Galderma S.A.

RD.06.SPR.118126

A Multicenter, Open-Label, Single-Group Clinical Trial to Assess the Pharmacokinetics, Safety and Efficacy of Nemolizumab (CD14152) in Pediatric Subjects (aged 2 to 11 years) with Moderate-to-Severe Atopic Dermatitis

21MAY2025

Final Statistical Analysis Plan

Version 5.0

Prepared by:

Client:	**GALDERMA S.A.**
Protocol Number:	**RD.06.SPR.118126**

Document Description:	Final Statistical Analysis Plan
SAP Title:	Final Statistical Analysis Plan. A Multicenter, Open-Label, Single-Group Clinical Trial to Assess the Pharmacokinetics, Safety and Efficacy of Nemolizumab (CD14152) in Pediatric Subjects (aged 2 to 11 years) with Moderate-to-Severe Atopic Dermatitis
SAP Version Number:	5.0 and corresponding SAP TLF Shells Version 4.0
Effective Date:	21MAY2025

Author(s):

PPD .

Approved by:

PPD

PPD

Document History – Changes compared to previous version of SAP:

Version	Date	Changes
0.1	13AUG2021	Initial draft
0.2	01OCT2021	Address sponsor comments
1.0	19NOV2021	Address sponsor comments and finalize
1.1	12JUL2022	Address sponsor comments and update as per protocol v6.0
1.2	08AUG2022	Stop date imputation updated
1.3	11AUG2022	Added details on flat doses changes (Section 4)
1.4	12AUG2022	Details on body weight added for PK (Section 8.1)
1.5	30AUG2022	Additional VS timepoints added (Section 8.2.4.7) and PK section updated (Section 8.1)
2.0	06SEP2022	Address sponsor comments and finalize
2.1	25NOV2022	Updates based on Protocol Amendment V7.0
2.2	16JUN2023	Minor updates on Version and Date
3.0	25AUG2023	Finalized SAP
3.1	26OCT2023	Compliance details added for dosage of 5 and 15 mg Adjusted period definition in section 8.1.2
4.0	3OCT2023	Finalized SAP
4.1	17FEB2025	Details added in Section 8.2.1.10 for LOCF imputation
5.0	21MAY2025	Section 8.2.4.2 update by adding Eosinophils to list of Hematology laboratory assessments. Final version before DBL

TABLE OF CONTENTS

List of Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP NRS	Average pruritus numeric rating scale
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time 0 extrapolated to infinity
BLQ	Below the limit of quantification
BSA	Body Surface Area
cACT	Childhood Asthma Control Test
cDLQI	Children´s Dermatology Life Quality Index
CPK	Creatinine phosphokinase
CL/F	Apparent total body clearance
C_{trough}	Trough serum concentration
CV	Coefficient of variation
DCS	Dual chamber, single-use syringe
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
EASI	Eczema Area and Severity Index
eCRF	Electronic Case Report Form
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IA	Interim analysis
IAC	Independent adjudication committee
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
iDQOL	Infants´ Dermatitis Quality of Life Index
IGA	Investigator´s Global Assessment
ITT	Intent-to-treat
k_a	Apparent terminal elimination rate constant
LDL	Low-density lipoprotein
LLT	Lowest level term
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
nBLQ	Number of samples below the limit of quantification

NRI	Non-responder imputation
NRS	Numeric rating scale
OC	Observed cases
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
PK/PD	Pharmacokinetic/pharmacodynamics
POEM	Patient-Oriented Eczema Measure
POPPK	Population PK
PP NRS	Peak pruritus numeric rating scale
PT	Preferred term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SD	Standard Deviation
SD NRS	Sleep disturbance numeric rating scale
SOC	System organ class
SOP	Standard operating procedure
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse events
TLFs	Tables, listings and figures
V_d/F	Apparent volume of distribution during the terminal phase

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population[1] and up to 25% of children[2]. During infancy, AD primarily involves the face and extensor surfaces of the extremities[1]. The disease is characterized by pruritus (itching), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. Approximately 60% of AD subjects have another concomitant atopic condition (e.g., asthma, allergic rhinitis, food allergy) and AD often constitutes the first step of atopic march (progression from one atopic disease to another). Although not a life-threatening disease, AD has a marked negative impact on subjects' quality of life (QoL), and depression and anxiety have been reported as comorbidities in AD subjects[3]. Existing literature suggests that the prevalence of AD is highest in young children and gradually reduces with age. Prevalence is higher in developed countries.

The purpose of the Statistical Analysis Plan (SAP) is to describe the analyses and data presentations used in determining the safety and efficacy of Nemolizumab in the treatment of pediatric subjects with Moderate-to-Severe Atopic Dermatitis. This SAP outlines the types of analyses that will address the study objectives and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis sets and statistical methods for the analysis of endpoints.

This statistical analysis plan was written in accordance with ICH E9, ICH E9 (R1) and PPD Global Biostatistics and Programming standard operating procedures (SOPs) and using the study protocol Version 7.0 dated 3rd October 2022.

2. Objectives

The primary objective of the study is to assess the pharmacokinetics (PK), safety, and tolerability of Nemolizumab administered concomitantly with topical corticosteroids (TCS) in pediatric subjects with moderate-to-severe atopic dermatitis (AD) not adequately controlled with topical treatments.

The secondary objective of the study is to assess the efficacy of Nemolizumab (CD14152) and to further characterize the relationship between Nemolizumab concentrations and clinical efficacy endpoints.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2, open label, single arm study of pediatric subjects (aged 2 to 11 years) with moderate-to-severe atopic dermatitis, who are inadequately controlled by or intolerant to topical therapies. Eligible subjects must have a documented history of inadequate response to topical AD medications. Approximately 45 study centers are planned in North America and the European Union.

The study will enroll approximately 105 subjects in three equal-sized cohorts:

- Cohort 1: Subjects aged 7-11 years
- Cohort 1.1: Subjects aged 7-11 years
- Cohort 2: Subjects aged 2-6 years

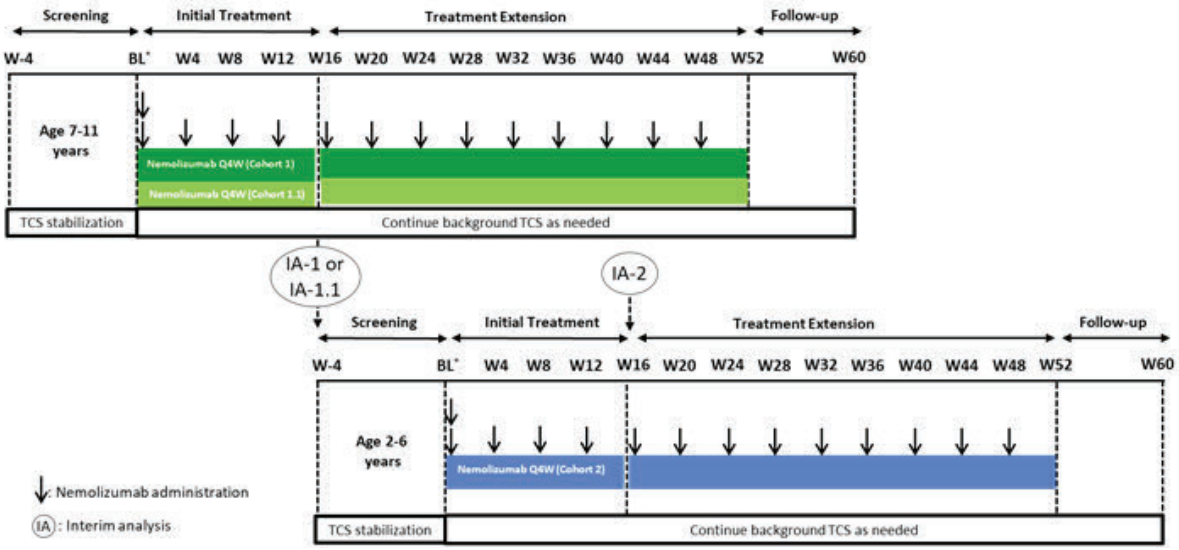
Each cohort will have two parts:

- Part A will have a 16-week treatment period
- Part B will have a 36-week extension of treatment

Cohort 1 subjects will be recruited first. An Interim Analysis (IA-1) focused on PK and safety will be performed after the first 18 subjects from Cohort 1 have completed the Week 16 visit. To allow recruitment of Cohort 1.1 subjects, the IA-1 of the Cohort 1 subjects will be assessed for safety by the independent data monitoring committee (IDMC) and the sponsor, and for drug exposure and dose confirmation by the sponsor. Cohort 1.1 cannot be enrolled until receiving written approval from Sponsor after the IA-1 of Cohort 1. A second interim analysis (IA-1.1) will be performed after approximately 18 subjects from Cohort 1.1 have completed the Week 16 visit. To allow recruitment of Cohort 2 subjects, the IA-1.1 of the Cohort 1.1 subjects will be assessed for safety by the IDMCand the sponsor, and for drug exposure and dose confirmation by the sponsor. Cohort 2 cannot be enrolled until receiving written approval from Sponsor after the IA-1.1 of Cohort 1.1. A third interim analysis (IA-2) will be performed after approximately 18 subjects from Cohort 2 have completed the Week 16 visit. IA-1, IA-1.1 and IA-2 will focus on PK and safety and will assess whether the observed safety and PK data from each cohort are similar to the data obtained in adolescent and adult subjects.

