CCI

Statistical Analysis Plan for Interventional Studies

Sponsor Name: Galderma Research & Development, LLC

Protocol Number: RD.06.SPR.116912

Protocol Title: A Multicenter, Open-Label, Single-Group Clinical Trial to Assess the Pharmacokinetics and Safety of Nemolizumab (CD14152) in Adolescent Subjects (12-17 years) with Moderate-to-Severe Atopic Dermatitis and Associated Pruritus

Protocol Version and Date: Version 6.0 (21-July-2020)

CCI

Authors: PPD, Principal Biostatistician

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
Stable 1.0	17-Jul-2019	PPD	Initial Document
Final 2.0	20-Nov-2019	PPD	Section for Biomarker added (section 10.9) Modification of in/exclusion criteria based on updated protocol version 4.0 in section 3.4.1 and 3.4.2 Addition of potentially clinically significant laboratory ranges added in section 21. Modification of potentially clinically significant ranges for vital signs and weight in section 10.4 One additional listing added for Biomarkers • Listing 16.2.8.2.13 Biomarkers Safety Population One table was modified to cover modified asthma score criteria • Table 14.3.4.4.6 Summary of Asthma Control Test (ACT) Score <= 19 Safety Population
Final 3.0	21-Sep-2020	PPD	Modification of inclusion criteria based on updated protocol version 5.0 and 6.0 Potentially clinically significant ranged (PCSV) added for Urinalysis in Appendix Definition of treatment period added. Definition of baseline clarified to handle the case of missing first treatment date. Shift tables on PCSV range replaced by a summary table since the PCSV range is not defined for baseline data. Therefore, the shift table is not relevant. Pk parameter are not presented for interim analysis. Modifications due to comments during dry-run

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

Approvals		
CCI Approval		
On behalf of PPD PPD Principal Biostatistician Name, Title Lead Biostatistician	PPD PPD Signature	Sep 22, 2020 Date (DD-Mmm-YYYY)
PPD PPD Name, Title PPD	PPD Signature	21-SEP-2020 Date (DD-Mmm-YYYY)
Galderma Approval		
PPD Biostatistician Name, Title Biostatistician	PPD Signature	22-SEP-2020 Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
ACT	asthma control test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BL	baseline
BLQ	below the limit of quantification
BSA	body surface area
cDLQI	children's Dermatology Life Quality Index
C_{max}	maximum drug concentration
CPK	creatinine phosphokinase
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C_{trough}	concentration before dosing
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
ITT	intent-to-treat
JAK	Janus kinase
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward

Abbreviation	Description
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects with an observation
N	number of subjects in the dataset or population
NAb	neutralizing antibody
NRS	numeric rating scale
OC	observed case
PD	pharmacodynamic
PEF	peak expiratory flow
PK	pharmacokinetic
PP NRS	peak pruritus numeric rating scale
PT	preferred term
Q4W	every 4 weeks
Q8W	every 8 weeks
QoL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	SCORing atopic dermatitis
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	half-life
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
W	week
WBC	white blood cell

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 are responsible for the production and quality control of all tables, figures and listings outlined in this document. The pharmacokinetic and pharmacodynamic parameters will be calculated by a dedicated contract research organization and further details are described in section 9.

2.2. Timings of Analyses

The final analysis of pharmacokinetics (PK), Immunogenicity and safety is planned after all subjects complete the final study visit or terminate early from the study.

An Independent Data Monitoring Committee (IDMC) will review and monitor subject safety. The IDMC will provide recommendations on the safety of subjects. Details on the IDMC, including the plan of analysis for IDMC outputs, the composition of the IDMC, the procedures, roles, responsibilities and their communications are provided in the IDMC charter.

An interim analysis is planned after approximately 10 subjects complete the Week 8 visit. The study will attempt to enroll at least 3 subjects with a low body weight (≤ 61 kg) for the interim analysis and approximately 6 total subjects with low body weight for the overall study population, with investigators attempting to enrol subjects at the lower age range (12-14 years old). The interim analysis will assess whether the observed safety and PK data from adolescents are similar to the data obtained in adults, which is the basis for allowing recruitment of adolescent subjects into the planned nemolizumab Phase 3 studies for AD (pivotal and open-label extension protocols).

3. Study Objectives

3.1. Primary Objective

The primary objective of the study is to assess the PK and safety of nemolizumab in adolescent subjects with moderate-to-severe atopic dermatitis (AD) and associated pruritus not adequately controlled with topical treatments, when administered concomitantly with topical corticosteroid (TCS).

3.2. Secondary Objective

The secondary objective of the study is to evaluate the efficacy of nemolizumab and to further characterize the relationship between nemolizumab concentrations and clinical efficacy endpoints.

3.3. Brief Description

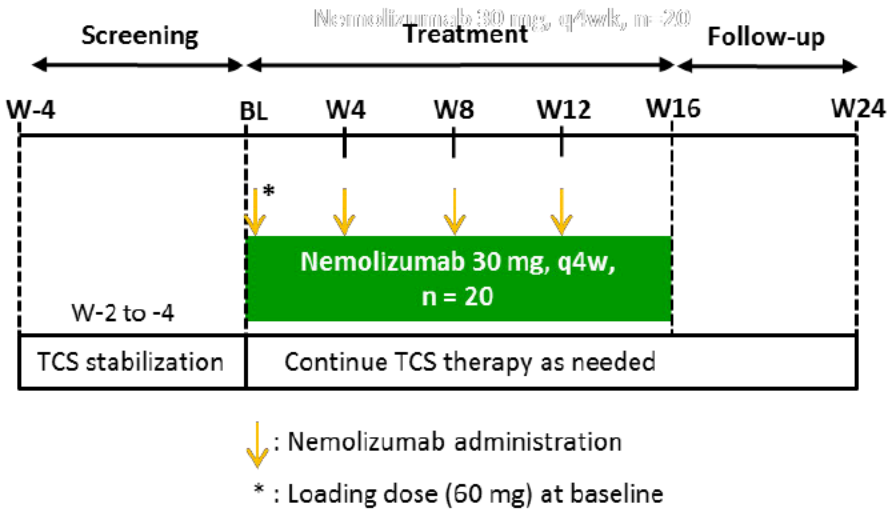
This is an open-label, single-group study to evaluate the PK and safety of 30 mg of nemolizumab in adolescent subjects (12 to 17 years of age), with moderate-to-severe AD and associated pruritus. Approximately 20 eligible subjects will be enrolled to receive subcutaneous injections of nemolizumab (30 mg) every 4 weeks over a 16-week treatment period, with a loading dose of 60 mg on Day 1.

Study participation may include a total of 28 weeks for subjects that complete the screening, treatment and follow-up periods. This study includes a 2 to 4-week run-in period followed by a 16-week treatment period. A follow-up visit (Week 24) is scheduled for subjects who will not immediately rollover (within 7 days following the Week 16 visit) into the nemolizumab open-label extension study. Subjects who prematurely discontinue the study before the Week 16 visit have to be followed for 12 weeks after their last dose of study drug.

Subjects will be screened and complete a run-in period of at least 14 days prior to the Baseline visit. Starting on Baseline/Day 1, all eligible subjects will receive nemolizumab administered subcutaneously, in the presence of background TCS therapy. A loading dose of nemolizumab (60 mg) is administered on Day 1, with subsequent nemolizumab dosing of 30 mg occurring every 4 weeks. The final dose of study medication will occur at Week 12 and subjects will complete the treatment period at the Week 16 visit. An 8-week follow-up period is scheduled (Week 24 visit) for subjects who do not immediately rollover (within 7 days following the Week 16 visit) into the nemolizumab open-label extension study. Subjects who prematurely discontinue the study prior to the Week 16 visit have to be followed for 12 weeks after their last dose of study medication.

Assessments of PK, safety, and efficacy will be conducted throughout the study. Subject-reported assessments of pruritus, sleep disturbance and use of topical medication for their eczema will be collected daily.

Figure 1 below shows a description of the Study Design:



Abbreviations: BL = Baseline; n = number of subjects; q4w = every 4 weeks; TCS = topical corticosteroid; W =week.

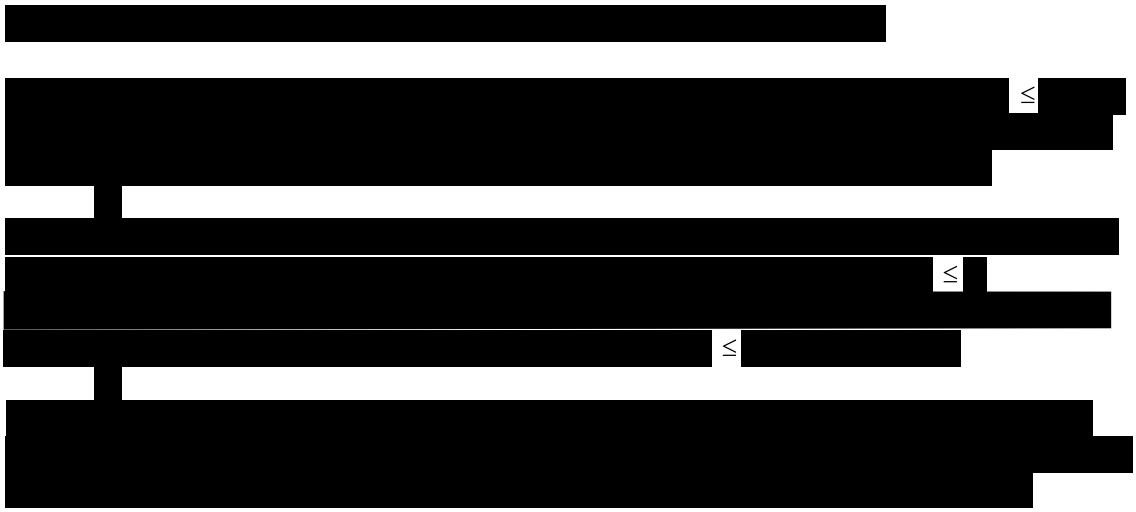
3.4. Subject Selection

It is anticipated that approximately 30 subjects will be screened, with at least 20 eligible subjects enrolled in approximately 10 study centers across the United States.

