CCI [redacted]

Statistical Analysis Plan

SAP Text Version Number: Final Version

SAP Text Date: 19-Jan-2024

Sponsor Name: Galderma S.A./Galderma R&D, LLC

Protocol Number: RD.06.SPR.203890

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

Protocol Version and Date:

V1.0, 20-Jul-2021

V2.0, 12-Dec-2022

V2.0, 22-Mar-2022 – For Germany

V3.0, 12-Dec-2022 – For Germany

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Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	11-Jan-2024	PPD	Final Version
2.0	19-Jan2024	PPD	• Protocol version update on the title page • Sample size section 4.3 updated with protocol Version 3.0

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

Approvals

CCI

PPD	PPD	
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Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
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
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

Abbreviation	Description
D	Depression
DBL	Data Base Lock
DCS	Dual-Chamber Syringe
DD	Drug Dictionary
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
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
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IGA	Investigator Global Assessment
IL-31	Interleukin-31
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System

Abbreviation	Description
IWRS	Interactive Web Response System
LDL	Low-Density Lipoproteins
LLN	Lower Limit of Normal
LTE	Long-Term Extension
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
MSD	Morning Sleep Diary
N/A	Not Applicable
NAb	Neutralizing Antibodies
NCS	Not Clinical Significant
NK	Neurokinin
NRS	Numeric Rating Scale
OC	Observed Case
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PDF	Portable Document Format
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PN	Prurigo Nodularis
POE	Proof of Exposure

Abbreviation	Description
PP NRS	Peak Pruritus Numeric Rating Scale
PP	Peak Pruritus
PPS	Per-Protocol Set
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

Abbreviation	Description
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
US	United States
W	Week
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

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

2.2. Timings of Analyses

The final analysis may 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 interim analysis may be conducted for the submission of the regulatory registration of nemolizumab.

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 (v1.0, dated 24-Aug-2020) and Appendix 2 of IAC charters (v1.0, dated 27-Aug-2020).

3. Study Objectives

3.1. Primary Objective

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

3.2. Secondary Objectives

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

4. Study Details/Design

4.1. Brief Description

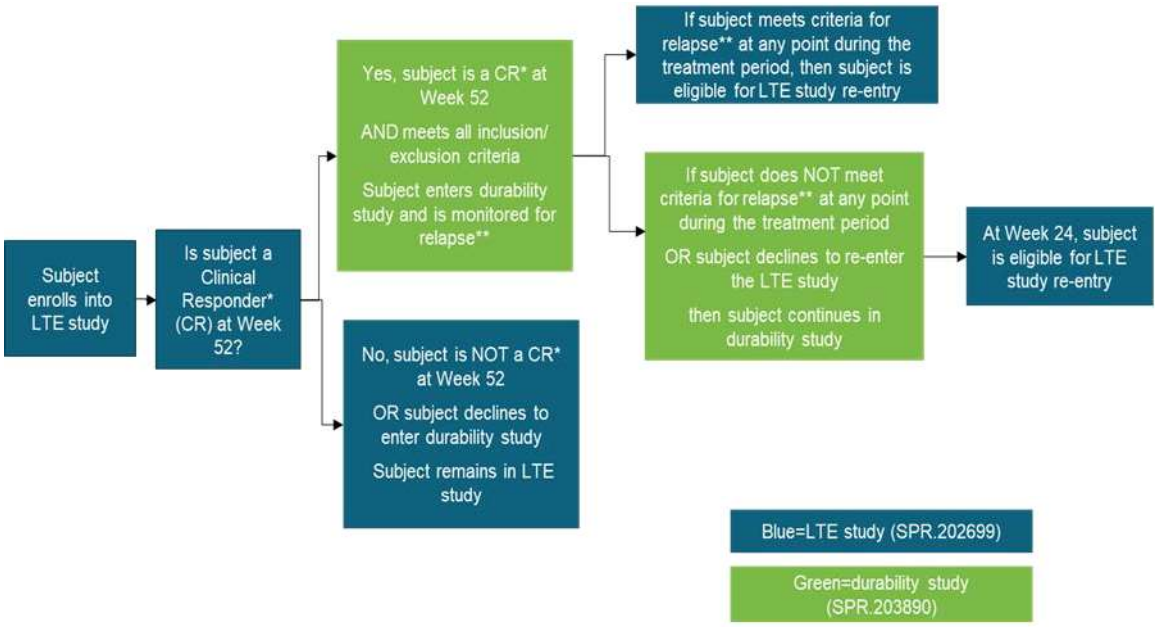
This is a Phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the durability of response and safety of nemolizumab in adult subjects who participated in the nemolizumab PN LTE study (RD.06.SPR.202699) and achieved a clinical response (i.e., IGA score of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

