Statistical Analysis Plan

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I confirm that I have reviewed this document and agree with the content.

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Syneos Health Approval

PPD		03-Mar-2023
Name, Title Developing Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD		06-Mar-2023
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

Galderma S.A./Galderma R&D, LLC Approval

PPD		03-Mar-2023
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
A	Anxiety
ACT	Asthma Control Test
ADA	Anti-Drug Antibodies
ADaM	Analysis Dataset Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Average Pruritus
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CHMP	Committee for Medicinal Products
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease-19
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinical Significant
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
D	Depression
DBL	Data Base Lock
DCS	Dual-Chamber Syringe

Abbreviation	Description
DD	Drug Dictionary
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcome
EQ-5D	EuroQoL 5-Dimension
ET	Early Termination
FSH	Follicle-Stimulating Hormone
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDL	High-Density Lipoproteins
HIV	Human Immunodeficiency Virus
IAC	Independent Adjudication Committee
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identifier
IDMC	Independent Data Monitoring Committee
IGA	Investigator Global Assessment
IL	Interleukin
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL	Low-Density Lipoproteins
LLN	Lower Limit of Normal
LLT	Lowest Level Term
LOCF	Last Observation Carried Forward
LTE	Long-Term Extension

Abbreviation	Description
LSMeans	Least Squares Means
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
min	Minutes
MMRM	Mixed-Effect Models for Repeated Measures
MNAR	Missing Not at Random
MSD	Morning Sleep Diary
N/A	Not Applicable
NAb	Neutralizing Antibodies
NCS	Not Clinical Significant
NRS	Numeric Rating Scale
OC	Observed Case
PAS	Prurigo Activity Score
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PDF	Portable Document Format
PEF	Peak Expiratory Flow
PGx	Pharmacogenomic
PGAD	Patient Global Assessment of Disease
PGAT	Patient Global Assessment of Treatment
PGIC-P	Patient Global Impression of Change – Pruritus
PGIC-SD	Patient Global Impression of Change – Sleep Disturbance
PGIS-P	Patient Global Impression of Severity – Pruritus
PGIS-SD	Patient Global Impression of Severity – Sleep Disturbance
pH	Potential of Hydrogen
PK	Pharmacokinetic
PN	Prurigo Nodularis
PopPK	Population Pharmacokinetic
PP NRS	Peak Pruritus Numeric Rating Scale

Abbreviation	Description
PP	Per-Protocol
PPS	Per-Protocol Set
PRO	Patient-Reported Outcome
PT	Preferred Term
Q1	1st Quartile
Q3	3d Quartile
Q4W	Every 4 Weeks
QC	Quality Control
QoL	Quality of Life
RNA	Ribonucleic Acid
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SD NRS	Sleep Disturbance Numeric Rating Scale
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
TMF	Trial Master File
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
USA	United States of America
VAS	Visual Analogue Scale
W	Week
WASO	Wakefulness after Sleep Onset

Abbreviation	Description
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective clinical study report (CSR).

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

Descriptive summary and listing will be provided for pharmacokinetic concentration. Definition of the Pharmacokinetic analysis population and derivation of Pharmacokinetic parameters will be performed by a designated CRO. This designated CRO will be responsible for the ad-hoc Modeling / Simulation Plan and the Modeling & Simulation Report. Any analysis of pharmacokinetic parameters will not be included in the CSR final TFLs but in the dedicated Modeling & Simulation Report. For further details see Section 11.2.

2.2. Timings of Analyses

The final analysis will be carried out once all subjects have completed the final study visit or terminate early from the study. No personnel directly involved with the conduct of the study shall have access to the unblinded data before the completion of the trial in order to avoid introducing bias to the remaining study data.

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 adverse events throughout the study. Details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities, and communications are provided in the respective IDMC (v2.0, dated 01-Nov-2021) and Appendix 2 of IAC charters (v2.0, dated 13-Jan-2022).

3. Study Objectives

3.1. Primary Objective

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

3.2. Secondary Objectives

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

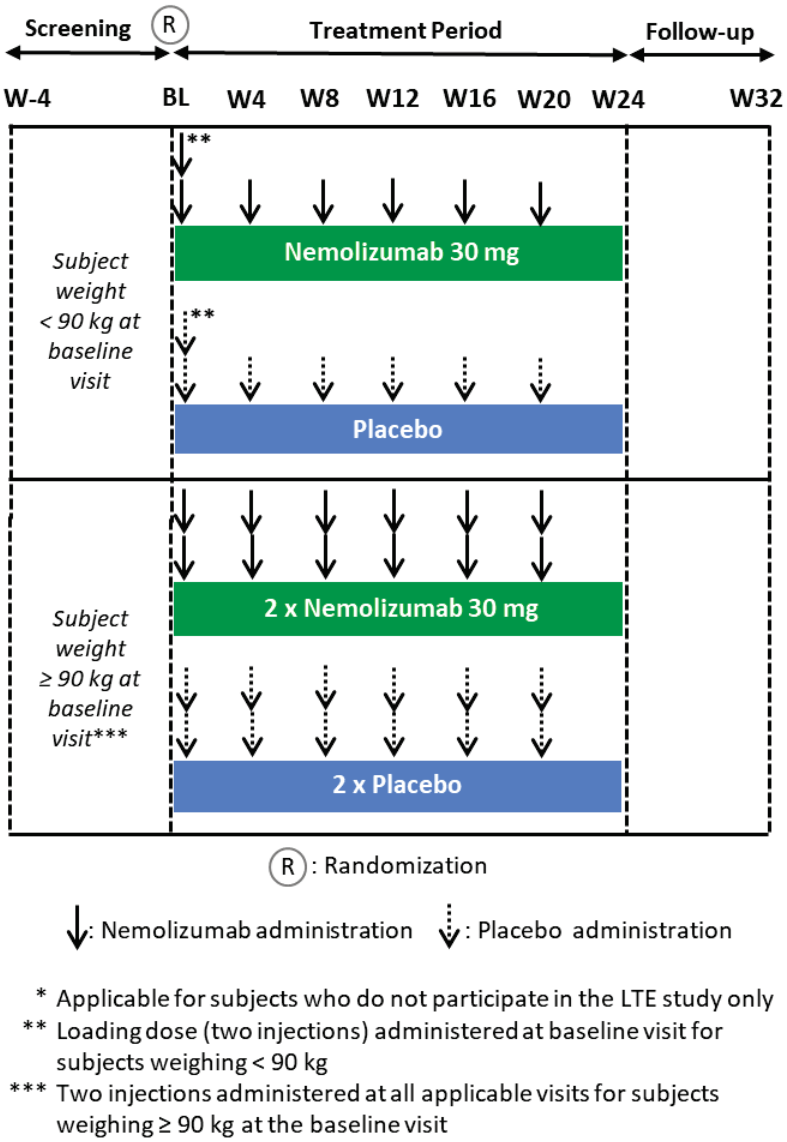
4. Study Details/Design

4.1. Brief Description

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

Subjects' participation in the study will be up to 36 weeks. The study consists of a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow up period (12 weeks after the last study drug injection). Refer to Figure 4-1 for an overview of study design.

Figure 4-1: Study Design



Abbreviations: BL = baseline; W = week.

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

At the end of the 24-week treatment period, consenting subjects may be eligible to enter an active treatment/long-term extension (LTE) study (RD.06.SPR.202699). Subjects who participate in the LTE are not required to complete the follow-up visit. Subjects who do not participate in the LTE will return for a follow-up visit at Week 32 (12 weeks after the last study drug injection).

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

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

A 16-week treatment period is considered adequate to evaluate the efficacy and safety of Nemolizumab based on the results of the phase 2a study (RD.03.SPR.115828) in subjects with PN. A further 8-week treatment period is included to provide additional data as requested by the European Medicines Agency for chronic diseases such as PN. All subjects who complete the treatment period (Week 24 visit) can be considered for LTE study eligibility. A 2-to-1 randomization is selected to minimize the number of subjects exposed to placebo for an extended period of time.

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

The study includes an 8-week follow-up period (i.e., 12 weeks after the last study drug injection) for subjects who decline or are not eligible to enroll in the LTE study. The duration of the follow-up period from the final Nemolizumab dose (12 weeks) corresponds to approximately 5 half-lives of Nemolizumab, which is

considered adequate to ensure subject safety. The follow-up visit is not required for subjects who participate in the LTE, where the primary objective is long-term evaluation of safety.

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

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

To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, blinded statistical team at Syneos Health, or other investigational study centers will not have access to any information that may lead to unblinding.

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including Week 24 or the last scheduled visit as indicated in the Schedule of Assessments (Table 4-2).

The end of the study will be the last subject's last visit or the last subject's scheduled visit as indicated in the Schedule of Assessments (Table 4-2).

4.2. Subject Selection

Eligible subjects for this clinical study will be adults with a clinical diagnosis of PN for at least 6 months, manifested by pruriginous nodular lesions on the trunk and/or limbs, and at least 20 nodules on the entire body bilaterally distributed. The inclusion criterion for IGA is consistent with the disease severity targeted in the study: An IGA of 3 or 4 corresponds to moderate or severe PN, at both the screening and baseline visits respectively. Severe pruritus will be defined by PP NRS scores ≥ 7.0 within the past 24 hours at screening and the mean PP NRS score ≥ 7.0 during the previous week at baseline. Subjects with chronic pruritus due to other active conditions or unilateral pruriginous lesions are ineligible. Further, subjects must undergo specific required washout periods from restricted topical and systemic treatments before enrolling in the study. The study population is selected based on the current unmet need in the management of PN, the mode of action of Nemolizumab (CD14152), and the need to understand the efficacy and safety of Nemolizumab (CD14152) in the adult population with PN.

4.2.1. Inclusion Criteria

For a detailed description of subject's inclusion criteria see protocol Section 8.1.

4.2.2. Exclusion Criteria

For a detailed description of subject's exclusion criteria see protocol Section 8.2.

4.3. Determination of Sample Size

In order to achieve at least 90% power for both primary endpoints at 5% significance level, 270 (180 Nemolizumab, 90 placebo) subjects will be randomized to detect the following differences in both primary

endpoints between treatment groups with 2:1 randomization, assuming a 15% dropout rate during treatment period.

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

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

Table 4-1 provides the resulting power with 270 subjects (180 Nemolizumab, 90 placebo) for different responses in primary endpoints.

Table 4-1: Results of Power Analysis

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

4.4. Treatment Assignment and Blinding

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

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

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

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 dual-chamber syringe (DCS) preparation, will not have access to the randomized treatment assignment.

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

As there may be detectable differences between active and placebo during the reconstitution process, the DCS is delivered for injection after the reconstitution is complete. The pharmacist (or other qualified personnel) preparing study drug should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments.

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

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 a minimum of 12 weeks after the last dose of study drug.

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

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

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

4.5. Administration of Study Medication

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

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

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

4.6. Study Procedures and Flowchart

See Table 4-2 for study procedures.

Table 4-2: Schedule of Assessments

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

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

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

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

Notes:

a) Screening visit must be performed at least 7 days prior to Day 1 visit. Subjects deemed eligible will be provided with electronic handheld devices.
b) Subjects will complete PGIS-P, PGIC-P, PGIS-SD, PGIC-SD, and PGAD assessments at Week 1 (ie, 7 days after the Day 1/Baseline visit) for test-retest validation of itch and sleep PRO measures.
c) The follow-up visit will be conducted for subjects who decline or are not eligible to enter the LTE study (including early termination) and should be conducted 12 weeks after the last study drug injection. (The follow-up visit is not required for subjects who will rollover to the LTE study.)
d) Assessments to be conducted at the unscheduled visit depend on the reason for the visit. PK and ADA analyses are required only at unscheduled visits that are conducted for safety reasons. Subjects requiring rescue therapy between scheduled visits should return to the clinic for an unscheduled visit for investigator assessments of efficacy before starting rescue therapy. See Section 10.2.1 for details.
e) SD NRS and sleep diary questions to be recorded by subjects once daily in the morning and if possible, within 1 hour of getting out of bed (Visit 1/Screening through Visit 8/Week 24). PP NRS and AP NRS to be recorded by subjects once daily in the evening (Visit 1/Screening through Visit 8/Week 24), beginning after the screening visit. On designated visits, PGIS-SD and PGIC-SD should be recorded after the SD NRS and sleep diary in the morning; PGIS-P and PGIC-P should be recorded after the PP NRS and AP NRS in the evening.
f) Pruritus assessments scheduled for clinic visit days that are recorded by subjects in the evening (ie, PP NRS, AP NRS, PGIS-P, PGIC-P) will be recorded the evening before the clinic visit.
g) Patient-reported outcome assessments and designated safety measurements should occur before investigator assessments, laboratory sample collections, and study drug administration.
h) Optional for consenting subjects and only for selected equipped sites; see Section 11.8 for details on clinical photographs.
i) Subjects with a medical history of asthma will complete the ACT testing at each scheduled visit. Subjects with de novo asthma will complete the ACT testing beginning from de novo diagnosis and at all subsequent scheduled visits.