3.4.1. Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria:

1. Subjects ≥ 12 to < 17 years of age at the screening visit.
2. Chronic AD for at least 2 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria at the time of the screening visit.
3. Eczema Area and Severity Index (EASI) score ≥ 16 at both screening and baseline visits.
4. Investigator's Global Assessment (IGA) score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both screening and baseline visits.
5. AD involvement ≥ 10% of Body Surface Area (BSA) at both screening and baseline visits.
6. Peak (maximum) pruritus numeric rating scale (PP NRS) score of at least 4.0 at both screening and baseline visits:
   - [redacted]
   - [redacted]
7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). [redacted]



8. Agree to apply a moisturizer throughout the study from the screening visit daily, and liberally as needed; agree to apply an authorized TCS from the screening visit and throughout the study as determined appropriate by the investigator.
9. Women of childbearing potential must agree either to be strictly abstinent throughout the study and for 12 weeks after the last study drug injection or to use an effective and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. This criterion also applies to a prepubertal female subject who begins menses during the study.

   Effective and approved methods of contraception applicable for the subject and/or their partner are defined below:

   - Progestogen-only oral hormonal contraception
   - Male or female condom
   - Cap, diaphragm or sponge with spermicide
   - Combination of male or female condom with cap, diaphragm or sponge with spermicide
   - Combined (estrogen and progestogen containing-) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices
10. Subject and guardian willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.
11. Understand and sign an Informed Consent Form (ICF) and Assent Form before any investigational procedures being performed.

3.4.2. Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criterion are applicable:

1. Body weight < 30 kg.
2. Subjects meeting one or more of the following criteria at screening or baseline:
   2a. Had an asthma exacerbation requiring hospitalization in the preceding 12 months.
   2b. Reporting asthma that has been not well-controlled (ie, symptoms > 2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the preceding 3 months.
   2c. Asthma Control Test ≤ 19 (applies only for subjects with a history of asthma).

2d. Peak expiratory flow < 80% of the predicted value.

3. Subjects with a current medical history of chronic obstructive pulmonary disease (COPD) and/or chronic bronchitis.
4. Cutaneous infection within 1 week before the screening visit or any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 1 week before the screening visit. Subjects may be rescreened once the infection has resolved.
5. Requiring rescue therapy for AD during the run-in period, or expected to require rescue therapy within 2 weeks following the baseline visit.
6. Positive serology results for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, or human immunodeficiency virus [HIV] antibody at the screening visit;

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

7. Having received any of the treatments within the specified timeframe before the baseline visit as described in Protocol Section 8.3.3 (Table 3: Prior Treatments).
8. Subjects who failed to respond clinically to previous treatment with a biologic (eg, dupilumab) or a Janus kinase (JAK) inhibitor.
9. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical trial.
10. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, actinic keratoses or squamous cell carcinoma in situ (Bowen's disease) that have been treated and have no evidence of recurrence in the last 52 weeks before the baseline visit, or (2) carcinoma in situ of the cervix.
11. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
12. History of intolerance to low or mid potency TCS or for whom TCS is not advisable (eg, hypersensitivity to TCS, significant skin atrophy, etc.).
13. Known active or latent tuberculosis (TB) infection.
14. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
15. History of or current confounding skin condition (eg, Netherton Syndrome, psoriasis, Cutaneous T-Cell Lymphoma [Mycosis Fungoides or Sezary Syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).
16. Any medical or psychological condition, or any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN), at the screening visit that may put the subject at significant risk according to the investigator's judgment if he/she participates in the clinical trial, or may interfere with study assessments (eg, poor venous access or needle-phobia).
17. Planned or expected major surgical procedure during the clinical trial.
18. Subjects unwilling to refrain from using prohibited medications during the clinical trial.
19. Currently participating in any other clinical trial of a drug or device, participated in a clinical trial within the past 3 months before the screening visit, or is in an exclusion period (if verifiable) from a previous clinical trial.

3.5. Determination of Sample Size

Based on the variability of nemolizumab serum concentrations (observed in adults during previous studies), a sample size of 20 was considered sufficient to calculate PK parameters with adequate precision and to ensure adequate representation across the adolescent age range. No formal powering of the trial was performed to determine sample size requirement.

It is anticipated that approximately 30 subjects will be screened, with at least 20 eligible subjects enrolled.

The study will attempt to enroll at least 3 subjects with low body weight (≤ 61 kg) for the interim analysis and approximately 6 total subjects with low body weight for the overall study population.

3.6. Treatment Assignment & Blinding

Eligible subjects will be sequentially assigned to receive treatment with open-label nemolizumab, based on the time of enrollment.

Although some subjects will be screened and assigned a subject identification number (SIN), they may not be eligible for enrollment/treatment, and thus they will not be enrolled in the study.

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

Any inadvertent dose modification(s) should be reported to the sponsor/CRO.

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

3.7. Administration of Study Medication

Dosing frequency is scheduled for every 4 weeks, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window, study drug can be administered with a minimum of 3 weeks since the last injection. Future visits should be scheduled within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between 2 injections.

As described in Table 1, Nemolizumab (CD14152) will be administered as a subcutaneous injection, with a loading dose of 60 mg on Day 1, followed by injections of 30 mg every 4 weeks for 12 weeks.

Table 1 Dosing Scheme

Group	Dose on Day 1	Dose at Weeks 4, 8 and 12
1	60 mg	30 mg

3.8. Study Procedures

Subjects will be screened and complete a run-in period of at least 14 days before the baseline visit. Eligible subjects will enter a 16-week treatment period with nemolizumab 30 mg administered subcutaneously every 4 weeks, with a loading dose of 60 mg at baseline/Day 1.
The final dose of study drug will occur at Week 12 and subjects will complete the treatment period at the Week 16 visit. An 8-week follow-up period is scheduled (Week 24 visit) for subjects who do not immediately rollover (within 7 days following the Week 16 visit) into the nemolizumab open-label extension study. Subjects who prematurely discontinue the study before the Week 16 visit have to be followed for 12 weeks after their last dose of study drug.

The Schedule of Assessments is described in the protocol (Section 8.1.1).

4. Endpoints

4.1. Pharmacokinetic Endpoints

- Nemolizumab serum concentrations at Baseline, Weeks 1-2, 4, 8, 12, 16, 24 and Unscheduled visits for safety reasons.
- Nemolizumab serum PK parameters at steady state extrapolated with a population PK analysis (Cl/F, V_d/F, T_{lag}, k_a, C_{max}, T_{max}, C_{trough}, AUC_{0-4w}, AUC_{0-8w}, AUC_{0-12w}, AUC_{0-16w}, AUC_{inf}, and $t_{1/2}$).

4.2. Immunogenicity Endpoints

- Anti-drug antibody (ADA) assessments (Screening, confirmatory, neutralizing antibody (NAb)), at Baseline, Weeks 4, 8, 16, 24 and Unscheduled visits for safety reasons.

4.3. Safety Endpoints

- Incidence of adverse events (AE), including treatment emergent adverse events (TEAEs), adverse events of special interest (AESIs) and serious adverse events (SAEs).
- Asthma Control Test (ACT): Screening, Baseline, Weeks 1-2, 4, 8, 12, 16, 24, and Unscheduled visits.
- Physical examination: Change from Baseline at all visits.
- Vital signs: Change from Baseline at all visits.
- Clinical laboratory values: Change from Baseline at Weeks 4, 8, 12, 16, 24 and Unscheduled visits for safety reasons.
- Spirometry (peak expiratory flow (PEF)): Change from Baseline at all visits.
- Electrocardiogram (ECG): Change from Screening at Week 16 and Unscheduled visits for safety reasons.

4.4. Secondary Endpoints

4.4.1. Pharmacokinetics

- Nemolizumab serum PK parameters calculated with a non-compartmental analysis (NCA): AUC_{0-4w}, AUC_{0-8w}, AUC_{0-12w}, and AUC_{0-16w}

4.4.2. Pharmacodynamics

- Blood biomarkers (eg, IL-31, TARC and/or other proteins) at baseline, Week 8, and Week 16
- Stratum corneum biomarkers (eg, IL-31 and/or other proteins) at baseline and Week 16

Biomarker analysis will be conducted by the designated CRO separately.

4.4.3. Efficacy

The following efficacy variables will be analyzed:

- Absolute and percent change in EASI score from Baseline to Week 16.

- IGA success rate from Baseline to Week 16.
- Change in BSA involvement of AD, reported as a percentage of all major body sections combined.
- Absolute and percent change in weekly average of peak pruritus numeric rating scale (NRS) score from Baseline to Week 16.
- Absolute and percent change in weekly average pruritus NRS score from Baseline to Week 16.
- Absolute and percent change in weekly sleep disturbance NRS score from Baseline to Week 16.
- Percent change in SCORing Atopic Dermatitis (SCORAD) score from Baseline to Week 16.
- Number of topical AD medication-free days AD medication-free days.

4.4.4. Quality of life

- Dermatology Life Quality Index (DLQI) for subjects > 16 years of age or Children's Dermatology Life Quality Index (cDLQI) for subjects 12-16 years of age at Baseline and Week 16.

5. Analysis Populations

Three analysis populations will be used for this study: the Intent-to-Treat Population, the Safety Population and the Pharmacokinetic population.

5.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all enrolled subjects who signed informed consent form. The ITT population will be used for all analyses of efficacy endpoints.

5.2. Safety Population

The Safety Population will include all subjects in the ITT who were administered at least one dose of study medication. Subjects will be analyzed according to the treatment actually received.

5.3. Pharmacokinetic Analysis Population

The Pharmacokinetic (PK) analysis population will include all subjects in the safety population who provide at least one post-baseline evaluable drug concentration value. PK endpoints will be analyzed using the PK population. Subjects will be analyzed according to the treatment actually received.

