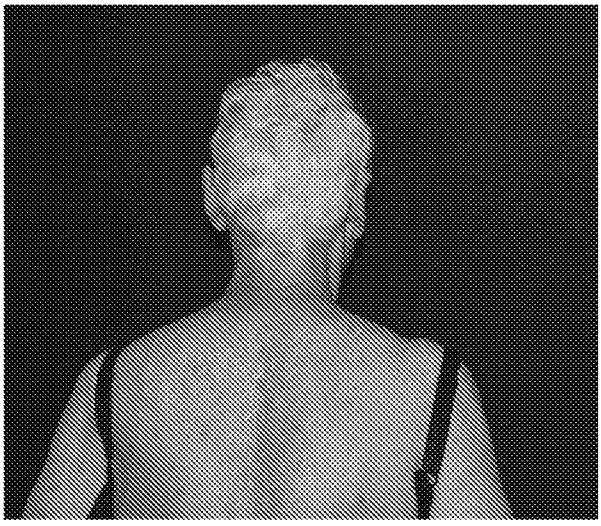


FIG. 13C

FIG. 13D

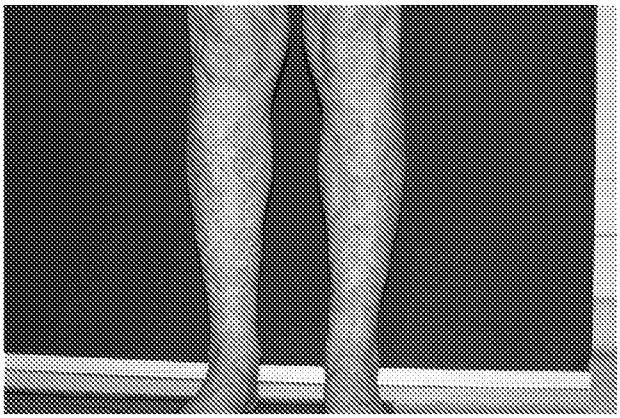


FIG. 14A

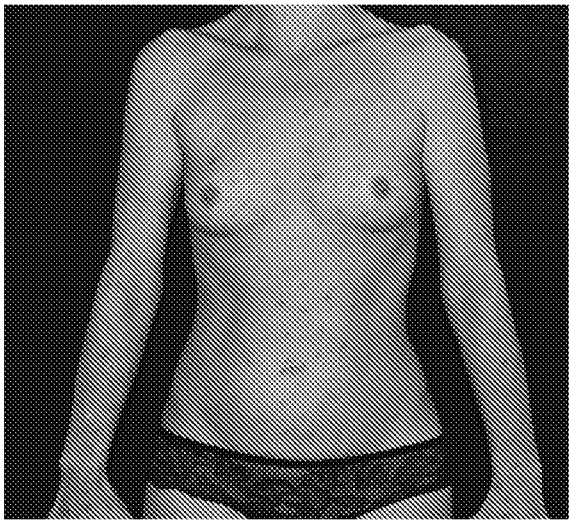


FIG. 14B

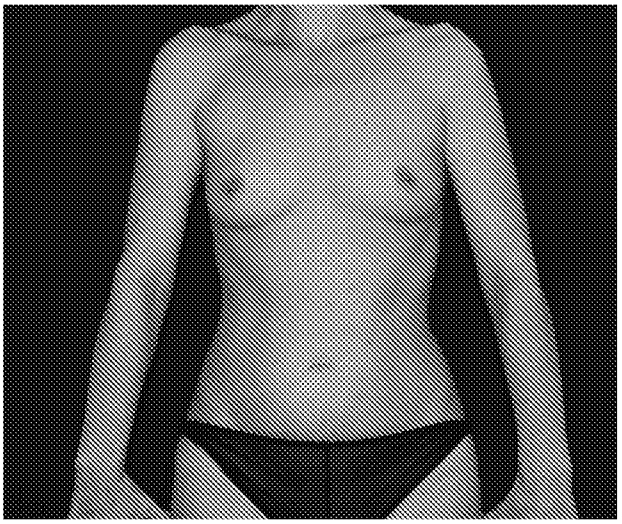


FIG. 14C

FIG. 14D

FIG. 15

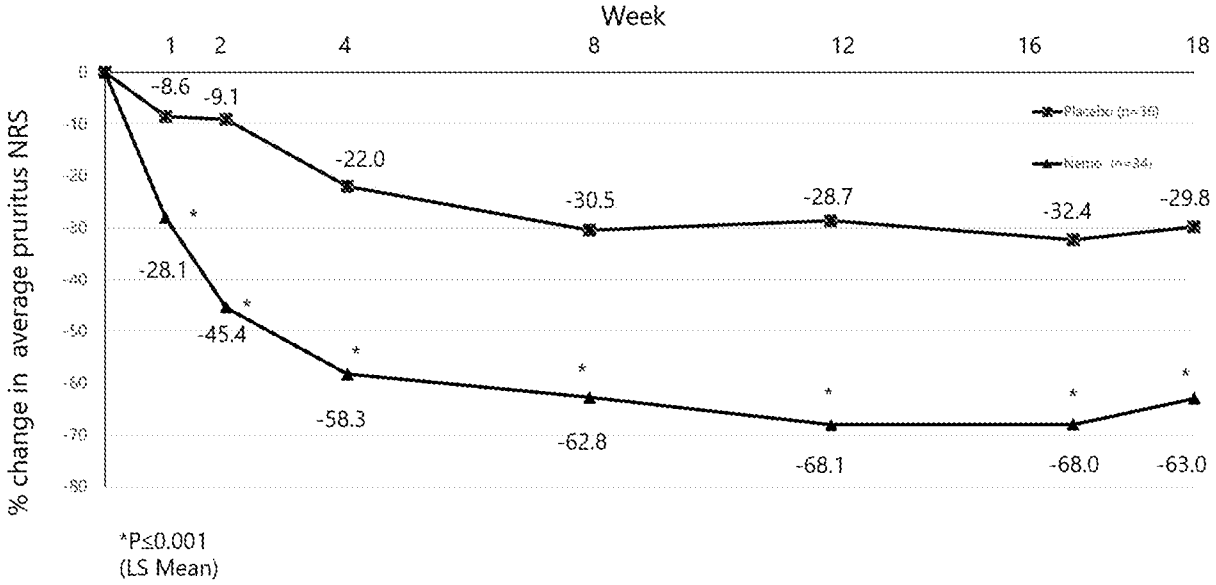

Week
1
2
4
8
12
16
18
% change in average pruritus NRS
0