Subjects who agree to enroll in this study must do so at the time of completion of the Week 52 visit in the LTE study (RD.06.SPR.202699) to prevent any lapse in study treatment. After the Week 52 visit of the LTE study is complete, approximately 100 subjects who choose to enter this study will be randomized 1:1 to receive either 1 or 2 injections of nemolizumab or placebo, stratified by dosing regimen. Subjects will continue to receive the same dosing regimen received in the LTE study (i.e., 1 or 2 SC injections of study drug administered every 4 weeks [Q4W]). Subjects with a body weight <90 kg in LTE study will receive a 30-mg dose. Subjects weighing ≥90 kg in the LTE study will receive a 60-mg dose.

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

Relapse is defined as an increase in (weekly average of the) PP NRS score ≥4 points from baseline or an increase in IGA score ≥ 2 from baseline at any point during the study. If a subject meets the criteria for relapse, then the subject may be considered for re-entry into the LTE study (RD.06.SPR.202699). Refer to Figure 4-1 for subject transition between studies 202699 and 203890.

Figure 4-1: Subject Transition between Studies 202699 and 203890



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

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

Baseline Assessment

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

Treatment Period

Eligible subjects will be randomized to receive either 1 or 2 injections of nemolizumab or placebo according to their dosage group in the LTE study, as assigned by interactive response technology (IRT). Study drug

will then be administered Q4W for 24 weeks with final dose administered at Week 20.

Refer to the below table for summary of the study treatment.

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

Abbreviation: LTE = long-term extension; Q4W = every 4 weeks.

[a] Dose will be assigned based on dose received in LTE lead-in study

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

If a subject meets the criteria for relapse at any point, the subject will exit the study and re-enter the LTE study (see Figure 4-1). Subjects who exit the study before Week 24 should complete an early termination (ET) visit. Subjects who complete the study through Week 24 are eligible to re-enroll in the LTE study.

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

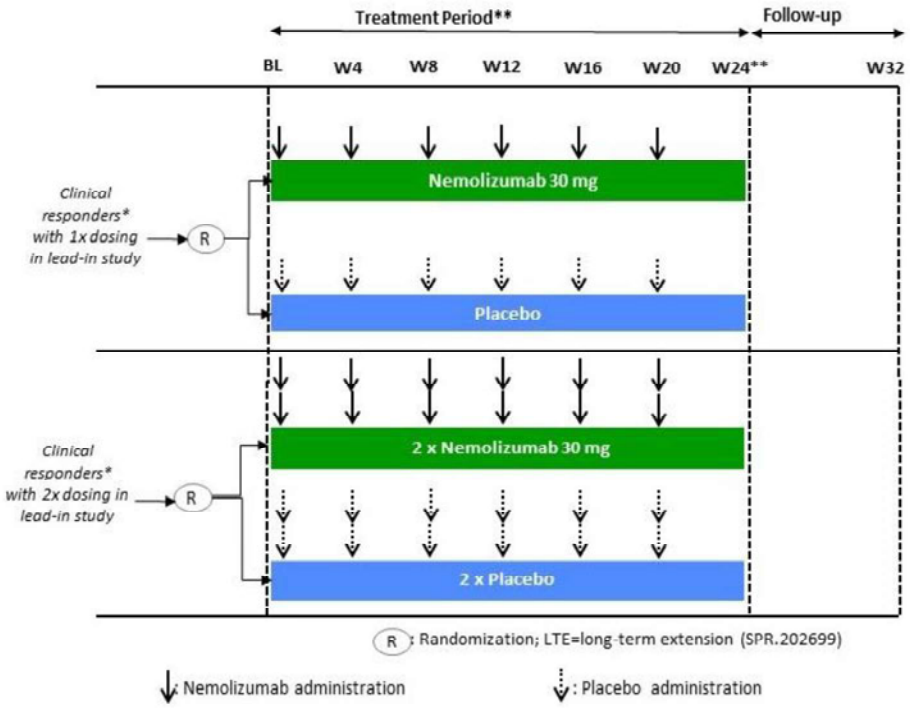
Subjects who discontinue the study for reasons other than relapse before Week 24 or who will not continue nemolizumab treatment in the LTE study should complete a follow-up visit, 12 weeks (±7 days) after the last study drug injection.