At baseline, subjects will enter a 16-week initial treatment period with Nemolizumab administered every 4 weeks. A loading dose will be given at Baseline/Day 1. The administered dose will be selected based on subject body weight as detailed in section 3.3. Subjects will continue to receive treatment for an additional 36 weeks after the initial 16-week treatment period and following this will enter an 8-week follow-up period. Subjects who withdraw from the study prior to Week 48 will be followed for 12 weeks after their last dose of study drug. **Figure 1** below presents the study design:

Figure 1 Overview of Study Design



* See Tables 1a and 1b above for the baseline dose and respective Nemolizumab presentation.
IA-1: Interim Analysis 1, will be performed after the first 18 subjects in the age 7 to 11 Cohort 1 have completed 16 weeks
IA-1.1: Interim Analysis 1.1, will be performed after approximately 18 subjects in the age 7 to 11 Cohort 1.1 have completed 16 weeks
IA-2: Interim Analysis 2, will be performed after approximately 18 subjects in the age 2 to 6 Cohort 2 have completed 16 weeks

The schedule of assessments is summarized in Appendix A.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoints for Pharmacokinetics are as follows:

- Nemolizumab serum concentrations at Weeks 4, 8, 12, 16, 32, and 52.
- Nemolizumab serum PK parameters extrapolated with a population PK analysis.

The primary endpoint for Safety is as follows:

- Incidence of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interests (AESIs), AEs leading to discontinuation and serious AEs (SAEs) through the study.

3.2.2. Secondary Endpoints

The secondary endpoints for the efficacy are as follows:

- Absolute and percent change in Eczema Area and Severity Index (EASI) score from baseline at each visit up to Week 16 and up to Week 52.
- Proportion of subjects achieving 50%, 75% or 90% response in EASI [EASI-50, EASI-75 and EASI-90] at each visit up to Week 16 and Week 52.
- IGA success rate (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥2-point improvement from baseline) at each visit up to Week 16 and up to Week 52.
- Change in BSA involvement of AD, reported as a percentage of all major body sections combined, from baseline at each visit up to Week 16 and up to Week 52.
- Absolute and percent change in weekly average of peak pruritus NRS (PP NRS) score from baseline at each visit up to Week 16 and up to Week 52.
- Proportion of subjects with an improvement of ≥4 from baseline in weekly average of PP NRS at visit up to Week 16 and up to Week 52.
- Absolute and percent change in weekly average of average pruritus NRS score from baseline at each visit up to Week 16 and up to Week 52.
- Absolute and percent change in weekly sleep disturbance NRS score from baseline at each visit up to Week 16 and up to Week 52.
- Proportions of subjects receiving any rescue therapy by rescue treatment type (e.g., topical, phototherapy, systemic) at any visit during the treatment period.
- Percent change in SCORing Atopic Dermatitis (SCORAD) score from baseline at each visit up to Week 16 and up to Week 52.
- Change in Children's Dermatology Life Quality Index (cDLQI) for subjects ≥4 years of age from baseline up to Week 16 and up to Week 52.
- Change in Infant's Dermatology Quality of Life Index (iDLQI) for subjects <4 years of age from baseline up to Week 16 and up to Week 52.
- Change in Patient-Oriented Eczema Measure (POEM) from baseline up to Week 16 and up to Week 52.

The secondary endpoints for PK/PD Analysis are as follows:

- Relationship between Nemolizumab concentrations and clinical efficacy endpoints (PP-NRS, EASI and IGA).

The secondary endpoints for immunogenicity are as follows:

- Anti-drug antibody (ADA) assessments (screening, confirmatory, neutralizing antibody [Nab]), at baseline, Weeks 16, 52 and unscheduled visits that are conducted for safety reasons.

3.3. Treatment

This is a single arm study where all subjects will receive a dose of Nemolizumab by injection every 4 weeks, with a loading dose at Baseline/Day 1. The dose level will be determined by subject weight at Baseline, Week 16 and Week 32 as shown in the **Table 1*a*** (for Cohort 1) and **Table 1.b** (for Cohort 1.1 and Cohort 2) below.
The dose should remain unchanged until Week 16. Then at week 16 the subject body weight will be re-assessed and, if necessary, a different dose should be selected based on **Table 1*a*** (for Cohort 1) and

Table 1.b (for Cohort 1.1 and Cohort 2). The dose will then remain unchanged until Week 32. At week 32 the subject body weight will be re-assessed and, if necessary, a different dose should be selected based on **Table 1*a*** (for Cohort 1) and

Table 1.b (for Cohort 1.1 and cohort 2). After the body weight assessment at week 32, the dose will remain unchanged until the end of the study.

Table 1a Selected Pediatric Dose for Cohort 1

	Q4W - dose			Baseline - loading dose		
Body Weight[a]	Dose	Formulation Presentation	# of injections	Loading Dose	Formulation Presentation	# of injections
≥10 kg and <20 kg	10 mg	10 mg vial	1	20 mg	20 mg vial	1
≥20 kg and <30 kg	20 mg	20 mg vial	1	40 mg	20 mg vial	2
≥30 kg	30 mg	30 mg DCS	1	60 mg	30 mg DCS	2

Abbreviation(s): DCS = dual chamber, single-use syringe
[a] Body weight at baseline, Week 16 and Week 32

Table 1.b Selected Pediatric Dose for Cohort 1.1 and Cohort 2

	Q4W - dose			Baseline - loading dose		
Body Weight[a]	Dose	Formulation Presentation	# of injections	Loading Dose	Formulation Presentation	# of injections
≥10 kg and <20 kg	5 mg	10 mg vial	1	10 mg	10 mg vial	1
≥20 kg and <30 kg	10 mg	10 mg vial	1	20 mg	20 mg vial	1
≥30 kg	15 mg	20 mg vial	1	30 mg	30 mg DCS	1

[a] Body weight at baseline, Week 16 and Week 32

The planned nemolizumab doses will be confirmed by the IA-1, IA-1.1, and IA-2.

4. General Statistical Considerations

All summaries and results in Tables, Listings and Figures (TLFs) will be presented for the following groups:

Table 2 Treatment Group Labels in TLFs

Groups	Label in TLFs
Nemoluzimab (CD14152) administrations on subjects in Cohort 1 aged 7-11 years	Cohort 1
Nemoluzimab (CD14152) administrations on subjects in Cohort 1.1 aged 7-11 years	Cohort 1.1
Nemoluzimab (CD14152) administrations on subjects in Cohort 2 aged 2-6 years.	Cohort 2

For the primary PK endpoints only (i.e. Nemolizumab serum concentrations and PK parameters) additional TLFs will be presented for the following groups too:

Table 3 Treatment Group Labels for Primary Endpoints in TLFs

Groups	Label in TLFs
Nemoluzimab (CD14152) administrations on subjects in Cohort 1 aged 7-11 years and weighting ≥10 kg and <20 kg	Cohort 1 (≥10 kg - <20 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 1 aged 7-11 years and weighting ≥20 kg and <30 kg	Cohort 1 (≥20 kg - <30 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 1 aged 7-11 years and weighting	Cohort 1 (≥30 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 1.1 aged 7-11 years and weighting ≥10 kg and <20 kg	Cohort 1.1 (≥10 kg - <20 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 1.1 aged 7-11 years and weighting ≥20 kg and <30 kg	Cohort 1.1 (≥20 kg - <30 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 1.1 aged 7-11 years and weighting	Cohort 1.1 (≥30 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 2 aged 2-6 years and weighting ≥10 kg and <20 kg	Cohort 2 (≥10 kg - <20 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 2 aged 2-6 years and weighting ≥20 kg and <30 kg	Cohort 2 (≥20 kg - <30 kg)
Nemoluzimab (CD14152) administrations on subjects in Cohort 2 aged 2-6 years and weighting ≥30 kg	Cohort 2 (≥30 kg)

Body weight at baseline will be used to determine the treatment group label from baseline to Week 16.
Body weight at Week 16 will be used to determine the treatment group label from Week 20 to Week 32.
Body weight at Week 32 will be used to determine the treatment group label from Week 36 to end of study.

Study days will be numbered relative to the date of the injection of loading dose on Day 1/Baseline which is treatment start date.
For assessments on or after the treatment start date, the study day of events from treatment start date is calculated as the date of event minus the date of treatment start + 1. For assessments before treatment start date, the study day of the assessment is defined as the date of assessment minus the date of treatment start.

Baseline is defined as the last non-missing measurement prior to first loading dose injection at Day1/Baseline. Measurements that are obtained after treatment start date/time will be considered as post-baseline values. Change from baseline is defined as post-baseline assessment minus baseline assessment.

All data summarized by visit will be based on the visit name collected on the electronic Case Report Form (eCRF) page. For data from unscheduled visits, these will be listed but not included in any by-visit summaries or analyses.

