CLINICAL STUDY PROTOCOL

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

Protocol Number:	RD.06.SPR.118126
EudraCT Number:	2021-000448-23
IND Number:	117122
Investigational Product:	Nemolizumab (CD14152)
Phase of Development:	2
Indication:	Moderate-to-severe atopic dermatitis
Sponsor:	Galderma S.A. Zählerweg 10 6300 Zug Switzerland Galderma Research & Development, LLC 2001 Ross Avenue Suite 1600 Dallas, TX 75201 United States
Protocol Date:	14OCT22
Protocol Version:	Version 7.0

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: 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

Protocol Number: RD.06.SPR.118126

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

Sponsor Signatory

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Sr. Medical Expert
R&D Medical Advisory
Galderma S.A.

PPD
Signatu

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2 STUDY PERSONNEL

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3 SYNOPSIS

Protocol Number:

RD.06.SPR.118126

Title:

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

Investigational Product:

Nemolizumab (CD14152)

IND Number:

117122

Study Centers:

Approximately 45 study centers are planned in North America (NA) and the European Union (EU).

Phase of Development:

Phase 2

Objectives:

Primary objective:

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.

Secondary objective:

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.

Study Design:

This is a phase 2, open-label, single arm study of pediatric subjects (aged 2 to 11 years) with moderate-to-severe AD, who are inadequately controlled by topical therapies. Eligible subjects must have a documented history of inadequate response to topical AD medications.

The study will enroll approximately 105 subjects in 3 cohorts of 35 subjects each:

Cohort 1: Subjects aged 7-11 years

Cohort 1.1: Subjects aged 7-11 years

Cohort 2: Subjects aged 2-6 years

Rationale:

An additional cohort (Cohort 1.1) was added based on the interim analysis of Cohort 1. The PK assessments at completion of the Week 16 visit, by the first 18 subjects of Cohort 1 showed that the steady state systemic exposure in children was approximately 2-fold higher than in the adult (SPR114322) and adolescent (SPR116912) studies without any safety signals to date. The independent data monitoring committee (IDMC) concluded that there were no safety concerns in the data presented and recommended to continue the existing Cohort 1 as intended in 7-11 year old subjects and agreed to an additional Cohort (1.1) in 7-11 year old subjects with decreased doses to re-evaluate the PK. Consequently, lower doses will be administered in

children of the same age group of Cohort 1, to match the systemic exposure in adult and adolescent populations.

Each cohort will include 2 parts; Part A will have a 16-week treatment period and Part B will have a 36-week extension of treatment. The investigator should make every effort to enroll subjects who can stay within the age group cohort throughout the study.

There are three Interim Analyses (IAs) planned for this study, IA-1 for Cohort 1, IA-1.1 for Cohort 1.1 and IA-2 for Cohort 2. IA-1 will be performed after the first 18 subjects in cohort 1 have completed the Week 16 visit. For subsequent Cohorts (1.1 and 2) the IA will be performed when approximately 18 subjects have completed the Week 16 visit. The recruitment will start with Cohort 1 (aged 7 to 11 years). 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.

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. Additional efficacy analysis may be performed at IA-1.1 and IA-2. During the interim analyses, enrollment will continue in each Cohort. Note: as mentioned above, enrollment in Cohort 1.1 and Cohort 2 will only start after completion of the IA-1 and IA-1.1, respectively, and Sponsor's written approval. Once enrollment starts in Cohort 1.1 and in Cohort 2, enrollment in these Cohorts will continue during IA-1.1 and IA-2, respectively.

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 subjects will receive a flat dose of nemolizumab every 4 weeks (Q4W) with a loading dose at baseline on the basis of body weight. The planned nemolizumab doses (see Table 1a and Table 1b below) will be confirmed by the IA-1, IA-1.1, and IA-2.

Table 1a. Selected Pediatric Dose for Cohort 1

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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 1b. Selected Pediatric Dose for Cohort 1.1 and Cohort 2

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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

Subjects meeting the eligibility criteria will initiate (or continue) use of a moisturizer beginning at screening. Subjects will also be provided or prescribed background topical therapy for AD (including a medium-potency TCS for the body, and low-potency TCS or topical calcineurin inhibitors [TCI] for sensitive areas such as the face, neck, intertriginous areas, etc.), for use throughout the study. Use of authorized background therapy is required for at least 14 days before baseline/Day 1. Subjects who continue to meet the eligibility criteria at the baseline visit will be enrolled in the study. Subjects may be rescreened once.