Follow-up Period

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

An overview of the study is presented in Figure 4-2.

Figure 4-2: Study Design



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

** Relapse is defined as an increase in weekly average of PP NRS score ≥4 points from baseline or an

increase in IGA score ≥2 from baseline at any point during the study. Subjects who relapse at any point during the treatment period or who complete through Week 24 are eligible for LTE re-entry.

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

The end of the study will be the last subject's last visit as indicated in the Schedule of Assessments (Table 4-1).

4.2. Subject Selection

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

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

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

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 1:1 ratio to receive treatment of either Nemolizumab (CD14152) or placebo. The randomization scheme will be stratified by dosing regimen (1 or 2 injections) 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 anti-drug antibody (ADA) 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. ADA results will be 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.

An independent unblinded team will perform unblinded analysis at the time of interim analysis. Further details are provided in unblinding plan.

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

“Study drug” or “study medication” refers to nemolizumab or placebo drug product for purposes of this double-blind study. The list of excipients is detailed in the Investigator’s Brochure(IB).

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

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

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

Subjects will have the option to self-inject study drug while at the study center under staff supervision. Subjects will be trained on injecting the study drug and will be allowed to inject study drug following

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

4.6. Study Procedures and Flowchart

See Table 4-1 for study procedures.

Table 4-1: Schedule of Assessments

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

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

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

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

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

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

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

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

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

g) Respiratory exams and PEF measurements are required at these visits for subjects with a medical history of asthma or newly-diagnosed (de novo) asthma only. Whenever possible, it is preferable that the PEF measurements be performed before noon or at the same time during each study visit. Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject.

h) Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least 5 minutes), and body temperature.

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

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

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

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

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

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

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

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

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

The dose will depend on the dose received in the LTE lead-in study RD.06.SPR.202699.

5. Endpoints

5.1. Primary Efficacy Endpoints

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

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

5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Proportion of subjects with increase in PP NRS score ≥4 points from baseline at each scheduled visit
- Proportion of subjects maintaining IGA success, defined as IGA score of 0 (clear) or 1 (almost clear) at each scheduled visit
- Proportion of subjects with increase in IGA ≥2 points from baseline at each scheduled visit
- Absolute and percent change from baseline in PP NRS at each scheduled visit
- Absolute and percent change from baseline in Sleep Disturbance Numeric Rating Scale (SD NRS) at each scheduled visit
- Change from baseline in DLQI at Week 16 and Week 24

5.3. Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence and severity of AEs, including treatment-emergent AEs (TEAEs), AESIs, serious AEs (SAEs), treatment-related AEs, and AEs that lead to discontinuation.
- Physical examination and Vital signs
- Clinical laboratory tests
- Electrocardiogram
- Peak expiratory flow
- Asthma Control Test (ACT)

- Anti-drug antibody (ADA) concentrations
- Incidence of positive ADA assays
- Nemolizumab (CD14152) serum concentrations

6. Analysis Sets

6.1. Intent-to-Treat Population

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

6.2. Safety Population

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

6.3. Proof of Exposure Analysis Population

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

6.4. Per-Protocol Population

The Per-Protocol (PP) population will consist of all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment (see Section 6.5). Only primary and selected secondary endpoints will be analyzed using the Per-Protocol Population, under the treatment group as randomized.