Continuous data will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum, and 25% and 75% quartiles (Q1 and Q3). Categorical data will be summarized using the frequency count (n) and percentage (%) of subjects for each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, Q1 and Q3 will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment within the Analysis Set of interest, unless otherwise specified. Percentages will be presented to one decimal place.

Any imputed data will be used in summary tables and figures and the original collected data will be displayed in listings.

Unless specified otherwise, all the summary tables will be presented by cohort and overall, and all the collected data will be presented in the listings. Data displayed in the listings will be sorted by cohort and subject identifier. Any imputed data will be used in summary tables and figures and the original collected data will be displayed in listings.

All analyses will be conducted using SAS Version 9.4 or higher.

4.1. Dates imputations

For the purpose of inclusion in prior and/or concomitant medication, prior and/or concomitant medical and surgical procedures and AE tables, incomplete medication start and stop dates will be imputed as follows:

Start Date Imputation (where UK, UNK and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date;

- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.

Stop Date Imputation:

- Completely missing and with outcome 'Not Recovered/Not Resolved' or 'Unknown' (Adverse Events): Leave it missing.
- Completely missing and flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures): Leave it missing.
- Completely missing and with an outcome different from 'Not Recovered/Not Resolved' and 'Unknown' (Adverse Events): Impute to the last contact date.
- Completely missing and not flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures, Medical History Diseases): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

4.2. Sample Size

No formal power analysis was performed to determine sample size requirement.

Approximately 105 subjects (35 per cohort) are planned to be enrolled in this study across 2 age groups: 70 subjects in age 7 to 11 years in two cohorts (Cohort 1 and Cohort 1.1) of 35 subjects, and 35 subjects in age 2 to 6 years in one cohort (Cohort 2). Based on the variability of

Nemolizumab serum concentrations, a sample size of approximately 35 was considered sufficient to calculate PK parameters with adequate precision and to ensure adequate representation across the pediatric age ranges.

4.3. Analysis Set

A summary of the analysis sets including the number and percentage of subjects for the following categories: subjects in the Enrolled Set, subjects in the ITT Set, subjects in the PK Set and subjects in the Safety Set will be presented. All percentages will be based on the number of subjects in ITT set. A corresponding listing will be displayed.

4.3.1. Enrolled Set

The Enrolled Set consists of all individuals who met the inclusion/exclusion criteria and signed the ICF and all individuals who did not met the inclusion/exclusion criteria but received at least 1 dose of study drug. This set will be used for the subject listings.

4.3.2. Intent-to-Treat (ITT) Set

The Intent-to-Treat Set consists of all enrolled subjects. As ITT Set and Enrolled Set are equivalent, only ITT Set will be used for the analyses. This set of population will be used for the subject listings and for the analysis of efficacy.

4.3.3. Safety Set

The Safety Set consists of all enrolled subjects who receive at least 1 dose of study drug. This set of population will be used for the analysis of safety.

4.3.4. Pharmacokinetic (PK) Set

The PK Set consists of all subjects who received at least 1 dose of study drug and have at least one measurable post-baseline concentration.

5. Subject Disposition

5.1. Disposition

Subject disposition including the number and percentage of subjects for the following categories will be summarized: subjects who screen failed, subjects who were enrolled, subjects who received any dose of Nemolizumab, subjects who completed the treatment, subjects who terminated

treatment early, subjects who completed the study and subjects who terminated early from the study. The reasons for screen failure will be summarized. The percentages of screen failure and subjects enrolled will be calculated based on number of subjects screened and other percentages will be based on the number of subjects in the ITT Set.

The reasons for study and treatment discontinuation will also be summarized in this table.

Subject disposition data will be presented in a listing. A corresponding listing will be provided for subjects with early treatment termination and for subjects with early study termination.

5.2. Protocol Deviations

All deviations will be identified, evaluated, and closed prior to database lock. Deviations from the protocol will be assessed as "Major" (or equivalently "Significant") and "Minor" (or equivalently "Not Significant") in cooperation with the sponsor.

Major protocol deviations will be summarized by cohort and overall in a table for the ITT Set and will be presented in a listing and summarized by category. All protocol deviations (major and minor) will be listed in a listing and summarized by category.

All COVID-19-related protocol deviations will be summarized by category and flagged in the corresponding listing.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

The demographics will be summarized by cohort and overall. The following variables will be included:

- Age (Years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown or Not reported)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other or Not reported)
- Weight (kg), Height (cm) and BMI (kg/m^2) at baseline

Baseline disease characteristics including EASI, IGA, BSA, SCORAD, PP NRS, AP NRS, SD NRS, cDLQI, iDQOL, POEM scores, Eosinophils at baseline will be summarized by cohort and overall presenting the different scores.
Percentages will be based on the total number of subjects in the ITT Set. Subject demographics and baseline characteristics will be presented in a listing.

6.2. Medical History

The number and percentage of subjects with any medical history will be summarized by cohort and overall and for each body system by system organ class (SOC) and preferred term (PT). Body systems will be included as recorded on the CRF. Percentages will be calculated based on number of subjects in the ITT Set.

Subject medical history data including specific details will be presented in a listing.

MedDRA dictionary Version 25.0 will be used for reporting and will be described in the relevant table and listing footnotes.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications used within 3 months prior to the date of screening through to the end of study will be collected on the CRF. All medications will be coded according to the World Health Organization drug dictionary Global B3 March 2022. The medication names will be coded according to the Anatomical Therapeutic Chemical (ATC) class level 4 and preferred terms provided in the dictionary.

A prior medication is defined as any medication that is taken or medical procedure undergone within 3 months prior to the date of the first dose. A concomitant medication is defined as any existing therapy ongoing at the time of the first dose, or any changes to existing therapies during the course of the study, or any new therapies the subject received since the date of the first dose.

Unless specified as prohibited in the protocol, all therapies are authorized for use during the study.

For missing start or end dates, the rules stated in Section 4.1 will be followed. Though note that if the start date is completely missing and end date is not prior to the first dose, then the medication will be classified as both prior and concomitant. It the start date is missing and end date is prior to the first dose, then the medication will be classified as prior. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as prior and concomitant.

Prior medications will be summarized by providing the number and percentage of subjects by ATC class level 2 and ATC class level 4 and preferred term for each cohort and overall. ATC classes will be sorted in decreasing order of frequency based on the total number of subjects who take each medication in the total column, while preferred terms within each drug class will be presented in decreasing order of frequency. In addition, the total number of prior medications and the number and percentage of subjects receiving at least one prior medication will also be presented in this table. If a subject has multiple medications for a given preferred term the subject will only be counted once. A similar table will be presented for concomitant medications.

All summaries will be performed using the ITT Set. Prior and concomitant medications will be presented in a listing for the ITT Set. Therapies will be flagged as prior (P), concomitant (C) or prior and concomitant (P/C).

7.2. Rescue Therapy

Rescue treatments are treatments that directly treat AD and include topical and systemic treatments as outlined. Rescue therapies include high- or ultra-high potency of TCS, oral corticosteroids, biologics (including their biosimilars), systemic nonsteroidal immunosuppressants /immunomodulators and phototherapy.

For the purpose of efficacy analysis, when description are not based on Observed Case (OC), subjects receiving any rescue therapies will be considered as treatment failures (i.e., non-responders). Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy.

Rescue treatments will be summarized for each cohort and overall, for the ITT Set. Rescue therapy data including specific details will be presented in a listing.

7.3. Prior and Concomitant Medical and Surgical Procedures

All relevant medical and surgical procedures done within 3 months prior to the date of screening through to the end of study will be collected on the CRF. Medical and surgical procedures will be coded according to MedDRA version 25.0.

A prior medical or surgical procedure is defined as any medical or surgical procedure that is done within 3 months prior to the date of screening. A concomitant medical or surgical procedure is defined as any medical or surgical procedure started or changed since the screening visit.

For missing start or end dates, the rules stated in Section 4.1 will be followed. Though note that if the start date is completely missing and end date is not prior to the first dose, then the medical or surgical procedure will be classified as both prior and concomitant. If the start date is prior to the first dose and end date is missing or if start date is prior to the first dose and end date is after the the first dose, then the medication will be classified as prior. If the end date is missing, then the medical or surgical will be classified as ongoing. Medical or surgical procedures for which the start and end dates are missing will be classified as prior and concomitant.

Prior medical or surgical procedures will be summarized by providing the number and percentage of subjects by system organ class (SOC) and preferred term (PT) for each cohort and overall. In addition, the total number of prior medical or surgical procedures and the number and percentage of subjects undergoing at least one prior medical or surgical procedures will also be presented in this table. A similar table will be presented for concomitant medical and surgical procedures.

All summaries will be performed using the ITT Set. Prior and concomitant medical or surgical procedures will be presented in a listing for the ITT Set. Procedures will be flagged as prior (P), concomitant (C) or prior and concomitant (P/C).

7.4. Study Treatments

7.4.1. Extent of Exposure

Exposure to study drug (in days) is defined as the number of days from the first study drug dose taken through the date of the last study drug dose taken, inclusive, adding 1 day.

The duration of exposure and the total dose received (mg) will be summarized by cohort and overall, in a table for the Safety Set.

