Name	Reason for Signature	Date
PPD	PPD	31-Jan-2023 00:07:43 UTC
PPD	PPD	31-Jan-2023 00:10:42 UTC
PPD	PPD	31-Jan-2023 09:26:30 UTC

1 CLINICAL STUDY PROTOCOL

Galderma S.A.

Galderma Research & Development, LLC

Protocol Title: A Double-Blind, Placebo-Controlled, Randomized Study to Assess the Durability of Effect and Safety of Nemolizumab for 24 Weeks in Subjects with Prurigo Nodularis

Protocol Number: RD.06.SPR.203890

IND Number:	CCI
EudraCT Number:	2021-003928-32
Name of Investigational Product:	Nemolizumab (CD14152)
Phase of Development:	3b
Indication:	Prurigo nodularis
Sponsor:	Galderma S.A. Zählerweg 10 6300 Zug Switzerland Galderma Research & Development, LLC 2001 Ross Avenue, Suite 1600 Dallas, TX 75201 United States

Protocol Version:	2.0
Protocol Date:	12 December 2022

PROTOCOL APPROVAL SIGNATURE

Protocol Title: A Double-Blind, Placebo-Controlled, Randomized Study to Assess the Durability of Effect and Safety of Nemolizumab for 24 Weeks in Subjects with Prurigo Nodularis

Protocol Number: RD.06.SPR.203890

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

PPD

PPD

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Double-Blind, Placebo-Controlled, Randomized Study to Assess the Durability of Effect and Safety of Nemolizumab for 24 Weeks in Subjects with Prurigo Nodularis

Protocol Number: RD.06.SPR.203890

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 (ICH) 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 study center'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 subjects' state of health will be regarded as confidential. No subjects' names 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.

Name, Title Investigator Signature

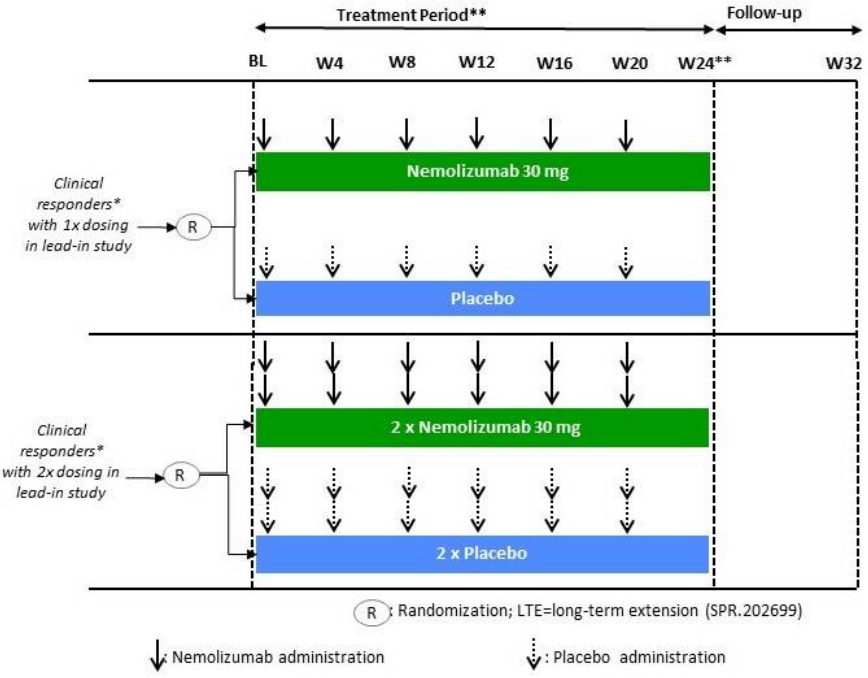
Institution Date (DD-Mmm-YYYY)

2 SYNOPSIS

Title of Study:	A Double-Blind, Placebo-Controlled, Randomized Study to Assess the Durability of Effect and Safety of Nemolizumab for 24 Weeks in Subjects with Prurigo Nodularis
Protocol Number:	RD.06.SPR.203890
Investigators/ Study Centers:	Centers enrolling subjects from the long-term extension (LTE) study (RD.06.SPR.202699) will be eligible to participate in this study
Phase of Development:	Phase 3b
Objectives:	Primary objective: To assess the long-term durability of response over a 24-week period following withdrawal of nemolizumab in subjects with prurigo nodularis (PN) who previously responded to treatment in the LTE study RD.06.SPR.202699 Secondary objective: To assess the safety of nemolizumab compared to placebo over a 24-week period in subjects with PN who previously responded to treatment in the LTE study
Study Endpoints:	**PRIMARY** Time from baseline to relapse, defined as meeting at least 1 of the following criteria: • Increase in (weekly average of the) Peak Pruritus Numeric Rating Scale (PP NRS) score ≥4 points from baseline • Increase in Investigator Global Assessment (IGA) score ≥2 points from baseline The estimand of primary endpoint is defined as the following: **Estimands** **Treatment:** randomized treatment with subcutaneous (SC) injections of nemolizumab or placebo at Week 0, 4, 8, 12, 16, and 20 **Population:** all randomized subjects (intent-to-treat [ITT] population) **Endpoint:** time to relapse meeting at least 1 of the defined criteria **Intercurrent events:** time to relapse will be censored at the last IGA or PP NRS assessment prior to treatment discontinuation or use of prohibited medication **Summary measure:** hazard ratio of nemolizumab and placebo **SECONDARY** The secondary efficacy endpoints include:

	• Proportion of subjects with increase in PP NRS score ≥4 points from baseline at each scheduled visit • Proportion of subjects maintaining IGA success, defined as IGA score of 0 (clear) or 1 (almost clear) at each scheduled visit • Proportion of subjects with increase in IGA ≥2 points from baseline at each scheduled visit • Absolute and percent change from baseline in PP NRS at each scheduled visit • Absolute and percent change from baseline in Sleep Disturbance (SD) NRS at each scheduled visit • Change from baseline in Dermatology Life Quality Index (DLQI) at Week 16 and Week 24 Safety endpoints: • Incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), serious AEs (SAEs), treatment-related AEs, and AEs that lead to discontinuation
Study Design:	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the durability of response and safety of nemolizumab in adult subjects who participated in the nemolizumab PN LTE study (RD.06.SPR.202699) and achieved a clinical response (i.e., IGA score of 0 or 1 and ≥4-point improvement in weekly average of PP NRS score from baseline of the lead-in study) at Week 52 of the LTE study. Subjects must enroll in this study at the time of completion of the Week 52 visit in the LTE study (RD.06.SPR.202699) to prevent any lapse in study treatment. After the Week 52 visit of the LTE study is complete, approximately 40 subjects will be randomized 1:1 to receive either 1 or 2 injections of nemolizumab or placebo, stratified by dosing regimen. Subjects will continue to receive the same dosing regimen received in the LTE study (i.e., 1 or 2 SC injections of study drug administered every 4 weeks [Q4W]). Subjects with a body weight <90 kg in the LTE study will receive a 30-mg dose. Subjects weighing ≥90 kg in the LTE study will receive a 60-mg dose. Subjects' participation in the study will be up to approximately 32 weeks. The study consists of a 24-week treatment period and an 8-week follow-up period (12 weeks after their last study drug injection at Week 20). Refer to Figure 1 for an overview of the study design.

Figure 1. Study Design (Synopsis)



* Clinical responder is defined as a subject with an Investigator Global Assessment (IGA) score= 0 or 1 and improvement in Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥4 points from baseline of the lead-in study at Week 52 visit of the LTE study. Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.

** Relapse is defined as an increase in weekly average of PP NRS score ≥4 points from baseline or an increase in IGA score ≥2 from baseline at any point during the study. Subjects who relapse at any point during the treatment period or who complete through Week 24 are eligible for LTE re-entry.

Abbreviations: BL = baseline; LTE = long-term extension; R = randomization; W = week.

Baseline Assessment

After signing the informed consent form (ICF), all subjects will be evaluated for study participation, based on eligibility criteria. The study assessments at the time of completion of the Week 52 visit from the PN LTE lead-in study RD.06.SPR.202699 will be used as baseline assessments for the current study.

Treatment Period

Eligible subjects will be randomized to receive 1 or 2 injections of nemolizumab or placebo according to their dosage group in the LTE study, as assigned by interactive response technology (IRT). Study drug will then be administered Q4W for 24 weeks with final dose administered at Week 20 (see Table 1).

Table 1. Treatment Summary (Synopsis)

LTE Lead-in Study	**Lead-in Study Assigned Treatment**	**Dose Q4W for 24 weeks** [a]
RD.06.SPR.202699	Nemolizumab 30 mg (1 injection)	Blinded Nemolizumab 30 mg (1 injection)
		Blinded Placebo (1 injection)
	Nemolizumab 2 × 30 mg (2 injections)	Blinded Nemolizumab 2 × 30 mg (2 injections)
		Blinded 2 × Placebo (2 injections)

Abbreviations: LTE = long-term extension; Q4W = every 4 weeks.
[a] Dose will be assigned based on dose received in LTE lead-in study.

Clinical assessments will occur according to the Schedule of Assessments in the protocol through the Week 24 visit.

If a subject meets the criteria for relapse at any point during the treatment period, the subject will exit the study and re-enter the LTE study (see Figure 2). Subjects who exit the study before Week 24 should complete an early termination visit. Subjects who complete the study through Week 24 are eligible to re-enroll in the LTE study.

Subjects who prematurely discontinue study drug for reasons other than relapse will be encouraged to complete the scheduled study visits. These subjects will only be eligible for re-enrollment in the LTE study if they continue with study visits through Week 24.

Subjects who discontinue the study for reasons other than relapse before Week 24 or who will not continue nemolizumab treatment in the LTE study should complete a follow-up visit, 12 weeks (±7 days) after the last study drug injection.

Follow-Up Period

A follow-up visit will be conducted 8 weeks after completing the treatment period and/or 12 weeks after the last study drug injection for all subjects who will not continue nemolizumab treatment in the LTE study.