-10
-20
-30
-40
-50
-60
-70
-80
-8.6
-9.1
-22.0
-30.5
-28.7
-32.4
-29.8
-28.1
-45.4
-58.3
-62.8
-68.1
-68.0
-63.0
*P≤0.001
(LS Mean)

FIG. 16

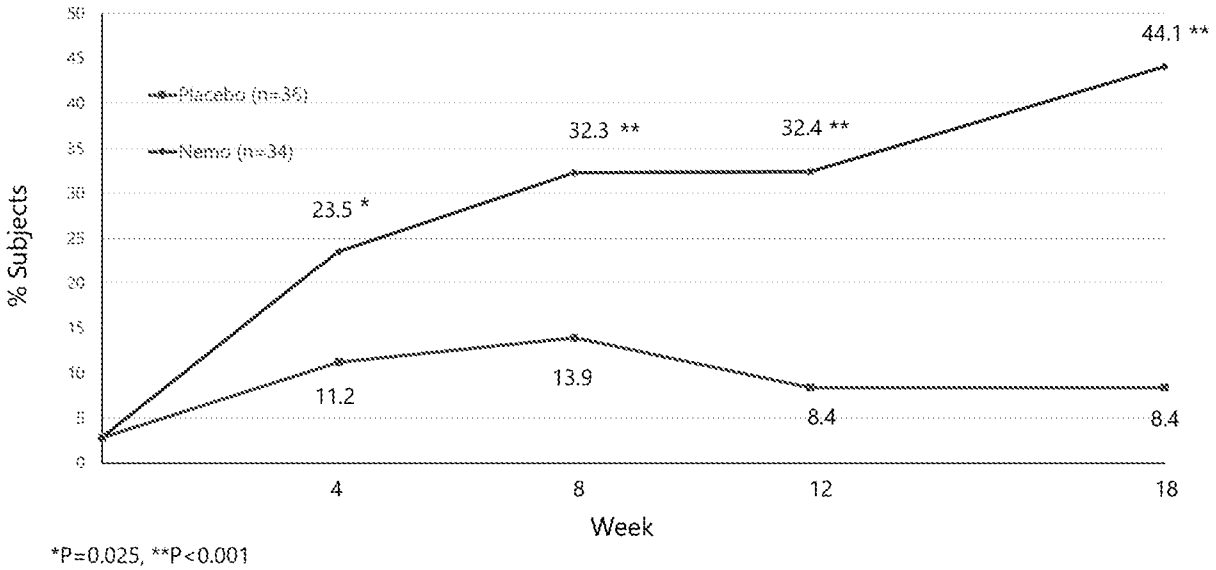

% Subjects
50
45
40
35
30
25
20
15
10
5
0
Placebo (n=36)
Nemo (n=34)
23.5 *
32.3 **
32.4 **
44.1 **
11.2
13.9
8.4
8.4
4
8
12
18
Week
*P=0.025, **P<0.001