7.4.2. Treatment Compliance

Treatment compliance will be assessed through the treatment records and drug dispensation logs. The dose should remain unchanged until Week 16. Then at Week 16 the subject body weight will be re-assessed and, if necessary, a different dose should be selected based on table presented in section 3.3. The dose will then remain unchanged until Week 32. At Week 32 the subject bodyweight will be re-assessed again and, if necessary, a different dose should be selected based on table presented in section 3.3. After the body weight assessment at Week 32, the dose will remain unchanged until the end of the study.

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 provided there is 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.

The overall compliance in percent will be calculated as the ratio of the total dose (mg) received during initial treatment and treatment extension divided by the total dose expected (mg) to be received during initial treatment and treatment extension multiplied by 100.
Dose compliance will be documented in the CRF, with the total volume (mL) of the study drug that was properly administered. Total volume injected in mL is converted into total dose administered in mg following the correspondence below:

Volume injected (mL)	Dose administered (mg)
0.2 mL (for 5 mg dose)	10mg Vial
0.4 mL	10mg Vial
0.6 mL (for 15 mg dose)	20mg Vial
0.8 mL	20mg Vial
0.49 mL	30mg DCS

Injected volume is assumed to be proportional to the dose administered.

A subject is considered as compliant when his compliance is ≥ 80% and ≤ 120%.

The overall compliance until Week 16, the overall compliance until end of the study and the compliance by visit will be presented in a table by cohort and overall for the Safety Set.
A corresponding listing will be provided for exposure and compliance.

8. Endpoint Analysis

The primary objective of the study is to assess the PK of Nemolizumab administered concomitantly with TCS in pediatric subjects with moderate-to-severe AD not adequately controlled with topical treatments.

8.1. Primary Endpoints Analysis

8.1.1. Pharmacokinetics

The primary endpoints for pharmacokinetics are as follows:

- Nemolizumab serum concentrations at Weeks 4, 8, 12, 16, 32, and 52.
- Nemolizumab serum PK parameters extrapolated with a population PK analysis.

The observed serum concentration at each time point (C_{trough}) will be presented in data listings and summarized separately using descriptive statistics (number of observations (n), arithmetic mean, standard deviation (SD), coefficient of variation (CV)%, 95% CI of arithmetic mean, geometric mean, minimum, first quartile (Q1), median, third quartile (Q3), maximum, and number of samples below the limit of quantification (nBLQ)) by cohort, body weight (in tables where applicable, see Section 4), and time point. Weight categories from Week 04 to Week 16 will be based on body weight at Baseline. Weight categories for Week 32 will be based on body weight at Week 16. Weight categories for Week 52 will be based on body weight at Week 32. Serum concentrations that are BLQ will be treated as missing for calculation of concentration descriptive statistics. The dose presented in the listing will be the actual dose.

Individual serum concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Individual ADA status (ADA+ at baseline, ADA+ (ADA- at baseline and ADA+ after treatment), and ADA- from baseline during the study) will also be displayed graphically. Mean serum concentrations will be plotted by cohort, body weight (in figures where applicable, see Section 4) and nominal time on both linear and semi-logarithmic scales.

Pharmacokinetic parameters will be derived using a non-linear mixed effect modeling approach. A pre-specified population PK model based on existing information from previous studies in adults and adolescents will be used to derive empirical Bayes estimates in the children population based on their baseline characteristics, dosing history and measured concentrations. The adequacy of the model to properly describe the pediatric data will be based on the model diagnostic tools and will be described in a separate PK modeling plan.

Estimates of population PK parameters used in the model (Cl/F, V_d/F, k_a), including inter-individual variability, covariate effects, residual error and their relative standard error (RSE), will be presented in a dedicated PK report attached to the CSR and not reported in the TLFs.

Individual PK parameters that will be derived using the popPK model will include Cl/F, V_d/F, k_a, AUC_{inf}, $t_{1/2}$, and predicted C_{trough}. Predicted C_{trough} will be estimated at week 4, week 8, week 12 and week 16. Estimates of the provided individual popPK derived parameters will be presented in data listings and summarized separately using descriptive statistics (n, arithmetic mean, SD, CV%, 95% of arithmetic mean, geometric mean, minimum, Q1, median, Q3, and maximum) by cohort and body weight (in tables where applicable, see Section 4).

The PK parameters derived from the popPK model will be regarded as primary endpoints for the PK analyses.

The popPK modeling will be conducted by an external CRO and will be detailed in a separate PK Modeling Analysis Plan. Individual popPK derived PK parameters will be provided to PPD by the external CRO for data presentation purposes.

All PK analyses will be based on Pharmacokinetic Set.

8.1.2. Safety

The primary endpoint for Safety is the incidence of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interests (AESIs), AEs leading to discontinuation and serious AEs (SAEs) through the study.

A treatment-emergent adverse event (TEAE) is defined as any adverse event with an onset date on or after the date of the first Nemoluzimab injection (Baseline/Day 1) through the last study visit (follow-up visit), whether or not it is considered causally related to the study drug.

Treatment Emergence:

Complete Missing Dates:

- If both the onset date and the end date are totally missing, then the adverse event is assumed to be treatment emergent.

Partial Missing Dates:

- If the onset date is missing and the non-missing end date is prior to first Nemoluzimab injection (Baseline/Day 1) date, then the AE is not considered treatment emergent.
- If the partial end date can be assumed to be prior to first Nemoluzimab injection (Baseline/Day 1) date (month and/or year before infusion date), then the AE is not considered treatment emergent.
- If the end date is after the first Nemoluzimab injection (Baseline/Day 1) date or the partial end date cannot be assumed to be prior to the first Nemoluzimab injection

(Baseline/Day 1) date (based on month and/or year), then the AE is assumed to be treatment emergent.

- If the onset date is partial and can be assumed to be prior to the first Nemoluzimab injection (Baseline/Day 1) date (based on the month and/or year) or the non-missing end date is prior to the infusion date then the AE is not considered treatment emergent.
- If the partial onset date cannot be assumed to be prior to the first Nemoluzimab injection (Baseline/Day 1) date, then the AE is assumed to be treatment emergent.

For missing start or end dates, the rules stated in Section 4.1 will be followed.

All AEs will be coded according to the most recent version of the MedDRA 25.0.

Incidence of Adverse Events

An overall summary table with count and percentage of subjects with TEAEs and count of events will include:

- TEAEs
- Serious TEAEs
- Severe TEAEs
- TEAEs related to study drug
- Serious TEAEs related to study drug
- TEAEs related to protocol procedure
- TEAEs leading to treatment discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death
- TEAE of Special Interest

The incidence of AEs will be summarized in tables with count and percentage of subjects with AEs and count of events by system organ class (SOC) and preferred term (PT). Unless otherwise specified, at each level of SOC or preferred term, a subject with multiple events will only be counted once per SOC or preferred term. AEs will be displayed by cohort and overall for the Safety Set.

The following categories of AE will be summarized by SOC and PT:

- TEAEs
- Serious TEAEs
- Severity of TEAEs
- TEAEs by relationship to study drug

- TEAEs by relationship to Protocol Procedure
- TEAEs leading to treatment discontinuation
- TEAEs leading to study discontinuation
- AEs of Special Interest
- Adjudicated TEAEs by Independent Adjudication Committee (IAC)
- TEAEs of asthma and asthma-related events reported by Investigator with adjudication outcome by IAC
- Confirmed asthma-related TEAEs adjudicated by IAC by maximum severity

At each level of SOC or preferred term, if a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in summary tables. All AEs will be presented in tables in descending order from the SOC with the highest total incidence (across all cohorts) to the SOC with the lowest total incidence. Within each SOC, AEs will be sorted in alphabetical order of PT. For AEs summarized by relationship to study drug, within each SOC and PT, AEs will be sorted in alphabetical order of relationship.

The overall summary table as well as the tables presenting AEs by SOC and PT will be displayed by period.

The Initial Treatment Period (also referred as "Week 16/ET") is defined as Day 1 (baseline) up to Week 16. For subjects who early discontinued during the initial treatment period, it is defined as the period until 4 weeks (28 days) after last dosing date or early termination date whichever occurs first.

The Treatment Period (also referred as "Week 52/ET") is defined as Day 1 (baseline) up to Week 52. For subjects who early discontinued during the treatment period, it is defined as the period until 4 weeks (28 days) after last dosing date or early termination date whichever occurs first.

Follow-up Period is defined as the post end of treatment period (i.e., 1 day after end of treatment period) to Follow-up visit.

A first table will present data collected during the initial treatment period (Week 16/ET) and the treatment period (Week 52/ET).

A second table will present data collected during the follow-up period.

TEAEs, SAEs, severe AEs, AESI, AEs leading to study discontinuation, AEs leading to study drug withdrawal, AEs leading to death, asthma-related TEAEs adjudicated by IAC and asthma-related TEAEs comments adjudicated by IAC will be listed.

Relationship of Adverse Events to Study Drug

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug and/or study procedure. The relationship

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

- Reasonable Possibility:
  According to the reporting investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between the study drug (Nemolizumab) and the AE, and/or between the clinical study protocol procedure (e.g., injection, topical background therapy, blood sample collection) and the AE.