6.5. 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 Per-Protocol Population will be specified in the BDRM Preparation Plan. Only major protocol deviation which have a significant effect on the efficacy will result in exclusion from the Per-Protocol Population.

Individual deviations (major and minor) will be presented in a data listing on the ITT 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 COVID-19) deviation will be provided by type of deviation and treatment group for the ITT population.

All protocol deviations will be listed.

7. Estimands

The primary 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 permitted 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

Table 7-1: List of Intercurrent Events

Intercurrent Event	Strategy to Deal With Intercurrent Event Within Analysis	Assessment of Subject
Treatment discontinuation	While on Treatment Strategy	Any data collected after a treatment discontinuation will be censored
Use of prohibited medication	While on treatment strategy	Any data collected after a use of prohibited medication will be censored

Table 7-2: Estimands for primary Endpoint

Endpoints	Estimands
Time to relapse meeting at least 1 of the defined criteria*	Treatment: randomized treatment with subcutaneous injections of nemolizumab or placebo at Week 0, 4, 8, 12, 16, and 20
	Population: ITT population
	Endpoint: Time to relapse meeting at least 1 of the defined criteria
	Intercurrent events: Time to relapse will be censored at the last observation prior to treatment discontinuation or use of prohibited medication

Endpoints	Estimands
	Summary measure: Hazard ratio of nemolizumab and placebo

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

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

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 , if indicated, by visit.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects
- 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

The 24-week **treatment period** is defined as Day 1/Baseline 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.

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 week 52 value from LTE trial.

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, then study day = event date - date of randomization.

A subject's **date of last participation** in the trial is the last date of contact.

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

8.3. Missing Data

When analyses are not based on OC, the primary method to impute the missing values will be as follows:

Continuous Endpoints: For continuous secondary endpoints during treatment period, the MMRM approach will be used to handle the missing data.

Binary Endpoints: For binary secondary endpoints during treatment period, missing data will be imputed to failure.

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 including 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 (IGA)	Visit Window (DLQI)
Baseline	1	≤ 1	≤ 1
Week 4	29	2 to 42	N/A
Week 8	57	43 to 70	N/A
Week 12	85	71 to 98	N/A
Week 16	113	99 to 126	2 to 140
Week 20	141	127 to 154	N/A
Week 24	169	155 to 210	141 to 210
Week 32 Follow-up	225	>211	N/A

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.

Consecutive daily assessment:

For the evening assessments (PP 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	1	-7 to -1	-6 to 1
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	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[a]	169	162 to 175	163 to 176
Early Termination*	UN	7 days prior until Early termination visit (excluding early termination visit date)	6 days prior until early termination visit (including early termination visit date)

[a] First 7 days data available will be used for weekly average calculation.

*For subjects with early termination, if weekly average is not available based on the slotting, additional analysis window was added and will be assigned to the week based on the slotting above. i.e., if subject

early terminated day 142, and week 21 is not available, the new window defined will be used to determine the weekly average at that week.

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

8.5. Subgroups

Subgroup analysis will not be conducted in this study, regarding the small sample size.

9. Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

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

Subject accounting will summarize subjects randomized and randomized but not treated for all subjects by overall 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) 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.

Subjects in each analysis population (ITT, SAF, PP, POE 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, visit dates will be listed for the ITT population. Additional listings of discontinuation reason, missed visit and 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.

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 POE 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, North America, and Asia Pacific),

race, ethnicity, and smoking history will be summarized using the summary statistics for categorical variables. Weight will additionally be presented for each subgroup < 90 kg and ≥ 90 kg as well as dosing regimen (1 or 2 injections).

The Baseline disease characteristics IGA, weekly average PP NRS, weekly SD NRS and baseline DLQI will be summarized. IGA, will be summarized as a categorical variable.