5.4. Protocol Deviations

Protocol deviations will be captured by the clinical monitoring team on an ongoing basis throughout the study. All protocol deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessments will be identified, evaluated, and resolved (if applicable) before the respective database lock (interim or final analysis).These deviations will be discussed in a case by case process and classified into major and minor deviations before the data base lock.

6. General Aspects for Statistical Analysis

6.1. General Methods

This section describes analytical analysis issues that relate to all or some of the analytic analysis sections that follow. It describes general guidelines for analysis as well as the following items:

- SAS version 9.4 or higher will be used.
- CCI will be responsible for reporting the demographic, safety, and efficacy data including listings of the administration information for collection of PK and PD samples.
- Unless otherwise specified, summaries will be presented by visit.
- The total number of subjects in the treatment group (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- 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) and percentages of subjects.
- Subject data listings will be presented with the ITT population for efficacy assessments, with the Safety Population for safety assessments and with the PK population for PK assessments, unless stated otherwise.
- In general, the listings will be sorted by subject number, and assessment date (and time) if applicable.
- Multiple assessments at a given time point (repeat, and unscheduled) will not be included in summary tables unless specified otherwise, but will be included in the listings.

6.2. Key Definitions

The date of first treatment is defined as the date of first injection of nemoluzimab.

The date of last treatment is defined as the date of last injection of nemoluzimab.

Study day is defined as the number of days from the date of first treatment and will be calculated as follows:

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

The baseline value will be taken as latest value prior to first injection of nemoluzimab. For subject enrolled but not treated, the baseline value will be the latest value prior to the treatment assignment.

A subject's date of last participation in the trial is the last date of contact and is recorded as the date of completion or date of withdrawal on the completion page of the CRF.

Treatment period is defined as the period between the date of first treatment.

- Up to the date of Week 16 for subjects who completed the treatment period
- Up to the earliest date between 4 weeks after the last study drug injection or the date of early termination for subjects discontinued the treatment period.

6.3. Missing Data

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

Continuous Endpoints: To impute the missing values for efficacy continuous endpoints, Last Observation Carried Forward (LOCF) approach will be used. Only post-baseline visits will be imputed. Screening or Baseline information will not be used for LOCF. As sensitivity analysis, observed case (OC) will be conducted.

Binary Endpoints: All missing values will be treated as a Non-Responder for the binary endpoints. LOCF and OC will be used to impute the missing values as sensitivity analysis.

LOCF and Non-Responder will be performed to all subsequent, scheduled, missing post-baseline assessments. And when impute the missing data using LOCF and Non-Responder, all efficacy data after use the rescue therapy will be considered as missing. There will be no imputations for missing PK and Safety parameters. Imputation rules for missing dates in AEs and medications are described in the corresponding sections.

6.4. Pooling of Centers

No pooling of centers is planned.

6.5. Subgroups

No subgroup analysis is planned.

6.6. Analysis Visit Window

Efficacy by-visit summaries will use the analysis visit. Unscheduled and early termination visits will be windowed based on the following analysis visit window. 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.

		Visit Window	
Analysis Visit	Target Study Day	EASI, IGA, BSA, SCORAD	DLQI/cDLQI
Baseline	1	<=1	<=1
Week 1-2	10	2 to 19	NA
Week 4	29	20 to 42	NA
Week 8	57	43 to 71	NA
Week 12	85	72 to 99	NA
Week 16	113	100 to 141	100 to 141
Week 24 Follow-up	169	> 141	> 141

Daily diary efficacy data (pruritus and sleep disturbance NRS) will be classified into analysis visits as follows considering the data during the 7 days immediately preceding each scheduled visit.

Analysis Visit	Target Study Day	Diary Data Window
Baseline	1	-7 to -1
Week 1-2	10	3 to 9
Week 4	29	22 to 28
Week 8	57	50 to 56
Week 12	85	78 to 84
Week 16	113	106 to 112
Week 24 Follow-up	169	162 to 168

Daily topical AD medication used data will be classified into visit intervals as follows.

Analysis Visit Interval	Target Study Day	Diary Data Window
Baseline to Week 1-2	10	1 to 9
Week 1-2 to Week 4	29	10 to 28
Week 4 to Week 8	57	29 to 56
Week 8 to Week 12	85	57 to 84
Week 12 to Week 16	113	85 to 112
Week 16 to Week 24 follow-up	169	113 to 168

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

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

Summary of accounting of subjects who enter the study will be provided.

Subject disposition will be summarized for all subjects. Subjects screened, screen failed with reason for screen failure, treated, completed the study, discontinued treatment with reason for discontinuation of treatment, and discontinued the study along with reason for discontinuation from the study will be summarized using number and percent of subjects. Percentage of screen failure reason will be based on the number of screen failures. Percentage of subjects treated, completed or discontinued will be based on the number of subjects in ITT population.

Subject disposition will also be summarized by site on the ITT population excluding summaries of subjects screened and screen failures.

Subjects in each analysis population (ITT, Safety, PK population) will be summarized separately.

Subject study completion status, study drug completion status, subjects not meeting eligibility criteria, subjects in analysis population will be listed.

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.

7.2. Protocol Deviations

Major protocol deviation will be summarized on the ITT population, and also summarized by site.

All protocol deviations (major and minor) will be listed on the ITT population.

7.3. Demographic and Other Baseline Characteristics

Age (years), height (cm) at screening, weight (kg) at baseline, weight (kg) by age group (12-14 years, 15-17 years), and BMI (kg/m^2) will be summarized using summary statistics for continuous variables. BMI will be calculated using height at screening and weight at baseline.

If height is recorded in inches (in) then height will be summarized in cm by the following:

$$\text{Height (cm)} = \text{Height (in)} * 2.54$$

If weight is recorded in pounds (lbs) then weight will be summarized in kilograms (kg) by the following:

$$\text{Weight (kg)} = \text{Weight (lbs)} * 0.4536$$

Age group (12-14 years, 15-17 years), sex, race, ethnicity will be summarized using the summary statistics for categorical variables. Summary statistics for demographic and baseline characteristics will be presented for the ITT population.

In addition, baseline disease characteristics will also be summarized for EASI, IGA, BSA involvement of AD, weekly average of peak pruritus NRS, weekly average of average pruritus NRS, weekly sleep disturbance NRS, SCORAD, DLQI, cDLQI.

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

7.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 21.1).

Medical History will be summarized using the number and percent of subjects reporting each system organ class (SOC) and preferred term (PT) and sorted alphabetically by SOC and descending frequency of PT within SOC. Summary tables will be presented for ITT population.

Medical history data listings will be sorted by subject number, onset date, end date, SOC, and PT.

7.5. Medical and Surgical Procedures

Medical and surgical procedures be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 21.1).

Medical and surgical procedures will be classified as follows:

- Prior procedure: defined as procedures that started and ended before first treatment date.
- Concomitant procedure: defined as procedures started or ongoing or ended on or after first treatment date.

Prior and concomitant medical and surgical procedures will be summarized separately using the number and percent of subjects reporting each system organ class (SOC) and preferred term (PT) and sorted alphabetically by SOC and in descending frequency of PT within SOC. Summary tables will be presented for ITT population.

Prior and concomitant medical and surgical procedures listings will be provided and sorted by subject number, onset date, end date, SOC, and PT.

7.6. Medication

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

- Prior medications: defined as medications that started and ended prior to the first treatment date.
- Concomitant medications: defined as medications that started or ongoing or ended on or after the first treatment date.
- Rescue Medication: only medication that directly treat AD (mainly those that are approved or are standard of care), and include topical and systemic treatments. And Rescue medications will be classified by period (treatment period, follow-up period).
    - Rescue medication during treatment period is a medication which started from the first treatment date to the date of Week 16 (for week 16 completers) or the earliest date between 4 weeks after the last study drug injection or the date of early termination (for discontinued subject).
    - Rescue medication during follow-up period is a medication which started from the date of the post end of treatment period to the date of follow up visit.
- Background topical corticosteroids (TCS): permitted background TCS used throughout the study.

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 medication unless the non-missing part of date proves it ended prior to the first treatment date.

Medications (prior, concomitant and rescue medications) will be coded using Version Sept 2018 of the World Health Organization's Drug Dictionary (WHO DD). Preferred Anatomical Therapeutic Chemical (ATC) coding will be performed. Background TCS will not be coded.

The number and percentage of subjects with prior and concomitant medications will be summarized for the ITT population by the ATC Level 4 and the preferred drug name (PT), and sorted alphabetically by ATC level term and descending frequency of PT within ATC level term.

All rescue medications and topical rescue medications (route=topical) will be summarized by period (treatment and follow-up periods) for the ITT population by the ATC Level 4 and PT.

Prior, concomitant and rescue medication summaries will be sorted alphabetically by ATC level term and sorted in descending frequency of PT within ATC level term.

Background TCS will be summarized (number and percentage) by medication name for the ITT population and sorted in descending frequency of medication.

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

8. Efficacy

All the efficacy analyses will be based on the ITT population. All efficacy variables will be summarized by visit from baseline unless specified otherwise. For efficacy analysis, unscheduled visit or ET visit data will be considered for by-visit summary.

All efficacy analysis will be performed using LOCF or Non-responder imputation (unless stated otherwise) and also performed with observed cases (OC) as sensitivity analysis (see Section 6.3 for more details). LOCF and Non-responder will be performed at all post-baseline visits up to Week 24.

In LOCF or Non-responder analyses, all efficacy data will be set to missing after rescue medication is used. In OC analyses, all data will be included even if subject has received rescue medication.