FIG. 17

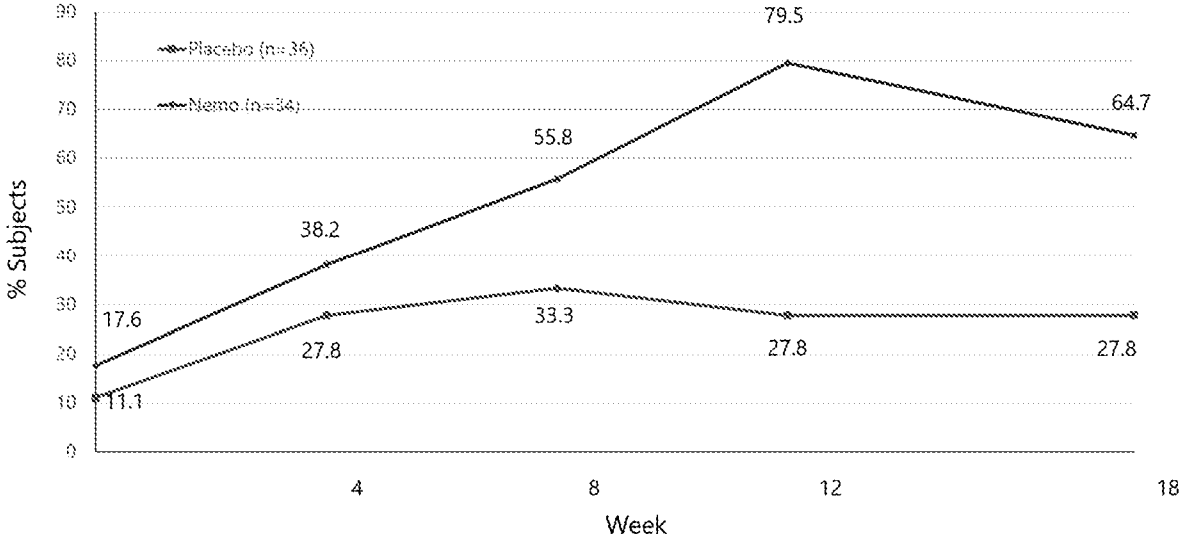

Placebo (n=36)
Nemo (n=34)
% Subjects
Week
0
10
20
30
40
50
60
70
80
90
4
8
12
18
17.6
38.2
55.8
79.5
64.7
11.1
27.8
33.3
27.8
27.8

FIG. 18

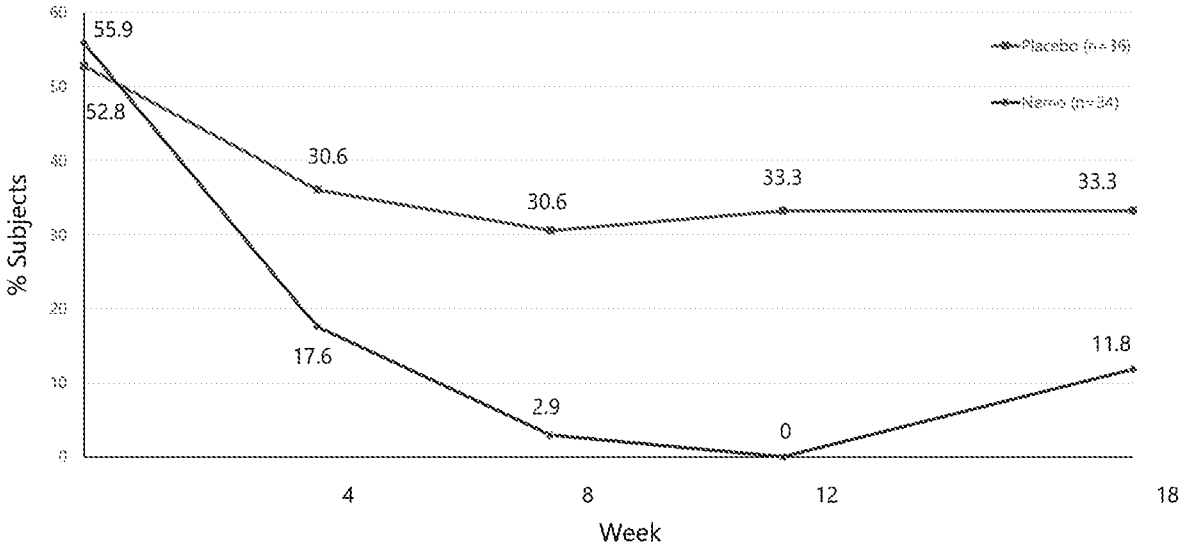

Placebo (n=36)
Nemo (n=34)
% Subjects
Week
0
10
20
30
40
50
60
4
8
12
18
55.9
52.8
30.6
30.6
33.3
33.3
17.6
2.9
0
11.8

FIG. 19

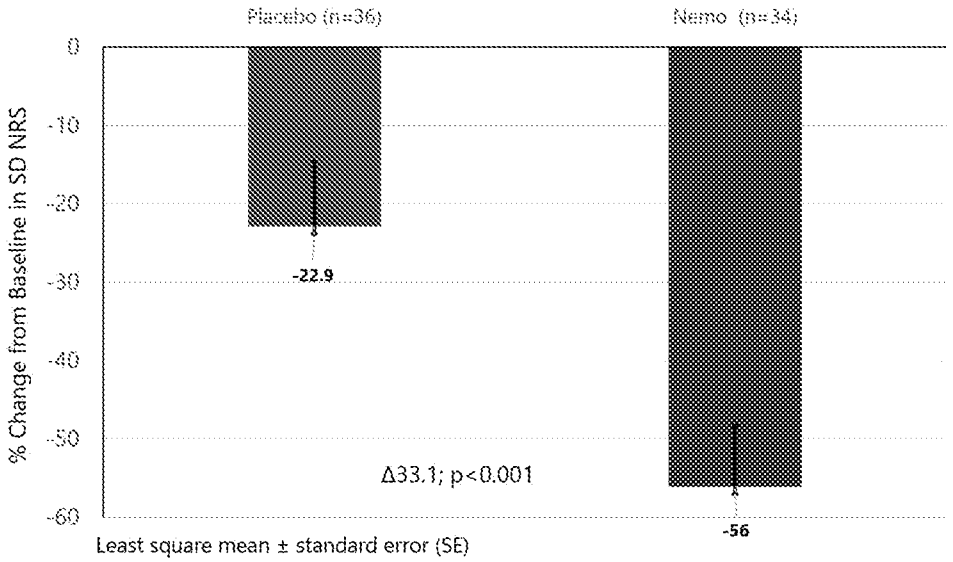
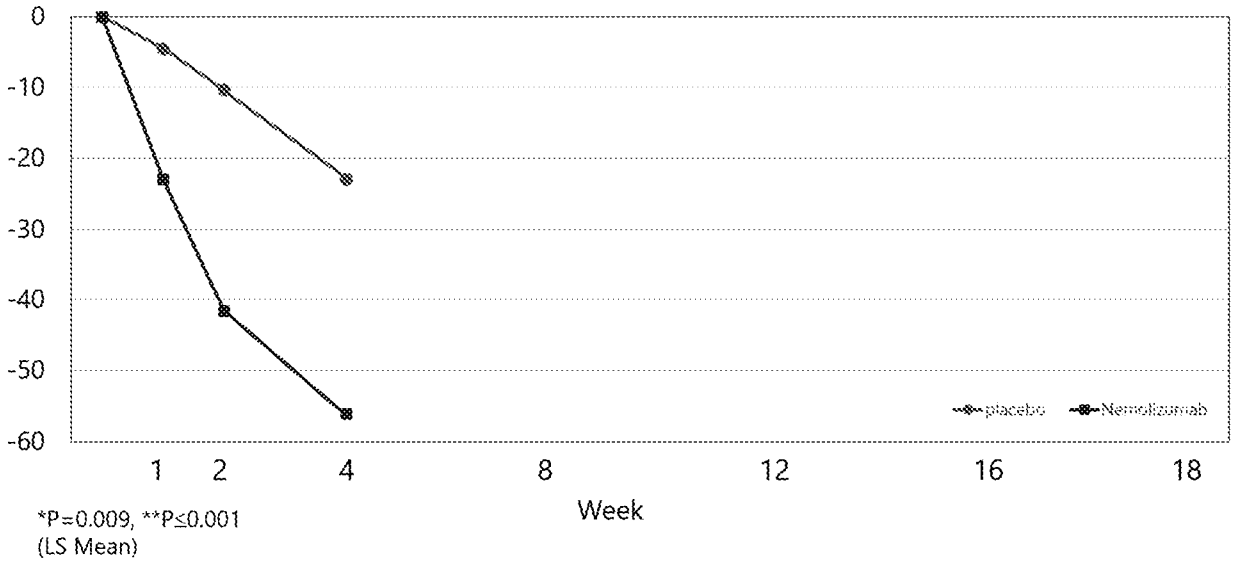

Placebo (n=36)
Nemo (n=34)
% Change from Baseline in SD NRS
0
-10
-20
-30
-40
-50
-60
-22.9
Δ33.1; p<0.001
-56
Least square mean ± standard error (SE)

FIG. 20


0
-10
-20
-30
-40
-50
-60
placebo
Nemolizumab
1
2
4
8
12
16
18
Week
*P=0.009, **P≤0.001
(LS Mean)