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

If the relationship to study drug is missing, then the adverse event is assumed to be related with reasonable possibility to the study drug.

Severity of Adverse Event

Severity will be categorized by the investigator as follows:

- Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If the severity is missing, then the adverse event is assumed to be severe.

If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in summary tables.

8.2. Secondary Endpoints Analysis

8.2.1. Efficacy and Patient-reported Outcome Assessments

The secondary endpoints for the efficacy are as follows:

- Absolute and percent change in Eczema Area and Severity Index (EASI) score from baseline at each visit up to Week 16 and up to Week 52
- Proportion of subjects achieving 50%, 75% or 90% response in EASI [EASI-50, EASI-75 and EASI-90] at each visit up to Week 16 and Week 52

- IGA success rate (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥2-point improvement from baseline) at each visit up to Week 16 and up to Week 52
- Change in BSA involvement of AD, reported as a percentage of all major body sections combined, from baseline at each visit up to Week 16 and up to Week 52
- Absolute and percent change in weekly average of peak pruritus NRS (PP NRS) score from baseline at each visit up to Week 16 and up to Week 52
- Proportion of subjects with an improvement of ≥4 from baseline in weekly average of PP NRS at visit up to Week 16 and up to Week 52
- Absolute and percent change in weekly average of average pruritus NRS score from baseline at each visit up to Week 16 and up to Week 52
- Absolute and percent change in weekly sleep disturbance NRS score from baseline at each visit up to Week 16 and up to Week 52
- Proportions of subjects receiving any rescue therapy by rescue treatment type (e.g., topical, phototherapy, systemic) at any visit during the treatment period
- Percent change in SCORing Atopic Dermatitis (SCORAD) score from baseline at each visit up to Week 16 and up to Week 52
- Change in Children's Dermatology Life Quality Index (cDLQI) for subjects ≥4 years of age from baseline up to Week 16 and up to Week 52
- Change in Infant's Dermatitis Quality of Life Index (iDLQI) for subjects <4 years of age from baseline up to Week 16 and up to Week 52
- Change in Patient-Oriented Eczema Measure (POEM) from baseline up to Week 16 and up to Week 52.

8.2.1.1 Eczema Area and Severity Index

The EASI is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs. The EASI score is a composite score ranging from 0 to 72. The severity of erythema, induration/papulation, excoriation, and lichenification will be assessed by the investigator or trained designee on a scale of 0 (absent) to 3 (severe) for each of the 4 body areas: head/neck, trunk, upper limbs, and lower limbs, with half points allowed.
In addition, the extent of AD involvement in each of the 4 body areas vary with age and are different in young children as compared to older children and will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6.
The EASI score will be calculated in the CRF at each visit from screening visit to Week 52 (end of treatment visit). EASI-50, EASI-75 and EASI-90 are defined respectively as a ≥50%, ≥75%, ≥90% improvement in EASI score from baseline.

8.2.1.2 Investigator's Global Assessment

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

success is defined as 0 (clear) or 1 (almost clear) and a minimum 2-point improvement from baseline.
IGA will be calculated in the CRF at each visit from screening visit to Week 52 (end of treatment visit).

8.2.1.3 Body Surface Area Involvement

The BSA involvement of AD varies with age and is different in young children as compared to older children and will be assessed by the investigator or trained designee for each part of the body (the possible highest score for each region is head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. The BSA will be derived from SCORAD data and will be assessed at each visit from screening visit to Week 52 (end of treatment visit).

8.2.1.4 Pruritus Numeric Rating Scale

The pruritus NRS is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours. Two measures of the pruritus NRS will be assessed: average pruritus (AP) and peak pruritus (PP).
The PP NRS has been validated in other AD clinical trials in adults, and the minimum clinically important difference was shown to be 4.25. The AP NRS provides a measure of overall pruritus intensity over a given period and has clinical relevance to both subjects and physicians because peak pruritus may show higher intensity but short duration.

Subjects will be asked the following questions:

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

The screening PP NRS and AP NRS will be determined by a single assessment using the PP NRS and AP NRS respectively (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. The baseline PP NRS and AP NRS will be determined based on the average of daily PP NRS and AP NRS respectively (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation. Subjects will receive instructions on how to record their pruritus NRS scores and will complete the assessment once daily in the evening throughout the clinical study (including the run-in and the follow-up period).
Post baseline values will be computed similarly, i.e. as an average of 7 values if at least 4 values are available. The computation will be performed:

- weekly from Week 1 to Week 16 (Week 1 will be the average of values from day 1 to day 7, Week 2 will be average from day 8 to day 14, and etc)

- based on study visit dates for Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52 (value at Week 20 will be the average of the 7 values prior to week 20 visit, etc.). (See Appendix D).

8.2.1.5 Sleep Disturbance Numeric Rating Scale

The sleep disturbance NRS is a 10-point scale ranging from 0 (no sleep loss) to 10 (I did not sleep at all) used by the subjects to report the degree of their sleep loss related to AD. Subjects will be asked the following question: "On a scale of 0 to 10, with 0 being "no sleep loss related to the symptoms of atopic dermatitis" and 10 being "I did not at all due to the symptoms of atopic dermatitis", how would you rate your sleep last night?" .
Subjects will receive instructions on how to record their sleep disturbance NRS scores and will complete the assessment once daily in the morning throughout the clinical study (including the run-in and the follow-up period).
The screening SD NRS will be determined by a single assessment using the SD NRS on the day of the screening visit. The baseline SD NRS will be determined based on the average of daily SD NRS during the 6 days immediately preceding baseline plus the value of SD NRS on the day of the baseline visit (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 6 days immediately preceding baseline plus baseline (7 scores in total) is required for this calculation. Post-baseline values will be computed similarly, i.e. as an average of 7 values if at least 4 values are available. The computation will be performed: weekly from Week 1 to Week 16 (Week 1 will be the average of values from Day 2 to Day 8, Week 2 will be average from Day 9 to Day 15 etc). The post-baseline values after Week 16 will be computed based on the 6 days immediately preceding the Week visit plus day at Week visit (see Appendix D).

8.2.1.6 Scoring Atopic Dermatitis

The 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. The SCORAD ranges from 0 to 103 and has 3 components: extent (BSA), intensity (signs), and subject-reported symptoms of pruritus and sleep loss. Investigator or trained designee will assess the severity of 6 signs of AD (erythema, edema/papulation, oozing/crust, excoriation, lichenification, and dryness), each on a scale ranging from 0 (absence) to 3 (severe). Investigator or trained designee will also ask the subjects to evaluate their symptoms of pruritus and sleep loss (average for the last 3 days/nights), each evaluated on a visual analogue scale from 0 to 10.
The SCORAD score will be recorded in the CRF at each visit from screening visit until Week 52 (end of treatment visit).

8.2.1.7 Children's Dermatology Life Quality Index

cDLQI is a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment. The subject will rate each question ranging from 0 (not at all) to 3 (very much). A higher total score indicates a poorer QoL.

cDLQI will be assessed at baseline, Week 8, Week 16, Week 32 and Week 52 for subjects >=4 years of age.

8.2.1.8 Infants' Dermatitis Quality of Life Index

iDQOL is a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, and treatment.
iDQOL will be assessed for the subject by the caregiver at baseline, Week 8, Week 16, Week 32, and Week 52 for pediatric subjects <4 years of age.

This index will not be assessed for Cohort 1 because all the subjects are over 4 years of age.

8.2.1.9 Patient-Oriented Eczema Measure

The POEM is a tool used for monitoring AD severity. It focuses on the illness as experienced by the patient. The POEM instrument consists of 7 questions for measuring patient-reported symptoms over the past week (in days). The subject or proxy will answer each question and the answer will be score from 0 to 4.
POEM will be assessed at baseline, Week 8, Week 16, Week 32 and Week 52.

8.2.1.10 Efficacy and Patient-reported Outcome Analyses

All descriptions of the continuous secondary efficacy (excluding PROs) endpoints will be performed based on Observed Cases (OC) and using Last observation carried forward (LOCF). In addition, IGA score will be summarized based on OC and LOCF as a continuous endpoint. LOCF approach will be used to impute any data not recorded at scheduled visits with most recent recorded data, considering data from any scheduled or unscheduled visit or early termination visit. For PP NRS, AP NRS and SD NRS, weekly derived scores will be used for LOCF imputation of missing weekly scores. The description of secondary efficacy endpoints referring to a response to treatment (IGA success, EASI-50, EASI-70, EASI-90, improvement in PP NRS >= 4) will be performed based on OC and using the non-responder imputation (NRI). For NRI, a non-response will be imputed for any missing data and for any data collected after the use of rescue therapy.
The PROs endpoints (POEM, cDLQI, IDQOL) will be summarized based on OC only.

Efficacy assessments including EASI, IGA, BSA, PP NRS, AP NRS, SD NRS and SCORAD will be summarized by visit and by cohort and overall as described in section 8.2.1. IGA changes from baseline will be summarized by visit by cohort and overall. PP NRS, AP NRS and SD NRS weekly scores will be plotted over time using LOCF approach for missing scores. In addition, the percentage of patients with an improvement of ≥4 from baseline in PP NRS will be displayed graphically over time with NRI approach for missing assessments.