8.1. Eczema Area and Severity Index

Eczema Area and Severity Index (EASI) is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs. EASI is a composite score ranging from 0 to 72. The severity of erythema, induration/papulation, excoriation, and lichenification will be assessed by the investigator on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe) for four body regions (head/neck, trunk, upper limbs, and lower limbs), with half points allowed. In addition, the extent of AD involvement in each of the four body regions (denoted as “Area”) will be assessed as a percentage and converted to a score ranging from 0 to 6 (0% no eczema; 1= 1% to < 10% affected; 2 = 10% to < 30% affected; 3 = 30% to < 50% affected; 4 = 50% to < 70% affected; 5 = 70% to < 90% affected; 6 = 90% to 100% affected). With this information an EASI score for each region will be obtained, and an Overall score as the sum of all body region scores. The EASI scores will be derived and recorded in the CRF as described in Table 2.

Table 2: EASI Score calculation

Body region	EASI score
Head/Neck	(Erythema + Induration/Papulation + Excoriation + Lichenification) x Area x 0.1
Upper limbs	(Erythema + Induration/Papulation + Excoriation + Lichenification) x Area x 0.2
Trunk	(Erythema + Induration/Papulation + Excoriation + Lichenification) x Area x 0.3
Lower limbs	(Erythema + Induration/Papulation + Excoriation + Lichenification) x Area x 0.4
EASI Overall	Sum of the above four body region scores

EASI will be summarized descriptively by visit using LOCF and OC. Absolute change and percent changes from baseline will also be included in the analysis.

For the LOCF analysis, the imputation will be performed for the EASI overall imputated score.

Percent change in EASI using LOCF will be displayed graphically.

All EASI data will be listed.

8.2. Investigator Global Assessment

The Investigator Global Assessment (IGA) is a 5-point scale (defined in Table 3) used by the investigator to evaluate the global severity of AD and the clinical response.

Table 3: IGA 5-point scale

Status	Score	Definition
Clear	0	Minor, residual hypopigmentation/hyperpigmentation, no erythema or induration/papulation, no oozing/crusting.
Almost clear	1	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting.
Mild	2	Faint pink erythema with mild induration/papulation and no oozing/crusting.
Moderate	3	Pink-red erythema with moderate induration/papulation with or without oozing/crusting.
Severe	4	Deep or bright red erythema with severe induration/papulation with oozing/crusting.

IGA score and change from baseline will be summarized by visit using LOCF and OC.

IGA success is defined as 0 (clear) or 1 (almost clear) and at least 2 grade improvement change from baseline. The IGA treatment success rate will be obtained as the ratio between the number of subjects achieving IGA treatment success and the number of subjects with available IGA result at the visit, and will also be summarized by visit from baseline using Non-Responder, LOCF and OC.

Proportion of subjects achieving IGA success using Non-Responder will be displayed graphically.

For the LOCF analysis, the imputation will be performed based on the recorded IGA per visit, and the imputed IGA treatment success rate will be based on the imputed values.

All IGA data will be listed.

8.3. Body Surface Area of AD Involvement

The Body Surface Area (BSA) of AD involvement will be assessed as a percentage for eight different parts of the body, and will be reported individually and as an overall BSA (calculated with the sum of all parts combined), as derived in the CRF. The body parts assessed and their highest possible scores are as follows: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%].

Overall BSA of AD involvement will be summarized descriptively by visit as continuous variables using LOCF and OC. Absolute change and percent from baseline will also be included in the descriptive analysis.

For the LOCF analysis, the imputation will be performed separately for each body part, and the imputed overall BSA will be obtained with the sum of the imputed body region scores.

All BSA data will be listed.

8.4. Scoring Atopic Dermatitis

Scoring Atopic Dermatitis (SCORAD) is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs and symptoms. SCORAD takes into account the extent and intensity of six types of basic lesions (erythema/darkening, edema/papule, oozing/crusting, excoriation,lichenification/prurigo and dryness) and symptoms (itching and loss of sleep). SCORAD ranges from 0 to 103 and has 3 components: extent, intensity, and subjective symptoms.

Calculation of SCORAD will be performed as follows: The extent of body surface area affected by atopic dermatitis will be the “extent of area involved component” (denoted with A).

Next, the intensity of all basic types of lesions is assessed. Depending on the intensity, each of these is assigned a score of 0 (absence), 1 (mild), 2 (moderate) or 3 (severe).The sum of these scores will estimate the “intensity component” (denoted with B).

Finally, based on a visual analog scale (recorded in centimeters), the presence of irritability and loss of sleep for the past three nights is evaluated as a value between 0 (no symptoms) and 10 (worst symptoms ever had). The sum of the two values will estimate the “subjective symptoms component” (denoted with C).

The SCORAD total score is then calculated as = A/5 + (7* B)/2 + C.

SCORAD will be summarized descriptively by visit using LOCF and OC. Absolute change and percent changes from baseline will also be included in the summary.

For the LOCF analysis, the imputation will be performed separately for each SCORAD component, and the imputated total score will be obtained with the imputed components.

All SCORAD data will be listed.

8.5. Pruritus Numeric Rating Scale

Subject-reported assessments of pruritus will be collected daily on a diary.

The Pruritus Numeric Rating Scale (NRS) will be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours. The scale for average itch intensity and maximum itch intensity has values in a range between 0 to 10, with 0 being ‘no itch’ and 10 being ‘worst itch imaginable’.

Average and peak Pruritus NRS scores will be obtained based on the average and maximum daily scores during the 7 days immediately preceding each scheduled visit (rounding is not permitted), and will be denoted as “weekly” scores (average weekly and peak weekly, respectively). A minimum of 4 daily scores is required for these calculations, and if less than 4 daily scores are available the respective weekly score will be a missing value.

Weekly average of peak pruritus NRS and weekly average of average pruritus NRS scores will be summarized descriptively by visit as continuous variables using LOCF and OC. Absolute and percent changes from baseline will also be included in the analysis.

Absolute and percent change from baseline in weekly average of peak pruritus NRS and weekly average of average pruritus NRS using LOCF will be displayed graphically.

For the LOCF analysis, the imputation will be performed separately for each weekly average or peak pruritus NRS score.

All pruritus NRS data will be listed.

8.6. Sleep Disturbance Numeric Rating Scale

Subject-reported assessments of sleep disturbance NRS will be collected daily on a diary.

Sleep disturbance NRS is a scale to be used by the subjects to report the degree of their sleep loss related to AD. The scale has values in a range between 0 to 10, with 0 being 'no sleep loss related to signs/symptoms of AD' and 10 being 'I cannot sleep at all due to the signs/symptoms of AD'.

Weekly sleep disturbance NRS scores will be obtained based on the average daily values during the 7 days immediately preceding each scheduled visit. A minimum of 4 daily scores is required for this calculation, and if less than 4 daily scores are available the respective weekly score will be a missing value.

Weekly average sleep disturbance NRS will be summarized descriptively by visit as continuous variables using LOCF and OC. Absolute and percent changes from baseline will also be included in the analysis.

Absolute and percent change from baseline in weekly average sleep disturbance NRS using LOCF will be displayed graphically.

For the LOCF analysis, the imputation will be performed for each weekly average sleep disturbance NRS score.

All sleep disturbance NRS data will be listed.

8.7. Application of Topical Medication for AD

Patient-reported assessments of the use of topical AD medication for their eczema will be collected daily on a diary.Subjects will be instructed to use the authorized background TCS, and will be asked to record the response (yes/no) to the following question, "Did you apply the eczema medication your doctor gave you, to your skin today?", on an electronic device (ie, diary), throughout the clinical trial (including the run-in and the follow-up period).

A topical AD medication free day is a day without use of topical AD medication. For each subject, each day will be classified as free or not. Days of topical AD medication use will be calculated by summing up the days recorded as yes on a diary. The daily values in visit interval will be used for calculation of visit informations.

Topical AD medication-free days in each visit interval (see section 6.6) will be calculated as follows:

Topical AD medication-free days in visit interval = Days in the interval– Days of topical AD medication use in the interval.

The number of topical AD free days will be summarized descriptively by visit interval as continuous variables. No imputation will be used.

All data for topical AD medication use will be listed.

8.8. Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) is a validated 10-item questionnaire for subjects aged > 16 years, covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment. DLQI data will be recorded in the CRF. Children's DLQI (cDLQI) is a

comparable validated 10-item questionnaire designed for pediatric subjects and cDLQI will be used if the subjects are aged 16 years or less. Each question in DLQI/cDLQI has values in a range between 0 (not at all) and 3 (very much) as defined in Table 4:

Table 4: DLQI and cDLQI question point score

Score	DLQI	cDLQI
0	Not at all	Not at all
1	A little	Only a little
2	A lot	Quite a lot
3	Very much	Very much

The DLQI/cDLQI total score is calculated by summing the score of each question resulting in a maximum score of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

DLQI and cDLQI scores and their change from baseline will be summarized descriptively by visit as continuous variables.

All DLQI/cDLQI data will be listed.

No LOCF analysis will be performed for DLQI/cDLQI.

9. Pharmacokinetics/Pharmacodynamics

PK analyses will be performed using the PK Population. No missing data imputation will be performed.

The serum concentration of nemolizumab will be assessed at baseline, Weeks 1-2, 4, 8, 12, 16, 24 and at any unscheduled visit for safety reasons. At the study drug injection visits (baseline, Weeks 4, 8 and 12), PK samples will be collected within 30 minutes before study drug injection (pre-dose samples). At Weeks 1-2, 16 and 24, attempts should be made to collect PK samples at approximately the same time of the day, to the extent possible.

9.1. Pharmacokinetic Concentration Presentation

Serum concentration data (unit: ng/mL) will be summarized by visit from baseline to Week 24 using the following statistics: n, arithmetic mean, standard deviation, %CV, geometric mean, %CV geometric mean, median, minimum, maximum, 95% CI of mean and number of BLQs (Below Limit of Quantification). BLQ will be considered as missing and excluded from the descriptive summary.

Individual serum concentration and mean concentration will be plotted by visit on both a linear and semi-logarithmic scale on the PK population (unit for x axis: week). For individual concentration plot, BLQ will be considered as missing. For mean concentration plot, mean concentration not calculated will be considered as missing. In addition, individual serum concentration will be plotted over time with different color for subjects with treatment related ADA+ (ADA- at baseline & ADA + after treatment), ADA + at baseline and ADA- from baseline during the study.