	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.
Selection of Subjects:	Inclusion Criteria Individuals must meet all the following criteria to be included in the study: 1. Subjects who achieved a clinical response at Week 52 of the LTE study RD.06.SPR.202699, defined as: • IGA score of 0 (clear) or 1 (almost clear) AND • ≥4 point improvement in weekly average of PP NRS score from baseline of the lead-in study *Note: Lead-in study baseline is defined as baseline PP NRS score in Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.* 2. Subjects with uninterrupted dosing of nemolizumab in the LTE study RD.06.SPR.202699 for 3 months before the Week 52 visit 3. Subjects willing and able to transfer into the study at the time of completion of the Week 52 visit in the LTE study RD.06.SPR.202699 4. Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile) must agree to use an 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception (see Appendix 2) • Progestogen-only oral hormonal contraception • Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods). Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) 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 partner at least 3 months before the study

5. Female subjects of non-childbearing potential must meet one of the following criteria:

   - Absence of menstrual bleeding for 1 year prior to baseline 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

Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential

6. Subject willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the subject using an electronic handheld device provided for this study

7. Understand and sign an ICF before any investigational procedure(s) are performed

Exclusion Criteria

Individuals meeting any of the following criteria are ineligible to participate in this study:

1. Subjects who, during their participation in a prior nemolizumab study, experienced an AE which in the opinion of the Investigator could indicate that continued treatment with nemolizumab may present an unreasonable risk for the subject

2. Body weight <30 kg

3. Receipt of prohibited medications, including rescue therapy, in the LTE study RD.06.SPR.202699 within 6 months of the Week 52 visit (Section 9.6.3).

4. Pregnant women (positive pregnancy test result at baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study

5. Any medical or psychological condition 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 (e.g., poor venous access or needle-phobia)

6. Planning or expected to have a major surgical procedure during the clinical study

7. Subjects unwilling to refrain from using prohibited medications during the clinical study

8. History of alcohol or substance abuse within 6 months of baseline

9. Subjects with confirmed or suspected coronavirus disease 2019 (COVID-19) infection within 2 weeks before baseline

	10. Any condition the Investigator deems incompatible with subject participation in the study
Planned Sample Size:	Approximately 40 subjects are planned to be enrolled in this study.
Investigational Therapy:	Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for injection for SC use only after reconstitution in a pre-filled, single-use, dual-chamber syringe (DCS). During the treatment period, eligible subjects will be randomized to receive either 1 or 2 injections of nemolizumab or placebo, administered Q4W for 24 weeks (last injection at Week 20). Subjects will receive the same dosage (1 or 2 SC injections) as received in the lead-in LTE study RD.06.SPR.202699, as assigned by IRT. 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 following appropriate training. If the subject does not wish to perform the injections, study staff can administer study drug at each visit. Table 2 presents details on the investigational therapy.

Table 2. Investigational Therapy

	Investigational product	**Comparator/Placebo**
Name	Nemolizumab	CD14152 placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder for solution for injection supplied in a DCS	Lyophilized powder for solution for injection supplied in a DCS
Packaging	DCS packaged with a plunger rod (not assembled) and a 27G ½'' safety needle	DCS packaged with a plunger rod (not assembled) and a 27G ½'' safety needle
Storage conditions	Stored between 2°C to 8°C (36°F to 46°F); protected from freezing; protected from light	Stored between 2°C to 8°C (36°F to 46°F); protected from freezing; protected from light
Dosage [a]	30 mg (1 injection) or 60 mg (2 injections); see Table 1	1 injection or 2 injections; see Table 1
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Dose regimen	Q4W	Q4W
Treatment duration	24 weeks with last injection at Week 20	24 weeks with last injection at Week 20

Abbreviations: DCS = dual-chamber syringe (single use); NA = not applicable; Q4W = every 4 weeks; SC = subcutaneous.

[a] Subjects will receive blinded study medication as assigned by IRT, based on the assigned dosage in the lead-in LTE study RD.06.SPR.202699.

If a subject relapses (i.e., experiences an increase in PP NRS score of ≥4 points from baseline or an increase in IGA score ≥2 points from baseline), the subject will exit the study and will be eligible to re-enter the LTE study for active treatment (see Figure 2).

Treatment Duration:	The expected duration of each subject's participation in the study is up to 32 weeks, including a 24-week treatment period and an 8-week follow-up period (12-weeks after the last study drug injection).
Efficacy:	The following efficacy assessments are planned according to the Schedule of Assessments (Table 7): • IGA • PP NRS • SD NRS The following quality of life assessment is planned according to the Schedule of Assessments (Table 7): • Dermatology Life Quality Index (DLQI)
Safety:	The following safety assessments are planned according to the Schedule of Assessments (Table 7): • AEs, including TEAEs, AESIs, SAEs, treatment-related AEs, and AEs leading to discontinuation • Physical examination and vital signs • Clinical laboratory tests • 12-lead ECGs • Respiratory examination and assessments
Proof of Exposure/ Immunogenicity:	Proof of exposure (POE) and immunogenicity assessments are planned according to the Schedule of Assessments (Table 7): • Serum nemolizumab concentrations for POE • Anti-drug antibody (ADA) assessments: screening, confirmatory, titer, and neutralizing antibody (Nab) assays
Statistical Methods and Planned Analyses:	The 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 POE analysis population will include all subjects in the safety population who provide at least 1 post-baseline evaluable drug concentration value. The per-protocol 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 per-protocol population will be used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints. **Primary Efficacy Endpoints:** Median time to relapse, 25^{th} and 75^{th} percentiles, and 95% confidence interval (CI) will be presented. Kaplan-Meier survival plots will be produced. Time to relapse from baseline will be analyzed using Cox proportional hazards model adjusted for dosing regimens, comparing the

nemolizumab group (30 mg or 60 mg Q4W) with placebo. Hazards ratio with 95% CI and survival curve will be presented. If the assumption of proportionality for Cox proportional hazards model is not met, then another appropriate method will be used.

If a subject withdraws from the study, takes prohibited medication, or completes the study without any relapse, time to relapse response will be censored respectively at the time of the last efficacy assessment (PP NRS and IGA) prior to study withdrawal, use of prohibited medication, or completion of the study. If a subject has no efficacy assessment after randomization, then time to relapse will be censored at Day 1.

Secondary Efficacy Endpoints:

Binary secondary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for randomized stratification variable. The estimate of the treatment difference (nemolizumab minus placebo), p-value and 2-sided 95% CI will be presented. These analyses will be based on observed case (OC) or imputation with the missing response considered as a non-responder for efficacy endpoints (i.e., IGA success) or as a relapse for relapse endpoints (i.e., increase in IGA or PP NRS score).

Continuous secondary endpoints will be analyzed using analysis of covariance (ANCOVA) based on OC with treatment group and dose regimen as factors, and baseline value as the covariate where applicable. They will also be analyzed using mixed effect model for repeated measure (MMRM) approach, including treatment group and dose regimen as factors, visit, interaction term between treatment and visit, and the corresponding baseline value as an independent 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. As sensitivity analyses, multiple imputation methods may be used to handle the missing data for some selected secondary endpoints. All secondary endpoints will be presented descriptively using OC.

Further details will be provided in the Statistical Analysis Plan.

Safety Analyses:

The incidence of TEAEs, AESIs, SAEs, treatment-related AEs, and AEs leading to study drug discontinuation will be included in incidence tables, summarized by system organ class and preferred term. Additionally, the incidence of TEAEs by maximum severity will be presented by system organ class and preferred term.

Clinical laboratory data and vital signs will be summarized, 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 be provided for 12-Lead ECG, Physical Examination (Full and Symptom-oriented), Asthma Control Test (ACT), peak expiratory flow (PEF), and respiratory examination by treatment group and visit where appropriate.

	Proof of Exposure and Immunogenicity Analyses: Summary statistics will be used to describe the POE to nemolizumab. Descriptive statistics (arithmetic and geometric mean, standard deviation, coefficient of variation [CV%], minimum [min], maximum [max], and median) of the serum concentrations versus time will be presented. Incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, and treatment-related ADA). **Sample size:** No formal sample size calculations were performed for this study. The sample size will be based on the sample size and the actual clinical response rate of the LTE study. Based on the current assumption, it is expected that approximately 40 subjects will be randomized.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Asthma Control Test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRO	contract research organization
CV	coefficient of variation
CYP450	cytochrome P450
DCS	dual-chamber syringe
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and 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
IFU	Instructions for Use

Abbreviation	Definition
IGA	Investigator's Global Assessment
IL-31	interleukin-31
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NK	neurokinin
NRS	numeric rating scale
OC	observed case
PD	pharmacodynamic
PEF	peak expiratory flow
PI	Principal Investigator
PK	pharmacokinetic
PN	prurigo nodularis
POE	proof of exposure
PP	peak pruritus
PTC	product technical complaint
QoL	quality of life
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SD NRS	sleep disturbance numeric rating scale
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPT	urine pregnancy test
US	United States
WHO	World Health Organization

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]

No reliable data exist for 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]

A large spectrum of underlying conditions that induce chronic pruritus can be associated with PN, including dermatological (e.g., atopic dermatitis [AD]), systemic (e.g., chronic kidney failure), neurological (e.g., brachioradial pruritus), psychiatric, or mixed origin disorders.[7] An atopic predisposition seemed to be most common, occurring in nearly half of subjects with PN. [4]

The goal of PN treatment is to break the itch-scratch cycle and allow the skin to heal. There is no standardized or approved therapy for PN to date and evidence from controlled studies is limited.[8]

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.[9] Phototherapy, oral or intra-lesional steroids, topical vitamin D3 (calcipotriol), capsaicin, cryotherapy, and antidepressants (amitriptyline, selective serotonin reuptake inhibitors) are used as second-line therapies with variable efficacy. In the third-line setting, systemic treatments such as cyclosporine,[10] antiepileptic drugs (gabapentin, pregabalin)[11] and thalidomide[12] 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),[13] NKR1-antagonists (aprepitant),[14] and antibiotics (roxithromycin, erythromycin).[15]

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 AD patients.[16]

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

5.2 Background on Nemolizumab

Nemolizumab (CD14152) is a humanized anti-human IL-31 receptor A monoclonal modified immunoglobulin G 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-31 receptor A and subsequent transduction of the IL-31 signal into the cell.