j) PEF testing will be performed for all subjects at screening, baseline, Week 8, Week 16, Week 24, and follow-up visits. For subjects reporting a medical history of asthma, PEF testing will be performed at all visits during the clinical study. For subjects diagnosed with de novo asthma, PEF testing will be performed at all visits, starting with the visit in which the diagnosis was confirmed. Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject. See Section 12.6.3 for details.
k) 12-lead ECGs should be performed in the supine position, before any scheduled vital sign measurements and blood draws. See Section 12.4.
l) In case of indeterminate result for TB test, the test should be repeated (only 1 retest is allowed). If the test is still indeterminate, the subject must not be included in the study, unless subject has a documented history of completion of an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed.
m) Subjects should be well hydrated and fast for at least 8 hours before the visit(s) when blood chemistry testing is planned, except for the screening visit.
n) At scheduled visits with laboratory, PK, and ADA assessments, samples are to be collected before study drug injection(s).
o) Only for females of childbearing potential. Serum pregnancy test to be performed at screening visit and UPT for all other visits. If UPT is positive, it must be confirmed with a serum pregnancy test. See Section 12.5.4 for details.
p) For postmenopausal subjects (ie, no menses for 12 consecutive months), confirm status with a high FSH level in the postmenopausal range.
q) As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples). See Section 13.1 for details on PK assessments.
r) Blood, stratum coreum, and biopsy samples for PD assessments are only collected at selected sites. Biopsy samples are optional and only for subjects who provide additional consent. See Section 14.3 for details.
s) Optional PGx sample collection is only for subjects who provide additional consent. See Section 14.1 for details.
t) Subjects weighing < 90 kg at baseline will receive a loading dose on Day 1 (ie, 2 injections of nemolizumab 30 mg or placebo) then single injections of either 30 mg nemolizumab or placebo Q4W. Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo via 2 injections Q4W at all study visits.
u) Study drug reconstitution will be performed by the pharmacist (or other qualified personnel) throughout the study, and complete reconstitution confirmed, prior to delivery for injection. Study center staff will provide study drug injection training for subjects willing and able to self-inject study drug. Based on the subject's preference, study center staff can also perform all injections.
v) After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. For the first 2 visits where study drug is administered, subjects should remain at the study center for at least 30 minutes following study drug administration.

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

5. Endpoints

5.1. Primary Efficacy Endpoints

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

5.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

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

5.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

- Proportion of subjects with AP NRS < 2 from baseline through Week 24
- Absolute change from baseline in AP NRS through Week 24
- Percent change from baseline in AP NRS through Week 24
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS through Week 24
- Absolute change from baseline in SD NRS through Week 24
- Percent change from baseline in SD NRS through Week 24
- Change from baseline in sleep diary endpoints (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN) based on recordings from subject sleep diary through Week 24
- Distribution of PN-associated pain frequency through Week 24
- Proportion of subjects with PN-associated pain frequency rating = 5 (every day) at each visit through Week 24
- Change from baseline in PN-associated pain intensity through Week 24
- Percentage change from baseline in PN -associated pain intensity at each visit through Week 24
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at Week 24
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at Week 24
- Proportion of subjects with an improvement of ≥ 4 in Dermatology Life Quality Index (DLQI) through Week 24
- Change from baseline in DLQI through Week 24
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) for each subscale (i.e., depression and anxiety) at Week 24
- Change from baseline in EuroQoL 5-Dimension (EQ-5D) at Week 24

5.4. Pharmacokinetic Endpoints

- Nemolizumab (CD14152) serum concentrations

5.5. Immunogenicity Endpoints

- ADA assay (screening, confirmatory, final, titer, NAb)

5.6. Safety Endpoints

- Incidence and severity of AEs, including TEAEs, AESIs, SAEs and Adjudicated AEs
- Clinical laboratory tests
- Vital signs
- Electrocardiogram
- Physical examination

- Respiratory assessment including respiratory examination, Peak expiratory flow, and Asthma Control Test (ACT)

6. Analysis Sets

6.1. Screened Population

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

Unless specified otherwise, this set will be used for subject listings and summaries of subject disposition.

6.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all randomized subjects. The ITT population will be the primary population for efficacy analyses. All analyses under the ITT population will be analyzed under the treatment group as randomized.

6.3. Per-Protocol Population

The Per-Protocol (PP) population will consist of all subjects in the ITT population and have no major protocol deviations that would have a significant effect on the efficacy of the study treatment (see Section 6.6). Primary, key secondary and selected secondary endpoints will be analyzed using the PP population, under the treatment group as randomized.

6.4. Safety Population

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

6.5. Pharmacokinetic Analysis Population

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

6.6. Protocol Deviations

Protocol deviations will be recorded by the Clinical Research Associate (CRA) in the Clinical Trial Management System (CTMS). All protocol deviations will be categorized by the associated deviation type and will be assessed individually on a regular basis on whether they are major or minor. Details can be found in the Protocol Deviation and Non-compliance Management Plan.

Major protocol deviations that are analysis relevant lead to an exclusion of the subject from the per-protocol population. A case by case decision regarding exclusions of subjects from the per-protocol analysis will be made in a blind data review meeting (BDRM) which will take place prior to unblinding the study. The criteria for exclusion from the PP population will be specified in the BDRM Preparation Plan. Only major protocol deviation which have a significant effect on the primary efficacy will result in exclusion from the PP population.

A summary table for number and percentage of subjects with major protocol deviation will be generated by type of deviation and treatment group for the ITT population.

Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded and presented as a COVID-19 deviation. The number and percentage of subjects with major (including major COVID-19) deviation will be provided by type of deviation and treatment group for the ITT population and additionally provided by Site.

All protocol deviations and the protocol deviations related to COVID-19 will be listed for the ITT population.

7. Estimands

The primary and key secondary efficacy endpoints will be evaluated and assigned to treatment at the time of randomization based on ITT population. The estimand is defined to address the scientific question relevant to subjects who are able to complete treatment with a response assessment without further medication being required, other than the allowed rescue medication.

An intercurrent event is an event which occurs after start of treatment and thus complicates the description and interpretation of treatment effects. Table 7-1 below lists potential intercurrent events and the strategy to deal with them for the estimand. The estimands for endpoints are defined in Table 7-2*: Estimands for Co-primary Endpoints (2 endpoints)* and Table 7-3.

Table 7-1: List of Intercurrent Events

Intercurrent Event	Strategy to Deal With Intercurrent Event (ICE) Within Analysis	Assessment of Subject
Treatment discontinuation	Treatment-policy strategy	Use observed response.
Rescue therapy	Composite strategy (Continuous endpoints & Binary endpoints)	Subjects will be treated as treatment failures on or after rescue therapy. The values of the variable of interest collected on or after the use of rescue therapy will be set to the worst possible value of the score. For diary data, if subject took rescue therapy within the analysis visit window, weekly average on or after visit window will be computed as 'worst-case value'. Subject's binary response will be calculated based on the underlying value.
Rescue therapy	Hypothetical strategy (Continuous endpoints)	Subject will be treated as treatment failures on or after intake of rescue therapy and will be considered as missing before running MMRM analysis. For diary data, if subject took rescue therapy within analysis visit window, weekly average on or after visit window will also be considered missing before running MMRM analysis. Treatment effect estimated by MMRM model assumes the subject with ICEs would have followed same as other subjects in the same treatment. Applicable only for the MMRM analysis.

Table 7-2: Estimands for Co-primary Endpoints (2 endpoints)

Endpoints	Estimands
Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 16	**Population:** ITT population
	Endpoint: a binary response indicates if subjects have a change from Baseline of ≥ 4 at Week 16
	Intercurrent events: use of rescue therapies on or prior to Week 16 is considered as treatment failure; the observed response at Week 16 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate
Proportion of subjects with an IGA success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at Week 16	**Population:** ITT population
	Endpoint: a binary response indicates if subjects have IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline at Week 16
	Intercurrent events: use of rescue therapies on or prior to Week 16 is considered as treatment failure; the observed response at Week 16 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate

Table 7-3: Estimands for Key Secondary Endpoints (5 endpoints)

Endpoints	Estimands
Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 4	**Population:** ITT population
	Endpoint: a binary response indicates if subjects with an improvement of PP NRS ≥ 4 at Week 4
	Intercurrent events: use of rescue therapies on or prior to Week 4 is considered as treatment failure; the observed response at Week 4 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate
Proportion of subjects with PP NRS < 2 at Week 16	**Population:** ITT population
	Endpoint: a binary response indicates if subjects with PP NRS < 2 at Week 16
	Intercurrent events: use of rescue therapies on or prior to Week 16 is considered as treatment failure; the observed response at Week 16 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate

Endpoints	Estimands
Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16	**Population:** ITT population
	Endpoint: a binary response indicates if subjects with an improvement of SD NRS ≥ 4 at Week 16
	Intercurrent events: use of rescue therapies on or prior to Week 16 is considered as treatment failure; the observed response at Week 16 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate
Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4	**Population:** ITT population
	Endpoint: a binary response indicates if subjects with an improvement of SD NRS ≥ 4 at Week 4
	Intercurrent events: use of rescue therapies on or prior to Week 4 is considered as treatment failure; the observed response at Week 4 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate
Proportion of subjects with PP NRS < 2 at Week 4	**Population:** ITT population
	Endpoint: a binary response indicates if subjects with PP NRS < 2 at Week 4
	Intercurrent events: use of rescue therapies on or prior to Week 4 is considered as treatment failure; the observed response at Week 4 after treatment discontinuation will be used in the analysis
	Summary measure: treatment difference of Nemolizumab and placebo in response rate

8. General Aspects for Statistical Analysis

8.1. General Methods

- All data will be listed, and summary tables will be provided.
- Unless otherwise specified, summaries will be presented for each treatment and overall, if indicated, by visit.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, 1st Quartile (Q1), 3rd Quartile (Q3), minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects in each category.
- Unless otherwise stated, all statistical tests will be two-sided and conducted at the 5% level; all presented confidence intervals (CIs) will be two-sided 95% CIs.

8.2. Key Definitions

Screening period is a period of up to 4 weeks before Baseline/Day 1 during which subject eligibility is evaluated. Subjects receiving rescue therapies during the screening period are not eligible to participate in the study.

The 24-week **treatment period** is defined as Baseline/Day 1 to Week 24. If early discontinued during treatment period, it is defined as the period until 4 weeks (<=28 days) after last dosing date or early termination date whichever is earlier.

Follow-up period is defined as the post end of treatment period to follow-up visit in respective treatment period.

The **Baseline value** is defined as the last non-missing value before the first dose of study drug. In case that the date of first injection is not available, the date of randomization is considered.

For diary data (PP NRS, SD NRS), the Baseline values will be derived from data collected during the 7 days prior to the first administration of study drug, if subject is treated. Otherwise, the data collected during 7 days prior to randomization will be used. Baseline score will be the weekly prorated average of non-missing subject diary scores reported during the 7 days. A minimum of 4 daily scores out of the 7 days is required to calculate the weekly prorated average score. If there are less than 4 non-missing assessments in the baseline diary window, the interval lower bound can be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values. For sensitivity analysis, a minimum of 2 or 3 daily scores out of the 7 days will be used to calculate the weekly prorated average score for primary and key secondary endpoints and the interval will not be extended with additional days.

The **date of first treatment** is defined as the date of first injection of study drug.

The **date of last treatment** is defined as the date of last injection of study drug.

Study day is defined as the number of days from the date of first treatment (randomization date if not treated) and will be calculated as follows:

- If the event date ≥ date of first treatment, then study day = event date - date of first treatment + 1.

  Treatment Day 1 is therefore defined as the day of first treatment.

- If the event date < date of first treatment, then study day = event date - date of first treatment.
- If subject is randomized, but not treated and event date ≥ date of first treatment, then study day = event date - date of randomization.
- If subject is randomized, but not treated and event date < date of first treatment, then study day = event date - date of randomization.

A subject's **date of last participation** in the trial is the last date of contact and is recorded as the date of completion or date of withdrawal on the completion page of the case report form (CRF).

Only the **subjects infected by COVID-19** during study participation will be considered subjects with COVID-19 infection.

8.3. Missing Data

The primary method to impute the missing values will be as follows:

Continuous Endpoints: For continuous secondary endpoints (except EQ-5D, HADS) during treatment period, the MI under MAR assumption approach and the MMRM approach will be used to handle the missing data.

Binary Endpoints: All missing values will be treated as a non-responder for the binary endpoints for primary, key secondary and secondary endpoints. To assess the robustness of non-responder analysis for primary and key secondary endpoints, a tipping point analysis will be performed. The MI under MAR assumption, last observation carried forward (LOCF) approach, and observed case (OC) approach will be used as sensitivity analysis to impute the missing values for the primary and key secondary endpoints. If applicable, the continuous response will be imputed first, and the response will then be categorized.