A summary table for the stratification factor dosing regimen 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 baseline and will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0).

Medical history will be summarized by treatment group. The summary will include number and percentage of subjects reporting each system organ class (SOC) and preferred term (PT) and will be 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.

Medical history data listings will be presented by subject number, start date, stop date, SOC, and PT for the ITT population.

9.4. Medical and Surgical Procedure

Medical and surgical procedures will be coded using the latest version of Medical Dictionary of Regulatory Activities (MedDRA).

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

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. If stop date is partially missing, the procedure will be considered concomitant unless the non-missing part of date proves it ended prior to the first treatment date.

The following medical and surgical procedures (prior and concomitant) 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
- Concomitant procedure during treatment period
- Concomitant procedure during follow-up period

Medical and surgical procedures listings 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.

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. If stop date is partially missing, the medication will be considered as concomitant unless the non-missing part of date proves it ended prior to the first treatment date.

Medications (prior, concomitant and prohibited medications) will be coded using Version B3 Sep2021 of the World Health Organization's Drug Dictionary (WHO DD). 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 ATC level alphabetically and descending frequency in PT within ATC level term.

- Prior medication
- Concomitant medication during treatment period
- Concomitant medication during follow-up period
- Prohibited medication during treatment period
- Prohibited medication during follow-up period

All medications (prior and concomitant medications, prohibited 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

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.

10.1. Primary Efficacy Endpoints

10.1.1. Primary Analysis of Primary Efficacy Endpoint

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

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

For primary endpoint, any subjects with missing data for PP NRS and IGA Score both at visit will be censored at the respective timepoint. If any one of PP NRS or IGA Score data is available for the visit, calculation for primary endpoint will be made using available results. If a subject has taken prohibited medication at any point of time during treatment period, then subject will be censored at the respective visit.

The primary endpoint will be analyzed using Cox proportional hazard model with treatment group, dosing regimen as a factor, and baseline PP NRS score and IGA score as covariates on ITT population. The estimated hazard ratio and the corresponding 95% CI will be presented. A supportive analysis also will be performed using Per-Protocol Population.

Kaplan-Meier survival plots will also be presented for time to relapse. The median time, 25th and 75th quantiles along with corresponding CI will be presented using ITT/PP.

Censoring rule for primary endpoint variable is as follows:

Situation	Date of Progression or Censoring	Outcome
Relapse as described	Date of Relapse	Event
Subject withdrawn without relapse	Date of last efficacy assessment (PP NRS and IGA) prior to withdrawal	Censored
Treatment Discontinuation	Date of last efficacy assessment (PP NRS and IGA) prior to Treatment Discontinuation	Censored
Prohibited medication without relapse	Date of last efficacy assessment (PP NRS and IGA) prior to prohibited medication	Censored
Completes the study without relapse	Date of Week 24 completion	Censored
No Efficacy assessment	Date of study Day 1	Censored

10.1.2. Sensitivity Analyses of Primary Efficacy Endpoint

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

- Same analysis on Per-Protocol Population as mentioned in 10.1.1.
- 'Actual strata of randomization' instead of 'stratum at the randomization' for subjects stratified incorrectly.
- Removal of COVID-19 affected visits (i.e. exclusion of subjects from visit, if visit was missed due to COVID-19.) This is analysis will be performed only if >2% subjects have missing data due to COVID-19.

10.2. Secondary Efficacy Endpoints

The following secondary endpoints are to be analysed at the scheduled visits:

Endpoint	Analysis Visit	Analysis to be done on which Population	Statistical Tests
Proportion of subjects maintaining IGA success at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT and Per-Protocol Population	CMH
Proportion of subjects with increase in IGA ≥2 points from baseline at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16	On the ITT and Per-Protocol Population	CMH
Proportion of subjects with increase in PP NRS score ≥4 points from baseline at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT and Per-Protocol Population	CMH
Absolute and percent change from baseline in PP NRS at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT and Per-Protocol Population	ANCOVA
Absolute and percent change from baseline in PP NRS at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT	MMRM