5.2.1 Nonclinical Studies

The Investigator's Brochure (IB) contains detailed information on nonclinical studies.[17]

5.2.2 Pharmacokinetic Profile

Nemolizumab PK profile was assessed in healthy volunteers and in subjects with AD after single and repeated doses with weight-based (0.1 mg/kg to 3 mg/kg) and flat (10 mg to 90 mg) doses. The PK profile of nemolizumab was also assessed in the Phase 2a study SPR.115828 with PN subjects, where a nemolizumab dose of 0.5 mg/kg was administered.

Overall PK assessments showed a dose proportional increase of nemolizumab serum concentrations after a single (mg/kg) injection and a less-than-proportional increase after repeated administrations of flat doses between 30 mg and 90 mg. Subcutaneous administration of nemolizumab results in slow absorption with peak serum concentrations achieved after 4 to 9 days. The terminal elimination half-life of nemolizumab was approximately 2 weeks after single and repeated administrations. No significant systemic accumulation was observed, and steady state concentrations were achieved from 16 weeks of treatment without a loading dose and from 4 weeks of treatment when a loading (flat 2×) dose was administered. The systemic exposure to nemolizumab appeared to be slightly lower in AD subjects compared to healthy volunteers.

Similar nemolizumab PK profiles were observed in subjects with AD and in subjects with PN. The similarity in nemolizumab exposure between the 2 populations was also confirmed using population PK modeling. The IB contains additional detailed information on the nemolizumab PK profile.[17]

A low immunogenicity potential was observed in subjects with PN and in subjects with AD. No subjects had positive anti-drug antibodies (ADA) that included immunoglobulin E (IgE), and no subjects developed neutralizing antibodies. In both subject populations, concentration-time profiles and PK parameters of ADA-positive subjects were not different from the ADA-negative subjects.

5.2.3 Clinical Studies

The IB contains detailed information on clinical studies.[17]

Studies have been completed in healthy subjects and subjects with AD, uremic pruritus, and PN (including the Phase 2a study RD.03.SPR.115828 and the Phase 3 pivotal study RD.06.SPR.203065).

Three additional Phase 3 studies in PN subjects are ongoing: 1 pivotal study (RD.06.SPR.202685), 1 long-term extension (LTE) study (RD.06.SPR.202699), and 1 dose optimization/long-term study (M525101-11) to assess the safety and efficacy of nemolizumab in subjects with a clinical diagnosis of PN.

There are also Phase 2 and Phase 3 studies in AD subjects, a Phase 3 study in subjects with pruritus associated with Chronic Kidney Disease and a Pharmacokinetic study for an Auto-Injector device ongoing.

5.3 Risk/Benefit Assessment

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 to allow skin healing and improvement in patients' QoL.

Results of a previous clinical study with nemolizumab demonstrated a marked effect on both PN lesions 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 scales (i.e., Investigator Global Assessment [IGA], Peak Pruritus [PP] Numeric Rating Scale [NRS], and Prurigo Activity Score). 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% confidence interval [CI] -51.0, -25.0; $p<0.001$). The statistically significant improvements in IGA success and Prurigo Activity Score observed in the nemolizumab group were greater than those observed in the placebo group.

Based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the important potential risks of nemolizumab treatment include local and systemic injection-related reactions, newly-diagnosed asthma or worsening of asthma, exacerbation of AD, and skin and non-skin infections.

The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

a. The protocol will exclude subjects who experienced an adverse event (AE) in the prior lead-in study that, in the opinion of the Investigator, could indicate continued treatment with nemolizumab would present an unreasonable risk for the subject.
b. In the Phase 2b dose-ranging study (RD.03.SPR.114322) in AD, 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 treatment arms, respectively) in subjects with pre-existing asthma was observed. Events were mostly mild or moderate (1 severe event with highest dose), manageable, and reversible under treatment with study drug. At all visits, subjects with a history of asthma will complete a respiratory exam, the Asthma Control Test (ACT), and peak expiratory flow (PEF) testing. Subjects diagnosed with de novo asthma will complete respiratory assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects without a medical history of asthma will undergo periodic respiratory assessments. 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 and/or respiratory assessments suggest a decline in subject's health. An independent adjudication committee (IAC) will review all asthma AEs reported during the course of the study.
c. As no data are available in pregnant or breastfeeding women, these patients are not eligible for this study.
d. 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 (Section 9.6.3). Administration of live vaccines is prohibited during the study. Administration of non-live vaccines is prohibited with the exception of seasonal, emergency, and coronavirus disease 2019 (COVID-19) vaccinations (Section 9.6.1). See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.
e. 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. Peripheral edema will be followed as an AE of special interest (AESI) in this study.
f. An independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study, including AESIs listed in Section 12.7.2, which were defined based on the currently available safety information on nemolizumab and the risks associated with biologic agents in general.

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

In the Phase 2 study (RD.03.SPR.115828), nemolizumab was tested as a 0.5 mg/kg subcutaneous (SC) injection administered Q4W in subjects with PN. The 0.5 mg/kg dose demonstrated efficacy in the treatment of PN with an acceptable safety profile and a very good immunogenicity profile.

The Phase 3 studies are conducted with a flat, fixed dose. The dose was selected with the aim of improving dosing convenience and avoiding potential errors that could be made while calculating, preparing, and/or administering a weight-based dose. The switch from weight-based dosing to a flat dose was based on an assessment of observed clinical data, and modeling & simulation tools.

Overall, subjects will continue to receive the same dose received in the LTE study (i.e., 1 or 2 SC injections of study drug administered Q4W). The dose was determined at baseline of the relevant lead-in study. Subjects with a body weight <90 kg were administered a 30 mg dose Q4W with a loading dose of 60 mg at baseline. Subjects weighing ≥90 kg were administered a 60 mg dose of nemolizumab Q4W (without loading dose). This dose adjustment was proposed to account for the impact of body weight on nemolizumab systemic exposure and subsequently to provide consistent efficacy response to nemolizumab across the body weight spectrum.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

To assess the long-term durability of response over a 24-week period following withdrawal of nemolizumab in subjects with PN who previously responded to treatment in the LTE study RD.06.SPR.202699

6.1.2 Secondary Objective

To assess the safety of nemolizumab compared to placebo over a 24-week period in subjects with PN who previously responded to treatment in the LTE study

6.2 Study Endpoints

6.2.1 Primary Endpoint

Time from baseline to relapse, defined as meeting at least 1 of the following criteria:

- Increase in (weekly average of the) PP NRS score ≥4 points from baseline
- Increase in IGA score ≥2 points from baseline

The estimand of primary endpoint is defined as the following:

Estimand
Treatment: randomized treatment with subcutaneous injections of nemolizumab or placebo at Week 0, 4, 8, 12, 16, and 20
Population: all randomized subjects (intent-to-treat population)
Endpoint: time to relapse meeting at least 1 of the defined criteria
Intercurrent events: time to relapse will be censored at the last assessment of IGA and PP NRS prior to treatment discontinuation or use of prohibited medication
Summary measure: hazard ratio of nemolizumab and placebo

6.2.2 Secondary Endpoints

6.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of subjects with increase in PP NRS score ≥4 points from baseline at each scheduled visit

- Proportion of subjects maintaining IGA success, defined as IGA score of 0 (clear) or 1 (almost clear) at each scheduled visit
- Proportion of subjects with increase in IGA ≥2 points from baseline at each scheduled visit
- Absolute and percent change from baseline in PP NRS at each scheduled visit
- Absolute and percent change from baseline in Sleep Disturbance Numeric Rating Scale (SD NRS) at each scheduled visit
- Change from baseline in DLQI at Week 16 and Week 24

6.2.2.2 Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence and severity of AEs, including treatment-emergent AEs (TEAEs), AESIs, serious AEs (SAEs), treatment-related AEs, and AEs that lead to discontinuation

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

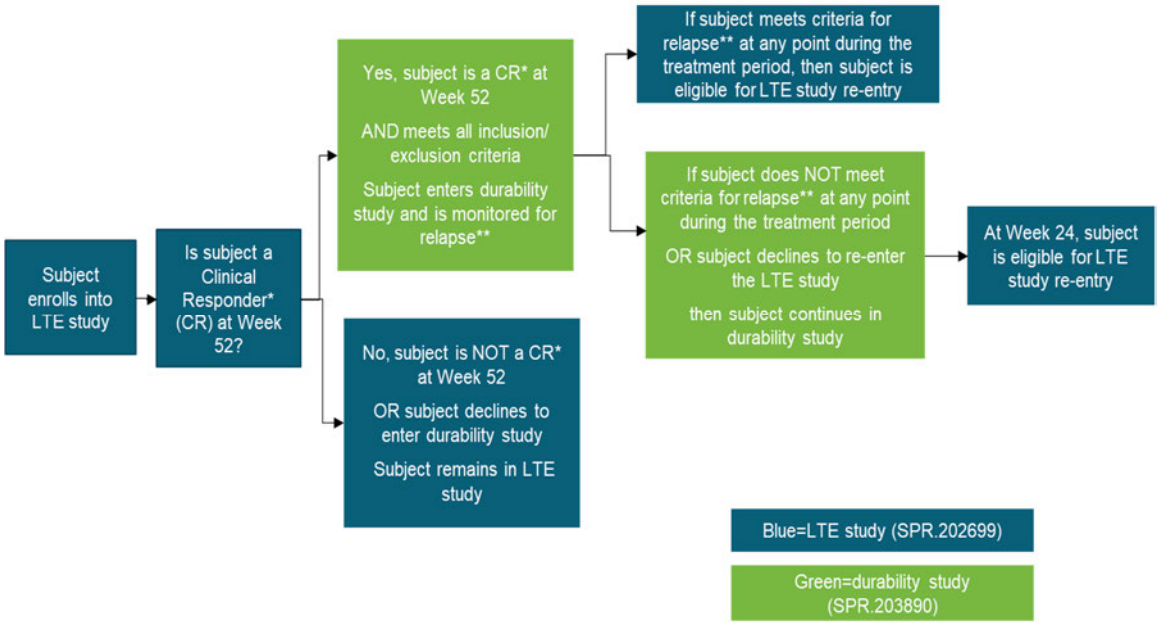
This is a Phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group withdrawal study to evaluate the durability of response and safety of nemolizumab in adult subjects with PN who participated in the nemolizumab PN LTE study (RD.06.SPR.202699) and achieved a clinical response (i.e., IGA score of 0 or 1 and ≥4-point improvement in weekly average of PP NRS score from baseline of the lead-in study) at Week 52 of the LTE study.