Use of rescue therapy: All efficacy data, except OC, will be treated as treatment failure. Binary endpoints will be based on the underlying values and continuous variables will be imputed using the worst case score (questionnaires) or worst case value (diary data), on or after rescue therapy is used, independent if visit was attended or not. This procedure will be completed before imputing missing data under different assumptions (i.e., non-responder, LOCF, MI under MAR/MNAR). A different approach will be applied for MMRM analysis where data on or after rescue therapy will be considered as missing before applying MMRM analysis.

In OC analysis, no observed data after subject has received rescue treatment will be excluded. There will be no imputations for missing data.

Adverse events and concomitant medications/procedures: Missing assessment times will have imputed times for the purposes of assessing treatment emergence for AEs or classifying medications/procedures into prior/concomitant. However, the assessment date and time (start date, stop date, and time if collected from CRF) without imputation will be presented in the listings.

For the start of a concomitant medication/procedure or AE:

- Only the year is reported: If the subject received the first study drug dose in the year reported, then the date of the first dose of study drug will be used as the start date; otherwise, January 1 of the year reported will be used as the start date.

- The month and year are reported: If the subject received the first study drug in the month and year reported, then the date of the first dose of study drug will be used as the start date; otherwise, the first day of the month and year will be used as the start date.

- The time is collected but missing: If the start date is the same as the date the subject started receiving study drug, then the time of the first dose of study drug will be used as the start time; otherwise, 00:00 will be used as the start time.

For the end of a concomitant medication/procedure or AE:

- Only the year is reported: The earlier between December 31 of the year reported and the date of the last study contact with the subject will be used as the stop date.

- The month and year are reported: The earlier between the last date of the month and year reported and the date of the final contact with the subject will be used as the stop date.

- The time is collected but missing: 23:59 (or 23:59:59 if collected up to seconds) will be used as the stop time.

If an AE has the start date completely missing and the stop date on/after the first dose date of study drug, this AE will be considered as treatment emergent (TEAE).

If a medication/procedure has the stop date completely missing, this medication/procedure will be considered as ongoing and concomitant. If the start date of a medication/procedure is completely missing and impossible to identify different by stop date, this medication will be considered as concomitant.

8.4. Visit Windows

Efficacy by-visit summaries will use the analysis visit. All visits (Scheduled, Unscheduled and early termination visits) will be windowed based on the analysis visit window in Table 8-1 which is based on study day. If multiple measurements are taken within the same window, the one taken closest to the target study day will be used for the analysis. If there are multiple measurements with same difference from target day, the later assessment should be used for the analysis.

Table 8-1: Analysis Visit Window

Analysis Visit	Target Study Day	Visit Window for IGA, PAS, PN associated Pain frequency and intensity	Visit Window for PGIS-P, PGIS-SD, PGIC-P, PGIC-SD, PGAD, PGAT, EQ-5D, HADS	Visit Window for DLQI
Baseline	1	≤ 1	≤ 1	≤1
Week 1	8	NA	2 to 60	NA
Week 4	29	2 to 42	NA	2 to 60
Week 8	57	43 to 70	NA	NA
Week 12	85	71 to 98	NA	NA
Week 16	113	99 to 126	61 to 154	61 to 154
Week 20	141	127 to 154	NA	NA
Week 24	169	155 to 210	155 to 210	155 to 210

Week 32 Follow-up	225	211 to 238	NA	NA

All daily diary efficacy data will be classified into analysis visits as described in Table 8-2 considering the data during the 7 days immediately preceding the target day of analysis visit.
Analysis visit of diary (ePRO) data will be defined depending on the data collection as below.

Diary data assessed within the extended timeframe below will be considered for analysis. The following rule will be applied for post-treatment assessments only.

- Evening assessment (PP/AP NRS) recorded from 17:00:00 to 00:59:59
- Morning assessment (SD NRS, morning sleep diary) recorded from 5:00:00 to 17:59:59

Consecutive daily assessment:
For the evening assessments (PP NRS, AP NRS), the daily data collected up to Week 24 will be classified into analysis visits considering the data during the 7 days immediately preceding the target study day of analysis visit. Similarly, for the morning assessment (SD NRS, morning sleep diary), the 7 days data up to the target study day will be classified into analysis visit. Details of the analysis visit window are in Table 8-2 below.

Table 8-2: Analysis Visit Window for Evening and Morning Assessments*

Analysis Visit	Target Study Day of Analysis Visit	Visit Window for evening assessment (PP NRS, AP NRS)	Visit Window for morning assessment (SD NRS, morning sleep diary)
Baseline[a]	1	-7 to -1	-6 to 1 before dosing
Week 1	8	1 to 7	2 to 8
Week 2	15	8 to 14	9 to 15
Week 3	22	15 to 21	16 to 22
Week 4	29	22 to 28	23 to 29
Week 5	36	29 to 35	30 to 36
Week 6	43	36 to 42	37 to 43
Week 7	50	43 to 49	44 to 50
Week 8	57	50 to 56	51 to 57
Week 9	64	57 to 63	58 to 64
Week 10	71	64 to 70	65 to 71
Week 11	78	71 to 77	72 to 78
Week 12	85	78 to 84	79 to 85
Week 13	92	85 to 91	86 to 92
Week 14	99	92 to 98	93 to 99
Week 15	106	99 to 105	100 to 106
Week 16[b]	113	106 to 112	107 to 113
Week 17	120	113 to 119	114 to 120
Week 18	127	120 to 126	121 to 127
Week 19	134	127 to 133	128 to 134
Week 20	141	134 to 140	135 to 141
Week 21	148	141 to 147	142 to 148
Week 22	155	148 to 154	149 to 155
Week 23	162	155 to 161	156 to 162

Week 24	169	162 to 168	163 to 169

[a] If there are less than 4 non-missing assessments within last 7 days prior to the first dose, the interval lower bound will be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values. The extension will not be applied for the sensitivity analysis by using a minimum of 2 (or 3) daily scores out of the 7 days.
[b] If there are less than 4 assessments during Week 16 visit window, upper bound of the visit window (106 - 112) or (107 - 113) will be extended for 5 additional days. If there are still less than 4 assessments after extending upper bound of the visit window, lower bound of the visit window will be extended for another 5 days until 4 assessments are reached.

* For diary data, if the intake date of rescue therapy is before and on the last day of the weekly visit window, this week will be treated as treatment failure except for OC analysis and the weekly average will be imputed using the worst case value, see Section 8.3. For MMRM analysis, values will be considered as missing.

Safety and pharmacokinetics data will not be windowed for by-visit summary. i.e., scheduled visit data will be used for analysis.

8.5. Pooling of Centers

A small center is defined as a center with less than 12 randomized subjects. Small centers will be pooled prior to analyses.

First, centers will be sorted by country, number of randomized subjects (descending order) and center number (ascending order). Pooling will start with combining the largest of the set of small centers with the smallest center within that country. If there is a further need to combine data (the size of the pooled centers includes less than 12 subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 12 subjects is met.

The process will continue until all pooled centers have a minimum of 12 subjects within the country. Any remaining centers will be pooled with the last pooled center within the country. In case after pooling of centers within country, there are countries with insufficient number of subjects (less than 12), those countries will be pooled to within the geographic region. Pooled centers will be referred to ‘analysis centers’ in the statistical analyses.

8.6. Subgroups

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

- Region (Europe, North America)
- Age groups (18-65, and > 65)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other (including Multiple))
- Weight at randomization (< 90 kg, ≥ 90 kg)
- Baseline IGA score (Moderate [3], Severe [4]).

9. Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

All subjects of the Screened population will be accounted for in this study.

Subject accounting will summarize subjects screened, re-screened, screen failed, randomized and randomized but not treated for all subjects by overall, country and site.

Subject accounting by visit will be summarized by treatment group and overall at each visit (scheduled visits only).

Subject disposition will be summarized based on the ITT population by treatment and overall. Summaries will include subjects randomized, subjects randomized but not treated, subjects treated, subjects completed treatment, subjects discontinued treatment, primary reason for discontinuation of treatment (including summary of subjects who stopped treatment due to COVID-19), subjects completed the study, subjects discontinued from the study, primary reason for discontinuation from the study (including summary of subjects who discontinued due to COVID-19), subjects rolled over to long term extension (LTE), and subjects completed Follow-up. Subjects who stopped treatment or discontinued study due to COVID-19 will be identified using other specify field in CRF.

Subject disposition will also be summarized by site on the ITT population.

Screen failure will be summarized for all screened subjects. Number of subjects screened and failed will be presented. Number and percentage of reason for screen failure (including summary of subjects who failed due to COVID-19) will be summarized.

Subjects in each analysis population (ITT, SAF, PP, PK analysis population) will be summarized by treatment group on the ITT population.

In addition, time (days since the first dose of study drug) to permanent discontinuation of study drug by reason for discontinuation will be displayed graphically in subjects having permanently discontinued from the study drug.

Randomization, study completion, drug completion, and visit dates will be listed for the ITT population. Screen failure reason will also be listed. Additional listing of missed assessment for subjects who discontinued due to COVID-19 will be presented for the ITT population.

Analysis populations will be summarized and listed on the ITT population.

All inclusion and exclusion criteria not met will be listed on the Screened population.

9.2. Demographic and Baseline Disease Characteristics

Summary statistics for demographic and other Baseline disease characteristics will be presented for the ITT, SAF, PP and PK analysis population.

Age (years), height (cm), weight (kg), and BMI (kg/m^2) will be summarized using summary statistics for continuous variables. Age groups (18-65, and > 65), sex, region (Europe and North America), race,

ethnicity, and smoking status will be summarized using the summary statistics for categorical variables. Weight will additionally be presented for each subgroup < 90 kg and ≥ 90 kg.

The Baseline disease characteristics IGA, weekly average PP NRS, weekly average AP NRS, weekly average SD NRS, pain frequency and intensity, PAS item 4 (number of lesion in representative area), item 5a (excoriation/crusts), item 5b (healed lesion stages), baseline DLQI, and time since PN diagnosis will be summarized. IGA, pain frequency, PAS item 5a and 5b, and atopy background will be summarized as a categorical variable.

Atopy background (Yes, No) will be defined based on the medical history terms selected by sponsor as atopy background.

Time since PN diagnosis (months) will be defined as [date of screening – date of start of PN (MHLLT = 'Prurigo nodularis') + 1] / 30.4375.

A summary table for the stratification factor weight at randomization will be provided to show any discrepancies between what was reported through Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) versus eCRF data (at baseline visit).

All demographic and baseline disease characteristics data will be listed on the ITT population.

9.3. Medical History

Medical history will be collected only at screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 25.0 or higher.

Medical history will be summarized by treatment group. The summary will include number and percentage of subjects reporting each system organ class (SOC), preferred term (PT) and lowest level term (LLT) and will be sorted alphabetically by SOC and descending frequency of PT within SOC and descending frequency of LLT within PT in the Nemolizumab treatment group. Summary tables will be presented for the ITT population.

Medical history data listings will be presented by subject number for the ITT population.

9.4. Medical and Surgical Procedure

Medical and surgical procedures will be coded using MedDRA, Version 25.0 or higher.

Prior medical and surgical procedures are defined as those which have been stopped before first treatment.

- *Procedure before informed consent signed* is defined as those stopped before the date of informed consent signed to the study.
- *Procedure during screening period* is defined as those stopped on or after the date of informed consent signed until before first treatment date.

Concomitant medical and surgical procedures will be defined as those started or stopped on or after the first treatment, or were ongoing during the study. If a procedure is started before the first treatment but is ongoing or stopped on or after the first treatment, it will be considered concomitant.

- *Procedures during treatment period* will be defined from start of treatment till 4 weeks (<= 28 days) after the last treatment or early discontinuation date whichever is earlier.
- *Procedures during follow-up period* is defined from post treatment period (4 weeks (> 28 days) after the last treatment or early discontinuation date, whichever is earlier) to follow-up visit date.

If the stop date and 'ongoing' are missing then the procedure will be considered concomitant.

The following medical and surgical procedures (prior, concomitant and rescue procedures) will be summarized by treatment group using the number and percent of subjects reporting each SOC and PT and sorted alphabetically by SOC and descending frequency of PT within SOC in the Nemolizumab treatment group. Summary tables will be presented for the ITT population.

- Prior procedure before screening (before informed consent date)
- Prior procedure before first dosing (from screening [informed consent date] before the first treatment)
- Concomitant procedure during treatment period
- Concomitant procedure during follow-up period
- Rescue procedure during treatment period
- Rescue procedure during follow-up period

Medical and surgical procedures listings and rescue procedure listing will be presented by treatment group on the ITT population and sorted by subject number, start date, stop date, SOC, and PT.

9.5. Medication

Medications will be classified and summarized on the ITT population as follows:

Prior medications are defined as those which stop before the first injection of study drug during the study.