Results of PROs including cDLQI, iDQOL and POEM will be summarized descriptively by visit as described in section 8.2.1 and by cohort and overall. Change in cDLQI will be summarized by visit for Cohort 1 and Cohort 2 and change in iDLQI will be summarized by visit for Cohort 2.

A corresponding listing will be provided for all the efficacy and PRO assessments scores.

The proportions of subjects receiving any rescue therapy will be summarized by rescue treatment type (e.g., topical, phototherapy, systemic) at any visit and by cohort and overall during the treatment period.

All efficacy analyses will be based on ITT Set.

8.2.2. PK/PD Analysis

The secondary endpoints for PK/PD analysis are as follows:

- Relationship between Nemolizumab concentrations and clinical efficacy endpoints (PP-NRS, EASI and IGA).

The PK/PD relationship between Nemolizumab observed serum concentrations and clinical efficacy endpoints (EASI, IGA and NRS) will be investigated, as appropriate, using a PK/PD model developed based on previous clinical data obtained in adults and adolescents. In addition, PK/PD modeling might be used to characterize the exposure /safety relationship. Estimates of main population PK/PD parameters used in the models, including inter-individual variability, covariate effects, residual error and their relative standard error (RSE), will be presented in a dedicated PK report attached to the CSR and not reported in the TLFs.

No individual PK/PD parameter that will be derived using the PK/PD models will be presented in the TLFs.

The PK/PD modeling will be conducted by an external CRO and will be detailed in a separate PK Modeling Analysis Plan.

All PK/PD analyses will be based on Pharmacokinetic Set.

8.2.3. Immunogenicity

The secondary endpoints for immunogenicity are as follows:

- Anti-drug antibody (ADA) assessments (screening, confirmatory, neutralizing antibody [Nab]), at baseline, Weeks 16, 52 and unscheduled visits that are conducted for safety reasons

Anti-drug antibody assessments (screening, confirmatory, titer, NAb) and incidence of positive ADA results (absolute occurrence, percent of subjects, and treatment-related ADA) will be summarized accordingly by visit and by cohort and overall. A treatment-related ADA is defined when at baseline, the screening or confirmatory ADA result is negative and the post-baseline confirmatory ADA result is positive. A corresponding listing will be displayed.

These analyses will be based on ITT Set.

8.2.4. Safety

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit as described in schedule of assessments in Appendix A.
All safety information will be summarized descriptively by each cohort and overall.

All safety analyses will be based on Safety Set.

8.2.4.2 Clinical Laboratory Evaluations

The safety laboratory assessments include the following parameters:

Hematology:

- Hemoglobin (g/L)
- Hematocrit (L/L)
- White blood cell count (with differential including eosinophils) (x10^9/L)
- Red blood cell count (x10^12/L)
- Platelet count (x10^9/L)
- Mean cell volume (fL)
- Eosinophils (x10^9/L)

Urinalysis:

- pH
- Glucose (mg/dL)
- Ketones (mg/dL)
- Blood (as reported negative, small, moderate, large)
- Protein (mg/dL)
- Leukocytes (as reported negative, trace, small, moderate, large)
- Nitrites (negative/positive)
- Bilirubin (as reported negative, moderate, large)
- Urobilinogen (mg/dL)
- Specific gravity (reported 1.001 to > 1.060)

Serum chemistry:

- Creatinine (mcmol/L)
- Aspartate Amino Transferase (AST) (U/L)
- Alanine Amino Transferase (ALT) (U/L)
- Gamma glutamyltransferase (U/L)
- Alkaline Phosphatase (U/L)
- Lactate Dehydrogenase (U/L)
- Total Bilirubin (mcmol/L)
- Direct Bilirubin (mcmol/L)
- Albumin (g/L)
- Total Protein (g/L)
- Uric Acid (mmol/L)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mmol/L)
- Chloride (mmolq/L)
- Glucose (mmol/L)
- Urea (mmol/L)
- Total cholesterol (mmol/L)
- Triglycerides (mmol/L)
- Low-density lipoprotein (LDL) (mmol/L)
- High-density lipoprotein (HDL) (mmol/L)
- Creatine phosphokinase (CPK) (U/L)

Summary statistics of the observed values and change from baseline for all laboratory parameters will be provided at the scheduled visits by cohort and overall.
Results will be presented for each parameter by cohort and overall in a shift table, using normal, abnormal not potentially clinically significant and abnormal potentially clinically significant categorization described in Appendix B and Central Lab Manual v2.0, between baseline and visits at Week 8, Week 16, Week 32 and at Week 52.

All laboratory data will also be presented in listings for each parameter with abnormal values flagged.

Boxplots presenting the distribution of AST, ALT, ALP, Total Bilirubin and CPK over the visits will be displayed by cohort. An additional boxplot will be presented on the figure considering the maximum post-baseline value.

8.2.4.3 Pregnancy Testing

Only female from Cohort 1 and Cohort 1.1 that are considered subjects of childbearing potential who is, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs)

at subsequent visits according to the schedule of assessments summarized in Appendix A. The data will be presented in a listing.

8.2.4.4 Premenses Status

Female subjects will be asked if they begin menses since the last visit at each visit. If yes, the data of first menses will be collected and the data will be presented in a listing.

8.2.4.5 Virology

Virology including HBsAg, HBcAb, hepatitis C, HIV-1, and HIV-2 antibody will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody. Subjects with positive hepatitis C antibodies will have a confirmatory test for HCV (e.g., PCR). The data will be presented in a listing.

8.2.4.6 Tuberculosis Testing

Immunosuppressant biologic treatments have been shown to increase the risk of TB infection or to cause conversion from latent to active TB in some circumstances. Because of this, subjects will be screened for active or latent TB before entry into this study. The data will be presented in a listing.

8.2.4.7 Vital Sign Measurements

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), body temperature (C), weight (kg), height (cm) and BMI (kg/m^2) will be assessed over time during the study. Descriptive statistics of observed values will be summarized by visit and by cohort and overall. Abnormal potentially clinically significant results will be presented for pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), and body temperature (C) by cohort and overall in a table at all visits (criteria are available in Appendix C).
A corresponding listing will also be provided.

8.2.4.8 Physical Examination and Respiratory Examination

Complete physical examination including a respiratory examination should be performed at all visits. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities. All physical examination and respiratory examination will be summarized by visit.

Results of physical examination is categorized into normal, abnormal and not done. If abnormal, results will be categorized with or without clinical significance. Corresponding listing will be provided with abnormal values flagged.

8.2.4.9 Respiratory Assessments

Subjects from Cohort 1 and Cohort 1.1 with no medical history will complete Peak Expiratory Flow (PEF) at certain visits, and subjects from Cohort 1 and Cohort 1.1 with de novo asthma will complete PEF and Childhood Asthma Control Test (cACT) at all subsequent visits.

1) In the case of subject has no asthma history, subject will undergo PEF testing at Screening, Baseline, Week 8, Week 16, Week 32 and Week 52.
2) If subject has asthma history, PEF and cACT will be performed at all visits according to the schedule of assessments in Appendix A.
3) Subjects with a new (de novo) diagnosis of asthma will complete PEF and cACT at all subsequent visits (taking into account that some subjects will have performed some PEF testing at prior visits as per (1))

cACT and PEF (absolute values and change from baseline) will be summarized by visit. A corresponding listing will be also provided for both assessments. For cACT, the numbers and percentages of subjects with an cACT score <=19 will be summarized by visit. For PEF, the numbers and percentages of subjects with PEF<80% will be presented by visit.

8.2.4.10 Electrocardiogram

A 12-lead ECG will be performed at specific visits regarding schedule of assessments in Appendix A. Electrocardiogram results are categorized into normal, abnormal and not done. If abnormal, results will be categorized with or without clinical significance. Results will be summarized by visit and by cohort and overall.
A corresponding listing will be provided with abnormal values flagged.

9. Interim Analyses

Three interim analyses (IA) will be performed for the study: IA-1 for Cohort 1, IA-1.1 for Cohort 1.1 and IA-2 for Cohort 2.
The first IA (IA-1) will be performed after the first 18 subjects have been enrolled into Cohort 1 (age 7-11 years) and have completed 16 weeks. The cut-off date for IA-1 is the date where 18 subjects from Cohort 1 have completed the Week 16 visit.
For the subsequent cohorts (Cohorts 1.1 and 2), the IA will be performed when approximately 18 subjects have completed 16 weeks. The cut-off date for IA-1.1 and IA-2 is the date where approximately 18 subjects from Cohort 1.1 and from Cohort 2 respectively have completed the Week 16 visit.
Cohort 1.1 cannot be enrolled until receiving written approval from the sponsor after the Interim Analysis of Cohort 1 (IA-1). Cohort 2 cannot be enrolled until receiving written approval from the

sponsor after completion of IA-1.1.
All the data collected up to the cut-off date for IA-1, IA-1.1 and IA-2 will be used for safety analysis, including the subjects who did not completed the Week 16 visit and including the data collected after week 16 but prior to the cut-off date for the first subjects who were enrolled and who already reached additional study visits.