Individual serum concentrations will be listed and BLQ will be listed as BLQ.

9.2. Pharmacokinetic Parameters Estimation

The PK parameters will be calculated by a dedicated CRO ([redacted]).

A population PK (popPK) model was developed using nemolizumab serum concentrations from 3 clinical studies conducted in adults (CIM001JP, CIM003JG, and SPR114322). The model developed in adult subjects will be used to derive empirical Bayes estimates in the adolescent population based on their baseline characteristics, their dosing history and their measured concentrations. The adequacy of the model to properly describe the adolescent data will be based on the model diagnostic tools described in a in dedicated PK modeling plan and report.

One interim PK analysis will be done with the available SPR116912 serum concentrations from the 10 first subjects up to the cut-off date corresponding to week 8. The interim PK analysis will be updated with final data when available and presented in the final report.

Estimates of main population PK parameters (Cl/F, V_d/F, T_{lag}, k_a), including inter-individual variability, covariate effects, residual error and their relative standard error (RSE), will be obtained using the popPK model described above.

Other individual nemolizumab PK parameters (C_{max}, T_{max}, $C_{trough\ 4w}$, $C_{trough\ 8w}$, $C_{trough\ 12w}$, $C_{trough\ 16w}$, $AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, $AUC_{0\text{-}16w}$, AUC_{inf} and $t_{1/2}$), will be derived using the same popPK model.

Some individual nemolizumab PK parameters ($AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, and $AUC_{0\text{-}16w}$) will be also calculated using a non-compartmental analysis (NCA) using only the observed serum concentrations from study SPR116912.

Details about calculation of PK parameters (NCA and popPK) will be described in a separated PK modeling plan.

9.3. Pharmacokinetic Parameters Presentation

Estimates of main population PK parameters (Cl/F, Vd/F, Tlag, ka), including inter-individual variability, covariate effects, residual error and their relative standard error (RSE), will be presented in a dedicated PK report.

Individual derived PK parameters at steady state estimated with the popPK model and individual observed PK parameters at steady state calculated with the NCA will be summarized using the following statistics: n, arithmetic mean, standard deviation, geometric mean, %CV, median, minimum, maximum and 95% CI. This descriptive statistics will be calculated CCI .

In addition, the comparison of the average observed trough (C_{trough}) nemolizumab concentration between ADA+ samples and ADA- samples will be performed using ANOVA and the comparison results will be presented.

All PK parameters will be listed by subject.

9.4. Pharmacokinetic/Pharmacodynamic Analysis

The PK/PD analysis will be done by a dedicated CRO (Certara).

Individual predictions and empirical Bayes post-hoc estimates generated from the popPK model will be used to develop PK/PD models for the following pharmacodynamic (PD) endpoints: eczema area and severity index (EASI), investigator's global assessment of dermatitis severity (IGA), and weekly average peak pruritus numeric rating scale (PP-NRS). For each patient, the concentration time-course will be predicted up to the last PD assessment time based on individual Bayes post-hoc estimates of the PK parameters, and will be used as a driver in the PD models. The PK/PD models will be described in a separate PK modeling plan.

10. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of adverse event (AE), adverse event of special interest (AESI), clinical laboratory data, ECG parameters, physical examinations, Asthma control test, respiratory and vital signs.

10.1. Extent of Exposure and Compliance

The extent of exposure (treatment duration, total dose administered, planned dose and treatment compliance percentage) will be summarized.

Treatment duration (in days) is calculated as follows:

[(date of last treatment – date of first treatment) + 1].

Treatment compliance will be summarized based on the treatment records and drug dispensation logs recorded in the CRF. The compliance percentage will be calculated as dose volume administered / planned dose volume *100, with the planned dose of 60 mg on Day 1, followed by injections of 30 mg every 4 weeks for 12 weeks. Once the dosing solution is prepared,1.0 mL of it will be drawn into a syringe, which will be administered subcutaneously in the abdomen of the subjects as planned dose.

Extent of exposure and treatment compliance will be presented in a listing for the Safety population.

10.2. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Summaries of AEs will include only treatment emergent AEs (TEAEs) defined as AEs with an onset date/time on or after the date/time of first treatment. AEs with completely missing onset dates/time will be considered as TEAEs. If AE onset date/time is partially missing, the AE will be considered as TEAE unless the non-missing part of date/time proves it started prior to the first treatment date/time.

AEs will be summarized using the number and percent of subjects reporting each system organ class (SOC) and preferred term (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. Percentages will be calculated using the total number of subjects in the Safety population.

The following summary tables for AEs will be presented:

- Overall Summary of Treatment Emergent Adverse Events (TEAEs), All Causalities
- Overall Summary of Treatment Emergent Adverse Events (TEAEs), Study Drug Related
- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities
- Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related
- Serious Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities
- Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related

- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Maximum Severity, All Causalities
- Severe Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities
- Severe Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related
- Treatment-Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term, All Causalities
- Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term, Study Drug Related
- Treatment-Emergent Adverse Events (TEAEs) of Special Interest by System Organ Class and Preferred Term, All Causalities
- Treatment-Emergent Adverse Events (TEAEs) Occurred in > 1 Subject by System Organ Class and Preferred Term, All Causalities
- Treatment Emergent Adverse Events (TEAEs) Occurred in > 1 Subject by Preferred Term, All Causalities

For the summary of TEAE by maximum severity, if a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity will be used in summary tables.

TEAEs related to study drug/study procedure are those that are identified as reasonable possibility. If relatedness is missing, the AE will be considered TEAE related to study drug/study procedure.
In addition TEAEs that occurred in > 1 subject at the PT level will be summarized by SOC and PT, and also by PT.

Subject listings will be presented for all TEAEs, TEAEs of special interest, serious TEAEs, TEAE leading to permanent discontinuation of study drug, Death and Pre-treatment AEs.

10.3. Laboratory Evaluations

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

Laboratory assessments are performed at Screening, Baseline, Week 4, Week 8, Week 12, Week 16, Week 24 follow-up, Unscheduled Visits and Early Termination Visit.

The following parameters are reported for laboratory data.

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

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

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

- For hematology and chemistry, descriptive statistics by visit and changes from baseline for each parameter using the results in standardized international (SI) units will be presented in summary tables. Urinalysis parameters will be summarized categorically by visit with percentage based on the number of subjects with available data at the visit. By visit summaries will be performed at all visits (scheduled visits only) from baseline. Last post-baseline results, minimum and maximum post-baseline values during treatment period will also be included in by visit summary tables.

- Shift tables will be provided for hematology and chemistry by visit (scheduled visits only) and last post-baseline results during treatment period will also be included in the shift tables. Hematology and chemistry results will be classified as low (L), normal (N), and high (H) by the laboratory parameter's normal range. Shift from baseline using low, normal, high will be provided by visit for hematology and chemistry parameters and will also presented for minimum and maximum post-baseline values.
- In addition, summary of hematology, chemistry and urinalysis using potentially clinical significant ranges will be provided by visit. Potentially clinically significant laboratory ranges are presented in section 21 (Potentially clinically significant ranges for laboratory tests).

Distribution of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Total bilirubin and Creatinine Phospokinease (CPK) will be displayed graphically with maximum post-baseline values. Also spaghetti plots over time will be displayed graphically for those five parameters.

By-subject listing for subjects with at least one abnormal results (out of reference range) will be provided for hematology and clinical chemistry.

By-subject listing for subjects with at least one potentially clinically significant results will be provided for hematology, clinical chemistry and urinalysis.

All laboratory data will be listed.

10.4. Vital Signs, Height and Weight

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 are performed at Screening, Baseline, Week 1- 2, Week 4, Week 8, Week 12, Week 16, Week 24 follow-up, Unscheduled Visits and Early Termination Visit.

Height will be measured at screening and designated visits; weight will be measured at all visits.

Vital signs, height and weight will be summarized descriptively by visit (scheduled visits only) as continuous variables. Absolute changes from baseline will be included in the summary tables. For vital signs parameters, last post-baseline results during treatment period will be summarized in the table.

Shift from baseline in vital signs using normal, abnormal cs, abnormal ncs results will be provided at post-baseline visits (scheduled visits only) and last post-baseline results during treatment period will be included in the shift table.

In addition, vital signs and weight will be summarized using potentially clinically significant ranges.

By-subject listing for subjects with at least one potentially clinically significant results will be provided for vital signs.

All vital signs, height and weight data will be listed.

Potentially Clinically Significant Ranges for Vital Signs and Weight:

Parameter	SI Units	Potentially Clinically Significant Ranges
Pulse rate	beats/min	< 50 (low) and a decrease > 20 from Baseline or >110 (high) and an increase > 20 from Baseline
Temperature	°C	< 35 (low) or > 38 (high)
Diastolic blood pressure	mmHg	< 50 (low) and a decrease > 10 from Baseline or >90 (high) and an increase > 10 from Baseline
Systolic blood pressure	mmHg	< 90 (low) and a decrease > 20 from Baseline or >135 (high) and an increase >20 from Baseline
Weight	kg	<95% or >105% of change from baseline

10.5. ECG

A 12-lead Electrocardiogram (ECG) will be performed at Screening, Week 16, Unscheduled visit and Early Termination visits.

ECG scan will be reviewed centrally by the designated vendor .

The overall results of the ECGs recorded as 'Normal', 'Abnormal, not Clinically Significant (NCS)' or 'Abnormal, Clinically Significant (CS)' will be summarized by visit (scheduled visits only). And the shift table will be provided.

All 12-Lead ECG data will be listed.

10.6. Physical Examination

A complete physical examination (PE) will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (with respiratory assessment), gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system.

Physical examination are performed at Screening, Baseline, Week 1- 2, Week 4, Week 8, Week 12, Week 16, Week 24 follow-up, Unscheduled Visits and Early Termination Visit.

The assessment results and shift from baseline of the physical examination will be summarized by body system and visit from baseline (scheduled visits only).