Subjects who agree to enroll in this study must do so at the time of completion of the Week 52 visit in the LTE study (RD.06.SPR.202699) to prevent any lapse in study treatment. After the Week 52 visit of the LTE study is complete, approximately 40 subjects who choose to enter this study will be randomized 1:1 to either continue the same dosing regimen received in the LTE study (i.e., 1 or 2 SC injections of study drug administered Q4W), or to discontinue nemolizumab and receive placebo.

Subjects' participation in the study will be up to approximately 32 weeks. The study consists of a 24-week treatment period and an 8-week follow-up period (12 weeks after their last study drug injection at Week 20).

Relapse is defined as an increase in (weekly average of the) PP NRS score ≥4 points from baseline or an increase in IGA score ≥ 2 from baseline at any point during the study. If a subject meets the criteria for relapse, then the subject may be considered for re-entry into the LTE study (RD.06.SPR.202699) (see Figure 2).

Figure 2. Subject Transition between CD14152 Studies 202699 and 203890



*Clinical responder (CR) is defined as a subject with an Investigator Global Assessment (IGA) score= 0 or 1 and improvement in Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥4 from baseline of the lead-in study at Week 52 visit of the long-term extension (LTE) study. Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.

** Relapse is defined as an increase in weekly average of PP NRS score ≥4 points from baseline or an increase in IGA score ≥2 from baseline at any point during the study

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

Baseline Assessment

After signing the informed consent form (ICF), all subjects will be evaluated for study participation, based on eligibility criteria. The study assessments at the time of completion of the Week 52 visit from the PN LTE lead-in study RD.06.SPR.202699 will be used as baseline assessments for the current study.

Treatment Period

Eligible subjects will be randomized to receive either 1 or 2 injections of nemolizumab or placebo according to their dosage group in the LTE study, as assigned by interactive response technology (IRT). Study drug will then be administered Q4W for 24 weeks with final dose administered at Week 20.

Refer to Table 3 for a summary of study treatment.

Table 3. Treatment Summary

LTE Lead-in Study	Lead-in Study Assigned Treatment	Dose Q4W for 24 weeks [a]
RD.06.SPR.202699	Nemolizumab 30 mg (1 injection)	Blinded Nemolizumab 30 mg (1 injection)
		Blinded Placebo (1 injection)
	Nemolizumab 2 × 30 mg (2 injections)	Blinded Nemolizumab 2 × 30 mg (2 injections)
		Blinded 2 × Placebo (2 injections)

Abbreviation: LTE = long-term extension; Q4W = every 4 weeks.
[a] Dose will be assigned based on dose received in LTE lead-in study.

Clinical assessments will occur according to the Schedule of Assessments in the protocol through the Week 24 visit.

If a subject meets the criteria for relapse at any point, the subject will exit the study and re-enter the LTE study (see Figure 2). Subjects who exit the study before Week 24 should complete an early termination (ET) visit. Subjects who complete the study through Week 24 are eligible to re-enroll in the LTE study.

Subjects who prematurely discontinue study drug for reasons other than relapse will be encouraged to complete the scheduled study visits. These subjects will only be eligible for re-enrollment in the LTE study if they continue with study visits through Week 24.

Subjects who discontinue the study for reasons other than relapse before Week 24 or who will not continue nemolizumab treatment in the LTE study should complete a follow-up visit, 12 weeks (±7 days) after the last study drug injection.

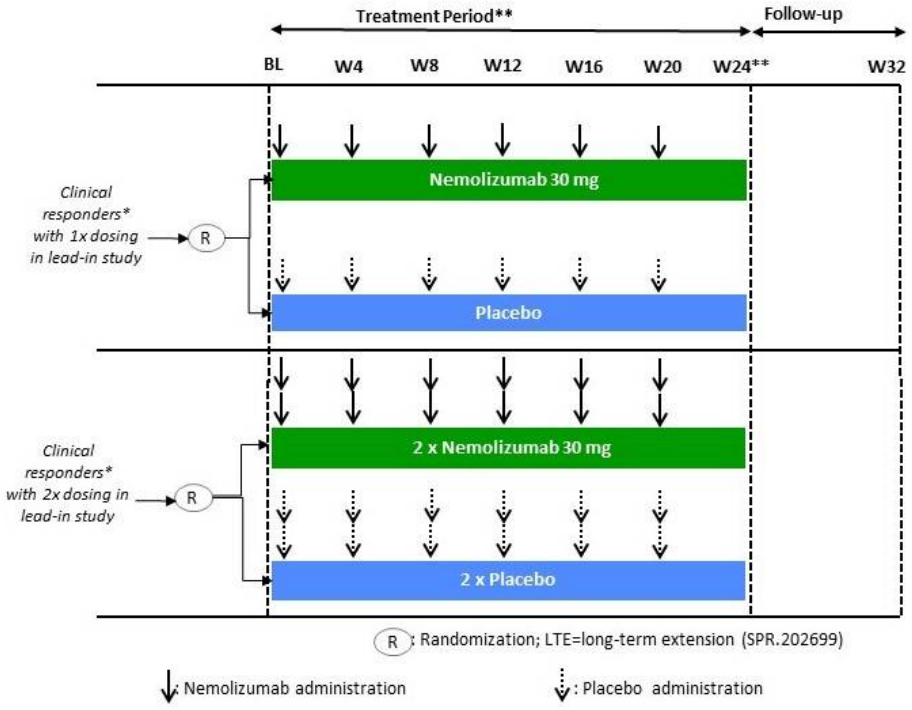
Follow-up Period

A follow-up visit will be conducted 8 weeks (±7 days) after completing the treatment period and/or 12 weeks (±7 days) after the last study drug injection for all subjects who will not continue nemolizumab treatment in the LTE study. Twelve weeks corresponds to approximately 5 half-lives of nemolizumab when administered subcutaneously Q4W at the doses used in this study.

7.1.1 Study Visit Schema

An overview of the study is presented in Figure 3.

Figure 3. Study Design



*Clinical responder is defined as a subject with an Investigator Global Assessment (IGA) score= 0 or 1 and improvement in Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥4 points from baseline of the lead-in study at Week 52 visit of the LTE study. Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.

** Relapse is defined as an increase in weekly average of PP NRS score ≥4 points from baseline or an increase in IGA score ≥2 from baseline at any point during the study. Subjects who relapse at any point during the treatment period or who complete through Week 24 are eligible for LTE re-entry.

Abbreviations: BL = baseline; LTE = long-term extension; R = randomization; W = week.

7.2 Discussion of Study Design

This study will evaluate the durability of response and safety of nemolizumab in adult subjects with PN. The general study design is based upon the prior Phase 3 and LTE study (RD.06.SPR.202699) designs conducted in adult subjects with PN. The rationale for the nemolizumab dose and dose regimen is provided in Section 5.4.

Eligible subjects for this clinical study will be adults who participated in the prior nemolizumab PN LTE study (RD.06.SPR.202699) with uninterrupted dosing for 3 months before the Week 52 visit and achieved a clinical response (i.e., IGA score of 0 or 1 and ≥4-point improvement in weekly average of PP NRS score from baseline of the lead-in study) at Week 52. By randomizing subjects from the PN LTE study who achieved a current clinical response to nemolizumab to either nemolizumab or placebo treatment arms, the durability of the response to nemolizumab following discontinuation of active treatment (i.e., in the placebo treatment arm) can be measured. This will be done to understand how long the effects of nemolizumab treatment are expected to last in controlling signs and symptoms of PN when treatment is removed. Subjects who experienced an AE during their participation in the prior lead-in study that in the opinion of the Investigator could indicate that continued treatment with nemolizumab might present an unreasonable risk for the subject are ineligible. Furthermore, subjects must not use restricted topical and systemic treatments, including rescue therapy, within 6 months of the Week 52 visit in the PN LTE study.

A 24-week treatment period is considered adequate to evaluate the long-term durability of response and safety of nemolizumab based on the results of the prior Phase 2a study.

The efficacy endpoints selected for the Phase 3b trial are relevant to the underlying long-term manifestations associated with the disease under study (i.e., skin lesions, chronic itch, sleep disturbance, and QoL impairment), and are designed to measure the maintenance or loss of clinical response.

The study includes an 8-week follow-up period and/or 12 weeks (±7 days) after the last study drug injection for subjects who will not continue in the LTE study. The duration of the follow-up period from the final nemolizumab dose (12 weeks [±7 days]) corresponds to approximately 5 half-lives of nemolizumab, which is considered adequate to ensure subject safety.

Blinding subjects and the designated study team to the dosing assignment(s) helps ensure objectivity and minimize bias. Randomization through the IRT guards against selection bias. To avoid bias further 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.

Differences may be detectable during the study drug reconstitution process between active study drug and placebo but they 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.

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 the follow-up visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 7).

The end of the study will be the last subject's last visit as indicated in the Schedule of Assessments (Table 7).

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be randomized. Refer to Section 14.1 for the statistical considerations on which the sample size is based.

8.1 Inclusion Criteria

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

1. Subjects who achieved a clinical response at Week 52 of the LTE study RD.06.SPR.202699, defined as:
   - IGA score of 0 (clear) or 1 (almost clear)

     AND
   - ≥4-point improvement in weekly average of PP NRS score from baseline of the lead-in study

     Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.
2. Subjects with uninterrupted dosing of nemolizumab in the LTE study RD.06.SPR.202699 for 3 months before the Week 52 visit
3. Subjects willing and able to transfer into the study at the time of completion of the Week 52 visit in the LTE study RD.06.SPR.202699
4. Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile) must agree to use an 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception (see Appendix 2).
   - Progestogen-only oral hormonal contraception

- Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods)

  Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) 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 partner at least 3 months before the study

5. Female subjects of non-childbearing potential must meet one of the following criteria:
   - Absence of menstrual bleeding for 1 year prior to baseline 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

Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential

6. Subject willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the subject using an electronic handheld device provided for this study
7. Understand and sign an ICF before any investigational procedure(s) are performed

8.2 Exclusion Criteria

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

1. Subjects who, during their participation in a prior nemolizumab study, experienced an AE which in the opinion of the Investigator could indicate that continued treatment with nemolizumab may present an unreasonable risk for the subject
2. Body weight <30 kg
3. Receipt of prohibited medications, including rescue therapy, in the LTE study RD.06.SPR.202699 within 6 months of the Week 52 visit (Section 9.6.3).

4. Pregnant women (positive pregnancy test result at baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study
5. Any medical or psychological condition 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 (e.g., poor venous access or needle-phobia)
6. Planning or expected to have a major surgical procedure during the clinical study
7. Subjects unwilling to refrain from using prohibited medications during the clinical study
8. History of alcohol or substance abuse within 6 months of baseline
9. Subjects with confirmed or suspected COVID-19 infection within 2 weeks before baseline
10. Any condition the Investigator deems incompatible with subject participation in the study

8.3 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 (i.e., consent withdrawal)
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs, including TEAE and 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
    - Serious worsening of asthma considered related to study drug administration
    - Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma [Bowen's disease], or basal cell carcinoma)

- Opportunistic infections such as but not limited to active tuberculosis (TB) and other infections whose nature or course suggest an immune-compromised or immune-suppressed status
- Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for >2 weeks considered related to study drug administration
- Confirmed or suspected COVID-19 infection (temporary discontinuation may be acceptable; for instructions on resuming study drug administration, see Section 8.3.2).

- Pregnancy (see Section 8.3.1)
- Use of non-permitted concurrent therapy (as specified in Section 9.6.3, unless discussed and agreed upon with the Investigator and Medical Monitor)
- Use of systemic rescue therapy (as specified in Section 9.6.2)
- Treatment failure (subjects who relapse may be eligible to re-enroll in the LTE study)
- Investigator request
- Sponsor request, including any of the above criteria

The reason(s) for withdrawal will be documented in the electronic case report form (eCRF). Subjects who have been enrolled and treated will not be replaced by another subject.

Subjects who prematurely discontinue study drug for reasons other than relapse will be encouraged to complete the scheduled study visits. These subjects will only be eligible for continued treatment with nemolizumab in the LTE study if they continue with study visits through Week 24.

When a subject is withdrawn from the study, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 10.3.1 (ET Visit).

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

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the Investigator(s) will be informed of the reason for study termination.

8.3.1 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 nonresponse/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., 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 [±7 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.

8.3.2 Coronavirus Disease 2019 (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 judgment 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 (e.g., cough, shortness of breath)
- For asymptomatic subjects: At least 21 days have passed since the positive polymerase chain reaction test and no symptoms

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

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

9 TREATMENTS

9.1 Details of Study Drug

9.1.1 Study Drug Administered

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

Study drug will be provided as lyophilized powder for solution for injection for SC use only after reconstitution in a pre-filled, single-use, dual-chamber syringe (DCS).

The DCS is a self-contained system that holds the lyophilized nemolizumab or placebo and solution (sterile water) for reconstitution, separately. The concentration of nemolizumab in the DCS will be 61.5 mg/mL once reconstituted (volume of 0.49 mL per injection).

Subjects will receive nemolizumab or placebo according to their dosage group (1 or 2 SC injections) in the LTE study, as assigned by IRT Q4W.

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 following appropriate training. If the subject does not wish to perform the injections, study staff can administer study drug at each visit.

9.1.2 Identity of the Study Drugs

Table 4 provides a description and overview of study drug usage.

Table 4. Description and Usage of Study Drug

	Investigational Product	*Comparator/Placebo*
Name (internal code)	Nemolizumab (CD14152)	CD14152 placebo (N/A)
Pharmaceutical form	Lyophilized powder for solution for injection in a DCS	Lyophilized powder for solution for injection in a DCS
Storage conditions	Stored between 2 to 8°C (36 to 46°F); protected from light; protected from freezing	Stored between 2 to 8°C (36 to 46°F); protected from light; protected from freezing
Dosage[a]	30 mg (1 injection) or 60 mg (2 injections); see Table 3	1 injection or 2 injections; see Table 3
Dose regimen	Q4W	Q4W
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Duration of treatment	24 weeks with last injection at Week 20	24 weeks with last injection at Week 20

Abbreviations: DCS = dual-chamber syringe (single use); N/A = not applicable; Q4W = every 4 weeks; SC = subcutaneous.

[a] Subjects will receive blinded study medication as assigned by IRT, based on the assigned dosage in the lead-in study RD.06.SPR.202699.

9.1.3 Preparation

A pharmacist (or other qualified personnel) will prepare study drug for injection according to instructions provided in the current version of the pharmacy manual and the "Instructions for Use" (IFU). Study medication 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 study drug and placebo, but active study drug 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 study drug should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in 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.

9.1.4 Injection

All study drug injections will occur at the study center, following instructions provided in the current versions of the pharmacy manual and IFU. 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 alternative injection site. A different injection site should be selected for each injection. Refer to the current versions of the pharmacy manual and the IFU 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.

Clinic staff will provide injection training (or re-training, as needed) for subjects willing and able to self-inject study drug. Subjects will then be allowed to inject study drug. Based on the subject's preference, clinic staff can also perform all injections.

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

9.1.5 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 trial. 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.

9.1.6 Storage

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 securely 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.

9.2 Dosage Schedule

Table 5 summarizes study drug dosing for the 24-week treatment period.

Table 5. Dosage Schedule by Treatment Group

Treatment Group	*Dose [a]/route*	*Week(s)*	*Schedule*
Clinical responders [b] with 1× dosing in lead-in LTE study	Nemolizumab (CD14152) 30 mg × 1 SC injection OR Placebo × 1 SC injection	0, 4, 8, 12, 16, 20	Q4W for 24 weeks
Clinical responders [b] with 2× dosing in lead-in LTE study	Nemolizumab (CD14152) 30 mg × 2 SC injections OR Placebo × 2 SC injections	0, 4, 8, 12, 16, 20	Q4W for 24 weeks

Abbreviation(s): IGA=Investigator Global Assessment; IRT=interactive response technology; LTE = long-term extension; PP NRS=Peak Pruritus Numeric Rating Scale; Q4W = every 4 weeks; SC = subcutaneous.

[a] Subjects will receive blinded study medication as assigned by IRT, based on the assigned dosage in the lead-in study RD.06.SPR.202699.

[b] Clinical responders are defined as subjects with IGA score of 0 or 1 and improvement in PP NRS score of ≥4 from baseline of the lead-in study at Week 52 visit of the LTE study. Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

9.3.1 Method of Study Treatment Assignment

At the baseline visit, a unique subject identification number will be assigned to an eligible subject via IRT. Subjects will be randomized in a 1:1 ratio to receive either 1 or 2 injections of nemolizumab or placebo. The randomization scheme will be stratified by dosing regimen.

9.3.2 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 or placebo treatments, according to the current version of the pharmacy manual, the IFU, and assigned DCS provided by the IRT system.

As there may be detectable differences between active study drug 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 medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

Local unblinding will occur for bioanalytical POE and ADA testing. POE and ADA sample assays will only be performed on samples from subjects treated with nemolizumab. Prior to sample assays, local unblinding at the bioanalytical CRO will be restricted to the bioanalytical manager and his/her direct reports only, in order to select the appropriate samples for the assay.

To maintain the integrity of the study blinding, the bioanalytical laboratory staff who process/analyze the proof of exposure (POE)/ADA samples will not provide any information to 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. The POE and ADA results will be released by the bioanalytical laboratory after database 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 (i.e., 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 12 weeks (±7 days) after the last dose of study drug.

The reporting requirements for unblinding are the same as the requirements for reporting an SAE (see Section 12.7.4).

The randomization code will remain blinded to all study centers and study team members until completion of the study and until 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 that treatment assignment remains undisclosed to all individuals involved in the direct execution and management of the study until the final database is locked.

9.4 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.

In the event of a missed dose (i.e., temporary discontinuation of the study drug), it will be documented in the eCRF that the drug has not been administered at the study visit, with the reason (e.g., 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 Section 10.

Dosing frequency of study drug (nemolizumab or placebo) is scheduled for Q4W, based on the baseline/Day 1 visit date. If a study visit occurs outside of the visit window, study drug can be administered provided there is a minimum of 3 weeks but not more than 5 weeks since the last injection. If 5 weeks or more, 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 doses.

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

9.5 Accountability and Compliance

Study drug (nemolizumab and placebo) will be provided to the investigational study center. Study center 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, the site personnel will notify the Sponsor/CRO and follow the guidelines according to the current version of the pharmacy manual.

The designated personnel will 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 units can be disposed of 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 9.6.4 for PTCs.

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 to the destruction depot. 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.

9.5.1 Dispensing and Return of Study Drug

All 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 study centers' standard operating procedures, local regulations, and best practices, as described in the current version of the pharmacy manual. The unused study drug will be returned to the drug depot for destruction.

9.5.2 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, the date, time, dose, injector (subject or study center staff), and site of injection should be accurately recorded to confirm that each dose of study treatment was properly administered.

9.6 Prior and Concomitant Therapies

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

Concomitant therapies/medications are defined as follows:

- Any existing therapies ongoing at the time of the baseline assessment
- Any changes to existing therapies (such as changes in dose, formulation, or application frequency) during the course of the study

- Any new therapies received by the subject since the baseline assessment

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, homeopathic preparations, and other alternative medications
- Medical and surgical procedures (e.g., phototherapy, exodontia). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included

Prior and concomitant therapies or 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. Contraceptive counseling should occur at baseline.

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.

Prohibited therapies are provided in Section 9.6.3.

9.6.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 9.6.3), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers (without “anti-itch” claim), bleach baths, and topical anesthetics.

Use of the following non-live vaccines is permitted in this study:

- seasonal vaccinations (e.g., influenza)
- emergency vaccinations (e.g., 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 that 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.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, and IL-10) during chronic inflammation. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab on such enzymes has not been studied. Therefore, Investigators should be attentive to clinical or laboratory signs that might indicate a potential effect of nemolizumab in subjects using other therapies that are CYP450 substrates and have a narrow therapeutic index. Typical examples of substrates with a narrow therapeutic range include warfarin, drugs that may cause torsades de pointes, almost all cytotoxic antineoplastic drugs, and aminoglycoside antibiotics.

9.6.2 Rescue Therapy

Rescue therapies are not permitted in this study. Subjects enrolled in this study have demonstrated a clinical response to nemolizumab; therefore, if a subject experiences relapse, they will be discontinued from this study and may be eligible to continue to receive nemolizumab by re-enrolling in the LTE study (see Figure 2).

9.6.3 Prohibited Therapy

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

Table 6. Prohibited Therapy

Treatments	***Timeframe***	
	Before Baseline/ Day 1	Day 1 – Week 32
Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) and topical corticosteroids	6 months	Prohibited
Topical vitamin D analogs	6 months	Prohibited
Topical or systemic PDE-4 inhibitors	6 months	Prohibited
Any other topical treatment other than moisturizer (e.g., capsaicin, cryotherapy for treatment of PN)	6 months	Prohibited
Emollients or moisturizers with menthol, capsaicin, polidocanol or other having “anti-itch” claim	6 months	Prohibited
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	6 months	Prohibited

Treatments	***Timeframe***	
	Before Baseline/ Day 1	Day 1 – Week 32
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine A, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	6 months	Prohibited
Biologics and their biosimilars (e.g., dupilumab, etanercept, adalimumab, infliximab, omalizumab, etc.)	6 months	Prohibited
Systemic retinoids	6 months	Prohibited
Systemic roxithromycin, erythromycin	6 months	Prohibited
Opioid antagonists (e.g., naltrexone, naloxone), opioid partial/mixed agonists (e.g., nalbuphine, butorphanol) or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (e.g., aprepitant)	6 months	Prohibited
Anti-epileptics (e.g., gabapentin, pregabalin) unless used at a stable dose for 6 months or for a non-pruritic condition	6 months	Prohibited
Alternative and complementary medicine for PN (e.g., traditional Chinese medicine)	6 months	Prohibited
Live attenuated vaccines	6 months	Prohibited
Non-live vaccines (excluding seasonal [e.g., influenza], emergency [e.g., rabies or tetanus], and COVID-19 vaccinations)	6 months (exceptions apply; Section 9.6.1)	Prohibited (exceptions apply; Section 9.6.1)
Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to baseline or for a seasonal allergy)	6 months	Prohibited
Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, or sedative antidepressants such as amitriptyline, paroxetine, except if these treatments were taken at a stable dose for at least 3 months before baseline	6 months	Prohibited
UVB Phototherapy or tanning beds, PUVA phototherapy	6 months	Prohibited
Cannabinoids (eg, dronabinol)	6 months	Prohibited

COVID-19=coronavirus disease 2019; JAK=Janus kinase; NK=neurokinin; PDE-4=phosphodiesterase-4; PN=prurigo nodularis; PUVA=psoralen+ultraviolet A; UVB=ultraviolet B.

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 (e.g., 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.

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 without compromising the health of the subject. See also Section 9.6.1.

Vaccinations during the study and follow-up period are not permitted, with the exception of the specified non-live vaccines in Section 9.6.1.

9.6.4 Product Technical Complaints

All DCS units 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. This also includes the DCS plunger rod. 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 study center personnel, pictures of the defective DCS 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.

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.

Upon ICF signature, each subject will be assigned, via electronic data capture (EDC), a unique subject identification number which will be used for the entire duration of the study.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 7).

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)
    - Electrocardiogram (ECG) should be done before vital signs measurements and blood draws (see Section 12.4).
3. Sample collections for laboratory assessments
4. Sample collections for correlative assessments (POE and ADA)
5. Administration of study drug injections

Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 7).

Efficacy assessments are described in Section 11 and include IGA, PP NRS, SD NRS, DLQI.

Safety assessments are described in Section 12 and include AEs, including TEAEs, AESIs, and SAEs, physical examination and vital signs, clinical laboratory tests, ECG, and respiratory assessments. Section 12.5 specifies laboratory assessment samples to be obtained.

The Investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures, for various reasons including occurrence of AEs, are described in Section 8.3.

Early termination visit procedures are described in Section 10.3.1 and unscheduled visit procedures are described in Section 10.3.2.

10.2.1 Schedule of Assessments

Table 7 outlines the timing of procedures and assessments to be performed throughout the study.

Table 7. Schedule of Assessments

	Baseline [a]	Treatment Period						FU	ET	Unscheduled
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**if applicable [b]**	**if applicable [c]**
Week	**W0 (Day 1)**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W32**		
Visit Window (days)		±1	±3	±3	±3	±5	±5	±7		
ICF [a]	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history, previous therapies and procedures, smoking status	X									
Patient-Reported Outcomes										
PP NRS/ SD NRS [d, e]	X----------						X		X	(X)
DLQI [e]	X				X		X		X	(X)
Efficacy Assessments										
IGA	X	X	X	X	X	X	X		X	(X)
Safety Assessments										
ACT [e, f]	X	X	X	X	X	X	X	X	X	(X)
Respiratory examination	X	X [g]	X [g]	X	X [g]	X [g]	X	X	X	(X)
PEF testing	X	X [g]	X [g]	X	X [g]	X [g]	X	X	X	(X)
Vital signs [h]	X	X	X	X	X	X	X	X	X	(X)
Full physical examination	X			X			X	X	X	(X)
Symptom-directed physical examination		X	X		X	X				
Height	X									(X)
Weight	X						X		X	(X)
12-lead ECG [i]	X						X		X	(X)
Contraceptive counseling	X									(X)

	Baseline [a]	Treatment Period						FU	ET	Unscheduled
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**if applicable [b]**	**if applicable [c]**
Week	**W0 (Day 1)**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W32**		
Visit Window (days)		±1	±3	±3	±3	±5	±5	±7		
Adverse events [e]	X	X	X	X	X	X	X	X	X	(X)
Concomitant therapies and procedures [e]	X	X	X	X	X	X	X	X	X	(X)
Laboratory Assessments										
Blood samples for hematology and clinical chemistry [j]	X			X			X	X		(X)
Urinalysis	X			X			X	X		(X)
Urine pregnancy test [k]	X	X	X	X	X	X	X	X	X	(X)
FSH [l]	X									(X)
Blood sample for virology (HIV, Hepatitis B and C test)										(X)
Blood sample for TB test										(X)
POE & Immunogenicity Assessments										
Blood sample for POE [c, m]	X						X		X	(X)
Blood sample for ADA [c, m]	X						X		X	(X)
Study Drug Administration										
Randomization	X									
Study drug injection [n, o, p, q, r]	X	X	X	X	X	X				(X)

ACT = Asthma Control Test; ADA = anti-drug antibody; AE = adverse event; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator Global Assessment; LTE = long-term extension; PEF = peak expiratory flow; POE = proof of exposure; PP NRS= peak pruritus numeric rating scale; SD NRS= sleep disturbance numeric rating scale; TB = tuberculosis; UPT = urine pregnancy test; V = visit; W = week.

a) After signing the ICF, all subjects will be evaluated for study participation, based on eligibility criteria. The Week 52 study assessments from the LTE lead-in study RD.06.SPR.202699 will be used as baseline assessments for the current study.

b) Subjects who relapse or discontinue prematurely (before the Week 24 visit) should complete an ET visit. If the subject discontinues for reasons other than relapse before Week 24, or will not continue with nemolizumab treatment in the LTE study, a follow-up visit should also be completed, 12 weeks (±7 days) after the last study drug injection.

c) Assessments to be conducted at the unscheduled visit depend on the reason for the visit. POE and ADA analyses should only be performed at unscheduled visits that are conducted for safety reasons when safety labs are collected for the management/monitoring of an AE. When a series of unscheduled visits is needed for the monitoring of the same AE, the POE and ADA collection is not required if already done at the first unscheduled visit of the series. Additional collection of samples for POE and ADA analysis should be performed per Investigator's judgment.

d) PP NRS to be recorded by subjects once daily in the evening. SD NRS to be recorded by subjects once daily in the morning and if possible, within 1 hour of getting out of bed.

e) Patient-reported outcome assessments and designated safety measurements (including AE and concomitant therapies/procedures assessments) should occur before Investigator assessments, laboratory sample collections, and study drug administration.

f) Subjects with a history of asthma will complete the ACT testing at all visits. Subjects with a new (de novo) diagnosis of asthma will complete the ACT testing beginning from de novo diagnosis and at all subsequent scheduled visits.

g) Respiratory exams and PEF measurements are required at these visits for subjects with a medical history of asthma or newly-diagnosed (de novo) asthma only. Whenever possible, it is preferable that the PEF measurements be performed before noon or at the same time during each study visit. 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.

h) 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.

i) 12-lead ECGs should be performed in the supine position and before any scheduled vital sign measurements and blood draws.

j) Subjects should be reminded to be well hydrated and fast for at least 8 hours before the visit(s) when clinical chemistry testing is planned. See Section 12.5 for details.

k) Only for females of childbearing potential. If UPT is positive, it must be confirmed with a serum pregnancy test. Pregnancy test results must be available prior to the administration of the study drug.

l) For postmenopausal subjects (i.e., no menses for 12 consecutive months), confirm status with a high FSH level in the postmenopausal range unless previously confirmed as part of a lead-in study. The blood chemistry sample at the baseline visit (V1) will also be used for an FSH test for the confirmation of postmenopausal status, if applicable.

m) At scheduled visits with laboratory, POE, and/or ADA assessments, the samples are to be collected before study drug injection(s). As a guideline, POE and ADA samples should be collected at approximately the same time of day throughout the study, to the extent possible.

n) Study drug reconstitution will be performed by the pharmacist (or other qualified personnel), and complete reconstitution confirmed, prior to delivery for injection.

o) Clinic staff will provide injection training (or re-training, as needed) for subjects willing and able to self-inject study drug. Subjects will then be allowed to inject study drug. Based on the subject's preference, clinic staff can also perform all injections.

p) After study drug administration, subjects should be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged.

q) If a study visit occurs outside of 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 5 weeks or more, 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 doses.

r) The dose will depend on the dose received in the LTE lead-in study RD.06.SPR.202699; see Table 3 for details.

10.3 Duration of Subject Participation

The expected duration for each subject's participation in the study is up to 32 weeks, including a 24-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection at Week 20).

10.3.1 Early Termination Visit

If a subject meets the criteria for relapse at any point during the treatment period, the subject will be eligible to re-enter the LTE study (see Figure 2). Subjects who exit the study before Week 24 should complete an ET visit. For subjects re-entering the LTE study, a minimum of 3 weeks is required between doses of study drug. Subjects who prematurely discontinue study drug for reasons other than relapse will be encouraged to complete the scheduled study visits. These subjects will only be eligible for re-enrollment in the LTE study if they continue with study visits through Week 24.

A follow-up visit will be conducted 8 weeks after completing the treatment period and/or 12 weeks (±7 days) after the last study drug injection for all subjects who will **not** continue nemolizumab treatment in the LTE study. Twelve weeks corresponds to approximately 5 half-lives of nemolizumab when administered subcutaneously Q4W at the doses used in this study.

10.3.2 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 7 may be conducted, but not all are required. Blood sample collection for POE and ADA analyses are required during unscheduled visits that are conducted for safety reasons when safety labs are collected for the management/monitoring of an AE. When a series of unscheduled visits is needed for the monitoring of the same AE, the POE and ADA collection is not required if already done at the first unscheduled visit of the series. Additional collection of samples for POE and ADA analysis should be performed per Investigator's judgment.

11 EFFICACY ASSESSMENTS

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) (see Appendix 3).

The same evaluator should perform all assessments for the same subject in order to reduce intra-subject variability.

11.2 Numeric Rating Scales

11.2.1 Peak Pruritus Numeric Rating Scales

An NRS relating to maximum intensity itch/pruritus (PP NRS) will be completed by the subject (see Appendix 4). The NRS will ask for a unit score on an 11-point scale (0 to 10) where 0 is "no itch" and 10 is the "worst itch imaginable". CCI [redacted]

11.2.2 Sleep Disturbance Numeric Rating Scale

An NRS relating to sleep disturbance (SD NRS) will be completed by the subject to report the degree of their sleep loss related to PN (see Appendix 5). The SD NRS will ask for a unit score on an 11-point scale (0 to 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 CCI [redacted]

11.3 Quality of Life Questionnaires

11.3.1 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 6).

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

12 SAFETY ASSESSMENTS

12.1 Vital Signs

Vital signs will be evaluated at all visits as indicated in the Schedule of Assessments (Table 7). 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 baseline visit identified as clinically significant by the Investigator will be recorded in the medical history form. Any clinically significant changes from the baseline 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 7).

12.3 Physical Examination

A complete physical examination should be performed according to the Schedule of Assessments (Table 7) at designated visits. 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.

A symptom-directed physical examination should be performed at all other visits according to the Schedule of Assessments (Table 7).

The Investigator should assess all abnormal findings for clinical significance. All clinically significant abnormal findings at the baseline visit will be recorded in the medical history form. Any clinically significant changes from the baseline 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 7). The 12-lead ECGs for each subject should be obtained using the electrocardiograph machine provided for the study. The 12-lead 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 at the baseline visit should be recorded in the medical history form. Results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. Any abnormalities considered by the Investigator to be clinically significant after the baseline visit are to be recorded as AEs and discussed with the Medical Monitor, as needed.

12.5 Clinical Laboratory Evaluation

Laboratory assessment samples are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 7).

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, e.g., 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 which 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 baseline visit will be recorded (report a diagnosis rather than the laboratory value whenever possible) in the medical history form. All clinically significant out-of-range laboratory values after the baseline visit are to be reported as an AE if this abnormality was not present at the baseline visit, or is assessed as having worsened since the baseline visit (i.e., changed significantly from the baseline 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. Laboratory testing conducted in a non-fasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual and in Appendix 8. Additional samples may be required if medically indicated (e.g., at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

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, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, 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 × upper limit of normal (ULN). The Investigator should also contact the Medical Monitor in such situations.

For postmenopausal subjects (i.e., no menses for 1 year), the blood chemistry sample at the baseline visit will also be used to confirm postmenopausal status by a high FSH level in the postmenopausal range, unless previously confirmed as part of the lead-in study.

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

Urine pregnancy tests (UPTs) will be conducted for all women of childbearing potential beginning at baseline and continuing at subsequent visits according to the Schedule of Assessments (Table 7). Pregnancy test results must be available prior to the administration of the study drug.

UPTs 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 Follicle-stimulating Hormone

The postmenopausal status (defined as no menses for 1 year) of a subject will be confirmed at the baseline visit, unless previously confirmed as part of the lead-in study. For these subjects, postmenopausal status will be confirmed with a FSH level in the postmenopausal range.

Blood chemistry sample at the baseline visit will also be used for an FSH test for the confirmation of postmenopausal status, if applicable.

12.5.6 Virology

Virology including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV), human immunodeficiency virus 1, and human immunodeficiency virus 2 antibodies may be assessed at unscheduled visits for safety purposes based on Investigator judgment. 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 (e.g., polymerase chain reaction).

12.5.7 Tuberculosis Testing

Subjects may be assessed for active or latent tuberculosis (TB) at unscheduled visits for safety purposes based on Investigator judgment. 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.

12.6 Respiratory Assessments

At baseline, the Investigator should specifically question all subjects about any medical history or changes in their asthma and respiratory health (e.g., 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 all visits according to the Schedule of Assessments (Table 7) before questioning and physical examination by the Investigator. Subjects with a new (de novo) diagnosis of asthma will take the ACT 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 7.

12.6.2 Respiratory Examination

A respiratory examination will be required to be performed for all subjects at specified visits according to the Schedule of Assessments (Table 7). Only subjects reporting a medical history of asthma will require a respiratory examination at all visits. Subjects with a new (de novo) diagnosis

of asthma will require a respiratory examination at all scheduled visits after the diagnosis is first made according to the Schedule of Assessments (Table 7).

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 (examination 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 specified visits according to the Schedule of Assessments (Table 7). Only subjects reporting a medical history of asthma will undergo PEF testing at all visits.

Subjects with a new (de novo) diagnosis of asthma will undergo PEF testing at all scheduled visits after the diagnosis is first made according to the Schedule of Assessments (Table 7).

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. [18, 19]

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 respiratory/asthma specialist physician whenever:

- Signs and/or symptoms suggestive of asthma are newly observed or reported
- Respiratory assessments (i.e., 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 baseline 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 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 (i.e., nemolizumab or placebo) and/or study procedure (e.g., 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 (International Council for Harmonisation [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 (i.e., 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 (e.g., 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 (±7 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, and 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 and the risks associated with biologics (and their biosimilar equivalents) in general (i.e., class effects), the following AEs will be considered AESIs:

- Injection-related reactions
  - Anaphylactic reactions
  - Acute allergic reactions requiring treatment
  - Severe injection site reaction (i.e., 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 is to be reported based on the investigator's clinical judgment, including consideration of the managing physician's report.
    - 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 (i.e., 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 (Section 8.3.2)
- 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, and/or
- 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 enrollment in the clinical trial, admission to a day care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., 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.

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

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 CCI [redacted] of an SAE report, by email or fax:
   CCI [redacted]

Note: Immediate SAE reporting is required by the Investigator if it occurs during the clinical study or within 12 weeks (±7 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 (e.g., laboratory test results) to the CCI [redacted] 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 (i.e., 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 suspected unexpected serious adverse reactions (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 (e.g., summary or listing of SAEs) from the Sponsor or its delegate (i.e., the CRO) will file it accordingly (i.e., 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 CCI [redacted] 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 (±7 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 (e.g., laboratory test results) to the CCI [redacted] 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 (i.e., the event is not consistent with the Reference safety information in the IB)
- there is at least a reasonable possibility for 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 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) within 7 days after the Sponsor (or CCI [redacted]) 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 CCI [redacted] first has knowledge of them.

The Sponsor (or CCI [redacted] 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 must have a negative pregnancy test result at baseline. 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 more injections 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 CCI [redacted]. 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 (±7 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 CCI [redacted] within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., 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 CCI [redacted] within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (i.e., 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 Medical Monitor of any occurrence of overdose with study drug.

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 OTHER ASSESSMENTS

13.1 Proof of Exposure

13.1.1 Blood Samples

Blood samples for proof of nemolizumab systemic exposure (POE) will be collected at the time points indicated in the Schedule of Assessments (Table 7) and the clinical laboratory manual. At each sampling time point for POE 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, POE 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, 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 (lower limit of quantification [LLOQ]: 100ng/mL). 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.

13.2 Immunogenicity Analysis

Blood samples will be collected at the time points indicated in the Schedule of Assessments (Table 7) and the clinical laboratory manual to assess anti-nemolizumab ADA.

The ADA will be determined by the designated CRO using a multi-tiered testing approach. A sensitive screening assay will first be used to assess clinical samples. Positive samples in the initial screening assay will be subjected to a confirmatory assay to demonstrate that ADA are specific for nemolizumab and not a result of non-specific interactions. Samples identified as positive in the confirmatory assay will be further characterized in 2 other assays, titering and neutralization antibody (Nab) assays.

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.

14 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed. All primary and secondary efficacy endpoints, and safety endpoints will be summarized. Summary statistics will be presented by treatment group and dose regimen. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group and dosing regimen. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group and dosing regimen. For time-to-event, data will be summarized using Kaplan-Meier method.

14.1 Determination of Sample Size

No formal sample size calculations were performed for this study. The sample size will be based on the sample size and the actual response rate of the LTE study. Based on the current assumption, it is expected that approximately 40 subjects will be randomized.

14.2 Analysis Populations

Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects. All primary and secondary efficacy endpoints will be analyzed based on the ITT population. All analyses on the ITT population will be analyzed under the treatment group “as randomized”.

Safety Population

The safety population will comprise all randomized subjects who receive at least 1 dose of study drug. All safety data will be summarized based on the safety population under the treatment group “as treated”.

Proof of Exposure Analysis Population

The POE analysis population will include all subjects in the safety population who provide at least 1 measurable post-baseline evaluable drug concentration value.

Per-Protocol Population

The per-protocol population will comprise 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. Only

primary and selected secondary efficacy endpoints will be analyzed using the per-protocol population, as defined in the SAP.

14.3 Efficacy Analysis

A summary based on observed case (OC) will be provided for all primary and secondary efficacy endpoints. For OC, no data will be imputed.

14.3.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the time to relapse which is defined as meeting at least 1 of the following criteria:

- Increase in (weekly average of the) PP NRS score ≥4 points from baseline
- Increase in IGA score ≥2 points from baseline

The estimand of primary endpoint is shown in Table 8. Treatment interruption and use of prohibited medication are considered as intercurrent events.

Table 8. Estimand of Primary Endpoint

Treatment	Population	Endpoint	Intercurrent events	Summary measure
Randomized treatment with subcutaneous injections of nemolizumab or placebo at Week 0, 4, 8, 12, 16 and 20	All randomized subjects (intent-to-treat population)	Time to relapse meeting at least 1 of the defined criteria	Time to relapse will be censored at the last observation prior to treatment discontinuation or use of prohibited medication	Hazard ratio of nemolizumab and placebo

As the primary analysis, the time to relapse will be analyzed using Cox proportional hazard model with treatment group, dosing regimen as a factor, and baseline PP NRS score and IGA score as covariates. The estimated hazard ratio and the corresponding 95% CI will be presented. If the assumption of proportionality is not met, other appropriate methods will be used and documented in the SAP.

In addition, Kaplan-Meier survival plots will be presented for time to relapse. The median time, 25th and 75th percentiles, and the corresponding CI will be reported.

If a subject withdraws from the study, takes prohibited medication, or completes the study without any relapse, time to relapse response will be censored respectively at the time of the last efficacy assessment (PP NRS and IGA) prior to study withdrawal, use of prohibited medication, or the completion of the study. If a subject has no efficacy assessment after randomization, then time to relapse will be censored at Day 1.

For the purpose of efficacy analysis, subjects receiving any prohibited therapies will be censored from the primary analysis.

As a supporting analysis, the time to relapse will also be analyzed using the same methods in the per-protocol population.

14.3.2 Analysis of Secondary Efficacy Endpoints

The following binary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for dosing regimen based on OC and imputation with missing efficacy response considered as the non-responder (i.e., IGA success) and missing relapse response considered as a relapse (i.e., increase in PP NRS or IGA):

- Proportion of subjects with increase in PP NRS score ≥2 points from baseline at each scheduled visit
- Proportion of subjects maintaining IGA success, defined as IGA score of 0 (clear) or 1 (almost clear) at each scheduled visit
- Proportion of subjects with increase in IGA ≥2 points from baseline at each scheduled visit

The estimate of treatment difference (nemolizumab minus placebo), the corresponding 2-sided 95% CI, and p-values will be presented.

The following continuous efficacy endpoints will be analyzed using analysis of covariance (ANCOVA) based on OC with treatment group and dose regimen as factors, and baseline value as the covariate. They will also be analyzed using the mixed effect model for repeated measure (MMRM) approach, including treatment group and dose regimen as factors, visit, interaction term between treatment and visit, and the corresponding baseline value as independent covariate.

- Absolute and percent change from baseline in PP NRS at each scheduled visit
- Absolute and percent change from baseline in SD NRS at each scheduled visit
- Change from baseline in DLQI at Week 16 and Week 24

The multiple imputation methods may be used as sensitivity analysis for some selected secondary efficacy endpoints.

14.4 Safety Analysis

Extent of Exposure

The duration of exposure will be summarized by treatment and dosing regimen. The number of subjects exposed to study medication will be summarized by visit, treatment group, and dosing regimen.

Adverse Events

All reported AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs, defined as those AEs occurring after the first administration of study treatment until the end of the follow-up period, will be tabulated in frequency tables by system organ class and preferred term. These TEAEs may also be reported separately for treatment period and follow-up period. Additional summary tables will be provided for SAEs, treatment-related AEs (reasonable possibility, no reasonable possibility), AESIs, and AEs leading to treatment discontinuation. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized by visit, treatment group and dosing regimen. In addition, the number and percentage of subjects below, within, and above the laboratory reference ranges, and the number and percentage of subjects who met criteria of potential clinically significant value will be summarized by visit, treatment group, and dosing regimen. Shift tables will be generated using the reference ranges. Reference ranges will be provided in the laboratory manual.

Vital Signs

All vital signs (absolute values and change from baseline) will be summarized by visit, treatment group, and dose regimen. In addition, the number and percent of subjects with clinically significant abnormal values (of clinical concern as identified by the Investigator) will be summarized by visit, treatment group, and dosing regimen.

12-Lead ECG

The number and percentage of subjects who have ECGs that are abnormal/clinically significant and abnormal/not clinically significant will be displayed by visit, treatment, and dosing regimen.

Respiratory Assessments

The results (absolute values and change from baseline) of PEF testing and respiratory examination will be summarized by visit, treatment group, and dose regimen. ACT for subjects with a medical history of asthma or newly-diagnosed asthma will be listed.

Concomitant Therapies and Procedures

Concomitant therapies will be coded according to the most recent version of the World Health Organization (WHO) Drug Dictionary Enhanced for Concomitant Medication. Concomitant therapies and procedures will be summarized.

Summary tables will be provided for concomitant medications initiated during the study period.

14.5 Proof of Exposure and Anti-Drug Antibody Analysis

The nemolizumab serum concentration and ADA will be summarized by visit in the POE analysis population.

For serum concentrations (POE), descriptive statistics will include arithmetic and geometric mean, standard deviation, coefficient of variation [%CV], median, minimum, maximum. A 95% confidence interval [CI] of mean and number of Below Limit of Quantifications will be presented. Any potential exposure-safety relationship will also be explored. Below Limit of Quantifications will be considered as missing and excluded from the descriptive summary.

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

14.6 Interim Analysis

An interim analysis may be conducted for the submission of the regulatory registration of nemolizumab. To maintain blinding, the interim analysis would be carried out by an independent group who are not directly involved in the conduct of the trial.

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 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 US Code of Federal Regulations (CFR), in compliance with ICH and Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study is conducted.

15.1.2 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.

15.1.3 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.

15.2 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.

15.3 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 study center'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.

15.4 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 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 (Health Insurance Portability and Accountability Act [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 and in a form satisfactory to the Sponsor.

15.5 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 PI will assure he/she and adequate study center 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.

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

15.6 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 centers and during data management to assure that safety and efficacy data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 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 acknowledgment 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 study centers until such approvals are received other than in the case of an urgent safety measure.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Protocol deviations will be reported to the IRB/IEC and in accordance with applicable regulatory authority mandates.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The Investigator should document and explain any deviation from the clinical study protocol. Major deviations are categorized into the following categories:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study medication
- Non-compliance with study medication per the Investigator's discretion

- Non-compliance with study procedures if the consequence of non-compliance would compromise either the subject's safety and/or the study integrity, primary endpoint, and/or is not in line with GCP/ICH guidelines
- Use of prohibited concomitant therapies
- Visit/treatment windows (i.e., 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 described 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.

15.8 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.

15.9 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.

15.10 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.

15.11 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s) approving this research, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identities will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations on personal data protection.

16 REFERENCES

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17 APPENDICES

Appendix 1 Specific Guidance for Study Conduct and Subject Safety during the Coronavirus Disease 2019 (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 of 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 enrollment 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 judgment. 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 8.3.2. Known or suspected COVID-19 infection will also be followed as an AESI.

New Subsection to Section 7.1, Description of 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 generic environmental risks (e.g., being outside of the 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 baseline, 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 enrollment.

Pre-baseline 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 and Prevention (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 8.3.2.
- 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) may be collected remotely (e.g., completed over the phone), as available.

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 IFU, including preparation of study drug by an independent pharmacist or other qualified personnel.
- ACT (for subjects with a medical history of asthma or newly-diagnosed asthma) and PEF (for all subjects at specified visits and more frequently for subjects with a history of asthma or newly-diagnosed asthma) should 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 on-site 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 examination, 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 9.4, Dosage 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 or newly-diagnosed asthma)
    - Concomitant therapies used
    - Urine pregnancy test results (for women of childbearing potential)
    - 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 trained on site at baseline visits.
- 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 depending on the judgment of the investigator (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 judgment.
  - Subject-reported assessments that would usually be collected on the site tablet (e.g., ACT) may be completed over the phone, as available.

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

New Subsection to Section 9.4, Dosage 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. 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 doses, the Investigator must contact the Sponsor for further guidance. Subjects will complete a follow-up visit 12 weeks after the last study drug injection.

15.5 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

Appendix 2 Contraception Guidelines

Women of childbearing potential (WOCBP) must use at least 1 adequate 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
- sexual 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.

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