Endpoint	Analysis Visit	Analysis to be done on which Population	Statistical Tests
Absolute and percent change from baseline in SD NRS at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT and Per-Protocol Population	ANCOVA
Absolute and percent change from baseline in SD NRS at each scheduled visit	Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24	On the ITT	MMRM
Change from baseline in DLQI at each visit	Baseline, Week 16, Week 24	On the ITT Population	ANCOVA

Abbreviations: CMH= Cochran-Mantel-Haenszel; DLQI=Dermatology Life Quality Index; IGA=Investigator Global Assessment; PP=Peak Pruritus; SD=Sleep Disturbance.

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

Continuous secondary endpoints will be analyzed using analysis of covariance (ANCOVA) based on OC with treatment group and dose regimen as factors, and baseline value as the covariate. In addition, for PPNRS and SDNRS endpoints, the mixed effect model for repeated measure (MMRM) approach based analysis will be repeated on OC, including treatment group and dose regimen as factor, visit, interaction term between treatment and visit along with corresponding baseline value as independent covariate. Kenward-Roger approximation is used to estimate denominator degrees of freedom. An unstructured covariance is used to model the within-patient errors in the analysis. While applying the model, if convergence criteria not met with unstructured covariance matrix, then "Type = CS or type =ar(1)" covariance matrix will be applied to achieve convergence of the model. The matrix with the minimum AIC criteria will be selected for the further analysis. For both analyses, the least squares means, estimated standard error, and 95% confidence interval (CI) for each endpoint will be presented for each treatment group and analysis visit; the estimated treatment difference for each endpoint at each analysis visit will be summarized by presenting the difference in least squares means between treatment groups, the two-sided 95% CI, and associated p-value as well.

All secondary endpoints will be presented descriptively using OC.

10.2.1. Investigator's Global Assessment (IGA)

The IGA is a 5-point scale used by the Investigator or trained designee to evaluate the global severity of PN and the clinical response to a treatment (see Table 10-1).

Table 10-1: 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.

IGA will be collected at Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 and Early Termination or any unscheduled visit. 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 Per-Protocol Population.

The proportion of subjects maintaining IGA success and subjects with increase in IGA ≥ 2 points from baseline will be summarized on the ITT based on OC. 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.

The analysis will be repeated:

- on Per-Protocol Population, based on OC
- on ITT population, imputing missing values with non-responder imputation

Line plot for proportion of subjects maintaining IGA success and proportion of subjects with increase in IGA ≥ 2 points from baseline, both using non-responder imputation, will be for the ITT Population.

10.2.2. 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.

Subjects will be asked the following question:

- CCI [redacted]

The Baseline PP NRS will be the score of Week 52 visit from LTE trial.

PP NRS at all follow-up visits will be determined as an average of 7 consecutive days data up to the target study day and will be set to missing if less than 4 days data are available. Subjects will receive instructions on how to record their PP 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 (OC) will be provided on the ITT and Per-Protocol Populations. Absolute change and percent change from Baseline for the PP NRS will also be included in the summary on the ITT and Per-Protocol Populations.

Absolute change from Baseline in PP NRS will be analyzed using ANCOVA based on OC, including treatment group dose regimen as factors with baseline value 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. Percentage change from Baseline in PP NRS will not be analyzed because of the small sample size and potential high skewness of the data.
The analysis will be repeated:

- on Per-Protocol Population, based on OC

on ITT population, based on OC and using MMRM approach, including treatment group and dose regimen as factor, visit, interaction term between treatment and visit, and baseline value as covariate. Kenward-Roger approximation is used to estimate denominator degrees of freedom. An unstructured covariance is used to model the within-patient errors in the analysis. While applying the model, if convergence criteria not met with unstructured covariance matrix, then below mentioned covariance matrix will be applied to achieve convergence of the model. The matrix with the minimum AIC criteria will be selected for the further analysis.

- Compound Symmetry (CS)
- Ar(1) – Autoregressive (1)

The proportion of subjects with PP NRS with ≥ 4 in increase from baseline will be summarized on the ITT based on OC. 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. The analysis will be repeated:

- on Per-Protocol Population, based on OC
- on ITT population, imputing missing values with non-responder imputation

Line plot for proportion of subjects with PP NRS ≥ 4 increase will be presented on the ITT Population using non-responder imputation.

10.2.3. 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 the score of Week 52 visit from LTE trial.

Subjects will be asked the following question:

- CCI [redacted]

Descriptive summary of SD NRS (OC) will be provided on the ITT and Per-Protocol Population. Absolute change and percent change from Baseline will also be included in the summary.

Absolute change from Baseline in SD NRS will be analyzed using ANCOVA based on OC, including treatment group dose regimen as factors with baseline value 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. Percentage change from Baseline in SD NRS will not be analyzed because of the small sample size and potential high skewness of the data.

The analysis will be repeated:

- on Per-Protocol Population, based on OC

on ITT population, based on OC and using MMRM approach, including treatment group and dose regimen as factor, visit, interaction term between treatment and visit, and baseline value as covariate. Kenward-Roger approximation is used to estimate denominator degrees of freedom. An unstructured covariance is used to model the within-patient errors in the analysis. While applying the model, if convergence criteria not met with unstructured covariance matrix, then below mentioned covariance matrix will be applied to achieve convergence of the model. The matrix with the minimum AIC criteria will be selected for the further analysis.

- Compound Symmetry (CS)
- Ar(1) – Autoregressive (1)
-

10.2.4. 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 score indicated a poorer quality of life.

DLQI will be collected at Baseline, Week 16, Week 24 and Early Termination. DLQI total score will be summarized as a continuous variable using OC on the ITT Population. Absolute change and percentage change from Baseline in DLQI total score will also be summarized.

Absolute change from Baseline in DLQI will be analyzed using ANCOVA based on OC, including treatment group dose regimen as factors with baseline value 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. Percentage change from Baseline in DLQI will not be analyzed because of the small sample size and potential high skewness of the data.

11. Pharmacokinetics

The serum concentration of Nemolizumab will be assessed at Baseline, Week 24 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 POE analysis population by visit and by dosing regimen from Baseline and Week 24, 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 dosing regimen on both a linear and semi-logarithmic scale on the POE analysis population (2 plots).

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

12. Immunogenicity

Blood samples to assess anti-Nemolizumab ADA will be collected at Baseline, Week 24 and Early Termination. Immunogenicity analyses will be summarized on the POE 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 positive ADA results will be summarized (absolute occurrence and percent of subjects) and plotted by dosing regimen at each visit. The concentration of ADA titer (ng/mL) and neutralizing antibodies (ng/mL) will be summarized as continuous variables.

The number and percentage of subjects with treatment related ADA will be summarized by visit and dosing regimen. A treatment-related ADA is defined when the Baseline or confirmatory ADA result is negative and the post-baseline confirmatory ADA result is positive in the Nemolizumab treated group only.

Individual trough serum drug concentrations will be plotted over time in ADA-positive versus ADA-negative subjects.

13. Safety

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

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

13.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1.

Treatment-emergent AEs (TEAEs), defined as those AEs occurring after the first administration of study treatment until the end of the follow-up period, will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA 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
- COVID-19 infections
- Peripheral edema: limbs, bilateral,
- Facial edema
- 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,
    - 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,
    - 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
- 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
-
- 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 AE

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 glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, creatine phosphokinase (CPK). CPK isoenzyme test will be performed only if CPK is elevated to >2.5 × upper limit of normal (ULN).
- **Urinalysis:** pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

Laboratory assessments are performed at Baseline/Day 1, Week 12, 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 (scheduled visits only) for hematology, chemistry. Last, worst and maximum post-baseline results will also be included in the summaries. Potentially CS ranges are listed in Section 20.2.

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.

By-subject listing will be presented for all laboratory data. By-subject listing for subjects with at least one abnormal result (out of reference range) 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.

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 baseline visit and urine pregnancy tests (UPTs) at Baseline, Week 4, Week 8, Week 12, Week 16, Week 20 and 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 confirmed pregnancy test results, premenses status and childbearing potential assessment results will be listed on the Safety population.

13.2.3. Virology and TB Testing

Virology including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV), human immunodeficiency virus 1, and human immunodeficiency virus 2 antibodies may be assessed at unscheduled visits for safety purposes based on Investigator judgment. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody. Subjects with positive HCV antibodies will have a confirmatory test for HCV (e.g., PCR). All virology results will be listed on the Safety population.

Subjects may be assessed for active or latent tuberculosis (TB) at unscheduled visits for safety purposes based on Investigator judgment. A subject who tests positive for latent TB (with a positive QuantiFERON-TB Gold test) should be referred to the subject's treating physician for appropriate follow-up. 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 at Baseline/Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24, Early Termination visit, and at Week 32/Follow-up.

Height and weight will be measured at Baseline for all subjects. Weight assessments will be conducted at Baseline/Day 1, and 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 20.2) 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 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 visit 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 Baseline/Day 1, Week 12, Week 24, Early Termination, and Week 32/Follow-up:

- Head, ears, eyes, nose, throat, neck (including thyroid),
- Skin/integumentary system (excluding PN),
- 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.

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. Asthma Control Test

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

13.6.2. 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 Baseline/Day 1, Week 12, 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

Only subjects reporting a medical history of asthma will require a respiratory examination at all visits. Subjects with a new (de novo) diagnosis of asthma will require a respiratory examination at all scheduled visits after the diagnosis is first made.

Newly diagnosed asthma or unexpected worsening of asthma are also reported as AESI. Respiratory examination questionnaire results will be listed on the Safety population.

13.6.3. 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 Baseline/Day 1, Week 12, Week 24, Early Termination, and Week32/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 new (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% 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.

14. Changes from Analysis Planned in Protocol

- Summary Statistics will be presented by Treatment Group instead of “by Treatment Group and dosing regimen’.

15. 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.

15.1. General Considerations

All TFLs will be produced in accordance to CCI [redacted] (see Section 16).

- 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.

15.2. Table, Figure, and Listing Format

15.2.1. 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 colour), 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.

15.2.2. Headers

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

```
Galderma                          Protocol                          RD.06.SPR.203890
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.

15.2.3. 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
```

15.2.4. 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.

15.2.5. Body of the Data Display

15.2.5.1. *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)"

15.2.5.2. *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 "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. *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.

15.2.5.4. *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.

15.2.6. 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
```

16. 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 CCI Developing Statistical Programs Standard Operation Procedure (SOP) (3907).

CCI 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”.

17. 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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	14.1.1.4	Summary of Subject Disposition by Site	ITT Population
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20. Appendices

20.1. Example SAS Code

1. The Example SAS code for Time to Event and Hazard Ratio

```
proc lifetest data=analysis_data;
    time aval*cnsr(1);
    strata trtp;
run;
proc phreg data=analysis_data;
    class trtp stratum;
    model aval*cnsr(1)=trtp stratum;
run;
```

2. 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;
```

3. *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;
```

4. *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;
```

20.2. Potentially Clinically Significant Ranges

Potentially clinically significant ranges for Hematology parameters are defined in Table 20-1.

Table 20-1 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
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)	158.00 (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 20-2 Potentially Clinically Significant Ranges for Blood Chemistry Parameters.

Table 20-2 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)
		3.23 (< 20 years old, Female)	5.48 (< 20 years old, Female)	

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		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)	
		40 (70 - < 80 years old, Male)	137 (70 - < 80 years old, Male)	

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		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)	
		0.41 (20 – < 30 years old, Female)	1.63 (20 – < 30 years old, Female)	

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

Test Parameter	Test Parameter Code	Normal Range Lower Limit (LLN)	Normal Range Upper Limit (ULN)	Potentially Clinically Significant Ranges
		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 20-3.

Table 20-3 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

CCI [redacted]

PPD

CCI