Clinically significant respiratory examination findings will be summarized separately.

Abnormal physical examination data will be listed.

10.7. Respiratory Assessment - Spirometry/Peak Expiratory Flow

At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, allergies and infections). All subjects will have spirometry/Peak Expiratory Flow (PEF) performed at screening and baseline. For subjects reporting a medical history of asthma, PEF will be performed at each visit during the clinical trial. For subjects diagnosed with de novo asthma, PEF will be performed at all visits starting with the visit in which the diagnosis was confirmed.

Actual PEF (L/min), Predicted PEF Rate (L/min) and Actual PEF Rate of the predicted value (%) will be summarized descriptively by visit (scheduled visit only) as continuous variables. Absolute change from baseline will also be included in the descriptive analysis.

Also spaghetti plots over time will be displayed graphically for Actual PEF (L/min).

Number of subjects with abnormal PEF (actual PEF < 80% of the predictive value) will be summarized separately.

PEF assessment will be presented in listings.

10.8. Asthma Control Test

Subjects with a medical history of asthma will take the Asthma Control Test (ACT) at each study visit before questioning and physical examination by the investigator. The ACT is a subject-completed assessment consisting of 5 questions. Each question is answered with a score in a range of 1 to 5 and lower score represents the more severe condition. A total ACT score is obtained as the sum of the 5 individual question scores.

ATC score and the change from baseline will summarized descriptively by visit (scheduled visits only) as continuous variables.

Also spaghetti plots over time will be displayed graphically for ACT.

Number of subjects with ACT score ≤ 19 will be summarized separately.

ACT assessment data will be presented in listings.

10.9. Other Safety

Confirmed pregnancy test results, childbearing potential, premense status results, biomarker and virology assessment data will be presented in a listing.

11. Immunogenicity

Blood samples will be collected to assess anti-drug (anti-nemolizumab) antibodies (ADA). Serum samples will be assessed for ADA at Baseline, Weeks 4, 8, 16, 24 and at any unscheduled visit for safety reasons.

Screening ADA, confirmation ADA, ADA titer, nutralizing antibodies, and treatment-related ADA will be will be summarized for the Safety population (scheduled visits only).

A treatment-related ADA is a post-baseline confirmatory ADA sample showing positive results while the baseline sreening or confirmatory ADA sample shows negative results.

All Immunogenicity data will be listed for the Safety population.

12. Health Economics

Not applicable.

13. Interim Analyses

An interim analysis is planned after approximately 10 subjects complete the Week 8 visit. The study will attempt to enrol at least 3 subjects with a low body weight (≤ 61 kg) for the interim analysis and approximately 6 total subjects with low body weight for the overall study population, with investigators attempting to enrol subjects at the lower age range (12-14 years old). The interim analysis will assess whether the observed safety and PK data from adolescents are similar to the data obtained in adults, which is the basis for allowing recruitment of adolescent subjects into the planned nemolizumab Phase 3 studies for AD (pivotal and open-label extension protocols).

Outputs presented for the interim analysis and for the IDMC are marked in Sections 18 (Index of Tables), Section 19 (Index of figures) and Section 20 (Index of Listings). But the selected output list for IDMC meeting can be updated by IDMC member's request.

14. Changes from Analysis Planned in Protocol

No changes to the methods planned in the protocol are foreseen.

15. Reference List

Not applicable.

16. Programming Considerations

All TLFs and statistical analyses will be generated using SAS® 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listings and figures (TLF) output will adhere to the following specifications.

16.1. General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word rtf format.
- The final TLFs will be provided in a combined pdf document including a table of contents which are hyperlinked to each output.
- Numbering of TLFs will follow International Conference on Harmonization (ICH) E3 guidance

16.2. Table, Listing, and Figure Format

16.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- 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.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, 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 TLFs. 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., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers

- All output should have the following header at the top left of each page:
- *Galderma* Protocol RD.06.SPR.116912
- CCI [redacted]

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

16.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis populations 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 column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Population

16.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the dose group column (Nemolizumab 30 mg).
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis population sizes will be presented for dose group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis population.

16.2.5. Body of the Data Display

16.2.5.1. General Conventions

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

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

16.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for dose group 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 (0.0).

- 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 are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median 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. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Min	XXX
Max	XXX

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100.0.
- 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. Within the

body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) are displayed in alphabetically order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing or not calculated descriptive statistics or p-values which cannot be estimated are reported as "-".

- 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. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note 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.

16.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Missing data are 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 are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

16.2.5.4. Figure Conventions

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

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six 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, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

17. Quality Control

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

CCI SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (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.

18. Index of Tables

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
14.1		Demographic Data Summary Tables			
14.1.1		Subject Disposition			
	14.1.1.1	Subject Accounting by Overall and Site	All Subjects		Yes
	14.1.1.2	Subject Accounting by Visit	ITT Population		Yes
	14.1.1.3	Summary of Subject Disposition	ITT Population		Yes
	14.1.1.4	Summary of Subject Disposition by Site	ITT Population		
	14.1.1.5	Summary of Screen Failure	All Subjects		Yes
	14.1.1.6	Summary of Analysis Populations	ITT Population		
14.1.2		Protocol Deviations			
	14.1.2.1	Summary of Major Protocol Deviations	ITT Population		
	14.1.2.2	Summary of Major Protocol Deviations by Site	ITT Population		
14.1.3		Demographic and Baseline Characteristics			
14.1.3.1		Subject Demographic and Baseline Characteristics			
	14.1.3.1.1	Summary of Demographics and Baseline Characteristics	ITT Population	Yes	Yes
	14.1.3.1.2	Summary of Baseline Disease Characteristics	ITT Population		Yes
14.1.3.2		Medical History			
	14.1.3.2.1	Summary of Medical History	ITT Population	Yes	Yes
14.1.3.3		Medical and Surgical Procedures			
	14.1.3.3.1	Summary of Prior Medical and Surgical Procedures	ITT Population	Yes	
	14.1.3.3.2	Summary of Concomitant Medical and Surgical Procedures	ITT Population	Yes	
14.1.4		Medications			
	14.1.4.1	Summary of Prior Medications by ATC level and Preferred Term	ITT Population	Yes	
	14.1.4.2	Summary of Concomitant Medications by ATC level and Preferred Term	ITT Population	Yes	
	14.1.4.3	Summary of Rescue Medications during Treatment Period by ATC level and Preferred Term	ITT Population	Yes	Yes
	14.1.4.4	Summary of Rescue Medications during Follow-up Period by ATC level and Preferred Term	ITT Population		Yes
	14.1.4.5	Summary of Topical Rescue Medications during Treatment Period by ATC level and Preferred Term	ITT Population		

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
	14.1.4.6	Summary of Topical Rescue Medications during Follow-up Period by ATC level and Preferred Term	ITT Population		
	14.1.4.7	Summary of Background Topical Corticosteroids (TCS) Dispensation	ITT Population		
14.1.5		Treatment Compliance			
	14.1.5.1	Summary of Exposure to Study Drug	Safety Population	Yes	Yes
14.2.1		Efficacy Data Summary reported on CRF			
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	14.2.1.1.1	Summary of Eczema Area and Severity Index (EASI) Score (LOCF)	ITT Population		
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14.2.1.2		Investigator Global Assessment (IGA)			
	14.2.1.2.1	Summary of Subjects Achieving Investigator Global Assessment (IGA) Success (Non-Responder)	ITT Population		
	14.2.1.2.2	Summary of Investigator Global Assessment (IGA) (LOCF)	ITT Population		
	14.2.1.2.3	Summary of Investigator Global Assessment (IGA) (OC)	ITT Population		
14.2.1.3		Body Surface Area (BSA)			
	14.2.1.3.1	Summary of Body Surface Area (BSA) of AD Involvement (LOCF)	ITT Population		
	14.2.1.3.2	Summary of Body Surface Area (BSA) of AD Involvement (OC)	ITT Population		
14.2.1.4		Scoring Atopic Dermatitis (SCORAD)			
	14.2.1.4.1	Summary of Scoring Atopic Dermatitis (SCORAD) Scores (LOCF)	ITT Population		
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14.2.2		Efficacy Data Summary reported on Diary			
14.2.2.1		Weekly Peak Pruritus NRS Score			
	14.2.2.1.1	Summary of Weekly Average of Peak Pruritus Numeric Rating Scale (NRS) Score (LOCF)	ITT Population		
	14.2.2.1.2	Summary of Weekly Average of Peak Pruritus Numeric Rating Scale (NRS) Score (OC)	ITT Population		
14.2.2.2		Weekly Average of Average Pruritus NRS Score			
	14.2.2.2.1	Summary of Weekly Average of Average Pruritus Numeric Rating Scale (NRS) Score (LOCF)	ITT Population		
	14.2.2.2.2	Summary of Weekly Average of Average Pruritus Numeric Rating Scale (NRS) Score (OC)	ITT Population		

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
14.2.2.3		Weekly Average of Sleep Disturbance Numeric Rating Scale (NRS) Score			
	14.2.2.3.1	Summary of Weekly Average Sleep Disturbance Numeric Rating Scale (NRS) Score (LOCF)	ITT Population		
	14.2.2.3.2	Summary of Weekly Average Sleep Disturbance Numeric Rating Scale (NRS) Score (OC)	ITT Population		
14.2.2.4		Topical AD Medication-free Days			
	14.2.2.4.1	Summary of Topical AD Medication-free Days	ITT Population		
14.2.2.5		Dermatology Life Quality (DLQI) Index			
	14.2.2.5.1	Summary of Dermatology Life Quality Index (DLQI) for Subjects aged > 16 years	ITT Population		
	14.2.2.5.2	Summary of Children's Dermatology Life Quality Index (cDLQI) for Subjects aged 12-16 years	ITT Population		
14.2.3		Pharmacokinetics			
	14.2.3.1	Summary of Nemolizumab Serum Concentrations (ng/mL)	PK Population	Yes	
	14.2.3.2	Summary of Nemolizumab Serum Pharmacokinetics Parameters estimated with PopPK Analysis	PK Population		
	14.2.3.3	Summary of Nemolizumab Serum Pharmacokinetic Parameters calculated with NCA	PK Population		
	14.2.3.4	Analysis on Through Concentrations Between Subject's Antibody to Nemolizumab Status using ANOVA	PK Population		
14.3		Safety Data Summary Tables			
14.3.1		Adverse Events			
	14.3.1.1.1	Overall Summary of Treatment Emergent Adverse Events (TEAEs), All Causalities	Safety Population	Yes	Yes
	14.3.1.1.2	Overall Summary of Treatment Emergent Adverse Events (TEAEs), Study Drug Related	Safety Population	Yes	Yes
	14.3.1.2.1	Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	Yes
	14.3.1.2.2	Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related	Safety Population	Yes	Yes
	14.3.1.2.3	Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	Yes