No individual PK parameter will be included in the 3 Interim Analyses.

IA-1, IA-1.1 and IA-2 cohorts will be assessed for:

1. Safety by the independent data monitoring committee (IDMC) and the Sponsor. The IDMC will review and monitor subject safety and will provide recommendations on the safety of the subjects.
2. Drug exposure and dose confirmation using a population PK analysis by the Sponsor

The IDMC will review and monitor subject safety and will provide recommendations on the safety of subjects.
Additional efficacy analysis may be performed at IA-1.1 and IA-2.

Dose selection will be completed in a stepwise approach, based on the Interim Analyses (IAs) planned for this study. Each IA will be performed after approximately 18 subjects in their respective cohort have completed the Week 16 visit. 2-6 year old subjects cannot be enrolled in Cohort 2 until suitable doses are confirmed in the 7 -11 year old subjects, i.e., after the Interim Analysis (IA-1.1) of Cohort 1.1.

An independent adjudication committee (IAC) will review all asthma-related events throughout the study. Details on the IDMC and IAC, including the plan of analysis for IDMC outputs, the composition of the committees; and the procedures, roles, responsibilities, and their communications will be provided in the IDMC and IAC charters.

10. Changes in the Planned Analysis

In the study protocol Version 7.0 dated 3rd October 2022, prior therapies are defined in section 8.4.7 as therapies that have been stopped or vaccinations received within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria; and concomitant medication is defined in section 8.4.7 as any existing therapy ongoing at the time of screening visit, or any changes to existing therapies during the course of the study, or any new therapies the subject received since the screening visit.
In order to be consistent with other studies, the date of the first dose will be used to consider the treatment as prior and concomitant instead of the date of the screening visit.

In the study protocol Version 7.0 dated 3rd October 2022, the enrolled population is defined in section 10.1.1.1 as all individuals who met the inclusion/exclusion criteria and signed the ICF. The definition of the enrolled set has been updated to add the individuals who did not met the inclusion/exclusion criteria but received at least 1 dose of study drug.

11. References

1. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-22.

2. Linnet J, Jemec GB. An assessment of anxiety and dermatology life quality in patients with atopic dermatitis. Br J Dermatol. 1999;140(2):268-72.

3. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116-32.

4. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-8.

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

6. Centers for Disease Control and Prevention. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection− United States, 2010. MMWR. 2010;59(RR05);1-25.

7. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6 Suppl 16:5-40.

8. Polgar G, Weng TR. The functional development of the respiratory system from the period of gestation to adulthood. Am Rev Respir Dis. 1979;120(3):625-95.

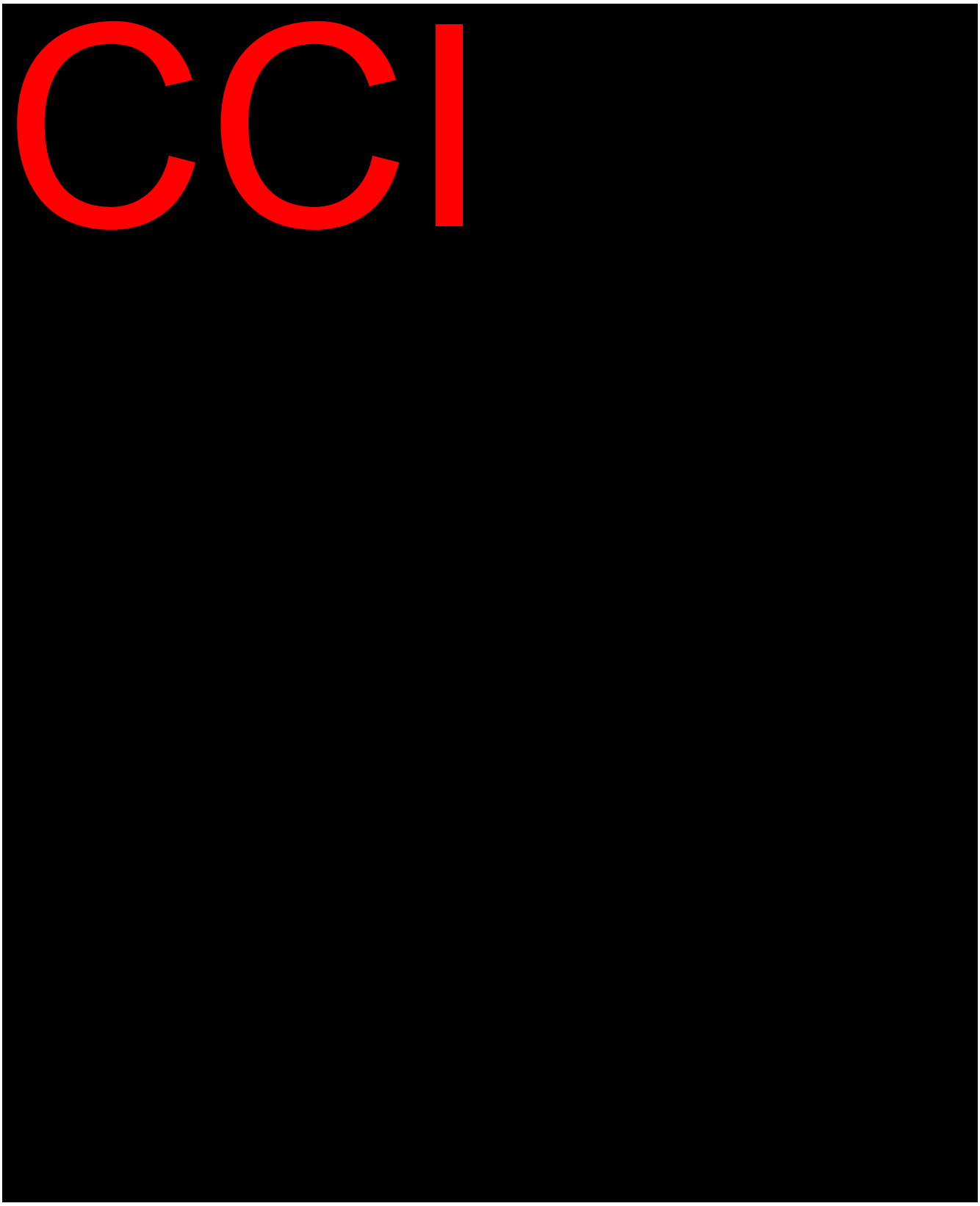
9. Lewis-Jones MS, Finlay AY. The Children’s Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132(6):942-9.

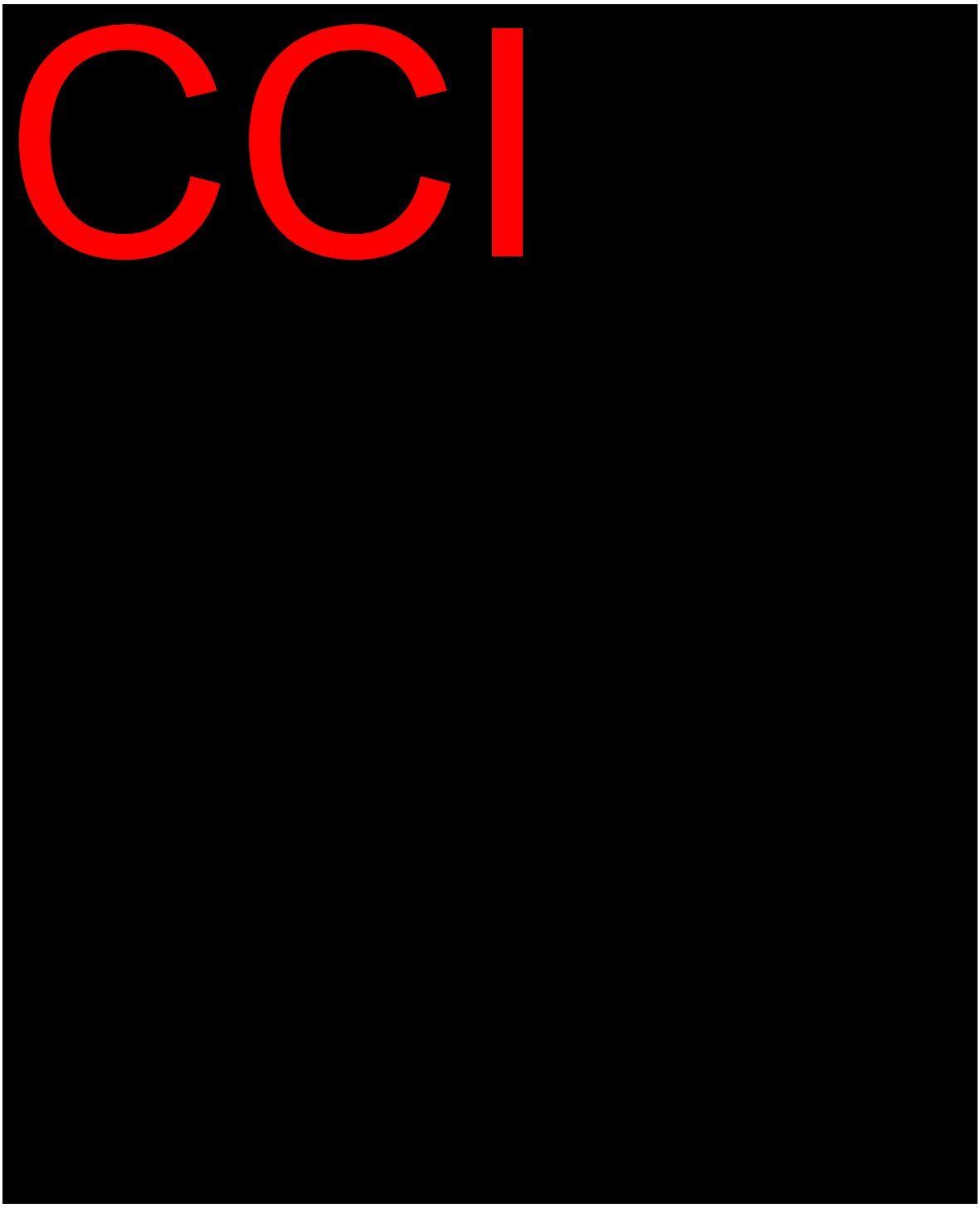
10. Lewis-Jones M S, Finlay A Y, Dykes P J. The Infants’ Dermatitis Quality of Life Index. Br J Dermatol 2001; 144: 104-10.

11. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients perspective. Arch Dermatol. 2004;140(12):1513-9.

12. Appendices

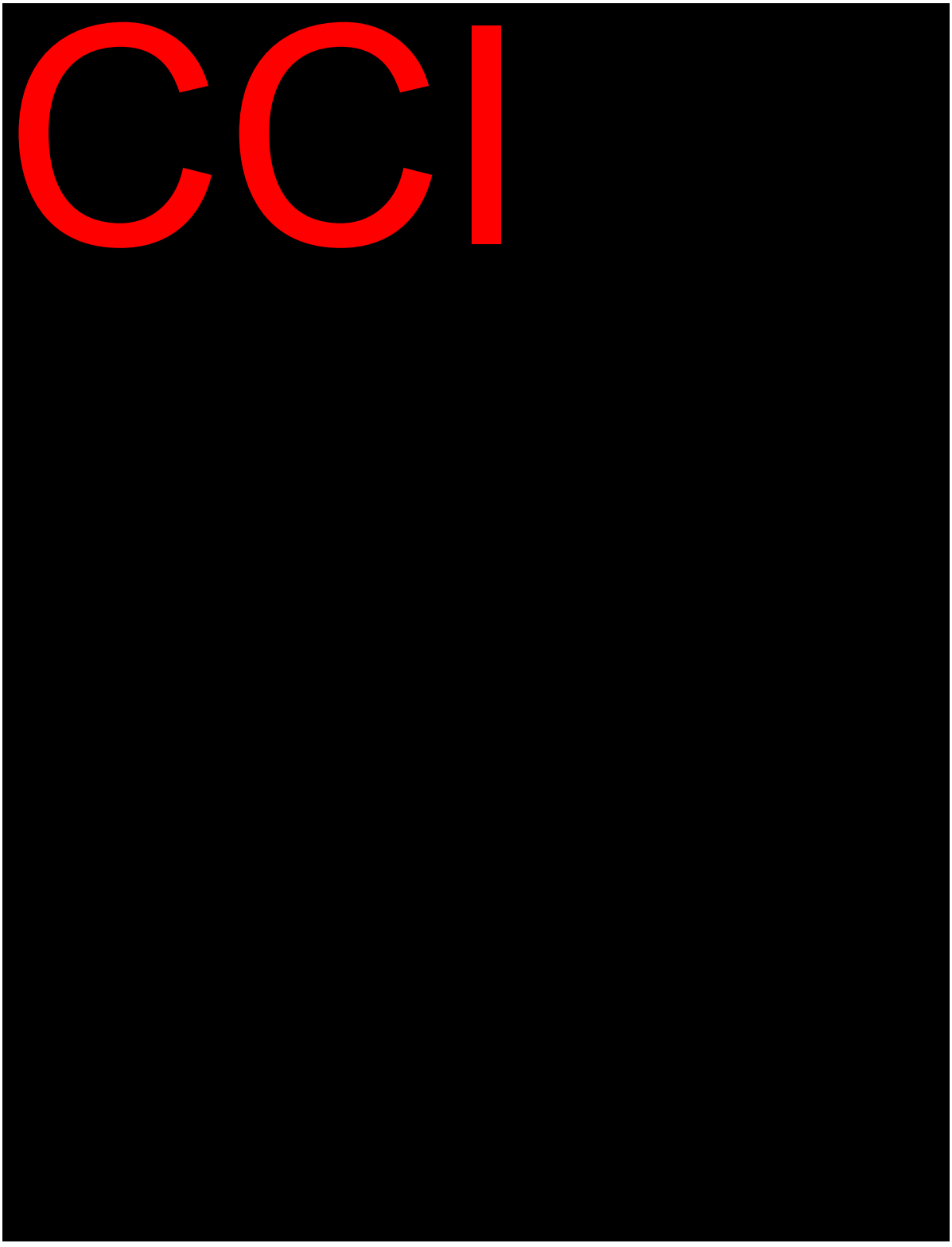
12.1. Appendix A: Schedule of Assessments


CCI


CCI


CCI


CCI


CCI


CCI

12.3. Appendix C: Potentially Clinically Significant Criteria of Vital Signs

Parameter	Criteria for subjects aged 7-11 years	Criteria for subjects aged 2-6 years
Pulse Rate (beats/min)	≤50 beats/min with a decrease from baseline ≥20 beats/min Or ≥120 beats/min with an increase from baseline ≥20 beats/min	≤75 beats/min with a decrease from baseline ≥20 beats/min Or ≥140 beats/min with an increase from baseline ≥20 beats/min
Systolic Blood Pressure (mmHg)	≤80 mmHg with a decrease from baseline ≥20 mmHg Or ≥108 mmHg with an increase from baseline ≥20 mmHg	≤70 mmHg with a decrease from baseline ≥20 mmHg Or ≥101 mmHg with an increase from baseline ≥20 mmHg
Diastolic Blood Pressure (mmHg)	≤48 mmHg with a decrease from baseline ≥10 mmHg Or ≥72 mmHg with an increase from baseline ≥10 mmHg	≤34 mmHg with a decrease from baseline ≥10 mmHg Or ≥59 mmHg with an increase from baseline ≥10 mmHg
Temperature (C)	>38°C with an increase ≥ 1.1°C	>38°C with an increase ≥ 1.1°C

12.4. Appendix D: Visit Windows for calculation of Weekly Average of AP NRS, PP NRS and SD NRS

Analysis Visit	Target Study Day of Analysis Visit	Visit Windows for AP NRS and PP NRS Evening Assessments	Visit Window for SD NRS Morning Assessment
Baseline	1	-7 to -1	-6 to 1 before dosing
Week 1	8	1 to 7	2 to 8
Week 2	15	8 to 14	9 to 15
Week 3	22	15 to 21	16 to 22
Week 4	29	22 to 28	23 to 29
Week 5	36	29 to 35	30 to 36
Week 6	43	36 to 42	37 to 43
Week 7	50	43 to 49	44 to 50
Week 8	57	50 to 56	51 to 57
Week 9	64	57 to 63	58 to 64
Week 10	71	64 to 70	65 to 71
Week 11	78	71 to 77	72 to 78
Week 12	85	78 to 84	79 to 85
Week 13	92	85 to 91	86 to 92
Week 14	99	92 to 98	93 to 99
Week 15	106	99 to 105	100 to 106
Week 16	113	106 to 112	107 to 113
Week 20	141	134 to 140	135 to 141
Week 24	169	162 to 168	163 to 169
Week 28	197	190 to 196	191 to 197
Week 32	225	218 to 224	219 to 225
Week 36	253	246 to 252	247 to 253
Week 40	281	274 to 280	275 to 281
Week 44	309	302 to 308	303 to 309
Week 48	337	330 to 336	331 to 337
Week 52	365	358 to 364	359 to 365

Certificate Of Completion

Envelope Id: C70C6F59-6D21-474E-9CA5-6DEC53E93F07
Status: Completed
Subject: Complete with Docusign: Galderma GLDRD6SPR118126 SAP_V5.0.pdf
Source Envelope:
Document Pages: 48
Signatures: 1
Envelope Originator:
Certificate Pages: 3
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Monrovia, Reykjavik

PPD

Record Tracking

Status: Original
21 May 2025 | 14:33
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): J'approuve ce document	Sent: 21 May 2025 | 14:39 Viewed: 21 May 2025 | 14:45 Signed: 21 May 2025 | 15:34

Electronic Record and Signature Disclosure:
Accepted: 21 May 2025 | 14:45
ID: b6566aaf-8c8c-4520-ba16-ac5435eec500

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	21 May 2025 | 14:39
Certified Delivered	Security Checked	21 May 2025 | 14:45
Signing Complete	Security Checked	21 May 2025 | 15:34
Completed	Security Checked	21 May 2025 | 15:34

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures