1 CLINICAL STUDY PROTOCOL

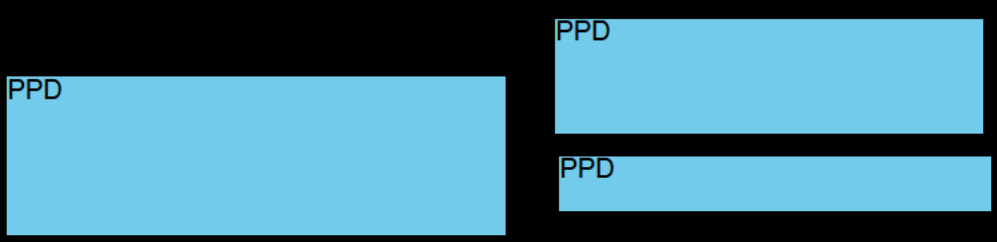
Galderma S.A.
Galderma Research & Development, LLC

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Prurigo Nodularis

Protocol Number: RD.06.SPR.202685

Short Title: A study to assess the efficacy and safety of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)

IND Number:	117122
EudraCT Number:	2019-004293-25
Name of Investigational Product	Nemolizumab (CD14152)
Phase of Development:	3
Indication:	Prurigo Nodularis
Sponsor:	Galderma S.A. Avenue Gratta-Paille 2 1018 Lausanne Switzerland Galderma Research & Development, LLC 14501 North Freeway Fort Worth, Texas 76177 United States
Protocol Version:	5.0
Protocol Date:	19 November 2021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INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation guidelines.
- I am thoroughly familiar with the appropriate use of the study drug as described in this protocol and any other information provided by Galderma S.A./Galderma R&D, LLC including, but not limited to, the current investigator's brochure
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Galderma S.A./Galderma R&D, LLC and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Galderma S.A./Galderma R&D, LLC and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Galderma S.A./Galderma R&D, LLC study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subject's state of health will be regarded as confidential. No

subject's name will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

- Information developed in this clinical study may be disclosed by Galderma S.A./Galderma R&D, LLC to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature	Date (DD-Mmm-YYYY)
Printed Name and Title	
Institution	

2 SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Prurigo Nodularis
Protocol Number:	RD.06.SPR.202685
Investigators/Study Sites/Centers:	Approximately 70 sites in Europe, North America, and Asia Pacific
Phase of Development:	Phase 3
Objectives:	The primary objective is to assess the efficacy of nemolizumab (CD14152) compared to placebo in subjects ≥ 18 years of age with prurigo nodularis (PN) after a 16-week treatment period. The secondary objectives are to assess the safety, pharmacokinetics, and immunogenicity of nemolizumab (CD14152) compared to placebo.
Study Endpoints:	Primary endpoints: • Proportion of subjects with an improvement of ≥ 4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16 • Proportion of subjects with an Investigator Global Assessment (IGA) success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at Week 16 Key secondary endpoints: • Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 4 • Proportion of subjects with PP NRS < 2 at Week 16 • Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16 • Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4 • Proportion of subjects with PP NRS < 2 at Week 4

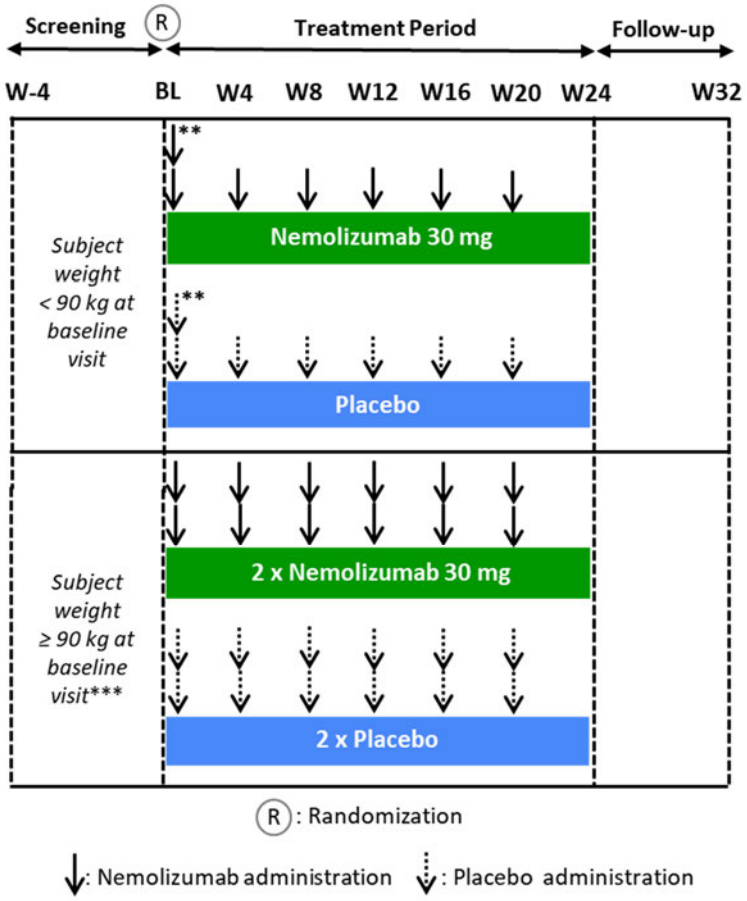
	Secondary efficacy endpoints: • IGA success rate at each visit through Week 24 • Percentage of pruriginous lesions with excoriations/crusts (Prurigo Activity Score [PAS] item 5a) at each visit through Week 24 • Percentage of healed prurigo lesions (PAS item 5b) at each visit through Week 24 • Change from baseline in number of lesions in representative area (PAS item 4) at each visit through Week 24 • Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS through Week 24 • Proportion of subjects with PP NRS < 2 from baseline through Week 24 • Proportion of subjects with PP NRS < 3 from baseline through Week 24 • Absolute change from baseline in PP NRS through Week 24 • Percent change from baseline in PP NRS through Week 24 • Proportion of subjects with an improvement of ≥ 4 from baseline in Average Pruritus (AP) NRS through Week 24 • Proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success at Week 16, Week 20, and Week 24 • Proportion of subjects with AP NRS < 2 from baseline through Week 24 • Absolute change from baseline in AP NRS through Week 24 • Percent change from baseline in AP NRS through Week 24 • Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS through Week 24 • Absolute change from baseline in SD NRS through Week 24 • Percent change from baseline in SD NRS through Week 24 • Change from baseline in sleep diary endpoints (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep

	time, sleep efficiency, WASO related to PN, number of WASO related to PN) based on recordings from subject sleep diary through Week 24 • Change from baseline in PN-associated pain frequency through Week 24 • Change from baseline in PN-associated pain intensity through Week 24 • Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at Week 24 • Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at Week 24 • Proportion of subjects with an improvement of ≥ 4 in Dermatology Life Quality Index (DLQI) through Week 24 • Change from baseline in DLQI through Week 24 • Change from baseline in Hospital Anxiety and Depression Scale (HADS) for each subscale (ie, depression and anxiety) at Week 24 • Change from baseline in EuroQoL 5-Dimension (EQ-5D) at Week 24 Safety endpoints: • Incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs). Pharmacokinetic endpoints: • Nemolizumab (CD14152) serum concentrations Immunogenicity endpoints: • ADA assay (screening, confirmatory, titer, NAb)
Study Design:	This phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study is designed to evaluate the efficacy and safety of nemolizumab in subjects with PN. Approximately 270 subjects with PN will be randomized 2:1 to receive either nemolizumab (CD14152) or placebo, stratified by study center and body weight (< 90 kg vs ≥ 90 kg). Subjects weighing < 90 kg at baseline will receive either

	30 mg nemolizumab (with 60 mg loading dose at baseline) or placebo every 4 weeks (Q4W). Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo Q4W (no loading dose at baseline). Subjects' participation in the study will be up to 36 weeks. The study consists of a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow up period (12 weeks after their last study drug injection). Refer to Figure 1 for an overview of study design. Following provision of written informed consent, subjects with PN will be screened for enrolment in the study. Eligible subjects will return for a baseline visit where, following randomization, they will be administered either a dose of 60 mg nemolizumab or placebo via 2 subcutaneous (SC) injections. Thereafter, study drug will be administered Q4W at Week 4, 8, 12, 16 and 20 by either a single SC injection of either nemolizumab 30 mg or placebo for subjects weighing < 90 kg at baseline or by two SC injections of either nemolizumab 30 mg or placebo for subjects weighing ≥ 90 kg at baseline. Refer to Table 1 for an overview of the study therapy. Efficacy and safety assessments will be performed at visits throughout the screening and treatment period, as outlined in the Schedule of Assessments (Table 5). At the end of the 24-week treatment period, consenting subjects may be eligible to enter an active treatment/long-term extension (LTE) study (RD.06.SPR.202699). Subjects who participate in the LTE are not required to complete the follow-up visit. Subjects who do not participate in the LTE will return for a follow-up visit at Week 32 (12 weeks after the last study drug injection). Subjects who prematurely discontinue the study drug will be asked to continue participation in the study and return for all remaining visits and assessments (including daily assessments of pruritus and sleep disturbance). Subjects who discontinue study drug due to required rescue therapy may be eligible to participate in the LTE study following completion of study visits through Week 24. Subjects who discontinue the study prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection. An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study. The IDMC

and IAC charters provide details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities and communications.

Figure 1. Study Schema



* Applicable for subjects who do not participate in the LTE study only
** Loading dose (two injections) administered at baseline visit for subjects weighing < 90 kg
*** Two injections administered at all applicable visits for subjects weighing ≥ 90 kg at the baseline visit

Abbreviations: BL, baseline; W, week.

Selection of Subjects:	Inclusion Criteria: Individuals must meet all of the following criteria to be included in the study: 1. Male or female and aged ≥18 years at the time of screening 2. Clinical diagnosis of PN for at least 6 months with: a. Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs b. At least 20 nodules on the entire body with a bilateral distribution c. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits 3. Severe pruritus defined as follows on the PP NRS: • At the screening visit (Visit 1): PP NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit • At the baseline visit (Visit 2): Mean of the daily intensity of the PP NRS score is ≥ 7.0 over the previous week; Note***:*** *PP NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean NRS score is not permitted.* 4. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below: • True abstinence, when in line with the preferred and usual lifestyle of the subject. See Appendix 1 for details. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Progestogen-only oral hormonal contraception

	• Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception) Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (eg, condom) together with a spermicide is not acceptable. • Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception • Injectable or implanted hormonal contraception • Intrauterine devices or intrauterine hormone releasing system • Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study • Bilateral vasectomy of male partner at least 3 months before the study 5. Female subjects of non-childbearing potential must meet 1 of the following criteria: • Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range • Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study 6. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study 7. Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed

	Exclusion Criteria: Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study: 1. Body weight < 30 kg 2. Chronic pruritus resulting from another active condition other than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorder, sporotrichosis, bullous autoimmune disease, end-stage renal disease, cholestatic liver disease (eg, primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care 3. Unilateral lesions of prurigo (eg, only one arm affected) 4. History of or current confounding skin condition (eg, Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis) 5. Subjects meeting 1 or more of the following criteria at screening or baseline: 5a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months 5b. Reporting asthma that has not been well-controlled (ie, symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months 5c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma) 5d. Peak expiratory flow (PEF) < 80% of the predicted value Note: In the event that PEF is < 80% of the predicted value at the screening visit in subjects without any history of asthma or in subjects with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours. 6. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis

	7. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.4.2. 8. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive confirmatory test for HCV [eg, polymerase chain reaction (PCR)], or human immunodeficiency virus antibody) at the screening visit Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study. In the event of rescreening, the serology tests results (eg, HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit. 9. Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit 10. Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months Note: Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (ie, specific immunoglobulin E), are eligible for the study. 11. Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis 12. Having received any of the following treatments in the table below within the specified timeframe before the baseline visit:

		Treatments	***Timeframe***
		Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids	2 weeks
		Topical vitamin D analogs	2 weeks
		Topical or systemic PDE-4 inhibitors	2 weeks
		Any other topical treatment other than moisturizer (eg, capsaicin, cryotherapy for treatment of PN)	2 weeks
		Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim	1 week
		Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks
		Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy)	1 week
		Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening	1 week
		Phototherapy or tanning beds	4 weeks
		Immunosuppressive or immunomodulatory drugs (eg, cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)
		Biologics and their biosimilars (eg etanercept, adalimumab, infliximab, omalizumab)	8 weeks or 5 half-lives (whichever is longer)
		Dupilumab	10 weeks
		Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)
		Systemic roxithromycin, erythromycin	1 week

Treatments	***Timeframe***
Opioid antagonists (eg, naltrexone, naloxone), opioid partial/mixed agonists (eg, nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (eg, aprepitant, serlopitant)	4 weeks or 5 half-lives (whichever is longer)
Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions	4 weeks
Cannabinoids (eg, dronabinol)	2 weeks
Alternative medicine for PN (eg, traditional Chinese medicine)	2 weeks
Live vaccines	12 weeks
Non-live vaccines	4 weeks

Abbreviations: JAK, Janus kinase; NK1, neurokinin; PDE-4, phosphodiesterase-4; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

13. Previous participation in a clinical study with nemolizumab
14. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study
15. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:
    - Basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or;
    - Actinic keratoses that have been treated
16. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients

	17. Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study. In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit. 18. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment 19. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia) 20. History of alcohol or substance abuse within 6 months of the screening visit 21. Planned or expected major surgical procedure during the clinical study 22. Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3) 23. Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected:

	24. History of coagulation disorders 25. Known sensitivity to local anesthetics 26. Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed) 27. History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.
Planned Sample Size:	Approximately 270 subjects are planned to be randomized in this study
Therapy:	Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for subcutaneous injection only after reconstitution in a single-use, pre-filled, dual-chamber syringe (DCS). During the treatment period, eligible subjects will be randomized to receive either nemolizumab (CD14152) or placebo, administered Q4W for 24 weeks (last injection at Week 20). Subjects weighing < 90 kg at baseline will receive either nemolizumab 30 mg or placebo via a single SC injection (with a loading dose of 60 mg on Day 1/baseline); subjects weighing ≥ 90 kg at baseline will receive either nemolizumab 60 mg or placebo via two SC injections at all visits (no loading dose). Subjects will have the option to self-inject study drug while at the study center under staff supervision. Subjects will be trained on injecting the study drug and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject does not wish to perform the injections, study staff can administer study drug at each visit.

Table 1. Investigational therapy

	Investigational product	Placebo
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Packaging	DCS	DCS
	Investigational product	**Placebo**
Storage conditions	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing
Dosage	Subjects weighing < 90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline; Subjects weighing ≥ 90 kg at baseline: 60 mg	Not applicable
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Dose regimen	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at baseline, then 2 injections Q4W	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at baseline, then 2 injections Q4W
Treatment duration	24 weeks with last injection at Week 20	24 weeks with last injection at Week 20

Abbreviations: DCS, dual chamber syringe; Q4W, every 4 weeks; SC, subcutaneous.

Rescue therapies

If deemed to be medically necessary by the investigator (eg, to control intolerable signs/symptoms of PN), rescue therapies can be prescribed to the subjects at any time during the study except during the screening period.

	Subjects receiving rescue therapies during the screening period are not eligible to participate in the study. As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure. Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. Whenever possible, investigators should first use topical medication or oral antihistamines as rescue therapy before escalating to other systemic therapies. If subjects receive topical treatments, oral antihistamines, or ultraviolet B (UVB) phototherapy as rescue therapy, study drug administration should be continued unless there is a concern according to the investigator's judgment. If subjects receive systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or oral psoralen + ultraviolet A (PUVA) treatment, the study drug administration must be permanently discontinued. See Section 9.10.2 for a complete list of allowed rescue therapies. Subjects requiring rescue medication (with or without study drug discontinuation) may be eligible for LTE participation. These subjects must continue with study visits through Week 24 to be considered for LTE participation.
Treatment Duration:	The expected duration of each subject's participation in the study is up to 36 weeks, including a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow-up period (12-weeks after the last study drug injection). Subjects who rollover into the LTE are not required to complete the follow-up visit.
Efficacy:	The following efficacy assessments are planned according to the Schedule of Assessments (Table 5): • IGA • Peak and Average Pruritus NRS • PAS • SD NRS • Subject Sleep Diary • PN-associated pain intensity and frequency • PGAD and PGAT

	• Clinical photographs (optional and subject to a specific, separate ICF at selected sites) The following quality of life assessments are planned according to the Schedule of Assessments (Table 5): • DLQI • HADS • EQ-5D Additional Patient-Reported Outcomes assessments are planned according to the Schedule of Assessments (Table 5), as follows: • Patient Global Impression of Severity-Pruritus • Patient Global Impression of Change-Pruritus • Patient Global Impression of Severity-Sleep Disturbance • Patient Global Impression of Change-Sleep Disturbance
Safety:	The following safety assessments are planned according to the Schedule of Assessments (Table 5): • AEs, including TEAEs, AESIs, and SAEs • Physical examination and vital signs • Clinical laboratory tests • Electrocardiogram (ECG) • Respiratory examination and assessments
Pharmacokinetics, Immunogenicity, Pharmacodynamics, and Pharmacogenomics:	The following assessments are planned according to the Schedule of Assessments (Table 5): • Serum nemolizumab concentrations • Anti-drug antibody (ADA) assessments (screening, confirmatory, titer, and neutralizing antibody (NAb) • Biomarkers (eg, interleukin-31 and/or other biomarkers) from blood, stratum corneum (D-Squames), and optional skin biopsies (subject to specific, separate ICF) (select centers only) • Pharmacogenomic testing (optional and subject to a specific, separate ICF)
Statistical Methods and Planned Analyses:	The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population will include all randomized subjects who receive at least 1 dose of study drug. The Per-Protocol (PP) population will consist of all subjects in the ITT population who have no major protocol deviations that would have a

	significant effect on the efficacy of the study treatment. The ITT population will be the primary population for all efficacy analyses, and all safety data will be summarized based on the safety population. The PP population will be used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints. **Primary Efficacy Endpoints:** There are 2 primary efficacy endpoints - The proportion of subjects with at least 4 points of improvement in PP NRS at Week 16. - The proportion of subjects reporting success on the IGA at Week 16, defined as an IGA response of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point reduction from baseline. Both primary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for randomized stratification variable analysis center and baseline body weight (< 90 kg and ≥ 90 kg). The estimate of the treatment difference (nemolizumab minus placebo), p-value and 2-sided 95% confidence interval will be presented. Missing data at Week 16, and any data for subjects in receipt of rescue medication up to Week 16, will be regarded as a non-responder for the primary analysis of the endpoint. A number of sensitivity analyses are included for the primary endpoints, as per Section 15.4.3. **Key Secondary Endpoints:** All binary key secondary efficacy endpoints will be analyzed as per the primary endpoint. Additionally, sensitivity analyses using multiple-imputation assuming missing at random (MAR) and observed case (OC) analysis will be performed for key secondary endpoints as outlined in Section 15.4.4. **Secondary Efficacy Endpoints:** Binary secondary endpoints will be analyzed in the same manner as the primary endpoint; missing values will be imputed as non-responder. Continuous secondary endpoints (except EQ-5D, HADS) will be analyzed using multiple-imputation assuming MAR and using mixed effect model for repeated measure (MMRM) approach, including analysis center as factor and baseline as

	covariate where applicable. The estimated treatment difference for each endpoint at each visit will be displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints will be analyzed using analysis of covariance (ANCOVA) including analysis center as factor and baseline as covariate. All secondary endpoints will be presented descriptively using OC. Further details will be provided in the Statistical Analysis Plan. **Multiplicity:** To control the type I error at 5%, a fixed sequential testing approach will be implemented. For testing purposes both primary endpoints will be tested first in a predefined order (as listed in Section 15.4.1) at 5% significance level, and testing of key secondary endpoints will start only if both primary endpoints are successful at 5% level of significance. Key secondary endpoints will be tested in an order listed in section 15.4.4, stopping when a non-significant result ($p > 0.05$) is found. **Safety Analyses:** The incidence of TEAEs, vital signs, laboratory values and ECG will be summarized by treatment groups. **Pharmacokinetics (PK):** Summary statistics will be used to describe the PK profile of nemolizumab. Individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics of the serum concentrations versus time will be presented as well as for the PK parameters. **Sample size:** In order to achieve at least 90% power for both primary endpoint at 5% significance level, 270 (180 nemolizumab, 90 placebo) subjects will be required to detect the following difference in both primary endpoints between treatment groups with 2:1 randomization, assuming 15% dropout rate during treatment period. NRS responders (≥4 point reduction from baseline): Based on phase 2a data, it is expected that the NRS response at Week 16 would be 50% in Nemolizumab group and 20% in placebo. IGA response (0/1): It is expected that the IGA response at Week 16 would be 30% in Nemolizumab group and 10% in placebo.

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3.2 LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Asthma Control Test
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	Average Pruritus
AST	aspartate aminotransferase
BDRM	Blind Data Review Meeting
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease-19
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
DBL	database lock
DCS	dual-chamber syringe
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EQ-5D	EuroQoL 5-Dimension
ET	early termination
GCP	good clinical practice
HADS	Hospital Anxiety and Depression Scale

Abbreviation	Definition
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability Accountability Act
HIV	human immunodeficiency virus
IAC	independent adjudication committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IGA	Investigator Global Assessment
IgE	immunoglobulin e
IgG	immunoglobulin g
IND	Investigational New Drug
IRB	institutional review board
IRR	injection-related reaction
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LOCF	last observation carried forward
LTE	long-term extension
MAR	missing at random
MI	multiple imputation
MMRM	mixed-effect models for repeated measures
NAb	neutralizing antibodies
NKR1	Neurokinin receptor 1
NONMEM	Nonlinear Mixed Effect Modeling
NRS	numeric rating scale
OC	observed case
PAS	Prurigo Activity Score

Abbreviation	Definition
PCR	polymerase chain reaction
PD	pharmacodynamic
PEF	peak expiratory flow
PGAD	Patient Global Assessment of Disease
PGAT	Patient Global Assessment of Treatment
PGIC-P	Patient Global Impression of Change - Pruritus
PGIC-SD	Patient Global Impression of Change – Sleep Disturbance
PGIS-P	Patient Global Impression of Severity - Pruritus
PGIS-SD	Patient Global Impression of Severity – Sleep Disturbance
PGx	pharmacogenomic
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic
PKAP	pharmacokinetic analysis population
PN	prurigo nodularis
PopPK	Population Pharmacokinetic
PP	per-protocol
PP NRS	Peak Pruritus Numeric Rating Scale
PRO	Patient-reported outcome
PT	preferred term
PTC	product technical complaint
Q4W	every 4 weeks
QoL	quality of life
RTSM	randomization and trial supply management
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	subcutaneous
SD NRS	Sleep Disturbance Numeric Rating Scale
SIN	Subject identification number
SNRI	serotonin-norepinephrine reuptake inhibitor

Abbreviation	Definition
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UP	uremic pruritus
UPT	urine pregnancy test
US	United States
VAS	visual analogue scale
WASO	wakefulness after sleep onset
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 BACKGROUND ON PRURIGO NODULARIS

Prurigo nodularis (PN) is characterized by the presence of multiple (up to hundreds), symmetrically distributed, highly pruritic, hyperkeratotic, erosive or crusted nodules and papules.[1] Chronic itching is believed to induce and maintain the characteristic PN skin lesions through an itch-scratch cycle.[2] This leads to an impaired quality of life (QoL) and high burden due not only to the severe itch but also the chronic skin lesions and lack of treatment options.[3]

Limited data exist about the incidence and prevalence of PN in the general population, but it seems to be more frequent and intense in females and the elderly.[4,5]

The physiopathology of PN is still not fully understood; however, the interactions between cutaneous nerve fibers, neuropeptides and immune cells seem to play an important role in the onset of PN.[6] The etiology of PN is associated with a subclinical small fiber neuropathy based on the observed reduction of intraepidermal nerve fiber density in patient biopsies and the epidemiological association of PN with various etiologies of peripheral neuropathies.[7,8,9] Further supporting this theory is the observation of a positive response in some patients to gabapentin and pregabalin, commonly utilized treatments for pain and neuropathy.[10] PN also has a neuroinflammatory component as changes in the morphology of skin nerve fibers and increased dermal neural hyperplasia are associated with concomitant inflammation caused by T lymphocytes, eosinophils, granulocytes and mast cells.[6]

As itch is the hallmark symptom of PN, a role for neural sensitization followed by lesion appearance and development of a chronic itch-scratch cycle has been suggested.

A large spectrum of underlying conditions that induce chronic pruritus can be associated with PN, including dermatological (eg, atopic dermatitis), systemic (eg, chronic kidney failure), neurological (eg, brachioradial pruritus), and psychiatric or mixed origin disorders.[11]

Only a few studies have described the incidence and the strength of association of different co-morbidities in a representative cohort of patients with PN.[4] A large study of PN patients at a major academic center in the United States noted associations of PN with chronic kidney disease, Type II Diabetes, and HIV.[12] Further, data from US claims databases confirmed these associations.[5] A subset of patients with PN also have a concomitant atopic diathesis, occurring in nearly half of subjects with PN in a small European study in a predominantly Caucasian population. Atopic diathesis was also found to predict a significantly earlier age of onset (median age of 19 years) compared to non-atopic patients (median age of 48 years).[13]

Psychosocial disorders are also significantly associated with PN. Rowland Payne et al.,[14] found that more than 50% of their PN patients had a history of depression or anxiety requiring medical intervention.

The goal of PN treatment is to break the itch-scratch cycle and allow the skin to heal. However, treatment of PN is notoriously challenging and frustrating for both dermatologists and patients, as the response to current therapy options is typically limited or associated with adverse events (AEs). There are no standardized or approved therapies for PN to date and evidence from controlled studies is limited.[10] The difficulty in treating this disease is reflected in the wide range of treatments proposed in the literature.

The current treatment recommendations for PN include identification and treatment of any underlying disease, moisturizers and antipruritics, topical therapies (corticosteroids, calcineurin inhibitors), and oral antihistamines as first-line agents.[15] Phototherapy, oral or intra-lesional steroids, topical vitamin D3 (calcipotriol), capsaicin, cryotherapy and antidepressants (amitriptyline, selective serotonin re-uptake inhibitors) are used as second-line therapies with variable efficacy. In third-line, systemic treatments such as cyclosporine,[16] antiepileptic drugs (gabapentin, pregabalin)[17] and thalidomide[18] showed moderate-to-good response in pruritus reduction after several months of administration, but their use is limited by their unfavorable safety profile. Other off-label therapeutic options proposed for pruritus based on limited evidence include opioid receptor agonists and antagonists (naltrexone),[19] NKR1-antagonists (aprepitant),[20] and antibiotics (roxithromycin, erythromicin).[21]

The T-cell-derived cytokine interleukin-31 (IL-31) has been suggested to be a key player in the development of pruritus in PN. Skin biopsies from PN patients with an atopic background showed a 50-fold upregulation of IL-31 mRNA compared to skin from healthy individuals and a 4.5-fold upregulation compared to skin from atopic dermatitis (AD) patients.[22] A significantly higher level of IL-31 mRNA was also observed in PN patients with unknown AD background compared to normal skin.[23]

IL-31 is preferentially produced by T helper 2 (Th2) cells, following induction by IL-4.[24] The IL-31 receptor A (IL-31RA) has been found to be expressed in several tissues including the dorsal root spinal ganglia, where the cell bodies of cutaneous sensory neurons reside,[22] as well as keratinocytes. IL-31 binds to IL-31RA, forming a heterodimer with Oncostatin M receptor (OSMR), which activates the down-stream JAK/STAT signaling pathway and transmits signals into the cell.[25, 26]

Taken together, IL-31 seems to be an important cytokine for the regulation of PN and a potential therapy target.

5.2 BACKGROUND ON NEMOLIZUMAB

Nemolizumab is a humanized anti-human IL-31 receptor A (RA) monoclonal modified immunoglobulin G (IgG) 2 antibody comprising a structure of 2 H-chains (445 amino acid residues) and 2 L-chains (214 amino acid residues) connected by 16 disulfide bonds. Nemolizumab inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction.

5.2.1 Nonclinical Studies

Non-clinical studies in mice, cynomolgus monkeys, and dogs have demonstrated a role for IL-31 in pruritus models that were inhibited by administration of anti-IL-31 or anti-IL-31RA monoclonal antibodies.[27-31] The Investigator's Brochure (IB) contains detailed information on nonclinical studies.

5.2.2 Clinical Pharmacokinetic Profile and Immunogenicity

Nemolizumab PK profile was extensively assessed in subjects with AD in Phase 1, 2, and 2b studies (Studies CIM001JP, CIM003JG, and RD.03.SPR.114322, respectively) and

after repeated doses and in subjects with PN (Phase 2 study, RD.03.SPR.115828). Similar nemolizumab systemic exposure was observed in subjects with AD and in subjects with PN when treated with the same dose (0.5 mg/kg).

The similarity in nemolizumab exposure between the PN and AD subjects was also confirmed using popPK modelling. Overall pharmacokinetic assessments after subcutaneous (SC) injections of weight-based (0.1 to 3 mg/kg) or flat (10 to 90 mg) doses showed a dose proportional increase of nemolizumab serum concentrations after a single (mg/kg) injection and a less than proportional increase after repeated (mg/kg and flat) administrations. The terminal elimination half-life of nemolizumab was around 2 weeks after single and repeated administrations. Steady state concentrations were achieved from week 16 of treatment following single SC injections and from Week 4 of treatment when a loading (flat 2x) dose was administered at the baseline injection. Limited systemic accumulation was observed after repeated administrations.

The IB contains additional detailed information on nemolizumab pharmacokinetics.

Immunogenicity results showed nemolizumab to have a very low potential of inducing ADA in subjects with AD or in subjects with PN. Only one treatment related ADA-positive subjects was reported out of the 34 subjects with PN receiving the treatment. No subjects had positive ADA that included IgE and no subjects developed neutralizing antibodies (NAb).

5.2.3 Clinical Studies

One phase 2 study with nemolizumab has been completed in PN subjects. Additional studies have been completed in healthy subjects, subjects with AD, and subjects with uremic pruritus. Results of phase 2 studies in PN and AD subjects are summarized below. The IB contains additional detailed information on clinical studies conducted with nemolizumab.

5.2.4 Phase 2a Safety and Efficacy Study: Prurigo Nodularis

The phase 2a study (RD.03.SPR.115828) was a randomized, placebo-controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of nemolizumab in subjects suffering from PN over a 12-week treatment period.

A total of 70 subjects were randomized: 36 subjects were randomized to placebo and 34 subjects were randomized to nemolizumab 0.5 mg/kg. Sixty subjects (85.7%) completed the study. Demographic characteristics were similar in both treatment groups. Disease characteristics at baseline were similar in both treatment groups, with the exception of the Prurigo Activity Score (PAS) at baseline, which was slightly higher in the placebo compared with the nemolizumab group, and more subjects in the nemolizumab group had a severe Investigator Global Assessment (IGA) score compared with the placebo group.

The primary efficacy endpoint was percent change from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) to Week 4 (weekly average of the peak). Nemolizumab was clinically and statistically significantly superior to placebo in reducing the PP NRS scores at Week 4 (difference between treatment groups -38.0%; 95% confidence interval [CI] -51.0, -25.0; $p<0.001$).

The proportion of subjects with IGA success, a secondary endpoint, was higher in the nemolizumab group compared with the placebo group at Week 12 and at a follow-up visit at Week 18, and the differences were statistically significant (Week 12: difference 17.2%; $p=0.020$; Week 18: difference 32.0%; $p=0.001$).

Secondary endpoints also included PP NRS scores at other time points, Average Pruritus (AP) NRS, PP and AP Verbal Rating Scale, Dynamic Pruritus Scale, and PAS. Improvements were statistically significantly greater in the nemolizumab group than in the placebo group at all time points for pruritus endpoints and at or before Week 12 for PAS endpoints.

The most frequently reported treatment-emergent adverse event (TEAE) was nasopharyngitis, the incidence of which was similar in the nemolizumab group (5 subjects, 14.7%) and the placebo group (4 subjects, 11.1%). The incidence of neurodermatitis was higher in the placebo group (5 subjects, 13.9%) compared with the

nemolizumab group (2 subjects, 5.9%). The incidence of atopic dermatitis was higher in the nemolizumab group (3 subjects, 8.8%) compared with the placebo group (0 subjects). The percentage of subjects with severe TEAEs was higher in the nemolizumab group (5 subjects, 14.7%) compared with the placebo group (1 subject, 2.8%). The incidence of TEAEs leading to permanent discontinuation of the study drug was similar between the nemolizumab and placebo groups.

The incidence of treatment-emergent SAEs was similar between the nemolizumab group (4 subjects, 11.8%) and the placebo group (3 subjects, 8.3%). Neurodermatitis was the most frequently reported treatment-emergent SAE, for which all subjects were in the placebo group (3 subjects, 8.3%). One subject in the nemolizumab group had a treatment-emergent SAE related to study drug (dermatitis psoriasiform). There were no deaths reported during the study.

5.2.5 Phase 2b Dose-Ranging Study: Atopic Dermatitis

The phase 2b study (RD.03.SPR.114322) was a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study to evaluate the efficacy, safety, and pharmacokinetics of various doses of nemolizumab in moderate-to-severe AD subjects with severe pruritus (PP NRS $\geq$ 7).

A total of 226 adult subjects were randomized: 57 subjects were randomized to placebo and 169 subjects were randomized to nemolizumab arms (55 subjects to 10 mg, 57 subjects to 30 mg, and 57 subjects to 90 mg). Overall, all demographic and baseline disease characteristics were similar in all treatment groups.

The primary efficacy endpoint was percent change from baseline in Eczema Area and Severity Index (EASI) to Week 24. At the Week 24 visit, a greater percent change reduction in EASI was observed with the nemolizumab 30-mg dose (least squares mean difference versus placebo = 16.7%) and the difference was statistically significant (95% CI = -30.2, -3.2; p = 0.016) compared to placebo. The nemolizumab 10-mg dose showed a marginally statistically significant difference versus placebo (least squares mean difference = 13.6%; 95% CI = -27.3, 0.0; p = 0.051). However, the difference between the nemolizumab 90-mg dose and placebo did not achieve statistical significance.

The PP NRS responder (PP NRS improvement ≥ 4) rate was statistically significant ($p < 0.05$) for all nemolizumab doses at all timepoints from Week 2.

All doses of nemolizumab were associated with a slightly higher incidence of TEAEs when compared to placebo. There was no increase in the incidence of skin infections in the nemolizumab compared to the placebo groups, although there was a higher incidence of non-skin infections with nemolizumab (mainly rhinopharyngitis and upper respiratory tract infections). There was a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) in subjects with pre-existing asthma. Events were mostly mild or moderate (1 severe event with the highest dose), manageable, and reversible under treatment with study drug. Local and systemic injection-related reactions (IRRs) occurred more frequently in the placebo group compared to the active treatment groups. Finally, there was a low incidence of peripheral edema, with no serious cases and no imbalance with the placebo arm. There was a comparable percentage of subjects discontinuing treatment due to TEAE in the placebo and active treatment arms.

There was 1 non-related AE with a fatal outcome (82-year-old subject treated with the 10-mg dose died due to non–study drug related aspiration pneumonia and cardiopulmonary arrest). Three suspected unexpected serious adverse reactions (SUSARs) were recorded in the study: exacerbation of AD (10-mg dose, withdrawal from study), septic shock (90-mg dose, sepsis, *Staphylococcus aureus*–positive blood culture, recovered/resolved without sequelae), and phlegmon/cellulitis of the right cheek (30-mg dose, recovered/resolved without sequelae). All doses of nemolizumab were associated with a slightly higher incidence of serious TEAEs (1 [1.8%], 3 [5.5%], 2 [3.5%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) but not severe TEAEs (6 [10.7%], 3 [5.5%], 5 [8.8%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) when compared to placebo.

The safety and efficacy data generated in the phase 2b dose-finding study supported the selection of the 30-mg dose as the treatment dose for the phase 3 studies in AD.

5.3 CLINICAL RISKS/BENEFITS OF NEMOLIZUMAB

Pruritus is the cardinal symptom in PN, and is often difficult to treat with current therapies. Chronic itching is believed to induce and maintain the characteristic PN skin lesions through an itch-scratch cycle. Therefore, the goal of PN treatments target pruritus remission in order to allow skin healing and improvement in patients' QoL.

Results from a previous clinical study with nemolizumab demonstrated a marked effect on PN and pruritus. The decrease in itching sensation was rapid, within the first week following the first injection and improved with subsequent administrations. This improvement in the signs and symptoms of PN was consistent with the observed improvement in QoL (evaluated using the Dermatology Life Quality Index [DLQI]). Continuous treatment with nemolizumab also led to an improvement in the overall severity of PN, which was evaluated with various validated scales (ie, IGA, PP NRS, and PAS). Based on the results of the phase 2a study (RD.03.SPR.115828) nemolizumab was clinically and statistically significantly superior to placebo in reducing the weekly average of PP NRS scores at Week 4 (difference between treatment groups -38.0%; 95% CI -51.0, -25.0; $p<0.001$). Improvements in IGA success and PAS observed in the nemolizumab group were also statistically significantly greater than those observed in the placebo group.

According to the currently available information on nemolizumab and the risks associated with biologic agents in general, the important potential risks for nemolizumab include IRRs (including local injection site reaction as well as systemic injection reaction), newly-diagnosed or worsening of asthma, skin and non-skin infections, and exacerbation of AD. The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

a. In the phase 2b dose-ranging study (RD.03.SPR.114322) in AD, a dose-dependent increase of asthma flares in subjects with pre-existing asthma was observed. The protocol will exclude subjects with asthma exacerbation requiring hospitalization in the preceding 12 months before screening, subjects whose asthma has not been well controlled (ie, symptoms > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the last 3 months before

the screening visit, Asthma Control Test (ACT) score ≤ 19, and subjects with peak expiratory flow (PEF) below 80% of the predicted value. At all visits, all subjects will be asked about respiratory changes and a respiratory examination will be performed. Peak expiratory flow measurements will be performed for all subjects at screening, baseline, and at intervals throughout the study. For subjects with a history of asthma, PEF measurements and ACT will be administered at all visits. Subjects diagnosed with de novo asthma will perform PEF and ACT assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects with a medical history of asthma will be referred to the physician managing their asthma if ACT ≤ 19, PEF < 80% of the predicted value, and/or unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. An independent adjudication committee (IAC) will review all asthma AEs reported during the course of the study.

b. The exclusion criteria of this clinical study (ie, restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections) will prevent non-eligible patients from receiving nemolizumab. As no data are available in pregnant or breastfeeding women, these patients are not eligible for this study. Patients who have recently received live or non-live vaccines may be considered for enrollment after an appropriate time has elapsed before baseline/Day 1. Administration of live vaccines is prohibited during the study. Administration of non-live vaccines is prohibited with the exception of seasonal, emergency, and COVID-19 vaccinations.
c. A slight trend of dose-dependent increase of peripheral edema was reported in the nemolizumab phase 2a study (CIM003JG) for AD. Most events were mild (11 of 21), no case was serious, and none resulted in premature treatment discontinuation; no case was associated with renal or cardiac AEs. The EASI values and thymus and activation-regulated chemokine levels were relatively higher in subjects with peripheral edema indicating that peripheral edema might be related to more severe AD. There were a few subjects reporting peripheral edema in the phase 2b (RD.03.SPR.114322) study (2 [3.6%], 2 [3.6%], 4 [7%], and 2 [3.5%] in placebo, 10-

mg, 30-mg, and 90-mg groups, respectively). Peripheral edema will be followed as an AE of special interest (AESI) in this study.

d. An independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study, including AESIs, which were defined based on the currently available safety information on nemolizumab and the risks associated with biologic agents in general. AESIs for this study are:
   - IRRs
     - Anaphylactic reactions
     - Acute allergic reactions requiring treatment
     - Severe injection site reaction (ie, lasting > 24 hours)
   - Newly diagnosed asthma or worsening of asthma
   - Infections
     - Any severe infection or any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for > 2 weeks
     - Any confirmed or suspected coronavirus disease (COVID)-19 infection
   - Peripheral edema: limbs, bilateral
   - Facial edema
   - Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

In conclusion, when taking into consideration the currently available data of nemolizumab and the risk-minimization approaches to be implemented, the benefit/risk ratio of nemolizumab is considered to be favorable in this study.

5.4 DOSE SELECTION RATIONALE

The dose was selected based on the phase 2 study results contained in PN subjects (RD.03.SPR.115828). PN subjects enrolled in the phase 2 study received a 0.5 mg/kg weight-based dose, administered every 4 weeks (Q4W), and successfully demonstrated efficacy in the treatment of PN with an acceptable safety profile. The same weight-based dose was administered in the phase 2a study CIM003JP in AD subjects, allowing a direct comparison between the two populations. Similarity in the PK profiles between subjects

with AD and subjects with PN was established, and no effect of disease on nemolizumab systemic exposure was identified.

This phase 3 study will utilize a flat dose. This fixed dose is considered safer and more efficient as it avoids errors that could be made in calculating, preparing, and administering a weight-based dose.

The switch from a body weight-based dose to a flat dose was supported by previous observed clinical data in subjects with AD. During the phase 2b study RD.03.SPR.114322 in AD subjects, a 30-mg flat dose (with 60-mg loading dose) administered Q4W provided the best benefit/risk ratio and produced a similar exposure compared to the 0.5 mg/kg dose used in the AD phase 2a study CIM003JG.

The switch from mg/kg to a flat dose was further supported by popPK and PK/PD modeling and simulation tools. PK/PD modelling was conducted using the two primary clinical efficacy endpoints, ie, PP NRS responder and IGA 0-1 success.

- The PK/PD model for PP NRS were initially developed based on data from AD subjects, tested against observations of study RD.03.SPR.115828 and considered suitable to be used for modelling and simulation in PN populations.
- Conversely, due to the difference in IGA scale between the two indications (ie, PN and AD), a PN-specific model was built based on data from study RD.03.SPR.115828.

Overall, the PopPK and PK/PD models were used to select a flat dose that produce similar systemic exposure and efficacy results than the ones observed in the phase 2 study RD.03.SPR.115828.

Dose for subjects with a body weight below 90 kg: The popPK and PK/PD modeling demonstrated that similar exposure and similar clinical efficacy are expected in this sub-population after a 30-mg dose administered Q4W (with a loading dose of 60 mg at baseline) compared to the dose regimen used in the phase 2 study (0.5 mg/kg Q4W).

Dose for subjects with a body weight superior or equal to 90 kg: The switch from a body weight-based dose (0.5 mg/kg) to a flat 30 mg dose (with a loading dose of 60 mg

at baseline) will produce a lower systemic exposure in the heavier subjects. The clinical relevance of this lower systemic exposure was assessed using PK/PD models.

- Simulations showed that no differences in PP NRS efficacy endpoint is expected for those subjects.
- Simulations with the PN-specific model for the IGA endpoint showed a lower responder rate for those subjects after administration of the 30-mg dose with a 60-mg loading dose. The PK/PD model confirmed that IGA responder rate would be comparable to that observed after 0.5 mg/kg administration when using a flat 60-mg dose without a loading dose.

For this reason, a 60-mg dose without a loading dose will be used for subjects with a body weight superior or equal to 90 kg, in order to guarantee an IGA responder rate comparable with that obtained in the overall population in study RD.03.SPR.115828.

Of note, for subjects with a body weight superior or equal to 90 kg, PopPK simulation showed that a 60-mg dose will provide similar nemolizumab exposure with respect to that observed with the 0.5 mg/kg dose. Based on the similarity in systemic exposure between the 2 doses, no major change in the drug safety is expected in adults.

Loading dose: Subcutaneous administration of nemolizumab results in slow absorption with peak serum concentrations achieved after 4 to 9 days. Plateau systemic exposure levels are achieved after at least 16 weeks of repeated monthly administrations. Therefore, loading doses are necessary to rapidly achieve targeted systemic levels, and to ensure a fast onset of action. Rapid inhibition of pruritus in PN is an important treatment goal in itself and is also expected to contribute to breaking the itch-scratch cycle and thus, to improve the skin condition in PN subjects. These outcomes were achieved in a phase 2b study in AD subjects using a 60-mg loading dose (ie, 2 doses of 30 mg nemolizumab) at the baseline visit. No loading dose will be used for the subjects with a body weight superior or equal to 90 kg.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 STUDY OBJECTIVES

6.1.1 Primary Objective

The primary objective is to assess the efficacy of nemolizumab (CD14152) compared to placebo in subjects ≥ 18 years of age with PN after a 16-week treatment period.

6.1.2 Secondary Objectives

The secondary objectives are to assess safety, pharmacokinetics, and immunogenicity of nemolizumab (CD14152) compared to placebo.

6.2 STUDY ENDPOINTS

6.2.1 Primary Endpoints

- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 16
- Proportion of subjects with an IGA success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at Week 16.

6.2.2 Secondary Endpoints

6.2.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 4
- Proportion of subjects with PP NRS < 2 at Week 16
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16

- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4
- Proportion of subjects with PP NRS < 2 at Week 4

6.2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- IGA success rate at each visit through Week 24
- Percentage of pruriginous lesions with excoriations/crusts (Prurigo Activity Score [PAS] item 5a) at each visit through Week 24
- Percentage of healed prurigo lesions (PAS item 5b) at each visit through Week 24
- Change from baseline in number of lesions in representative area (PAS item 4) at each visit through Week 24
- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS through Week 24
- Proportion of subjects with PP NRS < 2 from baseline through Week 24
- Proportion of subjects with PP NRS < 3 from baseline through Week 24
- Absolute change from baseline in PP NRS through Week 24
- Percent change from baseline in PP NRS through Week 24
- Proportion of subjects with an improvement of ≥ 4 from baseline in AP NRS through Week 24
- Proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success at Week 16, Week 20, and Week 24
- Proportion of subjects with AP NRS < 2 from baseline through Week 24
- Absolute change from baseline in AP NRS through Week 24
- Percent change from baseline in AP NRS through Week 24

- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS through Week 24
- Absolute change from baseline in SD NRS through Week 24
- Percent change from baseline in SD NRS through Week 24
- Change from baseline in sleep diary endpoints (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN) based on recordings from subject sleep diary through Week 24
- Change from baseline in PN-associated pain frequency through Week 24
- Change from baseline in PN-associated pain intensity through Week 24
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at Week 24
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at Week 24
- Proportion of subjects with an improvement of ≥ 4 in DLQI through Week 24
- Change from baseline in DLQI through Week 24
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) for each subscale (ie, depression and anxiety) at Week 24
- Change from baseline in EuroQoL 5-Dimension (EQ-5D) at Week 24

6.2.2.3 Safety Endpoints

The safety endpoints of this study are the incidence and severity of AEs, including TEAEs, AESIs, and SAEs.

6.2.2.4 Pharmacokinetic Endpoints

Nemolizumab (CD14152) serum concentrations

6.2.2.5 Immunogenicity Endpoints

ADA assay (screening, confirmatory, titer, NAb)

7 INVESTIGATIONAL PLAN

7.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study is designed to evaluate the efficacy and safety of nemolizumab in subjects with PN.

Considering a screen failure rate of 35-40%, 415-450 subjects will be screened so that approximately 270 adult subjects with PN will be randomized 2:1 to receive either nemolizumab (CD14152) or placebo. Subjects weighing < 90 kg at baseline will receive either 30 mg nemolizumab (with 60 mg loading dose at baseline) or placebo Q4W. Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo Q4W. Subjects will be stratified by study center and baseline body weight (< 90 kg and ≥ 90 kg). Subjects will be enrolled in approximately 70 study centers in Europe, North America, and Asia Pacific.

Subjects' participation in the study will be up to 36 weeks. The study consists of a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow up period (12 weeks after the last study drug injection). Refer to Figure 2 for an overview of study design.

Following provision of written informed consent, subjects with PN will be screened for enrolment in the study. Eligible subjects will return for a baseline visit where, following randomization, they will be administered either 60 mg of nemolizumab or placebo via 2 SC injections. Thereafter, study drug will be administered Q4W at Weeks 4, 8, 12, 16, and 20 by a single SC injection of either nemolizumab 30 mg or placebo for subjects weighing < 90 kg at baseline or by two SC injections of either nemolizumab 30 mg or placebo for subjects weighing ≥ 90 kg at baseline. Refer to Table 3 for an overview of the study therapy. Efficacy and safety assessments will be performed at visits throughout the screening and treatment period, as outlined in the Schedule of Assessments (Table 5).

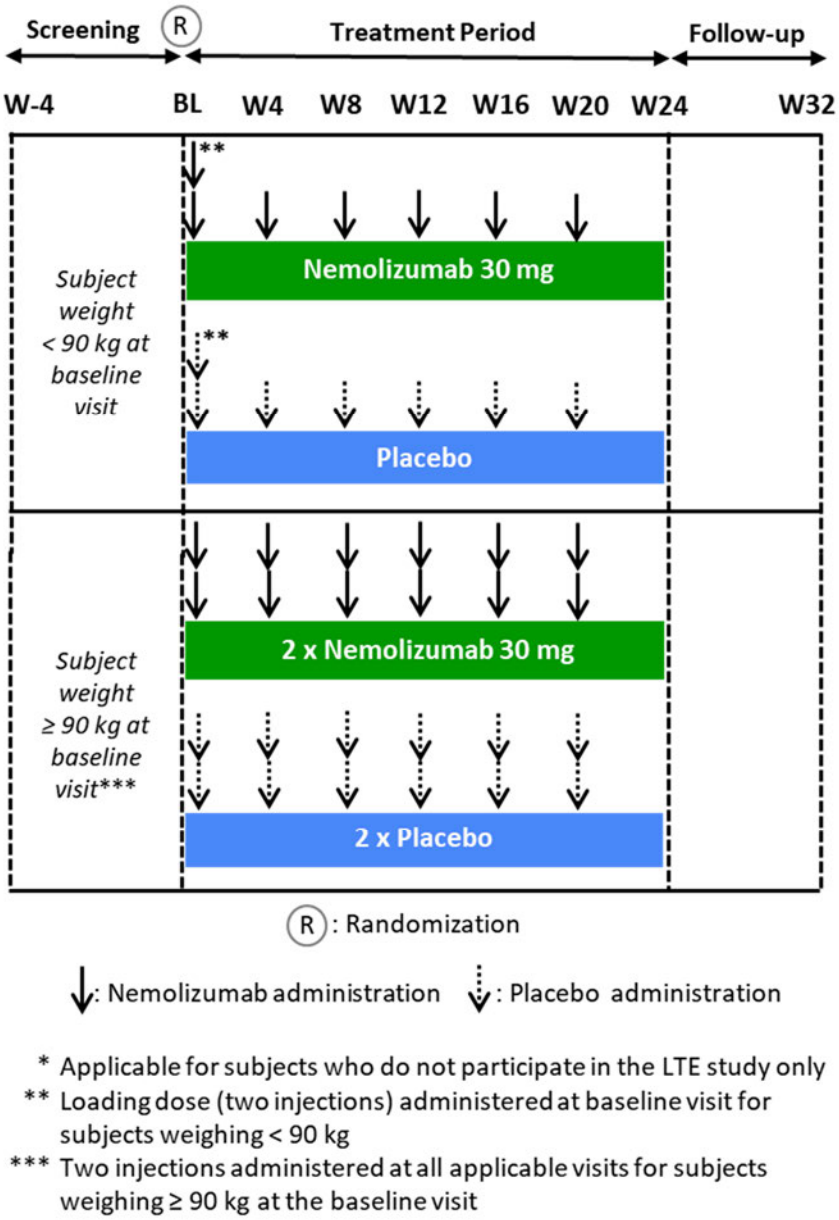
At the end of the 24-week treatment period, consenting subjects may be eligible to enter an active treatment/long-term extension (LTE) study (RD.06.SPR.202699). Subjects who participate in the LTE are not required to complete the follow-up visit. Subjects who do

not participate in the LTE will return for a follow-up visit at Week 32 (12 weeks after the last study drug injection).

Subjects who prematurely discontinue the study drug will be asked to continue participation in the study and return for all remaining visits and assessments (including daily assessment of pruritus and sleep disturbance). Subjects who discontinue study drug due to required rescue therapy may be eligible to participate in the LTE study following completion of study visits through Week 24. Subjects who discontinue the study prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection.

An IDMC will review and monitor subject safety throughout the study, and an IAC will review all asthma-related events throughout the study. The IDMC and IAC charters provide details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and procedures, roles, responsibilities and communications.

Figure 2. Study Design



* Applicable for subjects who do not participate in the LTE study only
** Loading dose (two injections) administered at baseline visit for subjects weighing < 90 kg
*** Two injections administered at all applicable visits for subjects weighing ≥ 90 kg at the baseline visit

Abbreviations: BL, baseline; W, week.

7.2 DISCUSSION OF STUDY DESIGN

This study will evaluate the safety and efficacy of nemolizumab (CD14152) in adult subjects with PN. The rationale for the general study design is based upon the prior phase 2a study design conducted in adult subjects with PN. The rationale for the nemolizumab dose/dose regimen is provided in Sections 5.2 and 5.4.

Eligible subjects for this clinical study will be adults with a clinical diagnosis (≥ 6 months) of PN, manifested by pruriginous nodular lesions on the trunk and/or limbs, and at least 20 nodules bilaterally distributed on the entire body. The inclusion criterion for IGA is consistent with the disease severity targeted in the study: An IGA of 3 or 4 corresponds to moderate or severe PN, respectively. Severe pruritus will be defined by PP NRS scores within the past 24 hours at screening and the mean PP NRS score during the previous week at baseline. Subjects with chronic pruritus due to other active conditions or unilateral pruriginous lesions are ineligible. Further, subjects must undergo specific required washout periods from restricted topical and systemic treatments before enrolling in the study. The study population is selected based on the current unmet need in the management of PN, the mode of action of nemolizumab (CD14152), and the need to understand the efficacy and safety of nemolizumab (CD14152) in the adult population with PN.

As no approved medicine for PN exists with which to compare nemolizumab, a placebo-controlled design was implemented in this study to allows blinding, randomization, and identical administration procedures to control for human bias or other influences on the disease (eg, natural disease course), while enabling demonstration of differences in clinical effect and safety profile of investigational treatment, if present. All subjects will have access to rescue medication to minimize risk and for ethical considerations. It is the position of the Committee for Medicinal Products for Human Use (CHMP) that, where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application.

A 16-week treatment period is considered adequate to evaluate the efficacy and safety of nemolizumab based on the results of the phase 2a study (RD.03.SPR.115828) in subjects with PN. A further 8-week treatment period is included to provide additional data as

requested by the European Medicines Agency for chronic diseases such as PN. All subjects who complete the treatment period (Week 24 visit) can be considered for LTE study eligibility. A 2-to-1 randomization is selected to minimize the number of subjects exposed to placebo for an extended period of time.

Although the pathophysiology of PN is still not fully understood, the efficacy endpoints selected for the phase 3 trial are relevant to the underlying manifestations associated with the disease under study (ie, skin lesions, chronic itch, sleep disturbance, and quality of life impairment). The selected endpoints for assessing the safety and PK of nemolizumab (CD14152) are in accordance with current standards. Blinding subjects and the designated study team to the treatment assignment(s) helps ensure objectivity and minimize bias. Randomization through the Interactive Response Technology (IRT) guards against selection bias.

The study includes an 8-week follow-up period (ie, 12 weeks after the last study drug injection) for subjects who decline or are not eligible to enroll in the LTE study. The duration of the follow-up period from the final nemolizumab dose (12 weeks) corresponds to approximately 5 half-lives of nemolizumab, which is considered adequate to ensure subject safety. The follow-up visit is not required for subjects who participate in the LTE, where the primary objective is long-term evaluation of safety.

Differences may be detectable during the study drug reconstitution process between active study drug and placebo but appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study drug for injection, including confirmation of complete reconstitution, prior to delivery of study drug for injection. The pharmacist (or other qualified personnel) preparing study drug should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments.

The placebo-controlled design includes a provision for rescue therapy for pruritus, based on the investigator’s clinical judgment. Subjects requiring rescue therapy may be eligible for the LTE study but will be required to continue scheduled study visits until the Week 24 visit before LTE eligibility will be assessed.

To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, contract research organization (CRO), or other investigational study centers will not have access to any information that may lead to unblinding.

7.3 END OF STUDY

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including Week 24 or the last scheduled visit as indicated in the Schedule of Assessments (Table 5).

The end of the study will be the last subject's last visit or the last subject's scheduled visit as indicated in the Schedule of Assessments (Table 5).

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be enrolled.

8.1 INCLUSION CRITERIA

Individuals must meet all of the following criteria to be included in the study:

1. Male or female and aged ≥18 years at the time of screening
2. Clinical diagnosis of PN for at least 6 months with:
   a. Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs
   b. At least 20 nodules on the entire body with a bilateral distribution
   c. Investigator Global Assessment (IGA) score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits
3. Severe pruritus defined as follows on the PP NRS:
   - At the screening visit (Visit 1): PP NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit
   - At the baseline visit (Visit 2): Mean of the daily intensity of the PP NRS score is ≥ 7.0 over the previous week;
     Note*: PP NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean PP NRS score is not permitted.*
4. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection.

   Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:
   - True abstinence, when in line with the preferred and usual lifestyle of the subject. See Appendix 1 for details. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Progestogen-only oral hormonal contraception
- Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception.)
  Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (eg, condom) together with a spermicide is not acceptable.
- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices or intrauterine hormone-releasing system
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Bilateral vasectomy of male partner at least 3 months before the study

5. Female subjects of non-childbearing potential must meet 1 of the following criteria:
   - Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range
   - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study
6. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study
7. Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed

8.2 EXCLUSION CRITERIA

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Body weight < 30 kg
2. Chronic pruritus resulting from another active condition other than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorder, sporotrichosis, bullous autoimmune disease, end-stage renal disease, cholestatic liver disease (eg, primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care
3. Unilateral lesions of prurigo (eg, only one arm affected)
4. History of or current confounding skin condition (eg, Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis)
5. Subjects meeting 1 or more of the following criteria at screening or baseline:

   5a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months

   5b. Reporting asthma that has not been well-controlled (ie, symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months

   5c. Asthma Control Test ≤ 19 (only for subjects with a history of asthma)

   5d. Peak expiratory flow < 80% of the predicted value

   Note: In the event that PEF is < 80% of the predicted value at the screening visit in patients without any history of asthma or in patients with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours.

6. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis
7. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected COVID-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.4.2.
8. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive confirmatory test for HCV [eg, polymerase chain reaction (PCR)], or human immunodeficiency virus antibody) at the screening visit

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

   In the event of rescreening, the serology tests results (eg, HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.
9. Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit
10. Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months

    Note: Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (ie, specific IgE), are eligible for the study.

11. Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis
12. Having received any of the following treatments in the table below within the specified timeframe before the baseline visit

Table 2. Restricted Prior Treatments

Treatments	Timeframe
Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids	2 weeks
Topical vitamin D analogs	2 weeks
Topical or systemic PDE-4 inhibitors	2 weeks
Any other topical treatment other than moisturizer (eg, capsaicin, cryotherapy for treatment of PN)	2 weeks
Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim	1 week
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy)	1 week
Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening	1 week
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (eg, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)

Treatments	Timeframe
Dupilumab	10 weeks
Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)
Systemic roxithromycin, erythromycin	1 week
Opioid antagonists (eg, naltrexone, naloxone), opioid partial/mixed agonists (eg, nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (eg, aprepitant, serlopitant)	4 weeks or 5 half-lives (whichever is longer)
Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions	4 weeks
Cannabinoids (eg, dronabinol)	2 weeks
Alternative medicine for PN (eg, traditional Chinese medicine)	2 weeks
Live vaccines	12 weeks
Non-live vaccines	4 weeks

Abbreviations: JAK, Janus kinase; NK1, neurokinin; PDE-4, phosphodiesterase-4; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

13. Previous participation in a clinical study with nemolizumab
14. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study
15. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:
    - Basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or;

- Actinic keratoses that have been treated

16. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients
17. Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines

    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

    In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit.
18. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment
19. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia)
20. History of alcohol or substance abuse within 6 months of the screening visit
21. Planned or expected major surgical procedure during the clinical study
22. Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3)
23. Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug,

whichever is longer), before the screening visit, or is in an exclusion period (if verifiable) from a previous study

For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected:

24. History of coagulation disorders
25. Known sensitivity to local anesthetics
26. Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed)
27. History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.

8.3 RESCREENING

Screen failures may be allowed to rescreen up to 1 time, unless the reason for screen failure is related to disease severity inclusion criteria. Subjects who screen fail due to disease severity are not allowed to rescreen. Subjects who are rescreened must sign a new ICF and be assigned a new subject identification number. See also Section 10.1.

In the event of rescreening, the serology and TB tests results from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.

In the event that PEF is < 80% of the predicted value at screening in patients without any history of asthma or in patients with history of asthma but with ACT score > 19, PEF testing can be repeated once within 48 hours.

8.4 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENTS

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and without any prejudice. No

constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Investigators or the Sponsor can also withdraw subjects from the clinical study if deemed to be necessary.

Reasons for discontinuing study drug include:

- Subject request (ie, consent withdrawal)
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs, including laboratory abnormalities, not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue, including but not limited to the following:
    - Serious immediate-type allergic manifestations including anaphylactic reaction
    - Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks considered to be related to study drug administration
    - Serious worsening of asthma considered to be related to study drug administration
    - Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma in situ [Bowen's disease], or basal cell carcinoma)
    - Opportunistic infections such as but not limited to active TB and other infections whose nature or course suggest an immune-compromised or immune-suppressed status
    - Confirmed or suspected COVID-19 infection (temporary discontinuation may be acceptable; for instructions on resuming study drug administration, see Section 8.4.2)
- Pregnancy
- Use of non-permitted concurrent therapy (unless discussed and agreed upon with the investigator and medical monitor)
- Use of systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or oral psoralen + ultraviolet A (PUVA) treatment, as specified in Section 9.10.2 and Table 4 of Section 9.10.3
- Treatment failure
- Investigator request

- Sponsor request, including any of the above criteria

If a subject is withdrawn from the study for any reason, the date and the reason for study withdrawal must be recorded on the electronic case report form (eCRF). Subjects who have been enrolled and treated will not be replaced by another subject. Once a subject is withdrawn from the study, the subject may not re-enter the study.

Subjects who prematurely discontinue from the study should undergo final study assessments and attend an Early Termination (ET) visit. Subjects should also complete a follow-up visit 12 weeks after the last study drug administration.

Subjects who prematurely discontinue study drug will be encouraged to complete all remaining visits and assessments (including daily assessment of pruritus and sleep disturbance).

Subjects requiring rescue medication (with or without study drug discontinuation) may be eligible for LTE participation, following completion of study visits through Week 24.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

In the event that a subject discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with GCP. This study may be terminated at the discretion of the Sponsor or any regulatory agency.

8.4.1 Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not receive any further injection(s) of the study drug.**

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 12.7.7) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 12.7.7).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide tri-monthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (ie, voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 12.7.4).

The investigator should also be notified of pregnancy occurring during the study (and within 12 weeks [± 5 days] after the last dose of study drug) but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 12.7.7.

8.4.2 COVID-19 Infection

Study drug administration will be discontinued in a subject in whom a COVID-19 infection is confirmed or suspected. COVID-19 must be specified as the reason for study drug discontinuation.

Study drug administration may resume in subjects with confirmed or suspected COVID-19 infection based on investigator judgement after discussion with the medical monitor or Sponsor and only if the following minimum conditions are met:

- For symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (eg, cough, shortness of breath)
- For asymptomatic subjects: At least 21 days have passed since the positive PCR test and no symptoms.

  Note: The above should be considered minimum criteria. Where the local guidelines are more stringent for infection resolution criteria, those must be applied.

See Appendix 2 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

9 STUDY TREATMENTS

"Study drug" refers to nemolizumab (CD14152) or placebo drug product for purposes of this double-blind study. The list of excipients are detailed in the IB.

9.1 DETAILS OF STUDY DRUG

Study drug will be supplied as a lyophilized powder in a pre-filled, single-use, dual-chamber syringe (DCS) for solution for subcutaneous injection only after reconstitution. The lyophilized nemolizumab (CD14152) powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30-mg dose of nemolizumab (CD14152) after reconstitution.

The study drugs to be used in this study are outlined in Table 3:

Table 3. Study Drugs

	Investigational product	Placebo
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Packaging	DCS	DCS
Storage conditions	Stored between 2°C to 8°C (36°F to 46°F); protected from light, protected from freezing	Stored between 2°C to 8°C (36°F to 46°F); protected from light, protected from freezing
Dosage	Subjects weighing < 90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline; Subjects weighing ≥ 90 kg at baseline: 60 mg	Not applicable
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution

	Investigational product	Placebo
Dose regimen	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at baseline, then 2 injections Q4W	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at baseline, then 2 injections Q4W
Treatment duration	24 weeks with last injection at Week 20	24 weeks with last injection at Week 20

Abbreviations: DCS, dual chamber syringe; Q4W, every 4 weeks; SC, subcutaneous.

9.2 PACKAGING AND LABELING

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products in the local language, national regulations/guidelines, and the relevant regulatory requirements, specifying that the drug is for use in a clinical study. Each DCS will be packaged in an individual carton, including a 27G 1/2" needle and a plunger rod (not assembled), and will be identified by a unique kit number. Local adaptation of the kit design may be required; specific details for each country are provided in the pharmacy manual.

9.3 STUDY DRUG PREPARATION

A pharmacist (or other qualified personnel) will prepare study drug for injection according to the instructions for use and instructions provided in the current version of the pharmacy manual. Study drug preparation should be conducted in a secured and clean area with limited access to only designated personnel at the time of the preparation. Good hygiene practices and clean techniques must apply at all times.

Differences may be detectable during the study drug reconstitution process between active and placebo, but active and placebo appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study drug for injection, including confirmation of complete reconstitution, prior to delivery of study drug for injection. The pharmacist (or other

qualified personnel) preparing the study drug should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments.

The study drug does not contain preservatives. From a microbiological point of view, the preparation of the study drug has to be done as close to subject administration as possible, and the study drug should be used immediately (less than 1 hour) after reconstitution. If not used immediately, the study drug has to be used within 4 hours maximum after reconstitution stored at room temperature (below 30°C) and only if the preparation has taken place applying strictly good hygiene practices and clean techniques to ensure controlled aseptic conditions.

9.4 STUDY DRUG INJECTION/ADMINISTRATION

All study drug injections will occur at the study center, following instructions provided in the instructions for use and the current version of the pharmacy manual. After confirming that the study drug is fully reconstituted, the pharmacist (or other qualified personnel) will deliver the DCS to the investigator or other qualified personnel, for SC injection in the subject's abdomen or an alternative injection site. A different injection site should be selected for each injection. Refer to the current version of the pharmacy manual and the instructions for use for further details. The site of injection should be recorded in the subject's treatment record as well as the eCRF at each time point.

For subjects willing and able to self-inject, study center staff will provide training on study drug injections. Subjects will be allowed to inject medication following appropriate training and under supervision by study center clinic staff (with DCS preparation including reconstitution performed by the pharmacist or other qualified personnel and delivered for injection after reconstitution is complete). Study center/clinic staff can perform all injections if the subject does not wish to perform injections. The eCRF will record who performed study drug injection at each visit.

After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. For the first 2 visits

where study drug is administered, subjects should remain at the study center for at least 30 minutes following study drug administration.

9.5 STUDY DRUG MANAGEMENT

9.5.1 Storage of Study Drug

All DCS units must be stored together in a safe and secure area with restricted access. Upon receipt, the DCS must be removed from the shipping cooler, kept in the outer carton until use, and stored in a refrigerator between 2°C to 8°C (36°F to 46°F), protected from light, and protected from freezing.

The refrigerator must be monitored daily, and if a temperature excursion occurs, the designated personnel should promptly inform the study monitor, as specified in the current version of the pharmacy manual.

9.5.2 Study Drug Accountability

Study drug will be provided to the investigational site and site personnel will acknowledge receipt of the study drug using IRT to confirm the shipment condition and content. If a damaged shipment is received and/or a temperature excursion has been experienced, he/she will notify the Sponsor/contract research organization (CRO) and follow the guidelines according to the current version of the pharmacy manual.

The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered and received DCS units, and the return/destruction of unused study drug as specified in the current version of the pharmacy manual. No unauthorized use is permitted. Used DCS units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected or an event occurs before, during, or just after the injection, the used DCS can be disposed in an appropriate sharps container and according to waste regulation(s) in the country. A DCS involved in a malfunction or an investigator or subject complaint must be retained on site and designated personnel must proceed as defined in the current version of the pharmacy manual. Refer to Section 9.6 for product technical complaints.

The study monitor may check the study supplies at each study center at any time during the study. It is the responsibility of the study monitor to ensure that the investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned/destroyed on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of any unused study drug not destroyed by the site. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

9.5.3 Dispensing and Return of Study Drug

All study drug preparation must be appropriately performed and documented by the designated personnel. Any error in the preparation of dosing solution must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/return/destruction process for all unused study drug will be conducted according to the sites' SOPs, local regulations, and best practices, as described in the current version of the pharmacy manual. If the site does not have the capability to destroy drug, then the unused study drug will be returned to the CRO/drug depot for destruction.

9.6 PRODUCT TECHNICAL COMPLAINTS

All DCS units, including the needle and plunger rod, must be inspected prior to preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to a DCS PTC. In case of doubt, the DCS should not be used, and the deficiency must be reported as defined in the pharmacy manual.

All PTCs should be reported to the Sponsor/designee by filing the relevant forms available in the Investigator Site File and the pharmacy manual and as required by local regulations. A PTC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, durability, effectiveness, or performance of a drug or delivery system. Examples may include but are not limited to appearance issues, discoloration, odor, broken/cracked syringe, missing parts, damaged stoppers, and foreign matter in lyophilized powder or diluent. These complaints may or may not represent a potential risk to the subject. For these types of events, a form must be

completed as per the specific instruction by the site personnel, pictures of the defective DCS/items must be attached, and forwarded to the Sponsor/designee at the latest on the next working day. Reporting to health authorities will be in accordance with local regulations. The defective DCS/items must be kept in case of investigation need as defined in the pharmacy manual and may be requested to be sent to the Sponsor/designee in accordance with regulations.

Refer to the current version of the pharmacy manual for further details.

9.7 MEASURES TO MINIMIZE BIAS: STUDY TREATMENT ASSIGNMENT AND BLINDING

9.7.1 Method of Study Treatment Assignment

Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number will be assigned to that subject via Interactive Response Technology (IRT).

The randomization number for a given subject will be used to identify the treatment arm the subject will be assigned to.

Subjects will be randomized in a 2:1 ratio to receive treatment of either nemolizumab (CD14152) or placebo. The randomization scheme will be stratified by the study site and baseline body weight (< 90 kg and ≥ 90 kg) using the IRT system.

9.7.2 Study Blinding

All attempts will be made to keep the study center staff and subjects blinded throughout the study. Members of the study center staff, including those responsible for DCS preparation, will not have access to the randomized treatment assignment.

To ensure double-blind administration of study drug, the study center pharmacist(s) or other qualified personnel will prepare all nemolizumab (CD14152) or placebo treatments, according to the current version of the pharmacy manual and assigned DCS provided by the IRT system.

As there may be detectable differences between active and placebo during the reconstitution process, the DCS is delivered for injection after the reconstitution is

complete. The pharmacist (or other qualified personnel) preparing study drug should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments.

To maintain the integrity of the study blinding, the bioanalytical laboratory staff who process/analyze the PK/anti-drug antibody (ADA)/pharmacodynamic (PD)/ pharmacogenomic (PGx) samples will not provide any information to the Sponsor, CRO, or investigational study center personnel directly involved with the ongoing conduct of the study that may lead to unblinding during the ongoing study. PK and ADA results will released by the bioanalytical laboratory after data base lock.

Unblinding of a subject's individual treatment code should occur only in case of a medical emergency or in the event of a serious medical condition that necessitates identification of the study drug for the welfare of that subject, as judged by the investigator. The emergency unblinding process utilizes IRT to allow the investigator to have unrestricted, immediate, and direct access to the subject's individual study treatment. When possible (ie, when the health of the subject is not immediately at risk), the investigator or sub-investigator is encouraged to consult with the medical monitor and the Sponsor before breaking the blind.

If emergency unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected subject will be unblinded.
- The IRT system will provide the treatment assignment to the investigator.

Refer to the Randomization and Trial Supply Management (RTSM) User Guide for information on the steps for breaking the blind in the IRT system.

When the blinding code is broken, the reason must be fully documented. If the code is broken by the investigator, the subject must be withdrawn from the study and must also be appropriately followed for a minimum of 12 weeks after the last dose of study drug.

The reporting requirements for unblinding are the same for reporting an SAE. See also Section 12.7.4.

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked.

The IDMC will review data at periodic intervals throughout the study as defined in the IDMC charter. The IDMC charter will specify the procedures for unblinding to ensure treatment assignment remains undisclosed to all individuals involved in the direct execution and management of the study until the final database is locked.

9.8 DOSAGE MODIFICATION

Dose modification of the study drug will not be permitted during the clinical study.

Any inadvertent dose modification(s) should be reported to the Sponsor/CRO and documented in the eCRF.

In the event of a missed dose (ie, temporary discontinuation of the study drug), it will be documented in the eCRF that the drug has not been administered at the study visit, together with the reason (eg, for safety). Subjects will be asked to return to the study centers for all remaining visits and complete all study assessments and procedures as described in the Schedule of Assessments (Table 5).

Dosing frequency is scheduled for Q4W, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window defined in the Schedule of Assessments (Table 5), study drug can still be administered provided there is a minimum of 3 weeks but not more than 5 weeks since the last injection. If beyond 5 weeks, the next injection should then occur at the next planned visit. Future visits should be scheduled as soon as possible and within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between 2 injections.

9.9 TREATMENT COMPLIANCE

Treatment compliance will be assessed through the treatment records and drug dispensation logs.

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, dose, injector (subject or site staff),

and site of injection should be accurately recorded to confirm that each dose of study treatment was properly administered.

9.10 PRIOR AND CONCOMITANT THERAPY

Prior therapies are defined as therapies that have been stopped within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, all prior therapies for PN should be documented.

Concomitant therapies/medications are defined as follows:

- Any existing therapies ongoing at the time of the screening visit,
- Any changes to existing therapies (such as changes in dose, formulation or application frequency) during the course of the study, or
- Any new therapies received by the subject since the screening visit

The following 2 categories are to be considered for prior and concomitant therapies:

- Drugs/Therapies include but are not limited to: prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures (eg, phototherapy, exodontia, etc); procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

Prior and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

At each visit, investigators should also confirm concomitant therapies for contraception. See Appendix 1 for details. Contraceptive counseling should occur at screening.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE form should be completed to account for the new therapy or change in therapy, except in some cases such as an inadvertent dose

modification (see Section 9.8), in which case the therapy/medication will be linked to an item in the subject's medical history.

9.10.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 9.10.3), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, and topical anesthetics.

Starting from the screening visit, subjects can use their daily moisturizer, if it does not contain any compound with known anti-itch effect (eg, menthol, polidocanol, etc.). Subjects should not change emollients or moisturizers or apply products for itching relief during the course of the study.

Sedatives and antidepressants as described in Table 4 are allowed if they have been administrated for at least 3 months at a stable dose before screening baseline and dose changes are not planned during the study.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, IL-10) during chronic inflammation. Treatment with a biologic agent with an anti-inflammatory effect such as nemolizumab may indirectly upregulate CYP450 expression by decreasing cytokine levels. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab (CD14152) on such enzymes has not been studied. Therefore, investigators should consider observing for clinical or laboratory signs that might indicate a potential effect of nemolizumab (CD14152) in subjects using concomitant therapies that are CYP450 substrates, particularly those with a narrow therapeutic index. Typical examples of substrates with a narrow therapeutic range include warfarin, drugs that may cause torsade de pointes, almost all cytotoxic antineoplastic drugs, and aminoglycoside antibiotics. A list of representative CYP450 substrates with narrow therapeutic index can be found in Appendix 3.

9.10.2 Rescue Therapy

If deemed to be medically necessary by the investigator (eg, to control intolerable PN signs/symptoms), rescue therapies can be prescribed to the subjects.

Rescue therapy must not be prescribed during the screening period.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure.

Rescue therapies include:

- Topical corticosteroids
- Topical calcineurin inhibitors
- Oral antihistamines
- Systemic or intralesional corticosteroids
- Biologics (including their biosimilars)
- Systemic nonsteroidal immunosuppressants/immunomodulators
- Phototherapy
- Gabapentinoids

Whenever possible, investigators should first use topical medication or oral antihistamines as rescue therapy before escalating to other systemic therapies. If subjects receive topical treatments, oral antihistamines, or ultraviolet B (UVB) phototherapy as rescue therapy, study drug administration should be continued unless there is a concern according to the investigator's judgment. If subjects receive systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or oral psoralen + ultraviolet A (PUVA) treatment, the study drug administration must be permanently discontinued. In the event study drug administration is discontinued due to receipt of systemic rescue therapy, subjects will be encouraged to complete the remaining scheduled study visits according to the Schedule of Assessments in Table 5. Subjects who complete the Week 24 visit may be eligible to participate in the LTE if screening criteria are met.

For the purpose of efficacy analysis, subjects receiving any rescue therapies will be considered as treatment failures. Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. Further, the use of any rescue therapies should be documented in the eCRF.

9.10.3 Prohibited Therapy

Treatment with the following concomitant medications/therapies in Table 4 is prohibited during the study unless otherwise specified.

Table 4. Prohibited Therapy

Treatments	***Timeframe***	
	Before Baseline/Day 1	Day 1 – Week 32
Topical calcineurin inhibitors (tacrolimus, pimecrolimus) and topical corticosteroids	2 weeks	Prohibited*
Topical vitamin D analogs	2 weeks	Prohibited
Topical or systemic PDE-4 inhibitors	2 weeks	Prohibited
Any other topical treatment other than moisturizer (eg, capsaicin, cryotherapy for treatment of PN)	2 weeks	Prohibited
Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim	1 week	Prohibited
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks	Prohibited*
Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy)	1 week	Prohibited*
Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg,	1 week	Prohibited

Treatments	***Timeframe***	
	Before Baseline/Day 1	Day 1 – Week 32
paroxetine), or SNRIs except if these treatments were taken at a stable dose for at least 3 months before screening		
Phototherapy	4 weeks	Prohibited*
Tanning beds	4 weeks	Prohibited
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)	Prohibited*
Biologics and their biosimilars (eg, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)	Prohibited*
Dupilumab	10 weeks	Prohibited*
Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)	Prohibited
Systemic roxithromycin, erythromycin	1 week	Prohibited
Opioid antagonists (eg, naltrexone, naloxone), opioid partial/mixed agonists (eg, nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (eg, aprepitant, serlopitant)	4 weeks or 5 half-lives (whichever is longer)	Prohibited
Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions	4 weeks	Prohibited*
Cannabinoids (eg, dronabinol)	2 weeks	Prohibited
Investigational topical or systemic medication	12 weeks or 5 half-lives	Prohibited

Treatments	***Timeframe***	
	Before Baseline/Day 1	Day 1 – Week 32
	(whichever is longer)	
Alternative medicine for PN (eg, traditional Chinese medicine)	2 weeks	Prohibited
Live vaccines	12 weeks	Prohibited
Non-live vaccines	4 weeks	Prohibited (exceptions apply)

Abbreviations: JAK, Janus kinase; NK1, neurokinin; PDE-4, phosphodiesterase-4; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
* Unless used as rescue therapy during the study.
Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the medical monitor and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical study (eg, inadvertent short-term use), the investigator should also notify the medical monitor and discuss whether or not it is acceptable for the subject to continue receiving the study drug.

Specifically, the use of systemic corticosteroids during the study is prohibited except when used as rescue therapy for PN (in accordance with the instructions in Section 9.10.2). If the use of systemic corticosteroids becomes necessary for the safety of the subject to treat condition(s) other than PN, the study drug should be temporarily discontinued for the duration of treatment with systemic corticosteroids plus 5 half-lives.

It is recommended that all subjects should be up to date with respect to standard of care vaccinations as defined by the local guidance. For subjects who have vaccination planned during the study, it will be determined after consultation with the treating physician, whether the administration of vaccine can be postponed until after the end of study, or preponed to before the start of the study, without compromising the health of the subject.

Vaccinations during the study and follow-up period are not permitted, except for use of the following non-live vaccines:

- seasonal vaccinations (eg, influenza)
- emergency vaccinations (eg, rabies or tetanus),
- COVID-19 vaccinations.

Wherever possible, it is recommended to avoid administration of seasonal and COVID-19 vaccinations within 1 week before or after study drug dosing, and a different anatomical location should be used for study drug administration and vaccine administration.

In the event of emergency vaccination during the study, the study drug administration should be discontinued until the immune response to vaccination is verified.

10 STUDY PROCEDURES

10.1 INFORMED CONSENT

Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject; including separate photography and PGx consent, if applicable.

Upon ICF signature, each subject will be assigned, via electronic data capture (EDC), a unique subject identification number (SIN) which will be used for the entire duration of the study. In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new subject identification number. See also Section 8.3.

10.2 STUDY ASSESSMENTS AND PROCEDURES

Assessments and procedures are to be performed as outlined in the Schedule of Assessments (Table 5).

At each visit, assessments/procedures should be performed in the following order:

1. Patient-reported efficacy and safety measurements
2. Investigator assessments (including efficacy and safety)
3. Sample collections for laboratory assessments
4. Sample collections for correlative assessments (PK, ADA, PD, and optional PGx)
5. Administration of study drug injections

Efficacy assessments are described in Section 11; quality of life assessments are described in Section 11.7. Safety assessments are described in further detail in Section 12. Section 12.5 specifies laboratory assessment samples to be obtained. Pharmacokinetic assessments are described in Section 13; pharmacogenomic and anti-drug antibody assessments are described in Section 14.

Study discontinuation procedures, including early termination visit and follow-up of TEAEs, are described in Section 8.4.

Unscheduled visit procedures are described in Section 10.2.1.

Table 5. Schedule of Assessments

Study period	Screening period (Day -28 to Day-1)	Treatment period								Follow-up [c]	Early Termination	Unsched-uled visit [d]
Visit	V1	V2	No visit [b]	V3	V4	V5	V6	V7	V8	V9	(if applicable)	(if applicable)
Week	Screening [a]	Baseline	W1	W4	W8	W12	W16	W20	W24	W32		
Day	D-28 to D-8	Day 1	Day 8	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 225		
Visit window			±0 days	±2 days	±2 days	±5 days	±5 days	±7 days	±7 days	±7 days		
Informed consent form	X											
Photography, skin biopsy, and PGx consent form(s) (if applicable)	X											(X)
Inclusion/exclusion criteria	X	X										
Demographics	X											
Medical history, previous therapies and procedures, smoking status	X											(X)
PATIENT-REPORTED OUTCOME ASSESSMENTS												
PP NRS/AP NRS/SD NRS/ subject sleep diary [e,f]	X----------									X	X	(X)
PGIS-P/PGIS-SD [e,f]		X	X [b]				X		X		X	(X)
PGIC-P/PGIC-SD [e,f]			X [b]				X		X		X	(X)
PGAD [g]		X	X [b]				X		X		X	(X)
PGAT [g]							X		X		X	(X)

Study period	Screening period (Day -28 to Day-1)	Treatment period								Follow-up [c]	Early Termination	Unsched-uled visit [d]
Visit	V1	V2	No visit [b]	V3	V4	V5	V6	V7	V8	V9	(if applicable)	(if applicable)
Week	Screening [a]	Baseline	W1	W4	W8	W12	W16	W20	W24	W32		
Day	D-28 to D-8	Day 1	Day 8	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 225		
Visit window			±0 days	±2 days	±2 days	±5 days	±5 days	±7 days	±7 days	±7 days		
PN-associated pain frequency and intensity [g]		X		X	X	X	X	X	X		X	(X)
DLQI [g]		X		X			X		X		X	(X)
EQ-5D/HADS [g]		X					X		X		X	(X)
CLINICAL PHOTOGRAPHS												
Full body clinical photographs (optional) [h]		X					X		X		X	(X)
CLINICAL EFFICACY ASSESSMENTS												
IGA	X	X		X	X	X	X	X	X		X	(X)
PAS	X	X		X	X	X	X	X	X		X	(X)
SAFETY ASSESSMENTS												
ACT [g, i]	X	X		X	X	X	X	X	X	X	X	(X)
Respiratory exam	X	X		X	X	X	X	X	X	X	X	(X)
PEF testing [j]	X	X		X[j]	X	X[j]	X	X[j]	X	X	X	(X)
Vital signs	X	X		X	X	X	X	X	X	X	X	(X)
Full physical examination	X	X			X		X		X	X	X	(X)
Height	X											(X)

Study period	Screening period (Day -28 to Day-1)	Treatment period								Follow-up [c]	Early Termination	Unsched-uled visit [d]
Visit	V1	V2	No visit [b]	V3	V4	V5	V6	V7	V8	V9	(if applicable)	(if applicable)
Week	Screening [a]	Baseline	W1	W4	W8	W12	W16	W20	W24	W32		
Day	D-28 to D-8	Day 1	Day 8	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 225		
Visit window			±0 days	±2 days	±2 days	±5 days	±5 days	±7 days	±7 days	±7 days		
Weight	X	X				X			X		X	(X)
12-lead ECG [k]	X	X							X		X	(X)
Contraceptive counseling	X											(X)
Adverse Events [g]	X	X		X	X	X	X	X	X	X	X	(X)
Concomitant therapies and procedures [g]	X	X		X	X	X	X	X	X	X	X	(X)
LABORATORY ASSESSMENTS												
Blood sample for virology (HIV, Hepatitis B, and C test)	X											(X)
Blood samples for TB test [l]	X											(X)
Blood samples for hematology and biochemistry [m, n]	X	X		X	X		X		X	X	X	(X)
Urinalysis [n]	X	X			X		X		X	X	X	(X)
Pregnancy test [o]	Serum	Urine		Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	(Urine)
FSH [p]	X											
PK, ADA, PD AND PGx ASSESSMENTS												
Blood sample for PK [d, n, q]		X		X	X	X	X		X	X	X	(X)

Study period	Screening period (Day -28 to Day-1)	Treatment period								Follow-up [c]	Early Termination	Unsched-uled visit [d]
Visit	V1	V2	No visit [b]	V3	V4	V5	V6	V7	V8	V9	(if applicable)	(if applicable)
Week	Screening [a]	Baseline	W1	W4	W8	W12	W16	W20	W24	W32		
Day	D-28 to D-8	Day 1	Day 8	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 225		
Visit window			±0 days	±2 days	±2 days	±5 days	±5 days	±7 days	±7 days	±7 days		
Blood sample for ADA [d, n]		X			X		X		X		X	(X)
Blood sample for PD [r]		X			X		X		X			(X)
Stratum corneum sample for PD [r]		X					X					(X)
Skin biopsy for PD (optional) [r]		X					X					(X)
PGx sample (optional) [s]		X										(X)
STUDY DRUG ADMINISTRATION												
Randomization		X										(X)
Study drug injection [t, u, v, w]		X [t]		X	X	X	X	X				(X)

Abbreviations: ACT, asthma control test; ADA, anti-drug antibodies; AP NRS, Average Pruritus Numeric Rating Scale; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EQ-5D, EuroQoL 5-Dimension; FSH, follicle-stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator Global Assessment; NRS, numeric rating scale; PAS, prurigo activity score; PD, pharmacodynamics; PEF, peak expiratory flow; PGAD, Patient Global Assessment of Disease; PGAT, Patient Global Assessment of Treatment; PGIC-P, Patient Global Impression of Change – Pruritus; PGIC-SD, Patient Global Impression of Change – Sleep Disturbance; PGIS-P, Patient Global Impression of Severity – Pruritus; PGIS-SD, Patient Global Impression of Severity – Sleep Disturbance; PGx, pharmacogenomic; PK, pharmacokinetic; PP NRS, Peak Pruritus Numeric Rating Scale; SD NRS, Sleep Disturbance Numeric Rating Scale; TB, tuberculosis; UPT, urine pregnancy test.

Notes:

a) Screening visit must be performed at least 7 days prior to Day 1 visit. Subjects deemed eligible will be provided with electronic handheld devices.

b) Subjects will complete PGIS-P, PGIC-P, PGIS-SD, PGIC-SD, and PGAD assessments at Week 1 (ie, 7 days after the Day 1/Baseline visit) for test-retest validation of itch and sleep PRO measures.

c) The follow-up visit will be conducted for subjects who decline or are not eligible to enter the LTE study (including early termination) and should be conducted 12 weeks after the last study drug injection. (The follow-up visit is not required for subjects who will rollover to the LTE study.)

d) Assessments to be conducted at the unscheduled visit depend on the reason for the visit. PK and ADA analyses are required only at unscheduled visits that are conducted for safety reasons. Subjects requiring rescue therapy between scheduled visits should return to the clinic for an unscheduled visit for investigator assessments of efficacy before starting rescue therapy. See Section 10.2.1 for details.

e) SD NRS and sleep diary questions to be recorded by subjects once daily in the morning and if possible, within 1 hour of getting out of bed (Visit 1/Screening through Visit 8/Week 24). PP NRS and AP NRS to be recorded by subjects once daily in the evening (Visit 1/Screening through Visit 8/Week 24), beginning after the screening visit. On designated visits, PGIS-SD and PGIC-SD should be recorded after the SD NRS and sleep diary in the morning; PGIS-P and PGIC-P should be recorded after the PP NRS and AP NRS in the evening.

f) Pruritus assessments scheduled for clinic visit days that are recorded by subjects in the evening (ie, PP NRS, AP NRS, PGIS-P, PGIC-P) will be recorded the evening before the clinic visit.

g) Patient-reported outcome assessments and designated safety measurements should occur before investigator assessments, laboratory sample collections, and study drug administration.

h) Optional for consenting subjects and only for selected equipped sites; see Section 11.8 for details on clinical photographs.

i) Subjects with a medical history of asthma will complete the ACT testing at each scheduled visit. Subjects with de novo asthma will complete the ACT testing beginning from de novo diagnosis and at all subsequent scheduled visits.

j) PEF testing will be performed for all subjects at screening, baseline, Week 8, Week 16, Week 24, and follow-up visits. For subjects reporting a medical history of asthma, PEF testing will be performed at all visits during the clinical study. For subjects diagnosed with de novo asthma, PEF testing will be performed at all visits, starting with the visit in which the diagnosis was confirmed. Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject. See Section 12.6.3 for details.

k) 12-lead ECGs should be performed in the supine position, before any scheduled vital sign measurements and blood draws. See Section 12.4.

l) In case of indeterminate result for TB test, the test should be repeated (only 1 retest is allowed). If the test is still indeterminate, the subject must not be included in the study, unless subject has a documented history of completion of an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed.

m) Subjects should be well hydrated and fast for at least 8 hours before the visit(s) when blood chemistry testing is planned, except for the screening visit.

n) At scheduled visits with laboratory, PK, and ADA assessments, samples are to be collected before study drug injection(s).

o) Only for females of childbearing potential. Serum pregnancy test to be performed at screening visit and UPT for all other visits. If UPT is positive, it must be confirmed with a serum pregnancy test. See Section 12.5.4 for details.

p) For postmenopausal subjects (ie, no menses for 12 consecutive months), confirm status with a high FSH level in the postmenopausal range.

q) As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples). See Section 13.1 for details on PK assessments.

r) Blood, stratum coreum, and biopsy samples for PD assessments are only collected at selected sites. Biopsy samples are optional and only for subjects who provide additional consent. See Section 14.3 for details.

s) Optional PGx sample collection is only for subjects who provide additional consent. See Section 14.1 for details.

t) Subjects weighing < 90 kg at baseline will receive a loading dose on Day 1 (ie, 2 injections of nemolizumab 30 mg or placebo) then single injections of either 30 mg nemolizumab or placebo Q4W. Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo via 2 injections Q4W at all study visits.

u) Study drug reconstitution will be performed by the pharmacist (or other qualified personnel) throughout the study, and complete reconstitution confirmed, prior to delivery for injection. Study center staff will provide study drug injection training for subjects willing and able to self-inject study drug. Based on the subject's preference, study center staff can also perform all injections.

v) After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. For the first 2 visits where study drug is administered, subjects should remain at the study center for at least 30 minutes following study drug administration.

w) If a study visit occurs outside the visit window, study drug injection(s) can still be administered provided there is a minimum of 3 weeks but not more than 5 weeks since the last injection. If beyond 5 weeks, the next study drug injection should then occur at the next planned visit. Future visits should be scheduled as soon as possible and within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between 2 injections.

10.2.1 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results, for follow-up of AEs, or to conduct efficacy assessments for subjects requiring rescue medication between regularly scheduled study visits. Visits occurring outside of the visit window are not considered unscheduled visits.

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit. Any of the procedures/assessments listed in Table 5 may be conducted, but not all are required. However, blood sample collection for PK and ADA analyses are required only during unscheduled visits that are conducted for safety reasons.

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 5) outlines the efficacy assessments to be performed throughout the study and their timing. Whenever possible, the same evaluator should perform all assessments for the same subject in order to reduce intra-subject variability.

11.1 INVESTIGATOR GLOBAL ASSESSMENT

The IGA is a 5-point scale used by the investigator or trained designee to evaluate the global severity of PN. The Investigator will review the subject's skin and give a score of 0 (Clear), 1 (Almost clear), 2 (Mild), 3 (Moderate), or 4 (Severe). Treatment response/success is defined as 0 (Clear) or 1 (Almost clear) and a ≥ 2-point improvement from baseline (see Appendix 4).

11.2 PRURIGO ACTIVITY SCORE

The Investigator or designee will use the PAS as an evaluation of the disease. This includes a count of the number of lesions in a representative area and a calculated staging (stage 0 to stage 4) based on the percentage of lesions with excoriations/crusts and healed lesions compared to all lesions.

A copy of the PAS can be found in Appendix 5.

11.3 NUMERIC RATING SCALES

11.3.1 Itch/Pruritus Numeric Rating Scales

Two NRSs relating to itch/pruritus (average and maximum intensity) will be completed by the subject once daily in the evening (see Appendix 6).[32] Each NRS will ask for a unit score on an 11-point scale (0 to10) where 0 is "no itch" and 10 is the "worst itch imaginable". The 2 questions asked will be:

- For average itch intensity (AP NRS): "On a scale of 0 to 10, with 0 being "no itch" and 10 being the "worst itch imaginable", how would you rate your itch overall during the previous 24 hours?"

- For maximum itch intensity (PP NRS): “On a scale of 0 to 10, with 0 being “no itch” and 10 being the “worst itch imaginable”, how would you rate your itch at the worst moment during the previous 24 hours?”

If a subject does not complete the NRS assessments in the evening before a scheduled visit, the subject will be allowed to complete the assessment the following day at the clinic visit. Site staff will be asked to ensure that the answer to the second question (PP NRS) is equal to or higher than the answer to the first question (AP NRS). If it is not, then further explanation will be given to the subject.

11.3.2 Sleep Disturbance Numeric Rating Scale

An NRS relating to sleep disturbance will be completed by the subject once daily in the morning and if possible, within 1 hour of getting out of bed, to report the degree of their sleep loss related to PN (see Appendix 7). Each NRS will ask for a unit score on an 11-point scale (0-10). The question asked will be “On a scale of 0 to 10, with 0 being “no sleep loss related to the symptoms of my skin disease (prurigo nodularis)” and 10 being “I did not sleep at all due to the symptoms of my skin disease (prurigo nodularis)”, how would you rate your sleep last night?”

If a subject does not complete the SD NRS in the morning before a scheduled visit, the subject will be allowed to complete the assessment at the clinic visit.

11.4 SUBJECT SLEEP DIARY

Subjects will be given a morning sleep diary to record the quality of their sleep. See Appendix 8. The subject sleep diary is a modification of the consensus sleep diary,[33] and is designed to gather information about the subject’s sleep pattern and how symptoms related to PN (eg, itching, burning) affect their sleep. Subject sleep diary items used to derive sleep parameters (eg, sleep onset latency, WASO) are defined in Appendix 8.

Subjects will be instructed to complete the sleep diary (Questions 1 to 11) once daily in the morning (ie, within 1 hour of getting out of bed), with the daily SD NRS (Appendix 7). If a subject does not complete the sleep diary in the morning before a scheduled visit, the subject will be allowed to complete the assessment at the clinic visit.

11.5 PAIN FREQUENCY AND INTENSITY

Subjects will be asked to report the frequency and intensity of pain they endure related to their skin disease (prurigo nodularis) (see Appendix 9). Subjects will rate the frequency of their pain on a 6-point scale (0-5) in response to the following question:

- "How often would you say that you experience pain from your skin disease (prurigo nodularis)?"

Subjects will rate the intensity of their pain using an 11-point NRS (0-10) in response to the following question:

- "On a scale of 0 to 10, with 0 being "no pain" and 10 being "the worst unbearable pain", how would you rate the pain associated with your skin disease (prurigo nodularis) at the worst moment during the past week?"

11.6 PATIENT-REPORTED OUTCOMES ASSESSMENTS

11.6.1 Patient Global Assessment of Disease

For the PGAD, subjects will be asked to rate their overall impression of their skin disease (prurigo nodularis) severity using a 5-point scale from "clear" to "severe" (see Appendix 10). Subjects will be asked the following question:

- "Overall, how would you describe your skin disease (prurigo nodularis) right now?"

The PGAD will also serve as an anchor for the patient-reported outcome (PRO) psychometric validation.

11.6.2 Patient Global Assessment of Treatment

The PGAT utilizes a 5-point Likert scale for subjects to rate the way they feel their skin disease (prurigo nodularis) is responding to the study treatment. See Appendix 11. Subjects will be asked the following question:

"How would you rate the way your skin disease (prurigo nodularis) responded to the study medication?"

11.6.3 Patient Global Impression of Severity - Pruritus

For the PGIS-P, subjects will be asked to rate their impression of their overall itch severity during the last week using a 5-point scale from "none" to "very severe" (Appendix 12). Subjects will record their PGIS-P scores in the evening after completing the Pruritus (PP and AP) NRS (Appendix 6). If a subject does not complete the PGIS-P in the evening before a scheduled visit, the subject will be allowed to complete the assessment the following day at the clinic visit. The PGIS-P will serve as an anchor for the PRO psychometric validation.

11.6.4 Patient Global Impression of Change - Pruritus

The PGIC-P utilizes a 5-point Likert scale (from "much better" to "much worse") for subjects to rate their impression of how their overall itch has changed since beginning study drug. See Appendix 13. Subjects will record their PGIC-P scores in the evening after completing the Pruritus (PP and AP) NRS (Appendix 6). If a subject does not complete the PGIC-P in the evening before a scheduled visit, the subject will be allowed to complete the assessment the following day at the clinic visit. The PGIC-P will serve as an anchor for the PRO psychometric validation.

11.6.5 Patient Global Impression of Severity - Sleep Disturbance

For the PGIS-SD, subjects will be asked to rate their impression of the severity of their sleep disturbance due to the symptoms of PN during the past week using a 5-point scale from "none" to "very severe" (See Appendix 14). Subjects will record their PGIS-SD score in the morning after completing the SD NRS and Subject Sleep Diary (Appendix 7 and Appendix 8, respectively). If a subject does not complete the PGIS-SD in the morning before a scheduled visit, the subject will be allowed to complete the assessment at the clinic visit. The PGIS-SD will serve as an anchor for the PRO psychometric validation.

11.6.6 Patient Global Impression of Change - Sleep Disturbance

The PGIC-SD utilizes a 5-point Likert scale for subjects to rate their impression of how their overall sleep disturbance, due to the symptoms of their skin disease (prurigo nodularis), has changed since beginning study drug (see Appendix 15). Subjects will record their PGIC-SD score in the morning after completing the SD NRS and Sleep Diary (Appendix 7 and Appendix 8, respectively). If a subject does not complete the PGIC-SD in the morning before a scheduled visit, the subject will be allowed to complete the assessment at the clinic visit. The PGIC-SD will serve as an anchor for the PRO psychometric validation.

11.7 QUALITY OF LIFE QUESTIONNAIRES

11.7.1 Dermatology Life Quality Index

The DLQI is a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment (see Appendix 16).[34]

The subject will rate each question ranging from 0 (not at all) to 3 (very much). A higher total score indicates a poorer QoL.

11.7.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-question validated questionnaire completed by the subject.[35] Each question has a multiple choice answer which is scored between 0 and 3. Questions are identified as relating to anxiety (A) or depression (D) and a summation for each area is performed leading to a total score of 0 to 21 for each area. Scores of 0 to 7 are considered normal, 8 to 10 are borderline, and ≥ 11 indicates clinical effects.

A copy of the HADS can be found in Appendix 17.

11.7.3 EuroQoL 5 Dimension Instrument

The EQ-5D instrument is a validated questionnaire, completed by the subject that consists of 2 parts. The first part consists of 5 multiple choice QoL questions and the

second is a 100 point VAS scale with 0 being “Worst imaginable health state” and 100 being “Best imaginable health state”.

A copy of the EQ-5D can be found in Appendix 18.

11.8 CLINICAL PHOTOGRAPHS

The optional clinical photography assessment will take place at selected equipped study centers. Subjects will be asked to provide separate consent to be involved in this section of the study. Declining to participate in this section of the study will not affect subject involvement in the main part of the study.

The Investigator or designee will be asked to take clinical photographs of the entire subject’s body on 2 occasions throughout the study. Additional details will be provided in the photographic manual.

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, respiratory examination and assessments, and clinical laboratory results [routine hematology and biochemistry]) are to be performed at protocol-specified visits, beginning at the screening visit (upon signing the ICF), as specified in the Schedule of Assessments (Table 5).

12.1 VITAL SIGNS

Vital signs will be evaluated at all visits, as indicated in the Schedule of Assessments (Table 5). Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least 5 minutes), and body temperature. All abnormal values at the screening visit identified as clinically significant by the investigator will be recorded in the medical history form. Any clinically significant changes from the screening visit (and onwards) will be recorded as an AE.

12.2 HEIGHT AND WEIGHT

Height and weight will be measured according to the Schedule of Assessments (Table 5).

12.3 PHYSICAL EXAMINATION

Complete physical examination should be performed at the screening, baseline, and specified subsequent scheduled visits, according to the Schedule of Assessments (Table 5). A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (for additional respiratory assessments, see Section 12.6), gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

The investigator should assess all abnormal findings for clinical significance. All clinically significant abnormal findings at the screening visit will be recorded in the medical history form. Any clinically significant changes from the screening visit will be recorded as an AE.

12.4 12-LEAD ELECTROCARDIOGRAM

A 12-lead, resting ECG will be performed and read centrally according to visits indicated in the Schedule of Assessments (Table 5) using the ECG machine provided. ECGs for each subject should be obtained using the electrocardiograph machine provided for the study. ECGs will be performed in the supine position and before any scheduled vital sign measurements and blood draws. Subjects should be monitored for potentially clinically significant ECG results (refer to the current version of the central laboratory manual). Tests with abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. ECG abnormalities present at screening should be recorded in the medical history form. Any abnormalities considered by the investigator to be clinically significant after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

12.5 CLINICAL LABORATORY EVALUATION

The hematology laboratory analyses, clinical chemistry laboratory analyses, and urinalyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

The investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the investigator or designee will evaluate whether he/she considers it to be clinically significant, defined as meeting at least 1 of the following conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management, eg, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

If the investigator observes a clinically significant laboratory result, the test will be repeated as soon as possible and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that may impact the safety of the subject or the interpretation of the trial results. This should occur only after discussion with medical monitor.

All clinically significant out-of-range laboratory values at the screening visit will be recorded in the medical history form (report a diagnosis rather than the laboratory value whenever possible). All clinically significant out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the screening visit (ie, changed significantly from the screening visit). Whenever possible, the investigator should provide a diagnosis of an AE when reporting the abnormal laboratory value. See Section 12.7 for details.

Subjects should be reminded to be well hydrated before all visits for phlebotomy purposes. Subjects should fast for at least 8 hours before the visits when blood chemistry testing is planned, except for the screening visit. The screening visit laboratory values must be available before the baseline visit. Laboratory testing conducted in a nonfasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual. Additional samples may be required if medically indicated (eg, at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

Laboratory assessment samples are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 5).

12.5.1 Hematology

The hematology tests include: hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, and mean cell volume.

12.5.2 Clinical Chemistry

The clinical chemistry tests include: creatinine, AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, creatine phosphokinase (CPK). CPK isoenzyme test will be performed only if CPK is elevated to > 2.5 × ULN. The investigator should also contact the medical monitor in such situations.

For postmenopausal subjects (ie, no menses for 12 consecutive months), postmenopausal status will be confirmed with a high follicle-stimulating hormone level in the postmenopausal range.

12.5.3 Urinalysis

The urinalysis tests include: pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

12.5.4 Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and UPTs at subsequent visits according to the Schedule of Assessments (Table 5). Pregnancy test results must be available prior to the administration of the study drug.

Subjects with a positive serum pregnancy test result at screening must not be enrolled.

Urine pregnancy tests with a sensitivity < 25 IU/L will be provided to the study centers for use in the trial.

UPTs will be performed at the study centers, and all other samples will be sent to central laboratory for analysis.

If the result of a UPT is positive, it must be confirmed with a serum pregnancy test, and no study drug should be administered pending the serum pregnancy test result. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

12.5.5 Virology

Virology including HBsAg, HBcAb, hepatitis C, human immunodeficiency virus 1, and human immunodeficiency virus 2 antibodies will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody. Subjects with positive HCV antibodies will have a confirmatory test for HCV (eg, PCR).

12.5.6 Tuberculosis Testing

Immunosuppressant biologic treatments have been shown to increase the risk of TB infection or to cause conversion from latent to active TB in some circumstances. Subjects will be screened for active or latent TB before entry into this study.

12.5.6.1 Tuberculosis Definitions

Active TB is a disease caused by *Mycobacterium tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or by radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with *M tuberculosis*, as evidenced by a positive Interferon Gamma Release Assay[36] such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

12.5.6.2 Tuberculosis Screening

Ideally, as part of the medical history, the subject should be asked if they have presented with active or latent TB in the past and whether they have received a bacillus Calmette-Guérin (BCG) vaccination. They should also be asked if they have been in contact with any individuals known to have active TB or been placed in any circumstances that may have exposed them to an increased risk of TB infection, such as travel to TB endemic regions, close contact with persons with active TB, or workplace risk (eg, prison, hospitals).

A subject who tests positive for latent TB (with a positive QuantiFERON-TB Gold test) should be referred to the subject's treating physician for appropriate follow-up, unless the subject has a documented history of completion of an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed. If the result is indeterminate, the test may be repeated once. If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

12.6 RESPIRATORY ASSESSMENTS

At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, coughing, allergies, and infections). Subjects with a history of asthma will be questioned about the seasonality of their asthma and known triggers, such as allergens. Newly-diagnosed asthma or worsening of asthma during the study will be reported as an AESI.

12.6.1 Asthma Control Test

Subjects with a medical history of asthma will take the ACT at visits according to the Schedule of Assessments (Table 5) before questioning and physical examination by the investigator. Subjects with a new (de novo) diagnosis of asthma will take the ACT beginning at the visit the diagnosis was first confirmed and thereafter, at all subsequent study visits. Subjects with an ACT score ≤ 19 will be referred to the physician managing their asthma.

The ACT is an assessment to determine if a subject's asthma symptoms are well controlled. The ACT is designed for adults and adolescents 12 years or older, and is composed of 5 questions. For each question, the subject will choose the best answer out of 5 possible answers. The test provides a numerical score ranging from 5 to 25 to assess asthma control; a higher score indicates better asthma control while a score of 19 or less indicates the subject's asthma may not be under control. A copy of the ACT can be found in Appendix 19.

12.6.2 Respiratory Examination

A respiratory examination will be required to be performed for all subjects at all scheduled visits, according to the Schedule of Assessments (Table 5). The ACT will also aid the investigator's questioning of subjects with a medical history of asthma and should be completed before the clinical questioning. All subjects will be asked non-leading questions about any respiratory changes. The investigator or designee will then perform a respiratory examination of all subjects at all visits.

Subjects with a medical history of asthma will be referred to the physician managing their asthma if unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma who experience respiratory changes (exam findings or newly-reported signs and/or symptoms suggestive of asthma) will be referred to a respiratory specialist.

12.6.3 Peak Expiratory Flow

All subjects will undergo PEF testing at screening, baseline, and specified visits according to the Schedule of Assessments (Table 5). For subjects reporting a medical history of asthma, PEF testing will be conducted at all visits.

In the event that PEF is < 80% of the predicted value at screening in patients without any history of asthma or in patients with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours.

Subjects with a new (de novo) diagnosis of asthma will undergo PEF testing at all visits after the diagnosis is first made according to the Schedule of Assessments (Table 5).

Peak expiratory flow testing during the clinical study will be performed under the supervision of qualified study personnel. Peak expiratory flow measurements should consist of 3 good efforts, with the best result documented. It is preferable that the PEF measurement be performed before noon or at the same time during each study visit whenever possible. Obtained PEF values will be compared to predicted values based on the subject's age, sex and height.[37,38]

To avoid interference with PEF measurements, attempts should be made to withhold asthma medication on study visit days until after PEF testing is complete; to the extent it does not pose an undue risk to the subject.

Subjects with a medical history of asthma with a PEF < 80% of the predicted value will be referred to the physician managing their asthma.

12.6.4 Respiratory Referrals

Subjects with a medical history of asthma will be referred to the physician who manages their asthma when:

- PEF < 80% of the predicted value
- ACT score ≤ 19 because an ACT score ≤ 19 conveys asthma that may not be adequately controlled
- Unexpected worsening of asthma is observed or reported at any time during the study

At any study visit, subjects without a medical history of asthma will be referred to an appropriate specialist physician whenever:

- Signs and/or symptoms suggestive of asthma are newly observed or reported.
- Respiratory assessments (ie, examination, PEF) suggest a decline in the subject's respiratory health.

12.7 ADVERSE EVENTS

12.7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments.

Note(s):

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms, or abnormal laboratory values.
- Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 12.7.7.
- Each worsening of a chronic disease from the screening visit should be reported as a new AE.

The investigator or designee will report all AEs that occur from the time the ICF is signed until the end of the study. The sponsor/CRO should be informed if the investigator becomes aware of any safety information that appears to be drug related, even after the subject has completed the clinical study.

At each post enrollment visit, the investigator (or sub-investigator) will question the subject about AEs using an open non persuasive question to elicit reporting of AEs (for example, “Have you noticed any change in your health since the last visit?”). Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug(s) or not, will be recorded immediately in the source document and described on the Adverse Event Form ("AE Form") along with the date of onset, severity, relationship to the study drug(s), and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

Adverse events assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug (ie, nemolizumab or placebo) and/or study procedure (eg, injection, blood sample collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the

pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression “reasonable causal relationship” is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during this clinical study:

Reasonable possibility:

According to the reporting investigator, there is a reasonable possibility (ie, suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered:

- Between the study drug (nemolizumab) and the AE, and/or
- Between the clinical study protocol procedure (eg, injection, blood sample collection) and the AE

No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or the clinical study protocol procedure and the AE.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication (any additions or discontinuations)
- Other, specify

Follow-up of Adverse Events

All investigators should follow-up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed up for 12 weeks (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

12.7.2 Adverse Events of Special Interest

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. See Section 12.7.5 for reporting procedure(s). An AESI can be either serious or nonserious.

Based on the potential risks of nemolizumab (CD14152) and the risks associated with biologics (and their biosimilar equivalents) in general (ie, class effects), the following AEs will be considered AESIs:

- Injection-related reactions (IRRs)
    - Anaphylactic reactions
    - Acute allergic reactions requiring treatment
    - Severe injection site reaction (ie, lasting > 24 hours)
- Newly diagnosed asthma or worsening of asthma
    - More specifically, subjects *with* a medical history of asthma will be referred to the physician who manages their asthma when:
        - ACT score ≤ 19: An ACT score ≤ 19 conveys asthma that may not be adequately controlled. An AESI is reported based on the investigator's clinical judgment, including consideration of the managing physician's report.
        - PEF < 80% of the predicted value: An AESI should be reported.
        - Unexpected worsening of asthma is observed or reported. An AESI is reported based on the investigator's clinical judgment.
    - Subjects *without* a medical history of asthma will be referred to an appropriate respiratory physician/specialist when:
        - Signs and/or symptoms suggestive of asthma have been observed or reported. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
        - Respiratory assessments (ie, examination, PEF) suggest a decline in the subject's respiratory health. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
- Infections
    - Any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks
    - Any confirmed or suspected COVID-19 infection
- Peripheral edema: limbs, bilateral
- Facial edema

- Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

12.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death
- is life-threatening
- results in inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE.

Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day care facility, social admission (eg, if the subject has no place to sleep), or administrative admission (eg, for a yearly examination).

SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.7.4 Procedure for Reporting Serious Adverse Events

For any SAE occurring during the clinical study, regardless of whether or not related to the study drug and/or procedure, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.

2. Ensure that the event is evaluated as an SAE. Immediately notify (**within 24 hours of receipt of the event**) the Syneos Health Safety and Pharmacovigilance group of an SAE report, by email or fax:

   Fax Number: 001-877-464-7787
   Safety email: SafetyReporting@SyneosHealth.com

   Note: Immediate SAE reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in the eCRF, at that time.

3. Send any relevant information or anonymized medical records (eg, laboratory test results) to the Syneos Health Safety and Pharmacovigilance group (see contact details above), within 24 hours of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, complete an updated SAE report **within 24 hours** of receipt of the updated information.

5. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, complete an updated SAE report, if appropriate.

7. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The Sponsor has a

legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor or its delegate (ie, the CRO) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, institutional review board (IRB)/independent ethics committee (IEC) and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements, and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the Sponsor or its delegate (ie, the CRO) will file it accordingly (ie, within the Trial Master File), and will notify the IRB/IEC, if appropriate according to local requirements.

8. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

12.7.5 Procedure for Reporting Adverse Events of Special Interest

For any AESI occurring during the clinical study, regardless of whether or not related to the treatment, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.

2. Ensure that the event is evaluated as an AESI. Notify (**within 3 days of receipt of the event**) the Syneos Health Safety and Pharmacovigilance group of an AESI report, by email or fax. Refer to Section 12.7.4.

   Note: AESI reporting is required by the investigator if it occurs during the clinical study following the first dose of study drug or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in the eCRF, at that time.

3. Send any relevant information or medical records (eg, laboratory test results) to the Syneos Health Safety and Pharmacovigilance group within 3 days of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AESI report within 3 days of receipt of the updated information.

5. Obtain and maintain in the files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, update the AESI report, if appropriate.

12.7.6 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as SUSARs and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) ≤ 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes, according to local requirements.

12.7.7 Procedures for Reporting Pregnancy

Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening. Following administration of study drug, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study.

Any pregnancy occurring during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome in order to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Withdraw the subject from the clinical study. The subject must not receive any injection of the study drug.
2. Complete as fully as possible the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy. Send by email or fax along with the exit form within 24 hours of receipt of the information, to the Syneos Health Safety and Pharmacovigilance group. Refer to Section 12.7.4.

Note: Immediate pregnancy reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, send the form by email or fax to the Syneos Health Safety and Pharmacovigilance group within 24 hours of receipt of the

information. If the subject can no longer be reached (ie, lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete as fully as possible the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. Print and send the form by email or fax to the Syneos Health Safety and Pharmacovigilance group within 24 hours of receipt of the information.
6. If the pregnancy leads to an abortion (ie, voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 12.7.4).

12.7.8 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. The investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

Although overdose of nemolizumab occurred in the phase 2 AD study (ie, accidental injection of more than 2.0 mg/kg SC), no related AEs were reported.

12.8 INDEPENDENT DATA MONITORING COMMITTEE

An IDMC will review and monitor subject safety throughout the study. The IDMC will provide recommendations on the safety of subjects. The IDMC charter will provide details on the IDMC, including the plan of analysis for IDMC outputs; the composition of the IDMC; and the procedures, roles, responsibilities, and communications.

12.9 INDEPENDENT ADJUDICATION COMMITTEE

An IAC will review all asthma-related AEs throughout the study. The IAC charter will provide details on the IAC, including the plan of analysis for IAC outputs; the composition of the IAC; and its procedures, roles, responsibilities, and communications.

13 PHARMACOKINETICS

13.1 PHARMACOKINETIC SAMPLING

13.1.1 Blood Samples

Blood samples for PK analysis of nemolizumab levels will be collected at the time points indicated in the Schedule of Assessments (Table 5) and the clinical laboratory manual to determine the PK profile of nemolizumab. At each sampling time point for PK assessments, the collected blood will be placed to clot at room temperature (no more than 60 minutes after collection) and then centrifuged. The serum will be collected into storage tubes.

As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples). The date and the time of each sample collection will be recorded in the eCRF, together with the time of study drug injection at the same visit (or missed injection if applicable).

13.1.2 CD14152 Quantification in Biological Sampling

Concentration of nemolizumab (CD14152) in the serum will be determined by the designated CRO using a validated enzyme-linked immunosorbent assay method. Details related to the processing of serum samples and the assessments of nemolizumab will be described in the bioanalytical plan, which will be finalized before the beginning of sample analysis. Results will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

13.1.3 PK parameters, PopPK and PK/PD analyses

Population PK parameters of nemolizumab (CD14152) will be derived, by a designated CRO, using a non-linear mixed effect modeling approach with NONMEM software. A pre-specified PopPK model based on existing information from previous studies in adults (first-order absorption and a 1-compartment distribution model) will be updated with the nemolizumab serum concentrations obtained in this study.

Observed C_{trough} will be listed for each subject and summarized with descriptive statistics (see Section 15.6).

In addition, PK/PD analyses will be conducted using pre-specified models based on existing information from previous studies in adults. For efficacy, PD endpoints are defined as the 2 primary clinical efficacy endpoints of the study: PP NRS responder and IGA success. If needed PK/PD analysis might be conducted for safety.

PopPK and PK/PD analyses will be described in an *ad hoc* Modeling & Simulation Plan. PopPK and PK/PD analyses results will be described in an *ad hoc* Modeling & Simulation Report.

14 OTHER ASSESSMENTS

14.1 PHARMACOGENOMICS

Pharmacogenomic testing (DNA analysis) is optional for this study, and will apply to subjects who provide written consent for this procedure. Subjects are not required to participate in the DNA analysis sub-study in order to enroll in the main study.

DNA analysis will be performed using a blood sample collected at baseline. If inadvertently not collected at baseline, the sample may be collected at a post-baseline visit.

Samples will be stored by the Sponsor or designated CRO for up to 15 years after the end of the study. Candidate sequences in DNA analysis may include but are not limited to genes that encode IL-31 and its receptor (IL-31RA). DNA analysis will be conducted for the purpose of understanding inter-individual variability in nemolizumab (CD14152) efficacy, safety, and PK.

These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence variation or single nucleotide polymorphism identification within candidate genes and surrounding genomic regions. Genome-wide studies may also be performed.

It is the intent of the Sponsor to assure that PGx information obtained remains confidential. The Sponsor maintains rigorous confidentiality standards for clinical studies by “coding” (ie, assigning a unique subject ID number at the investigational study center) for all subjects enrolled in the study. All samples taken for DNA analysis will undergo a second level of “coding” (each sample will receive a double-coded ID), according to the International Council for Harmonisation (ICH)-15 standards. Records will exist to trace double-coded samples to individual subjects for destruction if a subject provides a written request to withdraw their sample for DNA analysis. The data from samples that have already been analyzed will not be destroyed.

Blood samples for DNA analysis will be destroyed after 15 years have elapsed from the completion of this study.

14.2 IMMUNOGENICITY

Blood samples will be collected at the time points indicated in the Schedule of Assessments (Table 5) and the clinical laboratory manual to assess anti-nemolizumab ADA.

The ADA will be determined by the designated CRO using a validated electrochemiluminescence immunoassay (ECLIA). The serum concentration will be assessed using a multi-tiered approach.

Details related to the processing of serum samples and the assessments of ADA will be described in the bioanalytical plan, which will be finalized before the beginning of sample analysis. Results will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

If serum circulating ADA is detected, presence will be confirmed and characterized (eg, for titer and neutralizing potential). Incidence of positive ADA results will be summarized (absolute occurrence and percent of subjects).

14.3 PHARMACODYNAMIC BIOMARKERS

Blood and stratum corneum (D-Squames) samples will be collected from approximately 100 subjects at selected sites to investigate the effect of nemolizumab (CD14152) on selected RNA and protein biomarkers, including but not limited to IL-31. Optional skin biopsies for RNA and immunohistochemistry analyses will be collected from approximately 30 subjects at selected sites who sign the additional consent form. Samples will be collected according to Table 5.

The details of the procedures for PD samples and storage conditions are further described in the clinical laboratory manual. Samples will be shipped to the designated CRO for biomarker assessment, unless otherwise specified. Samples will be stored by the sponsor or designated CRO for up to 15 years after the end of the study.

14.3.1 Blood Samples for PD

Blood samples will be collected for assessment of IgE by the central laboratory. Additional blood samples will be collected and shipped to the designated CRO for RNA and protein biomarkers assessment. Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual.

14.3.2 Stratum Corneum (D-Squames) Samples for PD

Stratum corneum samples will be collected using D-Squames (ie, tape strips) to evaluate biomarker expression levels.[39,40,41] Body location for D-Squames sampling should be identified at baseline. D-Squames should be performed as much as possible in a clinically representative body location for all applicable subjects throughout the study and recorded on the central laboratory requisition form.

At baseline prior to administration of study drug, 1 lesional and 1 non-lesional area will be identified, and 20 consecutive D-Squames will be collected from each area, making 40 D-Squames in total (20 from lesional skin and 20 from non-lesional skin). At Week 16, 20 consecutive D-Squames will be collected from the exact anatomical location of the lesional area identified at baseline, regardless if the lesion has regressed (20 D-Squames in total). The samples will be shipped to the designated CRO for analysis of selected protein and RNA biomarkers.

14.3.3 Skin biopsies for PD (optional)

Three 4-mm punch biopsies will be performed (only for subjects who accept skin biopsies by signing the additional consent form) for RNA biomarkers and immunohistochemistry. Biopsies should be collected according to the investigator's usual procedure, including follow-up.

Body location for biopsy sampling should be identified at baseline. Biopsies should be performed as much as possible in a clinically representative body location for all applicable subjects throughout the study and recorded on the central laboratory requisition form.

The samples will be collected as much as possible on the same anatomical area as D-Squames, in an adjacent lesion with as much as possible a similar clinical presentation.

Skin biopsies will be performed as follows:

- Baseline visit:
  - One 4 mm punch biopsy on lesional skin (nodule)
  - One 4 mm punch biopsy on non lesional skin: approx. 5 cm apart from lesional skin
- Week 16 visit:
  - One 4 mm punch biopsy on lesional skin after treatment (on a nodule selected at baseline).

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be created and finalized before database lock (DBL). This document will provide details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will contain further detailed and technical descriptions of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in this protocol. Any changes made to the analysis after finalization of the SAP (ie, post-DBL) will be discussed and documented in the clinical study report.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

Unless otherwise stated, the baseline value for any variable will be the last non-missing value taken prior to the receipt of study treatment at the Baseline visit (Day 1).

Unless otherwise stated, all statistical tests will be 2-sided and conducted at the 5% level. All presented CIs will be 2-sided 95% CIs.

A Blind Data Review Meeting (BDRM) will be convened to finalize assignments to the analysis populations, including the Per-Protocol (PP) immediately prior to DBL, ie, once all subjects have completed the study and data cleaning activities are essentially complete. The agenda for this meeting, along with any decisions made to determine analysis population inclusion/exclusion, decisions on data handling and other topics will be documented in the BDRM Plan and subsequently in the BDRM Report.

15.1 DATASETS OR STUDY POPULATIONS ANALYZED

Screened Population

The Screened population comprises all subjects who signed the ICF and have screening data entered into the database. This population includes screen failures and randomized subjects. Screen failed subjects are defined as those subjects who fail to meet inclusion criteria or meet exclusion criteria and discontinue the study prior to randomization. Subjects that are re-screened will only be counted once, under the subject ID assigned for the repeat screening.

Intent-to-Treat Population (ITT)

The ITT population will consist of all randomized subjects. The ITT population will be the primary population for efficacy analyses. All analyses under the ITT population will be analyzed under the treatment group as randomized.

Per-Protocol Population (PP)

The PP population will consist of all subjects in the ITT population and have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. Only primary and key secondary endpoints will be analyzed using the PP population, under the treatment group as randomized. For further information on protocol deviations, please refer to Section 15.9.

Safety Population (SAF)

The SAF will consist of all randomized subjects who received at least 1 administration of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analyses of safety.

Pharmacokinetic (PK) Analysis Population (PKAP)

The PKAP will consist of all subjects included in the SAF, with at least one measurable post-baseline PK assessment. Similar to SAF, the treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the descriptive analyses of PK parameters.

15.2 SUBJECT DISPOSITION

The number of subjects screened and randomized in each analysis population will be presented. The number of subjects that discontinue the study and the reasons for discontinuation will be summarized. In addition, subjects' status with regard to study treatment and follow-up will also be summarized.

15.3 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics (eg, age, sex, race, height, body weight, body mass index, and applicable disease baseline characteristics) will be summarized for the ITT, PP, and SAF populations. Medical history, plus prior and concomitant therapies (including prohibited therapies) will be summarized for the SAF population.

15.4 EFFICACY ANALYSIS

Unless otherwise stated, all efficacy analyses will be performed on the ITT population.

15.4.1 Primary Efficacy Endpoints

The primary endpoints include the following endpoints:

1. The proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 16.
2. The proportion of subjects reporting success on the IGA at Week 16, defined as an IGA response of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point reduction from baseline;

For both primary endpoints, any subjects with missing data at Week 16 will be regarded as a non-responder for the respective endpoint. If a subject is in receipt of rescue medication at any point on or prior to Week 16, data after receipt of rescue medication will be set to missing, and subsequently regarded as a non-responder for respective primary endpoint based on the same imputation method as for purely missing data.

15.4.2 Analysis of Primary Efficacy Endpoints

The statistical hypotheses associated with the primary analysis of improvement in PP NRS ≥ 4 from baseline at Week 16 using treatment difference is, similarly:

$$H_0: P_{PP\ NRS\ nemo} - P_{PP\ NRS\ Pla} = 0;$$
$$H_1: P_{PP\ NRS\ nemo} - P_{PP\ NRS\ Pla} \neq 0,$$

where $P_{PP\ NRS\ nemo}$ and $P_{PP\ NRS\ Pla}$ are the proportion of subjects categorized as having a PP NRS improvement from baseline to Week 16 of ≥ 4, for nemolizumab and Placebo, respectively.

The statistical hypotheses associated with the primary analysis of IGA success at Week 16 using treatment difference is:

$$H_0: P_{IGA\ nemo} - P_{IGA\ Pla} = 0;$$
$$H_1: P_{IGA\ nemo} - P_{IGA\ Pla} \neq 0,$$

where $P_{IGA\ nemo}$ and $P_{IGA\ Pla}$ are the proportion of subjects categorized as success under IGA at Week 16 for nemolizumab and Placebo, respectively.

Both primary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization strata analysis center and baseline body weight cut-off (< 90 kg and ≥ 90 kg), in order to test the difference between nemolizumab and placebo for the proportion of subjects achieving success in each endpoint. The estimate of the treatment difference and corresponding 2-sided 95% CI and p-values will be presented. The confidence intervals will be based on Wald statistic controlling for stratification variables. Strata-adjusted proportion differences will be obtained using weighted average of stratum-specific proportion using CMH. This primary analysis will be conducted on the ITT population. To control type I error at 5% significance level, a fixed sequential testing approach, as described in Section 15.4.5, will be implemented.

15.4.3 Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses for both primary endpoints will be conducted in order to test for the robustness of the primary analyses. The following sensitivity analyses will be conducted:

- PP population
- To assess the robustness of non-responder analysis, a tipping point analysis will be performed by converting non-responders due to missing data to responders in successive increments (Δ) for both treatment groups. The value of Δ that overturns (ie, non-significant) the primary results will represent the tipping point. A graphic display of all possible combinations of the number of responders

among both treatment groups will be presented.

- Multiple Imputation (MI) method for missing data (or where rescue medication is received), assuming all missing data are Missing at Random (MAR)

The MI imputation will be carried out as follows:

Imputation Phase:

1. A 50 imputed datasets with a monotone missing pattern will be created using SAS MI procedure based on the observed data (Markov-Chain-Monte-Carlo method, MCMC). The seed to be used is 202685 (the Protocol number). Pattern of missing data will be evaluated and it is expected that the pattern of missing data will be monotonic. For non-monotone missing data patterns, MCMC method of MI procedure will be used to impute enough data so that the remaining missing data is monotone.

2. Each of the imputed datasets will be used to generate 50 complete datasets, using following approaches:

    a. A logistic regression method to impute the ordinal IGA missing data, including treatment, randomization strata, and assessments from earlier time points as covariates. IGA responder variable will be derived using these imputed data.

    b. For PP NRS endpoint, a linear regression model including treatment, randomization strata, and assessments from earlier time points as covariates will be used to impute the weekly average score. PP NRS responder variable will be derived using these imputed data.

Analysis Phase:

3. The complete datasets will be modelled for the endpoint using CMH method as per analysis described in Section 15.4.2. Proportion of responders in each treatment arm, difference and standard error will be calculated.

Pooling Phase:

4. The results from the CMH analysis of the multiple imputed datasets will be combined using the Rubin (1987) and Li et al (1991) approach to produce pooled CMH statistics and p-value. Proportion of responders in each treatment arm, difference and standard error will be combined using the MIANALYZE procedure in SAS.

- Pattern-mixture model under assumption Missing Not at Random (MNAR) controlled-based pattern imputation. MI-based imputation will be applied as described above. Under MNAR assumption, a controlled based pattern imputation where only observation in placebo treatment group will be used to impute.
- Last Observation Carried Forward (LOCF) imputation method for missing data (or where rescue medication is received)
- Observed Case (OC) - No data will be imputed. For this analysis, if any rescue medication is received, and data are collected post rescue receipt, data post-rescue will be analyzed as observed (ie, not set to missing) by ignoring the use of rescue medication

Sensitivity analyses may be performed to evaluate the impact COVID-19 deviations. Further details will be provided in SAP.

15.4.4 Key Secondary Efficacy Endpoints

The following key secondary endpoints are to be analyzed, in order:

1. Proportion of subjects with an improvement of ≥ 4 from baseline to Week 4 in PP NRS;
2. Proportion of subjects with PP NRS < 2 at Week 16
3. Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16
4. Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4
5. Proportion of subjects with PP NRS < 2 at Week 4

All key secondary endpoints will be analyzed on the ITT population as primary, and additionally on the PP population as supportive.

Additionally, the same sensitivity analyses as for the primary endpoints will be employed. For these endpoints, similar to the primary, the continuous response will be imputed first, and the response will then be categorized.

15.4.5 Multiplicity/Multiple comparisons

To control the type I error at 5%, a fixed sequential testing approach will be implemented. For testing purposes both primary endpoints will be tested first in a predefined order (as listed in Section 15.4.1) at 5% significance level, and testing of key secondary endpoints will start only if both primary endpoints are successful at 5% level of significance. Key secondary endpoints will be tested in an order listed in Section 15.4.4, stopping when non-significant result ($p > 0.05$) is found.

15.4.6 Secondary Efficacy/QoL Endpoints

The following secondary endpoints are to be analyzed at the following visits:

Endpoint	Analysis Visit
IGA success rate at each visit	Baseline, W4, W8, W12, W16, W20, W24
PAS items 5a (excoriation/crusts), 5b (healed lesion stages) at each visit	Baseline, W4, W8, W12, W16, W20, W24
Change from baseline in PAS item 4 (number of lesions in representative area) at each visit	Baseline, W4, W8, W12, W16, W20, W24
Proportion of subjects with PP NRS at each visit: a) Improvement ≥ 4 from baseline; b) < 2 at visit c) < 3 at visit	Baseline, W4, W8, W12, W16, W20, W24
Proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success	Baseline, W16, W20, W24
Absolute and Percent change from baseline in PP NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24

Endpoint	Analysis Visit
Proportion of subjects with AP NRS at each visit: a) Improvement ≥ 4 in change from baseline; b) < 2 at visit	Baseline, W4, W8, W12, W16, W20, W24
Absolute and Percent change from baseline in AP NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24
Proportion of subjects with change from baseline improvement ≥ 4 in SD NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24
Absolute and Percent change from baseline in SD NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24
Change from baseline in sleep diary endpoints at each visit (sleep onset latency, WASO, total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN)	Baseline, W4, W8, W12, W16, W20, W24
Change from baseline in PN-Associated Pain Frequency and Intensity at each visit	Baseline, W4, W8, W12, W16, W20, W24
Proportion of subjects reporting low disease activity (clear, almost clear, mild) based on Patient Global Assessment of Disease (PGAD) at each visit	Baseline, W16, W24
Proportion of subjects satisfied with study treatment (good, very good, excellent) based on Patient Global Assessment of Treatment (PGAT) at each visit	W16, W24
Proportion of subjects with an improvement of ≥ 4 in DLQI at each visit	Baseline, W4, W16, W24
Change from baseline in DLQI at each visit	Baseline, W4, W16, W24
Change from baseline in HADS for each subscale at each visit	Baseline, W16, W24
Change from baseline in EQ-5D for each subscale at each visit	Baseline, W16, W24

Abbreviations: AP, Average Pruritis; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL 5-Dimension; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; NRS, Numeric Rating Scale; PAS, Prurigo Activity Score; PGAD, Patient Global Assessment of Disease; PGAT, Patient Global Assessment of Treatment; PP, Peak Pruritis; SD, Sleep Disturbance; W, Week.

Binary secondary endpoints will be analyzed in the same manner as the primary endpoint; missing values will be imputed as non-responder.

Continuous secondary endpoints (except EQ-5D, HADS) will be analyzed using multiple-imputation assuming MAR and using mixed effect model for repeated measure (MMRM) approach, including analysis center and baseline body weight cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate where applies. The estimated treatment difference for each endpoint at each visit will be displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints will be analyzed using ANCOVA including analysis center and baseline body weight cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate. All secondary endpoints will be presented descriptively using OC.

Further details will be provided in the SAP.

15.4.7 Handling of small study sites

A small center is defined as a center which randomizes less than 12 subjects. Small centers will be pooled prior to analyses. First, centers will be sorted by country, number of randomized subjects (descending order) and center number (ascending order). Pooling will start with combining the largest of the set of small centers with the smallest center within that country. If there is a further need to combine data (the size of the pooled centers includes less than 12 subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 12 subjects is met. The process will continue until all pooled centers have a minimum of 12 subjects within the country. Any remaining centers will be pooled with the last pooled center within the country. The pooled centers will be referred to as ‘analysis centers’ in the statistical analyses.

15.4.8 Subgroup Analysis

Descriptive summary and analysis for primary and key secondary endpoints will be produced for the following subgroups:

- Region (Europe, North America, Asia-Pacific)
- Age groups (18-65, and > 65)

- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Baseline weight (< 90 kg, ≥ 90 kg)

15.5 SAFETY ANALYSIS

All safety analyses will be conducted on the SAF, by treatment group.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or later. A TEAE will be defined as those AEs occurring on or after the date/time of first administration of study treatment until the last study visit. The incidence of TEAEs (events with onset dates on or after the start of the study drug), drug-related TEAEs, SAEs, TEAEs leading to study drug discontinuation and TEAEs of Special Interest will be included in incidence tables, summarized by System Organ Class (SOC) and Preferred Term (PT). If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs causing discontinuation will be tabulated. The incidence of TEAEs by severity, counting multiple AEs under SOC and PT for a subject at the maximum severity will be presented. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including observed values and change from baseline values, as well as numbers of subjects with values outside limits of the normal range, including shifts from baseline at each time point.

Summary tables will also be provided for 12-Lead ECG, Physical Examination, ACT, PEF, and Respiratory Exam, by treatment group. Listings will also be provided.

15.6 PHARMACOKINETIC ANALYSIS

Descriptive statistics (arithmetic and geometric mean, standard deviation [SD], coefficient of variation [CV%], minimum [min.], maximum [max.], and median) will be used to summarize the observed nemolizumab C_{trough} in serum.

In addition, individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Treatment related positive ADA subjects and positive ADA subject will be identified in the graphs.

Incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, and treatment-related ADA). The ADA results presentation will be detailed in the SAP.

15.7 OTHER ANALYSES

Pharmacogenomic and pharmacodynamics analyses will be reported separately from the main study report.

Anti-drug antibody concentrations will be reviewed. Depending on the data provided, exploratory statistical analyses may be performed. Further details will be provided in the SAP.

15.7.1 Psychometric Validation Analyses

Confirmatory psychometric analyses will be conducted on the phase 3 data for the evaluation of the PP NRS, SD NRS, and subject sleep diary in the PN population. These analyses will be performed by the designated CRO on the basis of a separate psychometric validation SAP.

15.8 DETERMINATION OF SAMPLE SIZE

In order to achieve at least 90% power for both primary endpoints at 5% significance level, 270 (180 nemolizumab, 90 placebo) subjects will be randomized to detect the following differences in both primary endpoints between treatment groups with 2:1 randomization, assuming a 15% dropout rate during treatment period.

NRS responders (≥ 4 point reduction from baseline): Based on phase 2a data, it is expected that the NRS response at Week 16 would be 50% in Nemolizumab 30 mg and 20% in placebo.

IGA response (0/1): It is expected that the IGA response at Week 16 would be 30% in Nemolizumab 30 mg and 10% in placebo.

The table below provides the resulting power with 270 subjects (180 nemolizumab, 90 placebo) for different responses in primary endpoints.

Endpoint	Placebo	Nemolizumab 30 mg	Power at 5% significance level (N= 270 [180 nemolizumab, 90 placebo])
IGA responder	10%	30%	90%
	10%	27%	83%
	10%	25%	77%
PP-NRS Responder	20%	50%	>90%
	20%	45%	>90%
	20%	40%	84%
Assuming 15% attrition rate during treatment period. Based on continuity corrected Chi-square test.			

15.9 PROTOCOL DEVIATIONS

Major deviations are categorized into the following categories:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study drug
- Noncompliance with study drug per the investigator's discretion
- Noncompliance with study procedures if the consequence of noncompliance would compromise either the subject's safety and/or the study integrity, primary endpoint(s), and/or is not in line with Good Clinical Practice (GCP)/ICH guidelines
- Use of prohibited concomitant therapies
- Visit/treatment windows (ie, if a study visit occurs outside the visit window defined in the Schedule of Assessments)

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be discussed in the clinical study report. Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded as a COVID-19 deviation. Further details of protocol deviations will be provided in the Protocol Deviation and Non Compliance Management Plan.

15.10 INTERIM ANALYSIS

No interim analysis will be performed.

16 STUDY MANAGEMENT

16.1 APPROVAL AND CONSENT

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with ICH and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

16.2 DATA MANAGEMENT

The designated CRO will be responsible for activities associated with the data management of this study. This will include, but is not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and

resolution of queries. All data management activities will be detailed in the data management plan.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail.

16.3 SOURCE DOCUMENTS

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Sponsor monitors, auditors and regulatory inspectors should have direct access to source data.

16.4 RECORD RETENTION

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation (for US) or with applicable national and/or local laws and regulations and in a form satisfactory to the Sponsor.

16.5 MONITORING

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits and contacts will be made at appropriate times during the study. The Principal Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. See Section 15.9 for details. Protocol deviations will be reported to the IRB/IEC and in accordance with applicable regulatory authority mandates.

16.8 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

16.9 FINANCING AND INSURANCE

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 PUBLICATION POLICY/DISCLOSURE OF DATA

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

APPENDIX 1: CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) must use at least 1 effective method of contraception during the study and for 12 weeks after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Adequate methods of contraception include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods)
- bilateral tubal ligation or occlusion

- bilateral vasectomy (provided that the male partner has a medical assessment of surgical success) at least 12 weeks (3 months) before the study
- true abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the subject)

All subjects will be strongly advised that they should not become pregnant while on study treatment or for 12 weeks (3 months) after the last dose. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference:

1. Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Published September 15, 2014.

APPENDIX 2: SPECIFIC GUIDANCE FOR STUDY CONDUCT AND SUBJECT SAFETY DURING THE COVID-19 PANDEMIC

This guidance applies during the COVID-19 pandemic, as defined by regional and/or local authorities. The updates summarized below are relevant to the referenced sections of the protocol.

Section 5.3 Risk/Benefit Assessment

During the COVID-19 pandemic, additional risks to participants may exist, including general environmental risks (e.g. being outside the home, possible contact with unsanitized surfaces) and study-related activities (e.g. interaction with study staff). Potential new subjects with known or suspected COVID-19 infection are ineligible for study enrolment until the infection has resolved. Furthermore, potential new subjects in a high-risk population for COVID-19 (e.g. 60 years and older or with comorbidities), should be temporarily deferred until the COVID-19 risk has subsided at the location of the enrolling site, according to investigator judgement. Risk mitigation measures to be implemented for enrolled subjects and for new subjects during the COVID-19 pandemic are detailed in **Additional Measures for Subjects Amidst COVID-19 Pandemic** below. Subjects with a known or suspected COVID-19 infection will immediately discontinue study drug; instructions for resuming treatment are described in Section 8.4.2. Known or suspected COVID-19 infection will also be followed as an AESI.

New Subsection to Section 7.1, Overall Study Design and Plan: Additional Measures for Subjects Amidst COVID-19 Pandemic

All investigational sites should act according to applicable site regulations, to guidelines and restrictions implemented by local authorities, and to best practices for conducting clinical research during the COVID-19 pandemic.

- Guidance for New Subjects:

Best practices currently in place must be followed when evaluating eligibility of subjects to participate in the study during the COVID-19 pandemic.

For potential subjects in a high-risk population for COVID-19 as defined by the American Academy of Dermatology (AAD)[1] (e.g. 60 years and older or with

comorbidities) or local guidelines, deferring participation in the study should be considered. Deferment of enrollment is based on the potential risk posed by general environmental risks (e.g. being outside home, possible contact with unsanitized surfaces) and study-related activities (e.g. interaction with study staff).
For potential subjects in the low-risk population for COVID-19 (e.g. less than 60 years of age and without comorbidities), the risks and benefits of participation in the study should be assessed on a case by case basis.

If at the time of screening, in the opinion of the Investigator, the subject will not be willing and able to reach the investigational site and comply with all of the time commitments and requirements of the clinical study protocol, the subject should not be considered for enrolment. The subject may be rescreened at a later time.

Pre-screening phone calls should be conducted to exclude potential candidates/subjects who display possible symptoms of COVID-19 or are at high risk of having been exposed to COVID-19.

- Guidance for Enrolled Subjects:

If the local situation allows for subjects to reach the clinical investigational site and complete all study procedures, the following measures should be taken:

- Implement and document in the subject records regular communication with the subject between visits to attempt to ensure early detection of potential signs/symptoms of COVID-19 infection, and provide adequate advice, as per local medical practice and public health guidelines for suspected COVID-19 infection. Please refer to the Centers for Disease Control (CDC; https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html)/European CDC (https://www.ecdc.europa.eu/en/covid-19/questions-answers)/local disease prevention agency and applicable local guidelines for assessment of subjects' COVID-19 status.
- Following the same guidelines, implement and document in the subject records an additional communication to the subject just before the scheduled visit.

- Discontinue study drug administration in case of confirmed or suspected COVID-19 infection until the infection is resolved. See Section 8.4.2.
- Report any COVID-19 infection (confirmed or suspected) as an AE:
    - if any seriousness criterion is met, also report as an SAE (see Section 12.7.4).
    - if it occurs during the clinical study following the first dose of study drug administration, also report as an AESI (see Section 12.7.5).
- Implement preventive infection control measures against COVID-19 infection following local guidelines (e.g. good hygiene practice, clean techniques, and use of personal protective equipment such as gloves, goggles, and masks).
- Implement preventive measures in handling all subject-facing study-mandated assessment devices and parts:
    - PEF meter device body is to be cleaned after each use, with recommended wipes, as per user manual
    - PEF meter flow sensor is to be disposed of after each set of measurements is taken
    - Approved bacterial/virus filters may be used; if used, they must be disposed of after each set of measurements is taken
    - Offer protective gloves to subjects for use while filling out assessments on a tablet and provide training on hygienic removal and disposal of gloves

If the local situation allows for subjects to reach the investigational site and complete only some study procedures where visit duration needs to be limited, the above measures also apply. All assessments should be conducted if possible. Subject-reported assessments that would usually be collected on the site tablet (e.g. ACT, PGAD, PGAT, EQ-5D, DLQI, and PN-associated pain intensity and frequency) may be collected remotely (e.g. completed over the phone), as available. (See Appendix 20 for EQ-5D remote version.)

Subjects can be dosed only if, taking into account the local situation and risk of exposure to COVID-19, the site considers that:

- The study drug subcutaneous injection can be performed at the investigational site according to the instructions in the protocol, pharmacy manual and instruction for use, including preparation of study drug by an independent pharmacist or other qualified personnel.
- ACT (for subjects with a medical history of asthma) and PEF (for all subjects) can be performed according to the protocol.
    - Exceptionally, if sites cannot perform PEF safely on site, the subjects should perform it at home prior to the onsite visit, on the same day. See section below for remote PEF testing instructions.
- All other safety assessments are to be performed as per protocol: physical exam, vital signs, ECG, laboratory assessments, pregnancy test, monitoring of AEs and concomitant medications.
- All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

If the local situation does not allow for subjects to reach the investigational site:

- See New Subsection to Section 9.8, Dose Modification: **Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic** (below) for guidance on further dosing of subjects
- Remote collection of data by Investigator or delegate is still to be done for the following assessments at the regularly scheduled visit time, by phone or video call:
    - AE collection
    - ACT (for subjects with history of asthma)
    - Concomitant therapies used
    - Moisturizer use/background topical therapy

- UPT results (for WOCBP)
- PEF results

  Note: For remote PEF measurements the following should be done:
  - To prepare subjects to do remote PEF measurement at home in case it is needed during the course of the study, all subjects should be previously trained onsite.
  - During the remote visits, subjects can receive additional support (if needed) over the phone or video call by site staff when performing PEF
  - If a subject has a PEF <80% of the predicted value:
    - Site staff can try to evaluate whether this is due to poor technique and ask the subject to repeat the set of measurements
    - If the subject's best PEF measurement is still <80% of the predicted value or if there are other concerns regarding the subject's respiratory health, refer to appropriate physician and report an AESI (see Section 12.7.5)

- All laboratory samples should be collected at the site and analyzed at the central lab. Only in exceptional situations when subject safety cannot be assured otherwise and subject cannot reach the site, a local laboratory test (i.e. hematology, blood chemistry, urinalysis) can be performed and reported, based on investigator judgement.
- Subject-reported assessments that would usually be collected on the site tablet (e.g. ACT, PGAD, PGAT, EQ-5D, DLQI, and PN-associated pain frequency and intensity) may be completed over the phone, as available. (See Appendix 20 for EQ-5D remote version.)

All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

New Subsection to Section 9.8, Dose Modification:
Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic

If a subject misses a dose of study drug due to the COVID-19 pandemic, study drug administration may be continued. The following dosing schedules apply.

For subjects with a missed dose(s) during the treatment period, study drug administration can be continued based on one of the following scenarios (see also **Diagram 1**, below):

1) Subject has missed one or more doses between Baseline and Week 16 but can come to the clinical site at Week 16 (see also **Diagram 2a**)**:**

- Subjects who complete the Week 16 visit may be eligible to enroll in the long-term extension (LTE) study RD.06.SPR.202699 after the Week 24 visit is complete.
- Subjects who required rescue therapy before Week 16 may be considered for the LTE study but will be required to continue with study visits until Week 24 visit is due.

2) Subject has no missed doses through Week 12 but cannot reach the clinical site at Week 16 (see also **Diagram 2b**)**:**

- The Week 16 visit can be delayed by up to 4 weeks from the originally planned date. A remote Unscheduled visit should be planned between Week 12 and the delayed Week 16 visit for safety follow-up. Week 20 and Week 24 visits should be delayed by the same amount of time as the Week 16 visit.
    - Subjects who complete the rescheduled Week 16 visit may be eligible to enroll in the LTE study after the Week 24 visit is complete.
- If the subject still cannot come to the delayed Week 16 visit within 4 weeks of the originally planned date, the delayed Week 16 visit should be performed remotely at the rescheduled date as an early termination visit. A remote Unscheduled visit should be planned between Week 12 and the delayed Week 16 visit for safety follow-up. The Week 20 and Week 24 visits will be cancelled. The subject may be considered for rollover into the LTE study after the Week 24 timepoint is reached.

3) Subject has missed one or more doses between Baseline and Week 16 and cannot reach the clinical site at Week 16:

- For subjects who cannot come to the clinical site at week 12 but with an administered dose at Week 8 (with or without Week 4), the Week 12 visit can be delayed up to 3 weeks, and the Week 16 visit can be delayed up to 4 weeks from the rescheduled Week 12 visit (see also **Diagram 2c**). Week 20 and Week 24 visits should be delayed by the same amount of time as the Week 16 visit.
- For subjects with an administered dose at week 12 but with a missed dose at Week 4 and/or Week 8, the Week 16 visit can be delayed by up to 4 weeks from the originally planned date (see also **Diagram 2d**).
    - Subjects who complete the rescheduled Week 16 visit may be eligible to enroll in LTE study after the Week 24 visit is complete.
- For subjects with a missed dose at week 12, the Week 16 visit will be performed remotely at Week 16 (cannot be delayed) as an early termination visit. The Week 20 and Week 24 visits will be cancelled. The subject may be considered for rollover into the LTE study after the Week 24 timepoint is reached (see also **Diagram 2d**).

In all scenarios, study drug can be administered provided that there is a minimum 3-week interval between injections. If a subject cannot come to a planned visit due to COVID-19, the visit should be conducted remotely according to **Additional Measures for Subjects Amidst COVID-19 Pandemic**. If a subject misses 3 consecutive doses of study drug, an early termination visit should be conducted. Subject may still be eligible to participate in the LTE. Enrolment of subjects into the LTE study must be done in accordance with the LTE study protocol. Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after the last study drug injection.

16.5 Monitoring

On-site interim monitoring visits may not be feasible during COVID-19 restrictions; therefore, remote monitoring will be completed until on-site monitoring can be conducted again. Site monitoring activity will comply with the processes documented within the COVID-19 Site Management Risk Assessment Form.

[1] https://assets.ctfassets.net/1ny4yoiyrqia/PicgNuD0IpYd9MSOwab47/2461e6c12cd88953632a13cd68952b71/Guidance_on_medications__10-12-20.pdf

Diagram 1. Flow Chart of Management of Subjects with Missed Visits Before Week 16 due to COVID-19

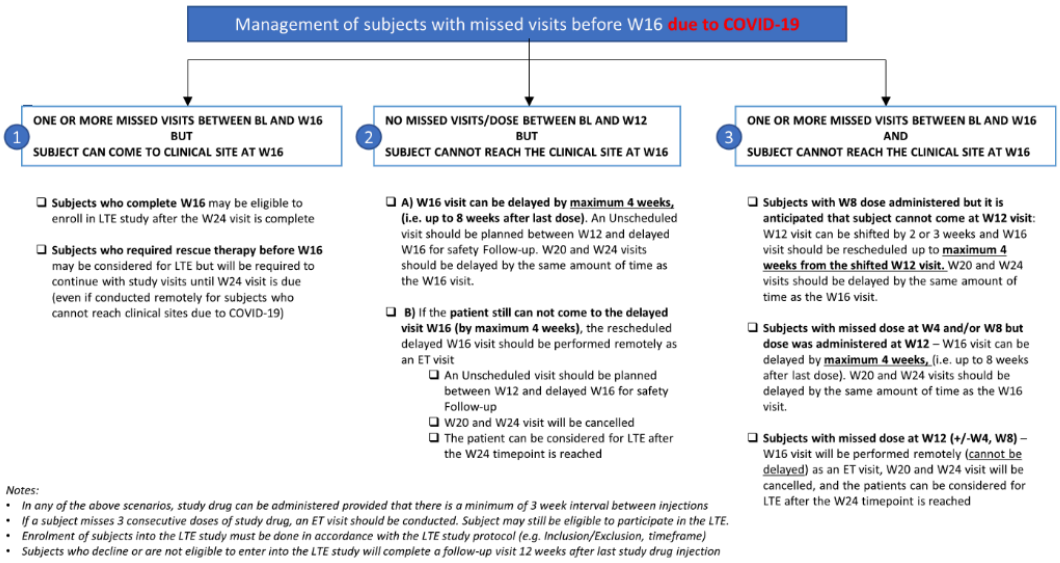
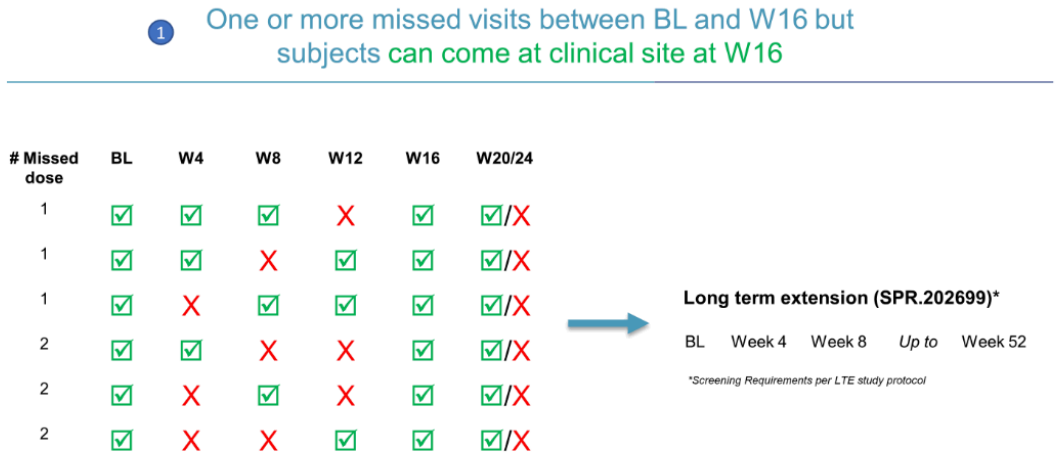
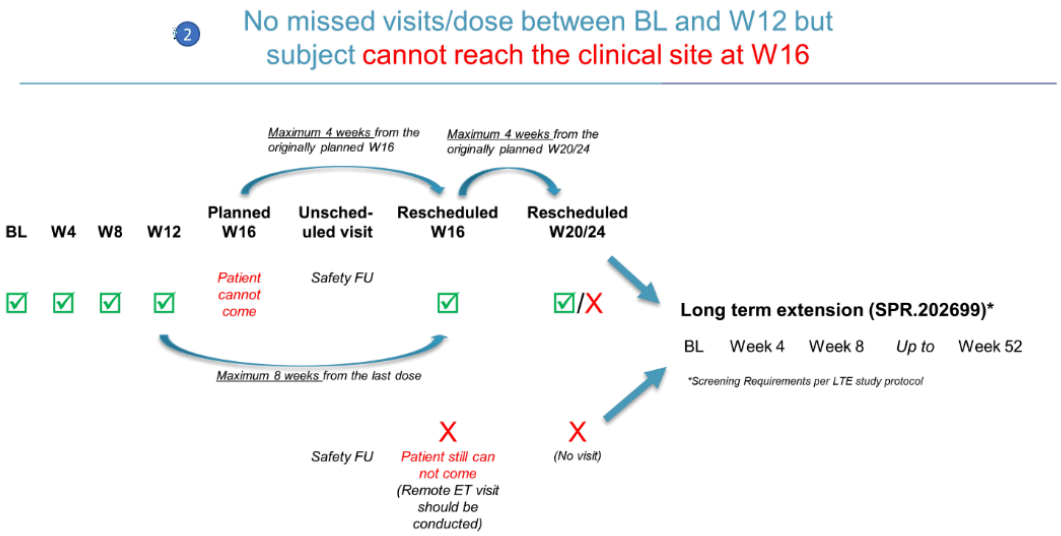


Diagram 2. Management of Subjects Based on Missed Dosing Scenarios

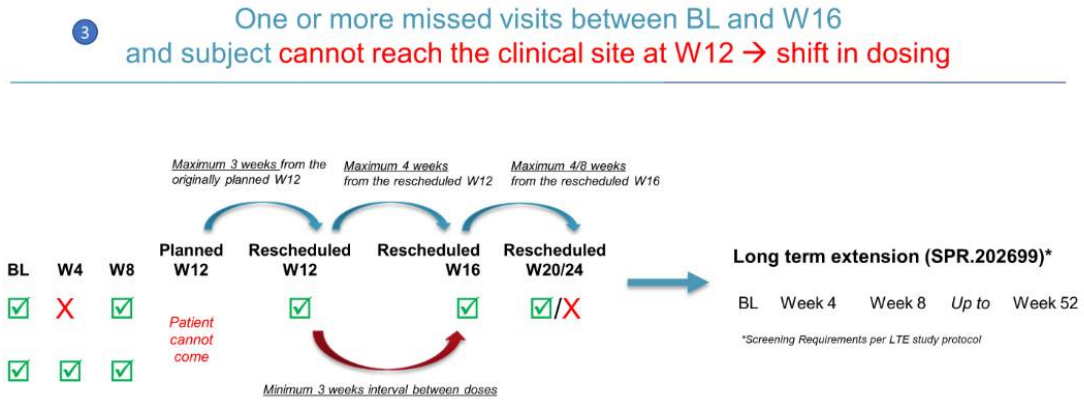
a. Diagram of Management of Subjects due to Scenario 1



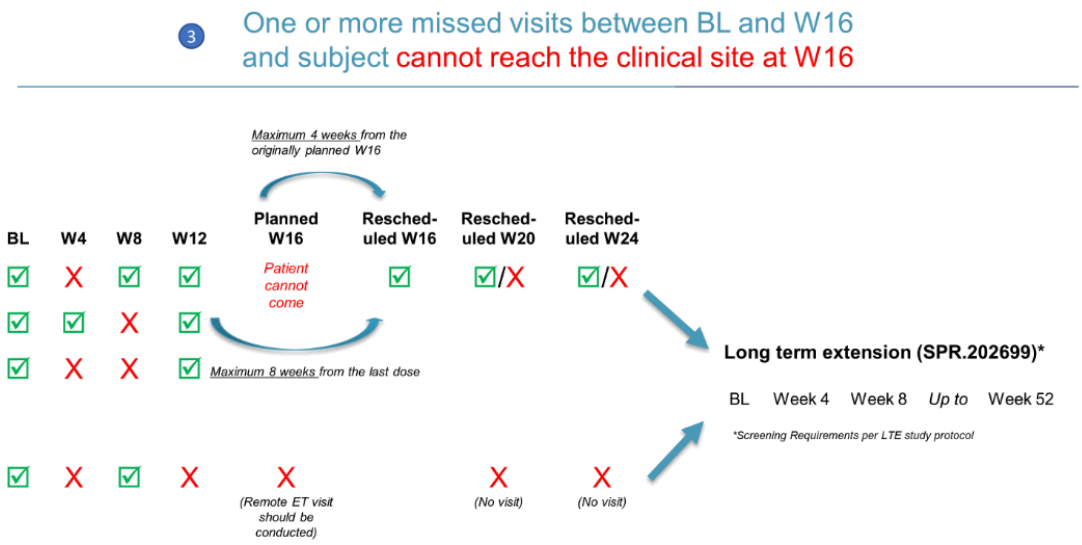
b. Diagram of Management of Subjects due to Scenario 2



c. Diagram of Management of Subjects due to Scenario 3: Cannot reach site at Visit 12



d. Diagram of Management of Subjects due to Scenario 3: Cannot reach site at Visit 16



APPENDIX 3: CYP SUBSTRATES WITH NARROW THERAPEUTIC INDEX

CYP enzymes	Substrates with narrow therapeutic index(1)
CYP1A2	Theophylline, Tizanidine
CYP 2B6	-
CYP2C8	Paclitaxel
CYP2C9	Warfarin, Phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, Astemizole, Cisapride, Cyclosporine, Dihydroergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine, Sirolimus, Tacrolimus, Terfenadine
CYP2D6	Thioridazine, Pimozide

(1) CYP substrates with a narrow therapeutic index refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes). This is not an exhaustive list.

Source: Center for Drug Evaluation and Research (CDER), Food and Drug Administration, U.S. Department of Health and Human Services. Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (Draft Guidance). February 2012.

APPENDIX 4: INVESTIGATOR GLOBAL ASSESSMENT (IGA)

Score	Category	Description
0	**Clear**	No nodules
1	**Almost Clear**	Rare palpable pruriginous nodules
2	**Mild**	Few palpable pruriginous nodules
3	**Moderate**	Many palpable pruriginous nodules
4	**Severe**	Abundant palpable pruriginous nodules

APPENDIX 5: PRURIGO ACTIVITY SCORE (PAS)

PAS: Baseline assessment

PAS, Version 1.0 (Baseline) _22.10.2019_English Copyright @ Center for Chronic Pruritus, University Hospital Münster

Prurigo Activity Score (PAS)© Name:_____ Date:_____

1a. Type of Prurigo: Which pruriginous lesions do you see? (multiple selection possible)

- □ hypo-/hyperpigmented maculae
- □ papules
- □ nodules
- □ plaques
- □ ulcerations
- □ umbilicated lesions

1b. Type of Prurigo: Which type of prurigo is predominant? (single choice)

- □ completely healed (only scars)
- □ Prurigo papular type
- □ Prurigo nodular type
- □ Prurigo plaque type
- □ Prurigo ulcerated type
- □ Prurigo umbilicated type
- □ Prurigo linear type

2. Number: How many pruriginous lesions do you see? (single choice)

- □ 0
- □ 1 - 19
- □ 20 – 100
- □ > 100

Guidance:
Count up to 20 pruriginous lesions;
If more than 20: estimate, do not count
Do not consider scars.

3. Distribution: Please mark the affected area(s) (for definition of trunk see fig. 1) (multiple selection possible)

Area	Affected (please tick as appropriate)	Code for item 4
Forearm left	( )	(1)
Forearm right	( )	(2)
Upper arm left	( )	(3)
Upper arm right	( )	(4)
Lower leg left	( )	(5)
Lower leg right	( )	(6)
Upper leg left	( )	(7)
Upper leg right	( )	(8)
Trunk ventral (see Fig.1)	( )	(9)
Trunk dorsal (see Fig.1)	( )	(10)
Capillitium (Scalp)	( )	(11)
Face	( )	(12)

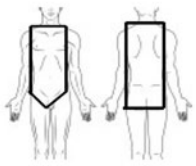


Fig. 1

4. Representative Area: Please choose a representative area (must be the same at each visit*).
(Do not change the representative area during the course of the disease, always count in the same area)

Representative Area (please insert code from item 3): _____
Exact number of pruriginous lesions in representative area (do not count scars): _____

5. Activity: Please mark the stage for the whole body (estimated percent compared to all pruriginous lesions). Item A and B do NOT need to add together to 100% (single choice in A and B)

a) Pruriginous lesions with excoriations/crusts on top of lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
b) Healed pruriginous lesions:	100 %	76-99 %	51 - 75 %	26 - 50 %	0 - 25 %

*in RCTs: select at screening visit and confirm at baseline visit if still valid. If not, determine a new representative area at baseline visit and keep this for all other visits.

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PAS: Follow-up assessment

PAS, Version 1.0 (Follow up) _22.10.2019_English

Prurigo Activity Score (PAS)© Name:_____ Date:_____

1a. Type of Prurigo: Which pruriginous lesions do you see? (multiple selection possible)

- □ hypo-/hyperpigmented maculae
- □ papules
- □ nodules
- □ plaques
- □ ulcerations
- □ umbilicated lesions

1b. Type of Prurigo: Which type of prurigo is predominant? (single choice)

- □ completely healed (only scars)
- □ Prurigo papular type
- □ Prurigo nodular type
- □ Prurigo plaque type
- □ Prurigo ulcerated
- □ Prurigo umbilicated type
- □ Prurigo linear type

2. Number: How many pruriginous lesions do you see? (single choice)

- □ 0
- □ 1 - 19
- □ 20 – 100
- □ > 100

Guidance:
Count up to 20 pruriginous lesions;
If more than 20: estimate, do not count
Do not consider scars.

3. Distribution: Please mark the affected area(s) (for definition of trunk see fig. 1) (multiple selection possible)

Area	Affected (please tick as appropriate)	Code for item 4
Forearm left	( )	(1)
Forearm right	( )	(2)
Upper arm left	( )	(3)
Upper arm right	( )	(4)
Lower leg left	( )	(5)
Lower leg right	( )	(6)
Upper leg left	( )	(7)
Upper leg right	( )	(8)
Trunk ventral (see Fig.1)	( )	(9)
Trunk dorsal (see Fig.1)	( )	(10)
Capillitium (Scalp)	( )	(11)
Face	( )	(12)

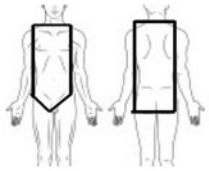


Fig. 1

4. Representative Area: Please use the representative area as defined at baseline. (Do not change the representative area during the course of the disease, always count in the same area)

Representative Area (please insert code from item 3): _____
Exact number of pruriginous lesions in representative area (do not count scars): _____

5. Activity: Please mark the stage for the whole body (estimated percent compared to all pruriginous lesions). Item A and B do NOT need to add together to 100% (single choice in A and B)

a) Pruriginous lesions with excoriations/crusts on top of lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
b) Healed pruriginous lesions:	100 %	76-99 %	51 - 75 %	26 - 50 %	0 - 25 %

These are instructions for filling out the Prurigo Activity Score 1.0.
Two versions of the PAS 1.0 exist:
1 baseline: For screening and the baseline visit
1 Follow up: For all subsequent visits
These differ in instructions for Item 4.

Item 1a) Please mark all existing lesions that you see with a cross. Multiple answers are possible.
Papules= Pruriginous, elevated, solid, palpable lesions≤1 cm diameter*
Nodules= Pruriginous, elevated, solid, palpable lesions>1 cm diameter
Plaques= Pruriginous, palpable and flat lesions>1 cm in diameter, often on the lower leg
Umbilicated= Ulcers surrounded by a raised, erythematous rim - formerly referred to as M. Kylre
Ulcers= Ulcerations, excoriations
Linear= linear pruriginous lesions
Hypo-/Hyperpigmented maculae= Maculae or scarification as a post-inflammatory reaction
*According to the definition of the ILDS (*Nast A et al. Br J Dermatol. 2016;174:1351-8*) and Task Force Pruritus (*Pereira et al. J Eur Acad Dermatol Venereol. 2018;32:1059-1065*)

Item 1b) Please mark the clinically predominant type of prurigo with a cross.
Please choose only one answer.

2) Please estimate how many palpable pruriginous lesions are present. Counting the exact number of lesions is necessary for the first 20 lesions; if over 20 lesions, estimate. Healed lesions, scars or excoriations without prurigo should not be considered. Please choose only one answer.

3) Please indicate all locations of the body with evidence of pruriginous lesions. Healed lesions, scars or excoriations without prurigo should not be considered. The gluteal region belongs to the trunk in this case (see figure). Multiple answers are possible.

4) Please select one area representing the dominant, representative type of prurigo. It is not necessary to select the most severe area. The purpose is to select an area in order to monitor the exact course of the lesions. **The representative area must be the same at each visit! Once determined, you will repeat counting in this area at each visit.**
It is thus advisable to select an area with lesions that are not bunched together. This should be the forearm or upper arm, if possible. Please avoid the lower legs. Please indicate the bodily localization code from Item 3a. Count the nodules (in case of prurigo nodularis) or the typical pruriginous lesions (in case of other types of prurigo) in that area. Please identify all lesions and count each. When nodules are merged, count only one.

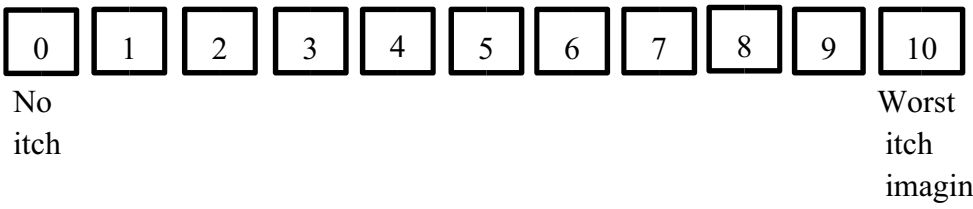
5) A. This item reflects the current itch/scratch activity. Please estimate what percentage of the pruriginous legions show excoriations/crusts.
100% = All pruriginous lesions have excoriations/crusts.

B. This item reflects the stage of the prurigo. Please estimate what percentage of the pruriginous lesions have healed.
100% = all pruriginous leasions have healed.

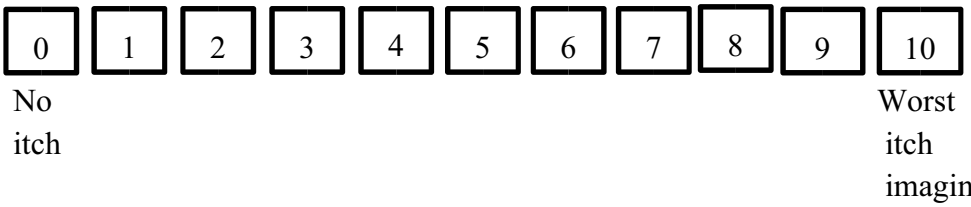
Items 7A and 7 B are to be considered separately and do not have to total 100% together.

APPENDIX 6: PRURITUS (PEAK AND AVERAGE) NUMERIC RATING SCALE (PP NRS and AP NRS)

For average itch intensity: "On a scale of 0 to 10, with 0 being "no itch" and 10 being the "worst itch imaginable", how would you rate your itch overall during the previous 24 hours?"



For maximum itch intensity: "On a scale of 0 to 10, with 0 being "no itch" and 10 being the "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?"



APPENDIX 7: SLEEP DISTURBANCE NUMERIC RATING SCALE (SD NRS)

"On a scale of 0 to 10, with 0 being "no sleep loss related to the symptoms of my skin disease (prurigo nodularis)" and 10 being "I did not sleep at all due to the symptoms of my skin disease (prurigo nodularis)", how would you rate your sleep last night?"

No sleep loss

I did not sleep at all

APPENDIX 8: MORNING SUBJECT SLEEP DIARY

Example

Items to be administered in the morning		
Question	**Example**	**Instructions**
Today's date	4/5/08	Write the date you are filling out the diary.
1. What time did you get into bed?	10:00 pm	Write the time that you got into bed. This may not be the time you began "trying" to fall asleep
2. What time did you try to go to sleep?	11:00 pm	Record the time that you began "trying" to fall asleep.
3. How long did it take you to fall asleep?	1 hour	**Beginning at the time you wrote in question 2**, how long did it take you to fall asleep.
4. How many times did you wake up **due to the symptoms of prurigo nodularis (for example itching, burning)**, not counting the final time you woke up for the day?	2 times	For example, if you fell asleep at 11pm, and woke up at 2am (to go to the bathroom), 4am (to scratch), 5am (to drink water), 6am (to scratch) and finally woke up at 7:30am, you woke up twice due to the symptoms of prurigo nodularis.
5. In total, how long did the **awakenings related to the symptoms of prurigo nodularis (for example itching, burning)** last?	55 min	For example, if you woke up 4 times during the night: 5 minutes (to go to the bathroom), 35 minutes (to scratch), 5 minutes (to drink water) and 20 minutes (to scratch), only two times were related to the symptoms of prurigo nodularis, for a total of 55 minutes awake (35+20=55 minutes).
6. How many times did you wake up, **for other things (for example to drink water, to go to the bathroom)**, not counting the final time you woke up for the day?	2 times	For example, if you fell asleep at 11pm, and woke up at 2am (to go to the bathroom), 4am (to scratch), 5am (to drink water), 6am (to scratch) and finally woke up at 7:30am, you woke up twice due to other things not related to prurigo nodularis.
7. In total, how long did these **awakenings related to other things (for example to drink water, to go**	10 min	For example, if you woke 4 times during the night: 5 minutes (to go to the bathroom), 35 minutes (to scratch), 5 minutes (to drink water) and 20 minutes (to scratch), only two

Items to be administered in the morning		
Question	**Example**	**Instructions**
to the bathroom) last?		times were related to other things, for a total of 10 minutes (5 + 5 =10 minutes).
8. What time did you wake up for the day?	6:35 am	Record the last time you woke up in the morning.
9. What time did you get out of bed for the day?	7:20 am	What time did you get out of bed with no further attempt at sleeping? This may be different from the time you wake in the morning (eg, you may have woken up at 6:35 am but did not get out of bed to start your day until 7:20 am)
10. How would you rate the quality of your sleep?	☐ Very poor ☒ Poor ☐ Fair ☐ Good ☐ Very good	"Sleep Quality" is your sense of whether your sleep was good or poor.
11. How rested or refreshed did you feel when you woke-up for the day?	☐Not at all rested ☒ Slightly rested ☐ Somewhat rested ☐ Well-rested ☐ Very well-rested	This refers to how you felt after you were done sleeping for the night, **during the first few minutes** that you were awake.

General Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? The morning sleep diary should be completed in the morning on designated days, and if possible, within one hour of getting out of bed, together with the daily Sleep Disturbance Numeric Rating Scale (SD NRS).

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Scoring Algorithm of Subject Sleep Diary

Sleep Parameter	SSD Items Used to Derive the Sleep Parameter
Sleep onset latency (SOL)	Q3
Wakefulness after sleep onset (WASO)	Q5 + Q7
Terminal WASO (TWASO)	Q9 – Q8
Total awake time (TWT)	SOL+ WASO + TWASO
Time in bed (TIB)	Q9 – Q1
Total sleep time (TST)	TIB – TWT
Sleep efficiency (SE)	TST/TIB
WASO related to PN (WASO-PN)	Q5
Number of WASO related to PN (NWASO-PN)	Q4
Sleep quality/refresh (SQR)	Q10 + Q11

Abbreviations: Q = question; SSD=Subject Sleep Diary

Reference:

Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*. 2012;35(2):287-302.

APPENDIX 9: PAIN FREQUENCY AND INTENSITY

How often would you say that you experience pain from your skin disease (prurigo nodularis)?

0. Never

1. Less than once a week

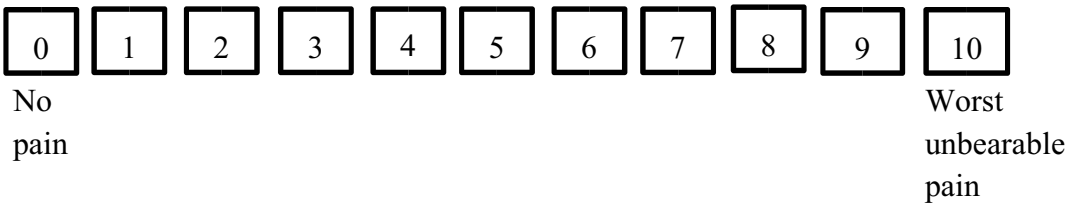
2. 1-2 days a week

3. 3-4 days a week

4. 5-6 days a week

5. Every day

On a scale of 0 to 10, with 0 being “no pain” and 10 being “the worst unbearable pain”, how would you rate the pain associated with your skin disease (prurigo nodularis) at the worst moment during the past week?



APPENDIX 10: PATIENT GLOBAL ASSESSMENT OF DISEASE (PGAD)

Overall, how would you describe your skin disease (prurigo nodularis) right now?

☐ Clear

☐ Almost clear

☐ Mild

☐ Moderate

☐ Severe

APPENDIX 11: PATIENT GLOBAL ASSESSMENT OF TREATMENT (PGAT)

How would you rate the way your skin disease (prurigo nodularis) responded to the study medication?

☐ Poor

☐ Fair

☐ Good

☐ Very Good

☐ Excellent

APPENDIX 12: PATIENT GLOBAL IMPRESSION OF SEVERITY – PRURITUS (PGIS-P)

Please choose the response below that best describes the severity of your overall itch over the past week:

☐ None

☐ Mild

☐ Moderate

☐ Severe

☐ Very severe

APPENDIX 13: PATIENT GLOBAL IMPRESSION OF CHANGE – PRURITUS (PGIC-P)

Please choose the response below that best describes the overall change in your itch since you started taking the study medication:

☐ Much better

☐ A little better

☐ No change

☐ A little worse

☐ Much worse

APPENDIX 14: PATIENT GLOBAL IMPRESSION OF SEVERITY – SLEEP DISTURBANCE (PGIS-SD)

Please choose the response below that best describes the severity of your sleep disturbance due to the symptoms of your skin disease (prurigo nodularis) over the past week:

☐ None

☐ Mild

☐ Moderate

☐ Severe

☐ Very severe

APPENDIX 15: PATIENT GLOBAL IMPRESSION OF CHANGE – SLEEP DISTURBANCE (PGIC-SD)

Please choose the response below that best describes the overall change in your sleep disturbance due to the symptoms of your skin disease (prurigo nodularis) since you started taking the study medication:

☐ Much better

☐ A little better

☐ No change

☐ A little worse

☐ Much worse

APPENDIX 16: DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Instructions for Dermatology Life Quality Index scoring:

3 = “Very much”

2 = “A lot”

1 = “A little”

0 = “Not at all”

0 = “Not relevant”

Question 7, “prevented work or studying/yes” = 3; “no or not relevant” = 0

The Dermatology Life Quality Index is calculated by summing the score of each question resulting in a maximum score of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Reference:

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-6.

APPENDIX 17: HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did Rather		0
		less than I used to Definitely		1
		less than I used to Hardly at all		2
		I get sudden feelings of panic		3
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

Questions relating to anxiety are indicated by an “A” while those relating to depression are shown by a “D”. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over (more) indicating clinical “caseness”.

APPENDIX 18: EUROQoL-5 DIMENSION (EQ-5D)

Appendix: The EQ-5D instrument

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*eg work, study, housework, family or leisure activities*)
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

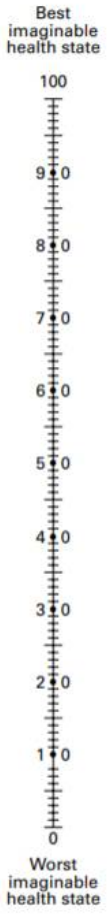
Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Note: The actual EQ-5D instrument spreads over two pages with the"thermometer" and explanation on page 2. To save journal space in this paper it has been compressed into one page.

Your own health state today



Source: European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23-31.

APPENDIX 19: ASTHMA CONTROL TEST (ACT)

Asthma Control Test™: This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an X in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX 20: EUROQoL-5 DIMENSION (EQ-5D) REMOTE VERSION

For use for remote collection of EQ-5D assessment during the COVID-19 pandemic only, according to Appendix 2.

EQ-5D-3L

Health Questionnaire

English version for the UK

VERSION FOR INTERVIEWER ADMINISTRATION

Note to interviewer: although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D-3L descriptive system on page 2 of the questionnaire, the precise wording must be followed.

If the respondent has difficulty choosing a response, or asks for clarification, the interviewer should repeat the question word for word and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION

(Note to interviewer: please read the following to the respondent.)

We are trying to find out what you think about your health. I will explain what to do as I go along, but please interrupt me if you do not understand something or if things are not clear to you. There are no right or wrong answers. We are interested only in your personal view.

First, I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: first read all three options for each question. Then ask the respondent to choose which one applies to him/herself. Repeat the question and options if necessary. Mark the appropriate box under each heading. You may need to remind the respondent regularly that the timeframe is TODAY.)

EQ-5D DESCRIPTIVE SYSTEM

First, I would like to ask you about MOBILITY. Would you say that:

1. You have no problems in walking about? ❑
2. You have some problems in walking about? ❑
3. You are confined to bed? ❑

Next, I would like to ask you about SELF-CARE. Would you say that:

1. You have no problems with self-care? ❑
2. You have some problems washing or dressing yourself? ❑
3. You are unable to wash or dress yourself? ❑

Next, I would like to ask you about USUAL ACTIVITIES, for example work, study, housework, family or leisure activities. Would you say that:

1. You have no problems doing your usual activities? ❑
2. You have some problems doing your usual activities? ❑
3. You are unable to do your usual activities? ❑

Next, I would like to ask you about PAIN OR DISCOMFORT. Would you say that:

1. You have no pain or discomfort? ❑
2. You have moderate pain or discomfort? ❑
3. You have extreme pain or discomfort? ❑

Finally, I would like to ask you about ANXIETY OR DEPRESSION. Would you say that:

1. You are not anxious or depressed? ❑
2. You are moderately anxious or depressed? ❑
3. You are extremely anxious or depressed? ❑

EQ-5D VAS

- **Now, I would like to ask you to say how good or bad your health is TODAY.**
- **I would like you to picture in your mind a vertical line that is numbered from 0 to 100.**
  (Note to interviewer: if interviewing face-to-face, please show the respondent the VAS line.)
- **100 at the top of the line means the best health you can imagine.**

  0 at the bottom of the line means the worst health you can imagine.
- **I would now like you to tell me the point on this line where you would put your health TODAY.**
  (Note to interviewer: mark the line at the point indicating the respondent's health today. Now, please write the number you marked on the line in the box below.)

THE RESPONDENT'S HEALTH TODAY = ☐

Thank you for taking the time to answer these questions.