- *Prior medication before informed consent signed* is defined as those stopped before the date of informed consent signed to the study.
- *Prior medication during screening period* is defined as those stopped during screening period (on or after the informed consent date, until before the first treatment date).

Concomitant medications are defined as those started, stopped, or ongoing on or after the first injection of study drug.

- *Medication during treatment period* is defined from start of treatment till 4 weeks (<= 28 days) after the last treatment or early discontinuation date whichever is earlier.
- *Medication during follow-up period* is defined from post treatment period (4 weeks (> 28 days) after the last treatment or early discontinuation date, whichever is earlier) to follow-up visit date

If the stop date and 'ongoing' are missing then the medication will be considered as concomitant medication.

Medications (prior, concomitant and rescue medications) will be coded using Version Global B3, March 2022 of the World Health Organization's Drug Dictionary (WHO DD) or higher. Preferred Anatomical Therapeutic Chemical (ATC) coding will be performed.

The following summaries by ATC level 2, ATC level 4 and preferred term (PT) will be produced on the ITT population. Subjects with more than one medication in a given ATC level and preferred name will be counted only once in that category. It will be sorted alphabetically by ATC level and by descending frequency in PT within ATC level term. Summary tables will be presented on the SAF.

- Prior medication before screening (before informed consent date)
- Prior medication before first dosing (from screening [informed consent date] before the first treatment)
- Concomitant medication during treatment period
- Concomitant medication during follow-up period
- Rescue medication during treatment period
- Rescue medication during follow-up period

All medications (prior and concomitant medications, rescue medications) will be listed for the ITT population.

9.6. Extent of Exposure

Following parameters will be summarized:

- Treatment duration (in days) is calculated as follows, where date of first treatment is defined as the first day: [(date of last treatment – date of first treatment) + 1].
- Total dose administered (mg) will be calculated as the sum of all doses of study drug administered.
- Total dose planned (mg) will be calculated as the sum of all doses of study drug planned (dispensed) according to the treatment schedule of the treatment group.
- The number of subjects who missed at least one dose
- The number of subjects who missed at least one dose due to COVID-19
- The number of doses missed
- The number of doses missed due to COVID-19
- Treatment Compliance as described in Section 9.7.

Note: The missed dose due to COVID-19 are captured as other-reason reported in CRF.

9.7. 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).

Treatment compliance (%) is calculated as the total number of actual injections / the total number of expected injections * 100. The total number of actual injections is counted based on collected study drug administration data. The total number of expected injections is counted based on the dosage schedule and dispensed as per protocol.

10. Efficacy

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

All efficacy variables will be summarized by treatment group at each analysis visit. The primary comparison of interest is Nemolizumab compared to placebo.

To control the type I error at 5%, a fixed sequential testing approach will be implemented. For testing purposes, both primary endpoints will be tested first in a predefined order as listed in Section 5.1 at 5% significance level, and testing of key secondary endpoints will start only if both primary endpoints are successful at 5% level of significance. Key secondary endpoints will be tested in an order listed in Section 5.2, stopping when non-significant result ($p > 0.05$) is found.

10.1. Primary Efficacy Endpoints

10.1.1. Primary Analysis of Primary Efficacy Endpoint

The primary endpoints include the following endpoints:

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

For both primary endpoints, any subjects with missing data at Week 16 will be considered as a non-responder for the respective endpoint. If a subject is in receipt of rescue medication at any point on or prior to Week 16, data on or after receipt of rescue medication will be regarded as a treatment failure and will be calculated based on the underlying imputed continuous value, see Section 8.3.

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

Null hypothesis H0: $P_{PP\ NRS\_nemolizumab} - P_{PP\ NRS\_placebo} = 0$;

Alternative hypothesis H1: $P_{PP\ NRS\_nemolizumab} - P_{PP\ NRS\_placebo} \neq 0$,

where $P_{PP\ NRS\_nemolizumab}$ and $P_{PP\ NRS\_placebo}$ are the proportion of subjects categorized as having a PP NRS improvement from baseline to Week 16 of ≥ 4, for Nemolizumab and placebo, respectively.

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

Null hypothesis H0: $P_{IGA\_nemolizumab} - P_{IGA\_placebo} = 0$;

Alternative hypothesis H1: $P_{IGA\_nemolizumab} - P_{IGA\_placebo} \neq 0$,

where $P_{IGA\_nemolizumab}$ and $P_{IGA\_placebo}$ are the proportion of subjects categorized as success under IGA at Week 16 for Nemolizumab and placebo, respectively.

Both primary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization strata analysis center and body weight at randomization (< 90 kg, ≥ 90 kg), in order to test the difference between Nemolizumab and placebo for the proportion of subjects achieving success in each endpoint. The estimate of the treatment difference and corresponding two-sided 95% CI and p-values will be presented. The confidence intervals will be based on Wald statistic controlling for stratification variables. Strata-adjusted proportion differences will be obtained using weighted average of stratum-specific proportion using CMH.

In addition an unadjusted CMH test will be performed.

Bar charts for the proportions of subjects with an improvement of ≥ 4 from baseline in PP NRS and IGA success at Week 16 will be presented.

10.1.2. Sensitivity Analyses of Primary Efficacy Endpoint

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

With the exception of OC analysis (where observed data will be used regardless of the use of rescue therapy), efficacy data collected on/after the use of rescue therapy will be treated as treatment failure. Continuous variables will be set to the worst case value and subject's binary response will be derived based on the underlying continuous value prior to impute missing data.

- Same analysis on PP population (including the bar charts for the proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS and IGA success at Week 16).
- Tipping point analysis: To assess the robustness of non-responder analysis, a tipping point analysis will be performed by converting non-responders due to missing data to responders in successive increments (Δ) for both treatment groups. The value of Δ that overturns (i.e., non-significant) the primary results will represent the tipping point (see Appendix 21.1). A graphic display of all possible combinations of the number of responders among both treatment groups will be presented.
- Multiple Imputation (MI) method for missing data, assuming all missing data are Missing at Random (MAR) (see Appendix 21.2).
- Pattern-mixture model under assumption Missing Not at Random (MNAR) controlled-based pattern imputation. MI-based imputation will be applied as described above. Under MNAR assumption, a controlled based pattern imputation where only observation in placebo treatment group will be used to impute.
- Last Observation Carried Forward (LOCF) imputation method for missing data. Missing post-baseline values will be carried forward from the last non-missing post-baseline value. Baseline value will not be carried forward to post-baseline value.
- Observed Case (OC) - no data will be imputed. For this analysis, if any rescue medication is received, data on or post rescue therapy will be analyzed as observed (i.e., not treated as non-responders).
- Removal of COVID-19 affected visits (i.e. exclusion of subjects from visit, if visit was missed due to COVID-19).
- 'Actual stratum' instead of 'stratum at the randomization' for subjects stratified incorrectly.
- Using at least 2 assessments for calculation of weekly average PP NRS instead of 4.
- Using at least 3 assessments for calculation of weekly average PP NRS instead of 4.

Tipping point analysis, multiple imputation methods, LOCF and OC analysis, analysis without COVID-19 affected visits and analysis with actual stratum will be performed on the ITT population. Except for OC and MMRM analysis, continuous assessments on or after rescue therapy used will be set to the worst case value.

10.1.3. Subgroup Analyses of Primary Efficacy Endpoints

In addition, the same analyses as described in Section 10.1.1 will be performed for the following subgroups:

- Region (Europe and North America)
- Age groups (18-65 and > 65)
- Sex (Male, Female)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other (including Multiple))
- Weight at randomization (< 90 kg, ≥ 90 kg)
- Baseline IGA Score (Moderate (3), Severe (4))

The subgroup analyses will be performed on the ITT population. Forest plot will be presented along with subgroup analysis results.

10.2. Key Secondary Efficacy Endpoints

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

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

All key secondary endpoints will be analyzed on the ITT population as primary endpoints (Section 10.1.1) including graphical presentation.

Additionally, the same sensitivity analyses as for the primary endpoints will be performed (Section 10.1.2), including bar charts for the key secondary endpoints or PP population.

Analysis of key secondary endpoints will be produced for the subgroups, too (Section 10.1.3).

10.3. Secondary Efficacy Endpoints

The following secondary endpoints are to be analyzed at the scheduled visits (Table 10-1):

Table 10-1: Secondary Efficacy Endpoints

Endpoint	Analysis Visit	Analysis to be done on which Population	Statistical Tests
IGA success rate at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT and PP population	CMH
Proportion of subjects with IGA <= 2 at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Percentage of pruriginous lesions with excoriations/crusts (PAS items 5a) at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT and PP population	CMH
Percentage of healed lesion stages (PAS items 5b) at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT and PP population	CMH
Proportion of subjects with number of pruriginous lesions (PAS item 2) < 20 at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Change from baseline in PAS item 4 (number of lesions in representative area) at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT and PP population	ANCOVA
Proportion of subjects with PP NRS at each visit: a) Improvement ≥ 4 from baseline; b) < 2 at visit c) < 3 at visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Absolute and Percent change from baseline in PP NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT	ANCOVA, MMRM
Proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success	Baseline, W16, W20, W24	On the ITT and PP population	CMH

Endpoint	Analysis Visit	Analysis to be done on which Population	Statistical Tests
Proportion of subjects with AP NRS at each visit: a) Improvement ≥ 4 in change from baseline; b) < 2 at visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Absolute and Percent change from baseline in AP NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	ANCOVA, MMRM
Proportion of subjects with change from baseline improvement ≥ 4 in SD NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Absolute and Percent change from baseline in SD NRS at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	ANCOVA, MMRM
Change from baseline in sleep diary endpoints at each visit (sleep onset latency, WASO, total awake time, total sleep time, sleep efficiency)	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	No hypothesis testing
Change from baseline in PN-associated pain intensity at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	MMRM
Percentage change from baseline in PN-associated pain intensity at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	MMRM
Proportion of subjects with PN-associated pain frequency rating = 5 (every day, non-responder) at each visit	Baseline, W4, W8, W12, W16, W20, W24	On the ITT population	CMH
Proportion of subjects reporting low disease activity (clear, almost clear, mild) based on Patient Global Assessment of Disease (PGAD) at each visit	Baseline, W16, W24	On the ITT population	CMH
Proportion of subjects satisfied with study treatment (good, very good, excellent) based on Patient Global Assessment of Treatment (PGAT) at each visit	W16, W24	On the ITT population	CMH
Proportion of subjects with an improvement of ≥ 4 in DLQI at each visit	Baseline, W4, W16, W24	On the ITT population	CMH
Change from baseline in DLQI at each visit	Baseline, W4, W16, W24	On the ITT population	ANCOVA, MMRM

Endpoint	Analysis Visit	Analysis to be done on which Population	Statistical Tests
Change from baseline in HADS for each subscale at each visit	Baseline, W16, W24	On the ITT population	ANCOVA
Change from baseline in EQ-5D for each subscale at each visit	Baseline, W16, W24	On the ITT population	ANCOVA

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

Binary secondary endpoints will be analyzed as described in Section 10.1.1. if not specified otherwise. Missing values will be imputed as non-responder except for OC analysis. If a subject is in receipt of rescue medication at any point, continuous data on or after receipt of rescue medication will be set to worst case value, except for OC analysis, , and the binary response are derived from the underlying value

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

Note: The strategy of dealing with ICE will be the same as defined in Table 7-2 for all secondary endpoints, unless it was specified (i.e., OC).

10.3.1. Investigator's Global Assessment (IGA)

The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the investigator or trained designee to evaluate the global severity of PN and the clinical response to a treatment (see Table 10-2).

Table 10-2: Investigator Global Assessment Scale

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

IGA treatment success is defined as 0 (clear) or 1 (almost clear) on the IGA scale and a ≥ 2-point reduction from Baseline.

IGA will be collected at Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 and Early Termination. In case of missing assessment at Baseline, the last available assessment prior study drug administration will be considered as Baseline.

IGA will be summarized as a categorical and continuous variable at each analysis visit. Absolute change from Baseline for the IGA score will also be presented in the summary on the ITT and PP population.

The proportion of subjects with IGA success (OC, non-responder, LOCF) will be summarized on the ITT and PP population. It will also be analyzed using non-responder imputation and a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization strata analysis center and body weight at randomization (< 90 kg, ≥ 90 kg).The estimate of treatment unadjusted and strata-adjusted differences with the corresponding two-sided 95% confidence intervals, and p-values from the CMH test will be presented.

Additionally, the proportion of subjects with IGA <= 2 (Responder) will be presented using missing as non-responder for ITT population up to Week 24.

Line plots for proportion of subject with IGA success using non-responder imputation will be generated for the ITT and PP population.