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
	14.3.1.2.4	Serious Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related	Safety Population	Yes	Yes
	14.3.1.2.5	Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Maximum Severity, All Causalities	Safety Population	Yes	
	14.3.1.2.6	Severe Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	Yes
	14.3.1.2.7	Severe Treatment Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term, Study Drug Related	Safety Population	Yes	Yes
	14.3.1.2.8	Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	Yes
	14.3.1.2.9	Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term, Study Drug Related	Safety Population	Yes	Yes
	14.3.1.2.10	Treatment Emergent Adverse Events (TEAEs) of Special Interest by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	Yes
	14.3.1.2.11	Treatment Emergent Adverse Events (TEAEs) Occurred in > 1 Subject by System Organ Class and Preferred Term, All Causalities	Safety Population	Yes	
	14.3.1.2.12	Treatment Emergent Adverse Events (TEAEs) Occurred in > 1 Subject by Preferred Term, All Causalities	Safety Population	Yes	
14.3.2		Listings of Deaths, Other Serious and Significant Adverse Events			
	14.3.2.1	Adverse Events leading to death	Safety Population	Yes	
	14.3.2.2	Listing of Serious Treatment Emergent Adverse Events (TEAEs)	Safety Population	Yes	
	14.3.2.3	Listing of Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug	Safety Population	Yes	
	14.3.2.4	Listing of Treatment Emergent Adverse Events (TEAEs) of Special Interest	Safety Population	Yes	
14.3.3		Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events			
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Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
14.3.4.1		Clinical Laboratory Data			
14.3.4.1.1		Hematology Data			
	14.3.4.1.1.1	Summary of Laboratory Data - Hematology	Safety Population	Yes	Yes
	14.3.4.1.1.2	Shift from Baseline for Hematology by Reference Range	Safety Population	Yes	Yes
	14.3.4.1.1.3	Summary of Potentially Clinically Significant Hematology Results	Safety Population		Yes
	14.3.4.1.1.4	Listing of Subjects with Abnormal Hematology Results	Safety Population	Yes	
	14.3.4.1.1.5	Listing of Subjects with Potentially Clinically Significant Hematology Results	Safety Population	Yes	
14.3.4.1.2		Blood Chemistry Data			
	14.3.4.1.2.1	Summary of Laboratory Data - Chemistry	Safety Population	Yes	Yes
	14.3.4.1.2.2	Shift from Baseline for Chemistry by Reference Range	Safety Population	Yes	Yes
	14.3.4.1.2.3	Summary of Potentially Clinically Significant Chemistry Results	Safety Population		Yes
	14.3.4.1.2.4	Listing of Subjects with Abnormal Chemistry Results	Safety Population	Yes	
	14.3.4.1.2.5	Listing of Subjects with Potentially Clinically Significant Chemistry Results	Safety Population	Yes	
14.3.4.1.3		Urinalysis Data			
	14.3.4.1.3.1	Summary of Laboratory Data - Urinalysis	Safety Population	Yes	
	14.3.4.1.3.2	Summary of Potentially Clinically Significant Urinalysis Results	Safety Population		Yes
	14.3.4.1.3.3	Listing of Subjects with Potentially Clinically Significant Urinalysis Results	Safety Population	Yes	
14.3.4.2		Vital Signs			
	14.3.4.2.1	Summary of Vital Signs, Height and Weight	Safety Population	Yes	Yes
	14.3.4.2.2	Shift from Baseline in Vital Signs by Clinically Significant Abnormality	Safety Population	Yes	
	14.3.4.2.3	Summary of Potentially Clinically Significant Vital Signs and Weight	Safety Population		Yes
	14.3.4.2.4	Listing of Subjects with Clinically Significant Vital Signs	Safety Population	Yes	
14.3.4.3		Electrocardiogram (ECG) Data			
	14.3.4.3.1	Summary of Eletrocardiogram (ECG) Interpretation	Safety Population		
	14.3.4.3.2	Shift from Screening in Eletrocardiogram (ECG) Interpretation	Safety Population		
14.3.4.4		Other Safety			
	14.3.4.4.1	Summary of Physical Examination	Safety Population	Yes	
	14.3.4.4.2	Shift from Baseline in Physical Examination	Safety Population		

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
	14.3.4.4.3	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF)	Safety Population	Yes	Yes
	14.3.4.4.4	Summary of Abnormal Peak Expiratory Flow (PEF)	Safety Population	Yes	Yes
	14.3.4.4.5	Summary of Asthma Control Test (ACT)	Safety Population	Yes	Yes
	14.3.4.4.6	Summary of Asthma Control Test (ACT) Score ≤ 19	Safety Population	Yes	Yes
	14.3.4.4.7	Summary of Clinically Significant Respiratory Examination Findings	Safety Population		Yes
14.3.4.5		Immunogenicity			
	14.3.4.5.1	Summary of Immunogenicity - Anti-drug Antibody (ADA) and Neutralizing Antibody	Safety Population	Yes	

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Header	Figure Number	Name	Analysis Population	Interim Analysis	IDMC
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	14.1.1.7	Time (days) to Permanent Discontinuation of Study Drug by Reason for Discontinuation Subjects who Discontinued from Study Drug	ITT Population		Yes
14.2.1.1		Eczema Area and Severity Index (EASI)			
	14.2.1.1.3	Plot of Percent Change in Eczema Area and Severity Index (EASI) Score over Time (LOCF)	ITT Population		
14.2.1.2		Investigator Global Assessment (IGA)			
	14.2.1.2.4	Plot of Proportion of Subjects Achieving Investigator Global Assessment (IGA) success (Non-Responder)	ITT Population		
14.2.2.1		Weekly of peak Pruritus NRS Score			
	14.2.2.1.3	Plot of Change from Baseline in Weekly Average of Peak Pruritus Numeric Rating Scale (NRS) Score over Time (LOCF)	ITT Population		
	14.2.2.1.4	Plot of Percent Change from Baseline in Weekly Average of Peak Pruritus Numeric Rating Scale (NRS) Score over Time (LOCF)	ITT Population		
14.2.2.2		Weekly of average Pruritus NRS Score			
	14.2.2.2.3	Plot of Change from Baseline in Weekly Average of Average Pruritus Numeric Rating Scale (NRS) Score over Time (LOCF)	ITT Population		
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14.2.2.3		Weekly of sleep disturbance NRS Score			
	14.2.2.3.3	Plot of Change from Baseline in Weekly Average Sleep Disturbance Numeric Rating Scale (NRS) Score over Time (LOCF)	ITT Population		
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14.2.3		Pharmacokinetics			
	14.2.3.5	Mean Nemolizumab Time-Concentration Profiles	PK Population	Yes	
	14.2.3.6	Individual Subject Nemolizumab Time-Concentration Profiles	PK Population	Yes	

Header	Figure Number	Name	Analysis Population	Interim Analysis	IDMC
	14.2.3.7	Individual Subject Nemolizumab Time-Concentration Profiles by ADA Result	PK Population	Yes	
14.3.4.1.2		Blood Chemistry Data			
	14.3.4.1.2.6.1	Distribution of Aspartate Aminotransferase (AST) by Visit with Maximum Post-baseline values	Safety Population		Yes
	14.3.4.1.2.6.2	Individual Subject Plot of Aspartate Aminotransferase (AST) by Visit with Maximum Post-baseline values	Safety Population		Yes
	14.3.4.1.2.7.1	Distribution of Alanine Aminotransferase (ALT) by Visit with Maximum Post-baseline Values	Safety Population		Yes
	14.3.4.1.2.7.2	Individual Subject Plot of Alanine Aminotransferase (ALT) by Visit	Safety Population		Yes
	14.3.4.1.2.8.1	Distribution of Alkaline Phosphatase (ALP) by Visit with Maximum Post-baseline Values	Safety Population		Yes
	14.3.4.1.2.8.2	Individual Subject Plot of Alkaline Phosphatase (ALP) by Visit	Safety Population		Yes
	14.3.4.1.2.9.1	Distribution of Total Bilirubin by Visit with Maximum Post-baseline Values	Safety Population		Yes
	14.3.4.1.2.9.2	Individual Subject Plot of Total Bilirubin by Visit	Safety Population		Yes
	14.3.4.1.2.10.1	Distribution of Creatinine Phosphokinase by Visit with Maximum Post-baseline Values	Safety Population		Yes
	14.3.4.1.2.10.2	Individual Subject Plot of Creatinine Phosphokinase by Visit	Safety Population		Yes
14.3.4.4		Other Safety			
	14.3.4.4.8	Individual Subject Plot of Respiratory Assessments – Peak Expiratory Flow (PEF) by Visit	Safety Population		Yes
	14.3.4.4.9	Individual Subject Plot of Asthma Control Test (ACT) by Visit	Safety Population		Yes

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	16.2.1.2	Study Drug Completion Status	ITT Population		
	16.2.1.3	Visit Dates	ITT Population		
16.2.2		Protocol Deviations			
	16.2.2.1	Protocol Deviations	ITT Population		
16.2.3		Subjects Excluded from Analysis Sets			
	16.2.3.1	Subjects in Analysis Populations	ITT Population		
	16.2.3.2	Inclusion and Exclusion Criteria Not Met	All Subjects		
16.2.4		Demographic Data			
	16.2.4.1	Demographics and Baseline Characteristics	ITT Population	Yes	
	16.2.4.2	Baseline Disease Characteristics	ITT Population		
	16.2.4.3	Medical History	ITT Population	Yes	
	16.2.4.4	Prior Medical and Surgical Procedures	ITT Population	Yes	
	16.2.4.5	Prior and Concomitant Medications	ITT Population	Yes	
	16.2.4.6	Rescue Medications	ITT Population	Yes	
	16.2.4.7	Background Topical Corticosteroids (TCS) Dispensation and Receipt	ITT Population		
16.2.5		Compliance and Study Drug Administration			
	16.2.5.1	Study Drug Administration	Safety Population	Yes	
	16.2.5.2	Study Drug Dispensation	Safety Population	Yes	
	16.2.5.3	Study Drug Compliance	Safety Population	Yes	
	16.2.5.4	Nemolizumab Serum Concentrations (ng/mL)	PK Population	Yes	
	16.2.5.5	Nemolizumab Serum PK Parameters estimated with PopPK Analysis	PK Population		
	16.2.5.6	Nemolizumab Serum PK Parameters calculated with Non-compartmental Analysis (NCA)	PK Population		
16.2.6		Individual Efficacy Response Data			
	16.2.6.1	Eczema Area and Severity Index (EASI)	ITT Population		
	16.2.6.2	Investigator Global Assessment (IGA)	ITT Population		

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
	16.2.6.3	Body Surface Area (BSA) of AD Involvement	ITT Population		
	16.2.6.4	Scoring Atopic Dermatitis (SCORAD)	ITT Population		
	16.2.6.5	Weekly Average Pruritus and Sleep Disturbance Numeric Rating Scale (NRS)	ITT Population		
	16.2.6.6	Daily Pruritus and Sleep Disturbance Numeric Rating Scale (NRS)	ITT Population		
	16.2.6.7	Topical AD Medication Use by Analysis Visit	ITT Population		
	16.2.6.8	Daily Topical AD Medication Use	ITT Population		
	16.2.6.9	Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (cDLQI)	ITT Population		
16.2.7		Adverse Event Listings			
	16.2.7.1	Treatment Emergent Adverse Events (TEAE)	Safety Population	Yes	
	16.2.7.2	Pre-Treatment Adverse Events	ITT Population	Yes	
	16.2.7.3	Adverse Events Comments	ITT Population	Yes	
16.2.8		Listing of individual laboratory measurements by subject			
16.2.8.1		Clinical Laboratory Data			
	16.2.8.1.1	Laboratory Data - Hematology	Safety Population	Yes	
	16.2.8.1.2	Laboratory Data - Chemistry	Safety Population	Yes	
	16.2.8.1.3	Laboratory Data - Urinalysis	Safety Population	Yes	
16.2.8.2		Other Safety Data			
	16.2.8.2.1	Vital Signs, Height and Weight	Safety Population	Yes	
	16.2.8.2.2	Electrocardiogram (ECG)	Safety Population		
	16.2.8.2.3	Electrocardiogram (ECG) Test Parameters	Safety Population		
	16.2.8.2.4	Physical Examination	Safety Population	Yes	
	16.2.8.2.5	Confirmed Pregnancy Test Results	Safety Population		Yes
	16.2.8.2.6	Respiratory Assessment – Peak Expiratory Flow (PEF)	Safety Population	Yes	
	16.2.8.2.7	Asthma Control Test (ACT)	Safety Population	Yes	
	16.2.8.2.8	Virology	Safety Population	Yes	
	16.2.8.2.9	Immunogenicity - Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb)	Safety Population	Yes	

Header	Table Number	Name	Analysis Population	Interim Analysis	IDMC
	16.2.8.2.10	Subjects with Childbearing Potential	Safety Population		
	16.2.8.2.11	Premenses Status	Safety Population		
	16.2.8.2.12	Subject with a drop by >= 15% from Baseline for either PEF or ACT	Safety Population		Yes
	16.2.8.2.13	Biomarker	Safety Population		
	16.2.8.2.14	All comments	Safety Population		

21. Potentially clinically significant ranges for laboratory tests

Test Parameter	Reference range (as per Lab Manual)		Potentially Clinically Significant Ranges (min and/or max limits)	SI Units
	LLN	ULN		
SERUM				
White Blood Cell Count (WBC)	4.00	10.70	<2.5 at post-baseline, if baseline value ≥2.5 >13.0 at post-baseline, if baseline value ≤13	x10E9/L
Neutrophils (absolute)	1.60	7.40	<1.5 at post-baseline, if baseline value ≥1.5 >9 at post-baseline, if baseline value ≤9	x10E9/L
Eosinophils (absolute)	0.00	0.70	>0.8 at post-baseline, if baseline ≤0.8	x10E9/L
Basophils (absolute)	0.00	0.20	>0.3 at post-baseline, if baseline value ≤0.3	x10E9/L
Monocytes (absolute)	0.10	0.90	>1 at post-baseline, if baseline value ≤1	x10E9/L
Lymphocytes (absolute)	1.00	4.00	<0.5 at post-baseline, if baseline value ≥0.5 >5.0 at post-baseline, if baseline value ≤5.0	x10E9/L
Red Blood Cell Count ***Male** ****Female**	4.00	* 5.80 ** 5.20	* <3.5 at post-baseline, if baseline value ≥3.5 ** >7.0 at post-baseline, if baseline value ≤7.0	x10E12/L
Hemoglobin ***Male** ****Female**	114.00	* 175.00 ** 160.00	* <100 at post-baseline, if baseline value ≥100 ** >190 at post-baseline, if baseline value ≤180	g/L
Hematocrit ***Male** ****Female**	0.36	* 0.52 ** 0.46	* <0.30 at post-baseline, if baseline value ≥0.30 ** >0.6 at post-baseline, if baseline value ≤0.6	L/L
MCV	78.00	98.00	<75 at post-baseline, if baseline value ≥75 >105 at post-baseline, if baseline value ≤105	fL
Platelets	150.00	420.00	<100 at post-baseline, if baseline value ≥100 >700 at post-baseline, if baseline value ≤700	x10E9/L
Sodium	135.00	148.00	<130 at post-baseline, if baseline value ≥130 >155 at post-baseline, if baseline value ≤155	mmol/L
Potassium	3.50	5.30	<3.1 at post-baseline, if baseline value ≥3.1 >5.9 at post-baseline, if baseline value ≤5.9	mmol/L
Calcium - total	2.14	2.62	<1.8 at post-baseline, if baseline value ≥1.8	mmol/L
Chloride	98.00	110.00	<95 at post-baseline, if baseline value ≥95 >115 at post-baseline, if baseline value ≤115	mmol/L
Glucose	3.90	6.90	<3 at post-baseline, if baseline value ≥3 >13.9 at post-baseline, if baseline value ≤13.9	mmol/L
Creatinine	31.00	106.00	>150 at post-baseline, if baseline value ≤150	µmol/L
Blood urea nitrogen (BUN)	1.80	7.14	>8 at post-baseline, if baseline value ≤8	mmol/L
AST	0.00	41.00	>3 x ULN at post-baseline, if baseline value ≤3 x ULN	U/L

Test Parameter	Reference range (as per Lab Manual)		Potentially Clinically Significant Ranges (min and/or max limits)	SI Units
	LLN	ULN		
ALT	5.00	* 30.00	>3 x ULN at post-baseline, if baseline value ≤3 x ULN	U/L
***Male**		** 20.00		U/L
****Female**				
Alkaline phosphatase	0.00	* 389.00	>2.5 x ULN at post-baseline, if baseline value ≤2.5 x ULN	U/L
***Male**		** 186.00		
****Female**				
Bilirubin total	0.00	21.00	>2 x ULN at post-baseline, if baseline value ≤2 x ULN	µmol/L
Bilirubin conjugated	0.00	7.00	>1.5 x ULN at post-baseline, if baseline value ≤1.5 x ULN	µmol/L
CPK	2.00	* 251.00	>2.5 x ULN at post-baseline, if baseline value ≤2.5 x ULN	U/L
***Male**		** 147.00	>2.5 x ULN at post-baseline, if baseline value ≤2.5 x ULN	
****Female**				
GGT	0.00	* 42.00	>2.5 x ULN at post-baseline, if baseline value ≤2.5 x ULN	U/L
***Male**		** 24.00	>2.5 x ULN at post-baseline, if baseline value ≤2.5 x ULN	
****Female**				
Protein total	60.00	85.00	<50 at post-baseline, if baseline value ≥50	g/L
			>95 at post-baseline, if baseline value ≤95	
Albumin	32.00	55.00	<30 at post-baseline, if baseline value ≥30	g/L
Uric acid	* 0.18	* 0.51	>0.6 at post-baseline, if baseline value ≤0.6	mmol/L
***Male**	** 0.13	** 0.45	>0.5 at post-baseline, if baseline value ≤0.5	
****Female**				
Cholesterol total	0.00	5.17	>6 at post-baseline, if baseline value ≤6	mmol/L
HDL	1.04	N/A	<0.75 at post-baseline, if baseline value ≥0.75	mmol/L
LDL	N/A	3.34	>4 at post-baseline, if baseline value ≤4	mmol/L
Triglycerides	0.00	2.25	>4 at post-baseline, if baseline value ≤4	mmol/L
LDH	NA	as in database	>3 x ULN at post-baseline, if baseline value ≤3 x ULN	mmol/L
URINE				
Urine specific gravity	1.003	1.030	<0.995 at post-baseline, if baseline value ≥0.995	
			>1.038 at post-baseline, if baseline value ≤1.038	
Urine pH	5.00	8.00	<4.5 at post-baseline, if baseline value ≥4.5	
			>8.5 at post-baseline, if baseline value ≤8.5	