10.3.2. Prurigo Activity Score (PAS)

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

Following items will be summarized at Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24:

- PAS item 1a/1b: Type of prurigo
- PAS item 2: Number of pruriginous lesions
- PAS item 3: Affected area(s)
- PAS item 4: Number of lesions in representative area.
- PAS item 5a: Pruriginous lesions with excoriations/crusts
- PAS item 5b: Healed prurigo lesions

PAS items will be summarized as a categorical or continuous variable at each analysis visit, respectively. Absolute change from Baseline for continuous parameter PAS item 4 will also be presented in the summary on the ITT and PP population.

The proportion of subjects with pruriginous lesions with excoriation/crusts (PAS item 5a = 0-25%) and of subjects with healed lesion stages (PAS item 5b = 76-100%) will be presented using non-responder approach. The estimate of treatment unadjusted and strata-adjusted proportion differences with the corresponding two-sided 95% CI, and p-values from the CMH test will be presented.

Absolute and percentage change from Baseline in PAS item 4 will be analyzed using ANCOVA with MI assuming MAR approach for missing data, including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate. The least squares means (LSMeans), standard error of LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented for ITT and PP population.

Additionally, the proportion of subjects with number of pruriginous lesions (PAS item 2) < 20 (Responder) will be presented using missing as non-responder for ITT population up to Week 24.

10.3.3. Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours. Peak pruritus (PP NRS) is an assessment of the maximum itch intensity in that period while average pruritus (AP NRS) provides a measure of overall pruritus intensity.

Subjects will be asked the following question:

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

The screening PP/AP NRS will be determined by a single assessment using the PP/AP NRS (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

The Baseline PP/AP NRS will be determined based on the average of daily PP/AP NRS (score ranging from 0 to 10) respectively during the 7 days immediately preceding Baseline (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding Baseline (up to one day before date of first treatment) is required for this calculation. If there are less than 4 non-missing assessments in the baseline diary window, the interval lower bound can be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values.

PP/AP NRS at all follow-up visits will be determined in the same manner, however if the intake date of rescue therapy is before and on the last day of the weekly visit window, this week will be treated as treatment failure except for OC analysis and the weekly average will be imputed using the worst case value, see Section 8.3.

Subjects will receive instructions on how to record their PP/AP NRS scores and will complete the assessment once daily in the evening throughout the clinical study (including the run-in and the follow-up period).

PP NRS will be determined by an average as described above at every week from Baseline to Week 24 as a continuous variable.

Descriptive summary of PP NRS will be provided on the ITT and PP populations using observed cases. Absolute change and percentage change from Baseline for the PP NRS will also be included in the summary on the ITT and PP populations.

AP NRS will be determined by an average as described above at every week from Baseline to Week 24 as a continuous variable. Descriptive summary of AP NRS will be provided on the ITT population. Absolute change and percent change from Baseline for the AP NRS score will also be included in the summary.

Absolute and percentage change from Baseline in PP/AP NRS will be analyzed using ANCOVA with MI assuming MAR for missing data including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate, and using MMRM, including visit, treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor, baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates on ITT population. The least squares means (LSMeans), standard error of

LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented.

Proportion of subjects with PP NRS at each analysis visit will be summarized:

- Improvement ≥ 4 from baseline
- < 2 at visit
- < 3 at visit

Proportion of subjects with AP NRS at each visit will be summarized:

- Improvement ≥ 4 in change from baseline
- < 2 at visit

The proportions of subjects will be presented on the ITT population using OC and non-responder for AP NRS and using OC, non-responder and LOCF for PP NRS. The estimate of treatment unadjusted and strata-adjusted proportion differences with the corresponding two-sided 95% CI, and p-values from the CMH test will be presented using non-responder.

Line plots for proportion of subjects with PP NRS improvement ≥ 4 and proportion of subjects with PP NRS < 2 using non-responder imputation will be presented on the ITT and PP population.

Additionally the weekly average PP NRS will be recalculated by using at least 2 assessments, or 3 assessments, instead of at least 4 assessments and without extending the visit window for sensitivity analysis.

The proportion of subjects with the weekly average PP NRS using 2, or 3 assessments, will be summarized at each analysis visit:

- PP NRS Improvement ≥ 4 from baseline
- PP NRS < 2

In addition, proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success (see Section 10.3.1) at Week 16, Week 20, and Week 24 will be summarized on the ITT and PP population. The proportion of subjects will be presented using OC, non-responder and LOCF. The estimate of treatment unadjusted and strata-adjusted proportion differences with the corresponding two-sided 95% CI, and p-values from the CMH test will be presented.

Line plots for the change and percentage change from Baseline in PP NRS using OC on the ITT population will also be presented.

10.3.4. Sleep Disturbance Numeric Rating Scale (SD NRS)

The SD NRS is a scale to be used by the subjects to report the degree of their sleep loss related to PN.

The Baseline SD NRS will be determined based on the average of daily SD NRS (score ranging from 0 to 10) during the 7 days up to the treatment start (including until treatment start time) (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days up to Baseline study day is required for this calculation. SD NRS at all following visits will be determined following the rules described in Table 8-2. If there are less than 4 non-missing assessments in the baseline diary window, the interval lower bound can be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values.

Subjects will be asked the following question:

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

Summary using OC will be provided on the ITT population. Absolute change and percentage change from Baseline will also be included in the summary.

Absolute and percentage change from Baseline at each analysis visits will be analyzed using ANCOVA with MI assuming MAR for missing data including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate, and using MMRM, including visit, treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor, baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates on ITT population. The LSMeans, standard error of LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented. Improvement in SD NRS will be calculated using Baseline as the reference point for change in SD NRS score.

The proportion of subjects with an improvement of SD NRS ≥ 4 will be summarized using OC and non-responder imputation on ITT population. The estimate of treatment unadjusted and strata-adjusted differences with the corresponding two-sided 95% confidence intervals, and p-values from the CMH test will be presented using non-responder imputation on ITT population.

Line plot for proportion of subjects with SD NRS improvement ≥ 4 using non-responder imputation will be presented on the ITT population.

Additionally the proportions of subjects with an improvement of SD NRS ≥ 4 from Baseline will be summarized by using at least 2 assessments, or 3 assessments, for calculation of weekly average SD NRS for sensitivity analysis. Proportions are summarized using non-responder imputation on ITT population.

10.3.5. Subject Sleep Diary

Subjects will be given a morning sleep diary (MSD) to record the quality of their sleep. The subject sleep diary is a modification of the consensus sleep diary and is designed to gather information about the subject's sleep pattern and how symptoms related to PN (e.g., itching, burning) affect their sleep.

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

The Baseline sleep diary metrics will be determined based on the average of daily sleep diary metrics respectively during the 7 days data up to the Baseline study day [including until treatment start time] (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days up to Baseline study day is required for this calculation. If there are less than 4 non-missing assessments in the baseline diary window, the interval lower bound can be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values. Sleep diary metrics at all other visits will be determined following the rules described in Table 8-2.

The sleep diary metrics will be derived as below (see Table 10-3: Sleep Diary Metrics) using questions in the morning based on morning sleep diary.

Table 10-3: Sleep Diary Metrics

Sleep Parameter	SSD Items Used to Derive the Sleep Parameter
Sleep onset latency (SOL)	Q3
Wakefulness after sleep onset (WASO)	Q5 + Q7
Terminal WASO (TWASO)	Q9 – Q8
Total awake time (TWT)	SOL+ WASO + TWASO
Time in bed (TIB)	Q9 – Q1
Total sleep time (TST)	TIB – TWT
Sleep efficiency (SE)	(TST/TIB)*100
WASO related to PN (WASO-PN)	Q5
Number of WASO related to PN (NWASO-PN)	Q4

Sleep diary metrics will be summarized as continuous variables on observed cases on the ITT population. Change from Baseline in sleep diary metrics will also be summarized.

If Q8 (wake up time) is after Q9 (get out of bed), then Terminal WASO (Q9-Q8) will be set to 0.

If Q8 (wake up time) is before Q1 (get into bed), the time on the next day will be considered for Q9 as only time is collected.

If the duration between Q1 and Q9 is >24 hours, this data will be considered as incalculable and the derived parameters (total awake time and total sleep time) are set to missing.

If total sleep time is negative, it will be considered as missing (not zero) for analysis. The same applies for total awake time.

No hypothesis testing will be performed.

10.3.6. PN Associated Pain Intensity and Frequency

Subjects will be asked to report the intensity and frequency of pain they endure related to their PN. Pain intensity is captured using a NRS.

Subjects will rate the frequency of their pain on a 6-point scale (0 = Never, 1 = Less than once a week, 2 = 1-2 Days a week, 3 = 3-4 Days a week, 4 = 5-6 Days a week, 5 = Every day) in response to the following question:

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

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

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

Summaries using OC will be generated for PN associated pain frequency and intensity at Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 on ITT population. Pain frequency will be summarized as a categorical variable. Pain intensity will be summarized as a continuous variable. Absolute change from Baseline in PN associated pain intensity will also be summarized.

Proportions of subjects with PN associated pain frequency rating = 5 (every day, non-responder) will be presented using missing as non-responder for ITT population up to Week 24.

Additionally, change and percentage from Baseline in PN associated pain intensity will be presented using MMRM model for ITT population up to Week 24.

No hypothesis testing will be performed.

10.3.7. Patient Global Assessment of Disease (PGAD)

For the PGAD, subjects will be asked to rate their overall impression of their skin disease (prurigo nodularis) severity using a 5-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe). Subjects will be asked the following question:

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

PGAD will be collected at Baseline/Day 1, Week 1, Week 16, Week 24 and Early Termination and be summarized for Baseline, Week 1 Week 16, and Week 24 as a categorical variable using OC on the ITT population.

The proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on PGAD will be summarized using OC on the ITT population. The estimate of treatment unadjusted and strata-adjusted differences with the corresponding two-sided 95% CI, and p-values from the CMH test will be presented.

10.3.8. Patient Global Assessment of Treatment (PGAT)

The PGAT utilizes a 5-point Likert scale (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent) or subjects to rate the way they feel their skin disease (prurigo nodularis) is responding to the study treatment. Subjects will be asked the following question at Week 16, Week 24 and Early Termination:

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

PGAT will be summarized as a categorical variable for Week 16 and Week 24 using OC on the ITT population.

The proportion of subjects satisfied with study treatment (good, very good, or excellent) based on PGAT will be summarized using OC on the ITT population. The estimate of treatment unadjusted and strata-adjusted differences with the corresponding two-sided 95% CI, and p-values from the CMH test will be presented.

10.3.9. 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.

The subject will rate each question ranging from 0 (not at all) to 3 (very much). The DLQI total score is calculated by summing each questionnaire. Total score will have a maximum score of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

DLQI will be collected at Baseline/Day 1, Week 4, Week 16, Week 24 and Early Termination. DLQI total score will be summarized as a continuous variable using OC on the ITT population for Baseline, Week 4, Week 16 and Week 24. Absolute change from Baseline in DLQI total score will also be summarized.

Absolute change from Baseline in DLQI total score at Week 4, Week 16 and Week 24 will be analyzed using ANCOVA with MI assuming MAR for missing data including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate, and using MMRM, including visit, treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor, baseline, the interaction term between baseline and visit, and the interaction term between treatment group and visit as covariates on ITT population. The LSMeans, standard error of LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented on ITT population.

Improvement of ≥ 4 in DLQI will be calculated using Baseline as the reference point for change in DLQI total score. The proportion of subjects with an improvement of ≥ 4 will be summarized on the ITT population using OC and non-responder imputation. The estimate of treatment unadjusted and strata-adjusted differences with the corresponding two-sided 95% CI, and p-values from the Cochran-Mantel-Haenszel test using non-responder will be presented for ITT population.

A line plot for proportion of subjects with DLQI improvement ≥4 using non-responder imputation will be presented on the ITT population.

10.3.10. Hospital Anxiety and Depression Scale (HADS)

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

HADS will be collected at Baseline/Day 1, Week 16, Week 24 and Early Termination and subscales will be summarized separately for each subscale (Total Score Anxiety and Total Score Depression) as continuous variable using OC for Baseline, Week 16 and Week 24 on the ITT population. Absolute change from Baseline in HADS subscale scores will also be summarized.

Absolute change from Baseline in HADS subscale scores will be analyzed for Week 16 and Week 24 using ANCOVA using observed case, including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate. The LSMeans, standard error of LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented.

10.3.11. EuroQoL 5 Dimension Instrument

The EQ-5D instrument is a validated questionnaire, completed by the subject and consists of 2 parts. The first part consists of 5 multiple choice QoL questions and the second is a 100 point VAS scale with 0 being “Worst imaginable health state” and 100 being “Best imaginable health state”.

EQ-5D VAS will be collected at Baseline/Day 1, Week 16, Week 24 and Early Termination and be summarized as a continuous variable using OC for Baseline, Week 16 and Week 24 on the ITT population. Absolute change from Baseline in EQ-5D VAS will also be summarized using OC.

Absolute change from Baseline in EQ-5D VAS at Week 16 and Week 24 will be analyzed using ANCOVA using observed case, including treatment group, analysis center and body weight at randomization cut-off (< 90 kg and ≥ 90 kg) as factor and baseline as covariate. The LSMeans, standard error of LSMeans, and 95% CI for change from baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented.

Five dimensions of EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized as a categorical variable using OC.

10.3.12. Rescue Therapy Used

Subjects who used either medication or procedure as rescue therapy will be summarized using OC.

The number and percentage of subjects receiving any concomitant rescue therapy will be summarized by rescue treatment type (topical, phototherapy, systemic, intralesional corticosteroids, and corresponding subgroups), preferred term within treatment type and overall. The number and percentage of subjects receiving any concomitant procedure of rescue therapy will be summarized by rescue treatment type (phototherapy), preferred term within treatment type and overall.

In addition, the time to first rescue therapy use will be calculated. The data will be analyzed using Kaplan-Meier methodology by presenting the point estimates of the quartiles estimates with the corresponding 95% CI. Kaplan-Meier estimates of time to first rescue therapy use will be summarized by visit. Subjects who do not use any rescue therapy will be censored for the analysis and the end of treatment period will be used as the censoring date. Subjects who discontinued without intake of rescue therapy will also be censored as described above. A Kaplan-Meier curve will also be provided.

Selected Prior Prurigo Nodularis medications and procedures will also be presented.

11. Pharmacokinetics

The serum concentration of Nemolizumab will be assessed at Baseline, Week 4, Week 8, Week 12, Week 16, Week 24, Week 32 Follow-up and Early Termination visit. PK analyses are required during any unscheduled visit conducted for safety reasons. As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples).

11.1. Pharmacokinetic Concentration Presentation

Serum concentration data (unit: ng/mL) will be summarized on the PK analysis population by visit and by body weight at baseline cut-off (< 90 kg or ≥ 90 kg) from Baseline to Week 32, using the following statistics: arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, maximum, 95% CI of the arithmetic mean, and number below the limit of quantification (BLQ).

Mean and individual (spaghetti plot) serum concentration(s) will be plotted by visit and by body weight at baseline cut-off (< 90 kg or ≥ 90 kg) on both a linear and semi-logarithmic scale on the PK analysis population (2 plots).

Individual serum concentrations will be listed on the PK analysis population.

11.2. Pharmacokinetic and Pharmacodynamics Parameters Estimation

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

Results of PopPK and PK/PD analyses will not be included in the CSR final TFLs. PopPK and PK/PD analyses will be described in an ad hoc Modeling & Simulation Plan. PopPK and PK/PD analyses results will be described in ad hoc Modeling & Simulation Report.

11.3. Biomarkers

Blood and stratum corneum (D-Squames) samples will be collected from approximately 100 subjects at selected sites to investigate the effect of Nemolizumab (CD14152) on selected RNA and protein biomarkers, including but not limited to IL-31. Optional skin biopsies for RNA and immunohistochemistry analyses will be collected from approximately 30 subjects at selected sites who sign the additional consent form. Samples will be collected at Baseline and Week 16 and blood samples will be collected at Week 8 and Week 24 additionally.

These biomarker data will be analyzed according to a separate Analysis Plan and presented in a separate biomarkers report.

12. Immunogenicity

Blood samples to assess anti-Nemolizumab ADA will be collected at Baseline, Week 8, Week 16, Week 24 and Early Termination. Immunogenicity analyses will be summarized on the PK analysis population.

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.

Incidence of ADA results will be summarized (absolute occurrence and percent of subjects) by body weight at baseline cut-off (< 90 kg or ≥ 90 kg) at each visit. The concentration of ADA titer and neutralizing antibodies will be summarized depending on the data requirement.

The number and percentage of subjects with treatment related ADA will be summarized. A treatment-related ADA is defined when the Baseline final ADA result is negative (i.e. either screening or confirmatory are negative) and the post-baseline final ADA result is positive (i.e. both screening and confirmatory are positive).

13. Safety

All safety data will be summarized and listed on the SAF population.

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit. Safety will be assessed on the basis of AEs (including TEAEs, AESIs, SAEs and adjudicated AEs), physical examination and vital signs, clinical laboratory tests, electrocardiogram (ECG), respiratory examination and assessments. Summary of all safety endpoints will be presented for each treatment group.

13.1. Adverse Events

AEs will be coded using MedDRA Version 25.0.

Treatment-emergent AEs (TEAEs), defined as those AEs occurring after the first administration of study treatment until the last study visit, will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities for treatment and follow-up periods. Missing date information will be handled using the algorithm described in Section 8.3.

TEAEs during treatment period are defined as AEs with onset date on or after the first dose date till 4 weeks after the last treatment or early discontinuation date whichever is earlier. TEAEs during follow-up period are defined as AEs with onset date post treatment period (4 weeks after the last treatment or early discontinuation date, whichever is earlier) to follow-up visit date.

AEs will be summarized using the number and percent of subjects reporting each SOC and PT and sorted alphabetically by SOC and by descending frequency of PT within SOC.

Subjects who experienced multiple events within the same SOC will be counted once in the SOC summary. Subjects who experienced multiple occurrences of events with the same PT will be counted once in the PT summary.

When summarizing by causality or maximum severity, if a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in summary tables. TEAEs related to study drug/study procedure are those that are identified as reasonable possibility. If relationship or severity are missing, the event will be considered as AE related to study drug/study procedure or severe AE.

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. An AESI can be either serious or non-serious. Based on the potential risks of Nemolizumab and the risks associated with biologics in general (i.e., class effects), the following AEs will be considered as AESIs:

- Injection-related reactions,
- Newly diagnosed asthma or worsening of asthma,
- Infections,
- Peripheral oedema: limbs, bilateral,
- Facial oedema
- Elevated ALT or AST (> 3 x ULN) in combination with elevated bilirubin (> 2 x ULN).

The following summary tables for TEAEs will be presented for all TEAEs (i.e., TEAE all causalities) and study drug related TEAEs separately by treatment period and follow-up period.

- Overall Summary of TEAEs :
    - Overall summary table includes summary of subjects reporting TEAEs,
    - Overall summary table includes summary of subjects reporting TEAEs by Country,
    - TEAE by maximum severity [Mild, Moderate, Severe],
    - TEAE related to study drug,
    - TEAE related to study drug by maximum severity [Mild, Moderate, Severe],
    - TEAE related to protocol procedure,
    - Serious TEAE,
    - Serious TEAE related to study drug,
    - Severe TEAE,
    - TEAE of special interest,
    - TEAE leading to study drug interruption,
    - TEAE leading to study drug withdrawal,
    - TEAE leading to study discontinuation,
    - TEAE leading to death,
    - TEAE related to study drug leading to death
- TEAEs by SOC and PT
- TEAEs by SOC and PT and by Country
- Serious TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum severity
- Severe TEAEs by SOC and PT
- TEAEs leading to study drug withdrawal by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs of special interest by category by SOC and PT
- TEAEs occurred in >= 5% of subjects by SOC and PT
- TEAEs occurred in >= 5% of subjects by Preferred Term
- Adjudicated TEAEs by SOC and PT
- TEAEs of Asthma and AESI reported by investigator with adjudication outcome by IAC
- Confirmed adjudicated TEAEs by SOC, PT and maximum severity
- TEAEs of special interest by category, SOC, PT and maximum severity

For overall study period which includes all periods (treatment and follow-up), the following summary tables will also be presented and repeated for all TEAEs (all causalities) and study drug related TEAEs.

- Overall Summary of TEAEs

- TEAEs by SOC and PT

For the subset of subjects with COVID-19 infection, the following summary tables will be provided additionally for all TEAEs and study drug related TEAEs, separately.

- Overall summary of TEAEs
- TEAEs by SOC and PT
- Serious TEAEs, by SOC and PT
- TEAEs of Special Interest by category by SOC and PT

In addition, the exposure-adjusted incidence rate (i.e., number of subjects per 100 patient-years) will be summarized for all TEAEs (all causalities) and study drug related TEAEs during treatment period.

Exposure-adjusted incidence rates of TEAEs is defined as the number of subjects exposed to treatment and experiencing a certain event divided by the total time of all subjects who are at risk for the event. Specially, for subjects with no event the exposure time is the time from the first drug intake to the end of treatment period. Exposure years is calculated as last study drug exposure date minus first study drug exposure date plus one, divided by 365.25 which is the number of days count in a year. This exposure year calculated for each subject is then added cumulatively and is derived for each treatment arm. So each treatment arm will have one value for exposure years (also known as “patient years”). The exposure year calculation is different in case of subjects who have completed the study or discontinued from the study or having withdrawn from the study due to any reason. Only the event occurred during the treatment period will account for calculation.

Subject listings will be presented for all

- TEAEs,
- TEAEs of special interest,
- Serious TEAEs,
- Severe TEAEs,
- TEAE leading to permanent discontinuation of study drug,
- TEAEs leading to deaths,
- Pre-treatment AEs,
- Adjudicated Asthma AEs,
- TEAE comments,
- Adjudicated Asthma AE comments by Independent Adjudication Committee.

Subject listings of TEAEs for subjects with COVID-19 infection will also be generated.

13.2. Laboratory Evaluations

13.2.1. Clinical Laboratory Evaluations

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. Reference ranges will be provided in the laboratory manual.

The following parameters will be reported for laboratory data.

- **Hematology:** Hemoglobin, hematocrit, white blood cell (WBC) count (with differential including eosinophils), red blood cell (RBC) count, platelet count, and mean cell volume (MCV).

- **Chemistry:** Creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, creatinine phosphokinase ([CPK], CPK isoenzyme test will be performed only if CPK is elevated to > 2.5 × ULN), albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Follicle-stimulating hormone (FSH) will be collected for postmenopausal subjects.

- **Urinalysis:** pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

Laboratory assessments are performed at Screening, Baseline/Day 1, Week 4, Week 8, Week 16, Week 24, Early Termination and Week 32/Follow-up.

Hematology and chemistry laboratory data (absolute values and change from Baseline) will be summarized as continuous variables by visit (Baseline and scheduled visits only). Urinalysis laboratory data will be summarized by visit (Baseline and scheduled visits only). Last post-baseline, worst post-baseline and maximum post-baseline results will also be included in the summaries and will include unscheduled visits in the derivation. Worst post-baseline value will be defined as the highest or lowest value relative to the reference range. Parameters will be presented in alphabetically order.

Shift tables will be generated using the reference ranges (Low, Normal, High and Missing) for hematology and chemistry laboratory data. The number and percentage of subjects shifting from reference ranges between Baseline and each visit (scheduled visits only) will be summarized. Last, worst and maximum post baseline values will also be included in the shift tables and will include unscheduled visits in the derivation.

Summary of the number and percentage of subjects who met criteria of potential clinically significant (CS) value will be summarized (Baseline and scheduled visits only) for hematology and chemistry laboratory data. Last, worst and maximum post-baseline results will also be included in the summaries. Potentially CS ranges are listed in Section 21.4.

For statistical and graphical summaries of the laboratory tests, values below or above the limit of detection (e.g. '< 3' or '> 500') are substituted with the lower limit of detection minus 1% for values below the lower limit and are substituted with the upper limit of detection plus 1% for values above the upper limit (e.g. '< 3' is substituted by '2.97', '> 500' is substituted by '505'). In data listings, the values are shown including the < or > sign.

Distribution of continuous hematology and chemistry laboratory data (in particular, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Total Bilirubin (BILI), Creatinine Kinase (CK) and Leukocytes (WBC)) will be displayed graphically as boxplot by treatment group for baseline and for each scheduled visits and the maximum post-Baseline (including unscheduled visits in the derivation) values.

Individual subject plots will be generated for all subjects with at least one abnormal result (outside of reference range). These plots will be provided for the chemistry laboratory parameters.

By-subject listing will be presented for all laboratory data. By-subject listing for subjects with at least one abnormal result will be provided for hematology and clinical chemistry. By-subject listing for subjects with at least one potentially CS result will be provided for hematology, clinical chemistry and urinalysis.

All laboratory data will be listed for the Safety population.

13.2.2. Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs) at Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Early Termination visit, and Week 32/Follow-up. Pregnancy test results must be available prior to the administration of the study drug.

All test results including Tests not done will be summarized by visit on the Safety population.

All confirmed pregnancy test results together with the premenses status and childbearing potential assessment results will be listed on the Safety population.

13.2.3. Virology and TB Testing

Virology including HBsAg, HBcAb, hepatitis C, human immunodeficiency virus 1, and human immunodeficiency virus 2 antibodies will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody. Subjects with positive HCV antibodies will have a confirmatory test for HCV (e.g., PCR). All virology and genomics results will be listed on the Safety population. All Immunoglobulin E results will also be listed on the Safety population.

Subjects will be assessed for TB infection with a QuantiFERON-TB Gold test at the screening visit. All TB test results will be listed on the Safety population.

13.3. Vital Signs

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.

Vital signs will be collected at the Screening visit and at Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Early Termination visit, and at Week 32/Follow-up.

Height and weight will be measured at Screening for all subjects. Weight assessments will be conducted at Baseline/Day 1, Week 12, Week 24 and Early Termination.

All vital signs including height and weight (absolute values and change from Baseline) will be summarized as continuous (Baseline and scheduled visits only). Last post-Baseline results (including unscheduled visits in the derivation) will also be included.

The number and percentage of subjects who met criteria of potential CS value (Section 21.4) for vital signs and weight will be summarized (Baseline and scheduled visits only). Last post-Baseline results (including unscheduled visits in the derivation) will also be included.

Distribution of pulse rate, systolic and diastolic blood pressure will be displayed graphically as boxplot by treatment group for Baseline and each scheduled visit and maximum post-Baseline (including unscheduled visits in the derivation) values.

By-subject listing of subjects with potentially CS vital signs and weight will be provided.

All vital signs results will be listed on the Safety population.

13.4. ECG

A 12-lead electrocardiogram (ECG) will be performed and read centrally at Screening, Baseline/Day 1, Week 24 and Early Termination visit.

All ECG data (absolute values and change from Baseline) will be summarized as continuous variables by visit (Baseline and scheduled visits only). All parameters will be presented in alphabetically order.

The overall results of the ECGs recorded as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS' will be summarized by treatment group and visit (scheduled visits only). Clinical significance will be determined by the investigator.

Additionally all ECG findings will be summarized with numbers and percentages by visit (Baseline and scheduled visits only.

All ECG results will be listed on the Safety population.

13.5. Physical Examination

Following body system assessments will be performed at Screening, Baseline/Day 1, Week 8, Week 16, Week 24, Early Termination, and Week 32/Follow-up:

- Head, ears, eyes, nose, throat, neck (including thyroid),
- Skin/integumentary system,
- Cardiovascular system,
- Respiratory system,
- Gastrointestinal system,
- Musculoskeletal system,
- Lymph nodes,
- Nervous system, and
- Extremities.

The number and percentage of subjects with physical examination results by body system classified as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS' will be summarized (Baseline and scheduled visits only).

Shift from Baseline of the physical examination category will also be summarized by body system and by visit.

By-subject listing will be provided for subjects who have at least one abnormal result from any body system or who missed the assessment due to any reason.

All physical examination results will be listed on the Safety population.

13.6. Respiratory Assessments

13.6.1. Respiratory Examination

A respiratory examination consists of medical interview. Questions regarding medical history of asthma, wheeze, dyspnea, and cough, will be performed for all subjects at Screening. At Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Early Termination and Week 32/Follow-up questions are asked regarding:

- newly diagnosed (de novo) with Asthma / experience a worsening of Asthma since last visit
- newly diagnosed with Wheeze since last visit / experience a worsening of Wheeze since last visit
- newly diagnosed with Dyspnea since last visit / experience a worsening of Dyspnea since last visit
- newly diagnosed with Cough since last visit / experience a worsening of Cough since last visit

Newly diagnosed asthma or unexpected worsening of asthma are also reported as AESI. All Respiratory examination questionnaire results will be summarized with numbers and percentages by visit and listed on the Safety population.

13.6.2. Peak Expiratory Flow

Peak expiratory flow (PEF) 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. Obtained PEF values will be compared to predicted values based on the subject's age, sex and height.

PEF testing will be performed for all subjects at screening, Baseline/Day 1, Week 8, Week 16, Week 24, Early Termination, and Week 32/Follow-up visits. For subjects reporting a medical history of asthma, PEF testing will be performed at all visits during the clinical study. For subjects diagnosed with de novo asthma, PEF testing will be performed at all visits, starting with the visit in which the diagnosis was confirmed.

Following PEF parameters will be summarized as a continuous variable (Baseline and scheduled visits only):

- Actual peak expiratory flow rate
- Predicted peak expiratory flow rate
- Actual PEF of predicted value (%).

These PEF parameters will be summarized separately for the subset of subjects with and without history of asthma.

The number and percentage of subjects with PEF < 80% of predicted value will be summarized by treatment group, visit (baseline and scheduled visits only), and medical history of asthma (with and without history of asthma).

All PEF results will be listed on the Safety population.

13.6.3. Asthma Control Test

Subjects with a medical history of asthma will take an Asthma Control Test (ACT) at Screening, Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Early Termination visit, and Week 32/Follow-up. Subjects with de novo asthma will complete the ACT testing beginning from de novo diagnosis and at all subsequent scheduled visits.

The ACT 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.

ACT total score (absolute values and change from Baseline) will be summarized as a continuous variable (Baseline and scheduled visits only).

The number and percentage of subjects with an ACT score ≤ 19 will be summarized (scheduled visits only).

The ACT results and the ACT score will be listed on the Safety population.

14. Changes from Analysis Planned in Protocol

In protocol Section 9.10 (Prior and Concomitant Therapy), concomitant medications/therapies are defined as any therapies taken during the study (i.e., from the screening visit to the end of study).

However, for the analysis purpose, concomitant medications/therapies are defined as medications/ therapies which start or stop or ongoing on or after the 1st injection of study drug.

In protocol stratification variable weight is named 'body weight at baseline'. This wording is corrected to 'weight at randomization', to clarify that this is the body weight at the time of randomization and how this information is provided by the investigator.

It has been further clarified how to deal with data collected on or after the use of rescue therapy in order to consistently treat subjects as treatment failures across all the analyses. Efficacy data collected on or after the use of rescue therapy will be set to the worst case value for continuous variables and subject's binary response will be calculated based on the underlying continuous values as stated in Section 8.3.

It has been further clarified for the definition of weekly dairy data: if the intake date of rescue therapy is before and on the last day of the weekly visit window, this week will be treated as treatment failure except for OC analysis and the weekly average will be imputed using the worst case value, refer to Section 8.3.

Additional secondary endpoints were added:

1) Proportion of subjects with IGA <= 2 (Responder) will be presented using missing as non-responder for ITT population up to Week 24
2) Proportion of subjects with number of pruriginous lesions (PAS item 2) < 20 (Responder) will be presented using missing as non-responder for ITT population up to Week 24.
3) PN associated pain frequency rating = 5 (every day, non-responder) will be presented using missing as non-responder for ITT population up to Week 24.
4) Change and percentage from Baseline in PN associated pain intensity will be presented using MMRM model for ITT population up to Week 24.

15. Reference List

1. Liublinska V., Rubin DB. Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial. Stat Med. 2014 October 30; 33(24): 4170–4185. doi:10.1002/sim.6197.

16. Programming Considerations

All TFLs and statistical analyses will be generated using SAS® 9.4 or higher (SAS® Institute Inc., Cary, NC, USA) on a SAS Server. Changes to the software version (e.g. upgrades), or use of additional software consistent with the SAP will not be considered a violation of the SAP.

16.1. General Considerations

All TFLs will be produced in accordance to Syneos Health QC Processes (see Section 17).

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be provided in separate Word rtf and as combined PDF format including all outputs in one PDF file.
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 Guidance.

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced on paper size A4 using the Courier New font, size 8.
- The data displays for all TFLs will have a 1 inch binding margin on top and bottom of a landscape oriented page and a minimum 1.25 inch margin on the left side and a minimum of 0.75 inch right side.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers

- All output should have the following header at the top left of each page:

```
Galderma Protocol RD.06.SPR.202685
Dry-run/Draft/Final
```

- All output should have Page n of N at the top corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

16.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1.1). ICH E3 numbering is used. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis population are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the table.
- Column headers. There will be 1 blank line between the last title and the solid line.

```
Table 14.1.1.1
Subject Disposition
Screened Population
```

16.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in Initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group column.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis population sizes will be presented for dose group in the column heading as “N=XX” (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis population.

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned. The “%” is not presented for example “`5 (0.6)`”

16.2.5.2. *Table Conventions*

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented are included.
- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean, median, Q1 and Q3 for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".
- Percentage values will be printed to one decimal place without the "%", with the "." in alignment, one space after the count (e.g., 7 (12.8), 13 (5.4)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC. The body system, drug class and SOC are displayed in alphabetically order. Within body system, drug class and SOC, preferred term will be display in descending frequency. If incidence for more than 1 preferred term is identical, they should then be sorted alphabetically.
- P-values will be output in the format: '0.xxxx', where xxx is the value rounded to 4 decimal places. Every p-value less than 0.0001 will be presented as "<0.0001". If the p-value is returned as >0.9999, then present as ">0.9999".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. These details are described in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, it is described in a footnote or programming note as needed if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(continued)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate.

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes will always begin with 'Notes:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes will be used sparingly and add value to the TFL. If more than 10 lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, the date of extraction indicated

with "Data Cut-off: DDMMMYYYY" and the listing source (i.e., '`Program: t-14-01-03-02-01.sas, Run date: 16MAR2021 12:57`', `date cut-off: DDMMMYYYY, Listing Source(s): 16.x.y.z`).

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed.
  Example
  `Listing source: 16.2.1.1`

17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs Standard Operation Procedure (SOP) (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (SDTM, ADaM, TFL) (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output. A detailed description of project specific QC procedure can be found in the document “SAS Programming and Validation Plan” (version 1.0, dated 18-May-2020).

18. Index of Tables

This section contains lists of the tables tentatively planned for this study. Changes in the number or content of planned listings are not considered deviations from this SAP.

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20. Index of Listings

This section contains lists of the listings tentatively planned for this study. Changes in the number or content of planned listings are not considered deviations from this SAP.

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21. Appendices

Efficacy data collected on/after the use of rescue therapy will be set to the worst case value for continuous variables (e.g. weekly averages of PP NRS) and subject's binary response will be calculated based on the underlying continuous data (see Section 8.3) prior to conducting the MI and Tipping Point analysis.

21.1. Tipping Point Analysis

Tipping point analysis will be performed by converting non-responders due to missing data to responders in successive increments (∆) for both treatment groups to assess the robustness of analysis (Liublinska, 2015, see Section 15). The value of ∆ that overturns (i.e. non-significant) the primary results will represent the tipping point. A graphic display of all possible combination of the number of responders among both treatment groups will be presented.

21.2. Multiple Imputation

Multiple imputation (MI) methods will be done for monotone missing data. The MI imputation will be carried out as follows.

21.2.1. Imputation Phase

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

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

- Binary endpoint: A logistic regression method to impute the ordinal missing data, including treatment, randomization strata, and assessments from earlier time points as covariates. Response or total score of the subjects will be derived using these imputed data.
- Continuous endpoint: A linear regression model including treatment, randomization strata, and assessments from earlier time points as covariates will be used to impute the score. Response or total score of the subjects will be derived using these imputed data.

21.2.2. Analysis Phase

The analysis will be conducted using the complete datasets.

- Binary endpoint: The complete datasets will be modelled for the endpoint using CMH method. Proportion of responders in each treatment arm, difference and standard error will be calculated.
- Continuous endpoint: The complete datasets will be analyzed using ANCOVA including treatment group and randomization stratification factors as factors and appropriate Baseline values as a covariate, if applicable. LSMeans in each treatment arm, difference and standard errors will be calculated.

21.2.3. Pooling Phase

The results from the analysis phase will be combined as follows.

- Binary endpoint: The results from the CMH analysis of the multiple imputed datasets will be combined using the Rubin (1987) and Li et al (1991) approach to produce pooled CMH statistics

and p-value. Proportion of responders in each treatment arm, difference and standard error will be combined using the MIANALYZE procedure in SAS.

- Continuous endpoint: The LSMeans in each treatment arm, difference and standard errors from the ANCOVA of the multiple imputed datasets will be combined using the MIANALYZE procedure in SAS.

21.3. Example SAS Code

1. The example SAS code for CMH model is listed as below:

```
proc freq data=analysis_data;
   tables stratum*trt*resp/ cmh alpha=0.1;
run;
```

2. The example SAS code for MMRM model is listed as below:

```
proc mixed data = analysis_data;
   class stratum trtp avisit subjid;
   model chg = base stratum trtp avisit trtp*avisit/ ddfm=kr;
   repeated avisit / subject=subjid(trtp) type=un;
   lsmeans trtp/ cl diff;
   lsmeans trtp*avisit/ slice=avisit cl diff;
run;
```

3. The example SAS code for ANCOVA model is listed as below:

```
proc mixed data = analysis_data;
   class stratum trtp;
   model chg = base stratum trtp;
   lsmeans trtp/ cl diff;
run;
```

4. The example SAS code for imputation phase by PROC MI:

```
proc mi data=analysis_data seed=202685 minimum=xx maximum=xx nimpute=50 out=out_data;
   mcmc impute=monotone chain = multiple;
   var base stratum y4 y8 y12 y16;
run;

proc mi data = analysis_data seed=202685 minimum=xx maximum=xx nimpute=number_of_imputations
out=out_data;
   by imputation;
   class trtp stratum;
   monotone reg (/details); [OR montone logistic;]
   mnar model (y4 / modelobs = (trtp = 'Placebo'));
   mnar model (y8 / modelobs = (trtp = 'Placebo'));
   mnar model (y12 / modelobs = (trtp = 'Placebo'));
   mnar model (y16 / modelobs = (trtp = 'Placebo'));
   var base stratum y4 y8 y12 y16;
run;
```

5. The example SAS code for pooling phase for ANCOVA model by PROC MIANALYZE:

```
proc sort data=diff;
   by avisitn trtp;
run;

proc sort data=lsm;
   by avisitn trtp;
run;

proc mianalyze data=diff;
   by avisitn trtp;
   modeleffects estimate;
   stderr stderr;
ods output ParameterEstimates=estdiff; run;

proc mianalyze data=lsm;
   by avisitn trtp;
   modeleffects estimate;
   stderr stderr;
ods output ParameterEstimates=estlsm; run;
```

21.4. Potentially Clinically Significant Ranges

Potentially clinically significant ranges for Hematology parameters are defined in Table 21-1:.

Table 21-1: Potentially Clinically Significant Ranges for Hematology Parameters

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
Basophils (x10^9/L)	BASO	0.00	0.20	> 0.2 at post-baseline, if baseline value ≤ 0.2
Eosinophils (x10^9/L)	EOS	0.00	0.57	> 0.7 at post-baseline, if baseline value ≤ 0.7
		80 (≥59 years old)	100 (≥59 years old)	> 105 at post-baseline, if baseline value ≤ 105
Hematocrit (L/L)	HCT	0.39 (12-<59 years old, Male)	0.54 (12-<59 years old, Male)	< 0.30 at post-baseline, if baseline value ≥ 0.30
		0.37 (≥ 59 years old, Male)	0.51 (≥ 59 years old, Male)	> 0.6 at post-baseline, if baseline value ≤ 0.6
		0.34 (Female)	0.48 (Female)	
Hemoglobin (g/L)	HGB	127 (12-<59 years old, Male)	181 (12-<59 years old, Male)	Male < 100 at post-baseline, if baseline value ≥ 100
		116 (12-<59 years old, Female)	164 (12-<59 years old, Female)	Male ≥ 200 at post-baseline, if baseline value < 200
		125 (≥ 59 years old, Male)	170 (≥ 59 years old, Male)	Female <90 g/L at post-baseline and ≥ 90 g/L at baseline
		115 (≥ 59 years old, Female)	158 (≥ 59 years old, Female)	Female ≥180 g/L at post-baseline and < 180 g/L at baseline
Leukocytes (x10^9/L)	WBC	3.80	10.70	< 3.0 at post-baseline, if baseline value ≥ 3.0
				> 15.0 at post-baseline, if baseline value ≤ 15.0
Lymphocytes (x10^9/L)	LYM	0.91 (18 – <59 years old)	4.28 (18 – <59 years old)	< 0.8 at post-baseline, if baseline value ≥ 0.8
		0.80 (≥ 59 years old)	3 (≥ 59 years old)	> 4.28 at post-baseline, if baseline value ≤ 4.28 (age 18 - < 59); > 3.00 at post-baseline, if baseline value ≤ 3.00 (age ≥ 59)
Monocytes (x10^9/L)	MONO	0.12	0.92	> 0.92 at post-baseline, if baseline value ≤ 0.92
Neutrophils, Segmented (GI/L)	NEUTSG	1.96	7.23	< 1.5 at post-baseline, if baseline value is ≥ 1.5
				> 9 at post-baseline, if baseline value is ≤ 9
Platelets (x10^9/L)	PLAT	140 (18 - <60 years old)	400 (18 - <60 years old)	< 100 at post-baseline, if baseline value ≥ 100

		130 (≥ 60 years old)	394 (≥ 60 years old)	> 700 at post-baseline, if baseline value ≤ 700

Potentially clinically significant ranges for Blood Chemistry parameters are defined in Table 21-2:.

Table 21-2: Potentially Clinically Significant Ranges for Blood Chemistry Parameters

Test Parameter	**Test Parameter Code**	**Normal Range Lower Limit (LLN)**	**Normal Range Upper Limit (ULN)**	**Potentially Clinically Significant Ranges**
Aspartate Aminotransferase (U/L)	AST	8.00	40.00	> 3 x ULN at post-baseline, if baseline value ≤ 3 x ULN
Alkaline Phosphatase (U/L)	ALP	55 (< 19 years old, Male)	149 (< 19 years old, Male)	> 2.5 x ULN at post-baseline, if baseline value ≤ 2.5 x ULN
		45 (< 19 years old, Female)	87 (< 19 years old, Female)	
		40 (≥ 19 years old, Male)	129(≥ 19 years old, Male)	
		35 (≥ 19 years old, Female)	104 (≥ 19 years old, Female)	
Alanine Aminotransferase (U/L)	ALT	5 (Male)	48 (Male)	> 3 x ULN at post-baseline, if baseline value ≤ 3 x ULN
		4 (Female)	43 (Female)	
Bilirubin (umol/L)	BILI	3.00	21.00	> 1.5 x ULN at post-baseline, if baseline value ≤ 1.5 * ULN
Calcium (mmol/L)	CA	2.07	2.64	< 2 at post-baseline, if baseline value ≥ 2
				> 2.9 at post-baseline, if baseline value ≤ 2.9
Chloride (mmol/L)	CL	94.00	112.00	< 94 at post-baseline, if baseline value ≥ 94
				> 115 at post-baseline, if baseline value ≤ 115
Cholesterol (mmol/L)	CHOL	2.95 (< 20 years old, Male)	5.12 (< 20 years old, Male)	> 7.75 at post-baseline, if baseline value ≤ 7.75 (Female ≤ 60 years old, Male ≤ 70 years old); > 8.28 at post-baseline, if baseline value ≤ 8.28 (Female < 60 - 70 years old); > 7.76 at post-baseline, if baseline value ≤ 7.76 (Male > 70 years old); > 9.10 at post-baseline, if baseline value ≤ 9.10 (Female > 70 years old)

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		3.23 (< 20 years old, Female)	5.48 (< 20 years old, Female)	
		3.31 (20 - < 30 years old, Male)	6.10 (20 - < 30 years old, Male)	
		3.31 (20 - < 30 years old, Female)	5.64 (20 - < 30 years old, Female)	
		3.88 (30 - < 40 years old, Male)	6.83 (30 - < 40 years old, Male)	
		3.65 (30 - < 40 years old, Female)	6.21 (30 - < 40 years old, Female)	
		4.19 (40 - < 50 years old, Male)	7.24 (40 - < 50 years old, Male)	
		4.01 (40 - < 50 years old, Female)	6.85 (40 - < 50 years old, Female)	
		4.40 (50 - < 60 years old, Male)	7.53 (50 - < 60 years old, Male)	
		4.42 (50 - < 60 years old, Female)	7.53 (50 - < 60 years old, Female)	
		4.53 (60 - < 70 years old, Male)	7.71 (60 - < 70 years old, Male)	
		4.86 (60 - < 70 years old, Female)	8.28 (60 - < 70 years old, Female)	
		4.58 (≥ 70 years old, Male)	7.76 (≥ 70 years old, Male)	
		5.35 (≥ 70 years old, Female)	9.10 (≥ 70 years old, Female)	
Creatinine (umol/L)	CREAT	40 (18 - < 50 years old, Male)	110 (18 - < 50 years old, Male)	> 1.5 x ULN at post-baseline, if baseline value ≤ 1.5 x ULN
		31 (18 - < 50 years old, Female)	101 (18 - < 50 years old, Female)	
		40 (50 - < 70 years old, Male)	119 (50 - < 70 years old, Male)	
		31 (50 - < 70 years old, Female)	101 (50 - < 70 years old, Female)	

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		40 (70 - < 80 years old, Male)	137 (70 - < 80 years old, Male)	
		31 (70 - < 80 years old, Female)	110 (70 - < 80 years old, Female)	
		40 (≥ 80 years old, Male)	145 (≥ 80 years old, Male)	
		31 (≥ 80 years old, Female)	128 (≥ 80 years old, Female)	
Creatine Kinase (U/L)	CK	39 (Male)	308 (Male)	> 2.5 x ULN at post-baseline, if baseline value ≤ 2.5 x ULN
		26 (Female)	192 (Female)	
Direct Bilirubin (umol/L)	BILDIR	<2.00	7.00	> 1.5 x ULN at post-baseline, if baseline value ≤ 1.5 x ULN
Gamma Glutamyl Transferase (U/L)	GGT	10 (< 59 years old, Male)	61 (< 59 years old, Male)	> 2.5 x ULN at post-baseline, if baseline value ≤ 2.5 x ULN
		4 (< 59 years old, Female)	49 (< 59 years old, Female)	
		10 (≥ 59 years old, Male)	50 (≥ 59 years old, Male)	
		5 (≥ 59 years old, Female)	50 (≥ 59 years old, Female)	
Glucose (mmol/L)	GLUC	3.90	5.60	< 3 at post-baseline, if baseline value ≥ 3
				> 13.9 at post-baseline, if baseline value ≤ 13.9
Potassium (mmol/L)	K	3.5	5.2	< 3.5 at post-baseline, if baseline value ≥ 3.5
				> 5.5 at post-baseline, if baseline value ≤ 5.5
Sodium (mmol/L)	SODIUM	132 (18 – < 59 years old)	147 (18 – < 59 years old)	< 129 at post-baseline, if baseline value ≥ 129
		135 (≥ 59 years old)	145 (≥ 59 years old)	> 150 at post-baseline, if baseline value ≤ 150
Triglycerides (mmol/L)	TRIG	0.42 (< 20 years old, Male)	1.67 (< 20 years old, Male)	> 3.69 at post-baseline, if baseline value ≤ 3.69
		0.44 (< 20 years old, Female)	1.40 (< 20 years old, Female)	
		0.50 (20 – < 30 years old, Male)	2.81 (20 – < 30 years old, Male)	

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		0.41 (20 – < 30 years old, Female)	1.63 (20 – < 30 years old, Female)	
		0.56 (30 – < 40 years old, Male)	3.62 (30 – < 40 years old, Male)	
		0.44 (30 – < 40 years old, Female)	1.99 (30 – < 40 years old, Female)	
		0.62 (40 – < 50 years old, Male)	3.69 (40 – < 50 years old, Male)	
		0.51 (40 – < 50 years old, Female)	2.42 (40 – < 50 years old, Female)	
		0.65 (50 – < 60 years old, Male)	3.61 (50 – < 60 years old, Male)	
		0.59 (50 – < 60 years old, Female)	2.96 (50 – < 60 years old, Female)	
		0.65 (≥ 60 years old, Male)	2.94 (≥ 60 years old, Male)	
		0.63 (≥ 60 years old, Female)	2.71 (≥ 60 years old, Female)	
Urate (mmol/L)	URATE	125 (< 50 years old, Male)	488 (< 50 years old, Male)	> 494 at post-baseline, if baseline value ≤ 494 (Male); > 446 at post-baseline, if baseline value ≤ 446 (Female)
		125 (< 50 years old, Female)	428 (< 50 years old, Female)	
		149 (50 - < 70 years old, Male)	494 (50 - < 70 years old, Male)	
		149 (50 - <70 years old, Female)	446 (50 - < 70 years old, Female)	
		149 (≥ 70 years old, Male)	494 (≥ 70 years old, Male)	
		149 (≥ 70 years old, Female)	446 (≥ 70 years old, Female)	
Urea Nitrogen (mmol/L)	UREAN	1.40 (< 70 years old)	8.60 (< 70 years old)	> 8.6 at post-baseline, if baseline value ≤ 8.6 (<70 years old); > 10.4 at post-baseline, if baseline value

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
				≤ 10.4 (70 - <80 years old); > 12.1 at post-baseline, if baseline value ≤ 12.1 (≥ 80 years old)
		1.40 (70 - < 80 years old)	10.40 (70 - < 80 years old)	
		1.40 (≥ 80 years old)	12.10 (≥ 80 years old)	

Potentially clinically significant ranges for vital signs parameters are defined in Table 21-3.

Table 21-3: Potentially Clinically Significant Ranges for Vital Signs Parameters

Test Parameter	Test Parameter Code	Potentially Clinically Significant Ranges
Pulse rate (beats/min)	PULSE	≥120 bpm and increase from baseline ≥20 bpm
		≤50 bpm and decrease from baseline ≥20 bpm
Diastolic blood pressure (mmHg)	DIABP	≥110 mmHg and increase from baseline ≥10 mmHg
		≤45 mmHg and decrease from baseline ≥10 mmHg
Systolic blood pressure (mmHg)	SYSBP	≥160 mmHg and increase from baseline ≥20 mmHg
		≤95 mmHg and decrease from baseline ≥20 mmHg
Weight	WEIGHT	≥5% increase from baseline
		≥5% decrease from baseline

PPD

PPD