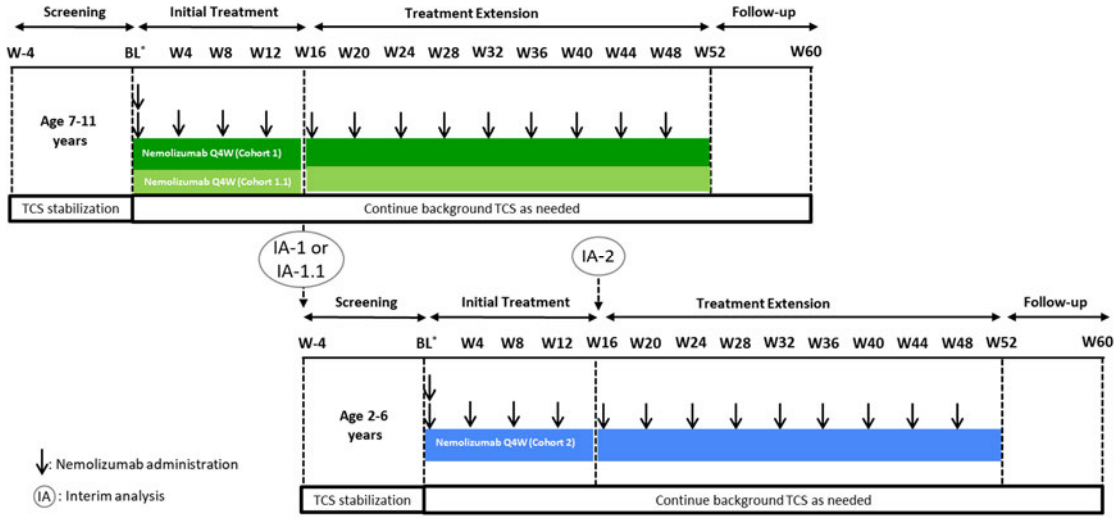
Figure 1 provides an overview of the open-label study design. Subjects will be screened and complete a run-in period of at least 14 days before the baseline visit. At baseline, eligible subjects will enter a 16-week initial treatment period with nemolizumab administered subcutaneously (SC) Q4W, with a loading dose at baseline/Day 1 for each cohort. The administered dose will be selected based on subject body weight as defined in Table 1a and Table 1b.

Subjects will continue to receive treatment for an additional 36 weeks in the treatment extension period. Following the treatment extension period, subjects will enter an 8-week follow-up period. Subjects who prematurely discontinue the study before the Week 48 visit will be followed for 12 weeks after their last dose of study drug.

The Schedule of Assessments is summarized in Table 5. Assessments of PK, safety, and efficacy will be conducted throughout the study. Subject-reported assessments of pruritus, sleep disturbance and the use of topical AD medication will be collected daily.

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

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

Number of Subjects:

Approximately 105 subjects are planned to be enrolled in this study with approximately 35 subjects in each cohort.

Treatments:

Investigational therapy

Subjects will receive a flat dose of nemolizumab Q4W for 52 weeks, with a loading dose at Baseline (2x dose). The flat dose will be defined for a range of body weight (see Table 1a and Table 1b).

For subjects with body weight <30 kg at baseline, nemolizumab will be provided as a lyophilized powder in a single dose vial. Injection will be performed after reconstitution with sterile water for injection.

For subjects with body weight ≥30 kg, nemolizumab will be provided as a lyophilized powder and water for injection for solution for injection for SC use after reconstitution in a single dose, pre-filled dual chamber syringe (Cohort 1 and baseline doses for Cohort 1.1 and Cohort 2) or a lyophilized powder in a single dose vial (for all doses in Cohort 1.1 and Cohort 2, except for baseline).

Background therapies are used throughout the study (screening through the follow up visit), as described below.

Moisturizer

Subjects/caregivers will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions throughout the study. The subject's current moisturizer or a moisturizer recommended by the investigator may be used. Use should not occur within 8 hours before each clinic/office visit.

Background topical therapies

Subjects will be prescribed authorized background topical therapy for use during the study, beginning within the screening period and ≥14 days before Day 1 (i.e., run-in):

Medium-potency TCS therapy for non-sensitive areas: Subjects/caregivers will apply the authorized medium-potency TCS background therapy in areas of the body where use of medium-potency TCS is considered safe (e.g., trunk and extremities).

Low-potency TCS or TCI therapy for sensitive areas: Subjects/caregivers will apply an authorized background therapy (i.e., low-potency TCS or TCI) to areas of the body considered TCS-sensitive (e.g., face, neck, intertriginous areas) or in cases where medium-potency TCS is not tolerated. The investigator may select either low-potency TCS or TCI for each subject, per investigator discretion. The subject/caregiver may only apply **one** medication to each affected area; concomitant use of low-potency TCS and TCI on the same lesion is not permitted.

Subjects/caregivers will apply a thin layer of authorized background topical therapy on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare, but which does not exceed the daily frequency recommended in the product labeling. Refer to the current pharmacy materials for the authorized topical medications and permitted daily frequency of use. "As needed" (PRN) use of TCS or TCI is not permitted. Only topical therapies specifically provided or prescribed for use in this study are permitted. Background therapy for sensitive areas should not be used in non-sensitive areas or vice versa.

Background therapy use should be adjusted according to the disease activity and tolerability of the subject, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, at the discretion of the investigator.

Rescue Therapies

If deemed to be medically necessary by the investigator (e.g., to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects at any time during the study except during the run-in period. Subjects receiving rescue therapies during the run-in period are not eligible to participate in the study. As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks after baseline to allow a minimum period for study drug exposure in the presence of background therapy. Rescue treatments are only treatments that directly treat AD (mainly those that are approved or are standard of care) and include topical and systemic treatments as outlined. Rescue therapies include:

- High- or ultra-high potency of TCS
- Oral corticosteroids
- Biologics
- Systemic nonsteroidal immunosuppressants/immunomodulators
- Phototherapy

Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams are not considered to be rescue therapy because they do not directly treat AD.

Whenever possible, investigators should first use topical medications as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy, the study drug administration must be permanently discontinued.

Study Duration:

The expected duration of each subject's participation in the study is up to 64 weeks, including a 4-week screening period, a 16-week initial treatment period, a 36-week treatment extension period, and an 8-week follow-up period (12-weeks after the last study medication injection).

Study Population:

Inclusion Criteria:

[redacted]

2. Chronic AD that has been documented for at least 6 months for subjects aged 2-6 years and at least 1 year for subjects aged 7-11 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria (Appendix 1) 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]

8. Agree to apply a moisturizer throughout the study from the screening visit daily, and liberally as needed; agree to apply an authorized TCS, with or without TCI, from the screening visit and throughout the study as determined appropriate by the investigator.
9. CCI [redacted]
10. Subject and caregiver willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.
11. CCI [redacted]

Exclusion Criteria:

1. Body weight <10 kg.
2. Child in Care: a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation.
3. CCI [redacted]

CCI [redacted]

4. Subjects with a current medical history of chronic bronchitis.
5. CCI [redacted]
6. Requiring rescue therapy for AD during the run-in period or expected to require rescue therapy within 2 weeks following the baseline visit.
7. Positive serology results for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), hepatitis C (HCV) antibody with positive confirmatory test for HCV (e.g., polymerase chain reaction [PCR]), or human immunodeficiency virus (HIV) antibody at the screening visit.

CCI [redacted]

8. CCI [redacted]
9. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years or since birth for subjects <5 years of age.
10. CCI [redacted]

12. Known or suspected immunosuppression.
13. CCI [redacted]

CCI [redacted]

19. Subjects unwilling to refrain from using prohibited medications during the clinical trial.
20. CCI [redacted]

Study Endpoints:

Primary endpoints:

Pharmacokinetics (PK):

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

Safety:

- 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

Secondary endpoints:

Efficacy:

- Absolute and percent change in 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 baseline and 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 Week 52
- Absolute and percent change in weekly average of average pruritus NRS score from baseline at each visit and up to Week 16 and up 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
- Proportion 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 Infants' Dermatitis Quality of Life Index (IDQOL) 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

PK/PD Analysis:

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

Immunogenicity:

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

Procedures and Assessments:

Efficacy:

The following efficacy assessments are planned according to the Schedule of Assessments:

- EASI
- IGA
- BSA
- SCORAD
- Peak pruritus NRS (patient reported outcome [PRO])
- Average pruritus NRS (PRO)
- Sleep disturbance NRS (PRO)

Safety:

The following safety assessments are planned according to the Schedule of Assessments:

- AEs, including TEAEs, AESIs, and SAEs
- Physical examination and vital signs
- Clinical laboratory tests
- Electrocardiogram
- Respiratory examination and assessments

Pharmacokinetics:

The following PK assessments are planned according to the Schedule of Assessments:

- Serum nemolizumab concentrations
- Serum nemolizumab PK parameters

Immunogenicity:

The following immunogenicity assessments are planned according to the Schedule of Assessments:

- ADA assessments
- Nab assessments

Statistical Methods and Planned Analyses:

Analysis population:

The safety population will include all enrolled subjects who receive at least 1 dose of study drug. This population will be used for the analysis of safety. The PK population will include all subjects who received at least 1 dose of study drug and have at least one measurable post-baseline concentration and will be used for the PK analysis. Intent-to-treat (ITT) population will include all enrolled subjects and will be used for efficacy analysis.

Demography and efficacy analyses:

The demographics and baseline characteristics, efficacy and QoL endpoints will be summarized using descriptive statistics by each age cohort and overall.

PK analysis:

- Pharmacokinetic parameters will be derived using a non-linear mixed effect modeling approach. The 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.
- Exposure-response (E/R) analysis: pharmacokinetic pharmacodynamics (PKPD) relationship between nemolizumab plasma concentrations and the selected clinical outcomes (EASI, IGA and NRS) will be investigated, as appropriate, using a PKPD model development based on previous clinical data.
- Descriptive statistics will be provided for all individual popPK-derived parameters and for nemolizumab observed serum concentrations per time point.

Safety Analysis:

Treatment Emergent Adverse Events (TEAEs) and other safety information (e.g., clinical laboratory, vital signs, ECG, ADA, etc.) will be summarized descriptively by each age cohort and overall.

An interim analysis (IA-1) will be performed to assess the PK and Safety of nemolizumab once at least 18 subjects have been enrolled into Cohort 1 (aged 7-11 years) and completed Week 16 assessment.

IA-1.1 will be performed to assess the PK and Safety of nemolizumab once approximately 18 subjects have been enrolled into Cohort 1.1 (aged 7-11 years) and completed the Week 16 assessment, to determine if recruitment to Cohort 2 (aged 2-6 years) should start.

IA-2 will be performed to assess the PK and Safety of nemolizumab once approximately 18 subjects have been enrolled into Cohort 2 (aged 2-6 years) and completed their Week 16 assessment.

Sample size assumption:

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

Based on the observed variability of nemolizumab serum concentrations (observed in adults and adolescents during previous studies), a sample size of approximately 35 children per cohort is considered sufficient to calculate PK parameters with adequate precision and to ensure adequate representation across the pediatric age ranges.

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4.1 List of In-text Tables

4.2 List of In-text Figures

5 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	Average pruritus
AST	aspartate aminotransferase
BCG	bacillus Calmette-Guérin
BL	baseline
cACT	Childhood Asthma Control Test
CDC	Centers for Disease Control and Prevention
cDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
COVID	coronavirus disease
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CS	clinically significant
CV	coefficient of variation
CYP450	cytochrome P450
DCS	dual chamber, single-use syringe
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ELISA	Enzyme linked immunosorbent assay

Abbreviation	Definition
ET	early termination
EU	European Union
FOCBP	female of childbearing potential
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
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
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
IRB	Institutional Review Board
IRR	injection-related reaction
JAK	Janus kinase
LDH	lactate dehydrogenase
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NAb	neutralizing antibody

Abbreviation	**Definition**
NRS	numeric rating scale
PCR	Polymerase chain reaction
PDE	phosphodiesterase
PEF	peak expiratory flow
PK	pharmacokinetics
PKPD	pharmacokinetic pharmacodynamics
POEM	Patient-Oriented Eczema Measure
PopPK	population-pharmacokinetic
PP NRS	peak pruritus numeric rating scale
PRN	pro re nata (when necessary or as needed)
PRO	patient-reported outcome
PTC	product technical complaint
Q4W (q4wk)	every 4 weeks
Q8W (q8wk)	every 8 weeks
QoL	quality of life
RA	receptor A
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
Th_2	type 2 helper T [cell]
TMF	Trial Master File

Abbreviation	**Definition**
ULN	upper limit of normal
UPT	urine pregnancy test
US	United States

6 INTRODUCTION

6.1 Background and Rationale

Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population (Weidinger 2016) and up to 25% of children (Eichenfield 2014). During infancy, AD primarily involves the face and extensor surfaces of the extremities (Weidinger 2016). 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 (Linnet 1999). 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 overall lifetime prevalence of AD has increased over the past 30 years (Eichenfield 2014). In most countries, there has been an increase in AD prevalence over a 5 to 10-year period (Williams 2008). In the United States (US), the prevalence of AD in children has been reported between 10% and 13% in 2 studies (Shaw 2011), (Silverberg 2014). Many environmental and geographic factors were shown to contribute to incidence rate and severity in both studies. These variables included urban living, household income, parental education level, and race.

The majority of AD cases can be regarded as "mild", with 10% to 20% of subjects suffering from severe eczematous skin lesions, although the percentage of individuals experiencing severe disease appears to be higher in the adult AD population (Kunz 1997). Whereas the prevalence of moderate-to-severe AD is up to 71% in adults suffering from AD, the prevalence of moderate and severe AD in children with AD was found to be 14% and 2%, respectively (Emerson 1998). Evaluation of AD data collected through the US 2007 National Survey of Children's Health showed that 67% of pediatric AD subjects had mild disease, 26% had moderate disease, and 7% had severe disease, which translates to approximately 5.6, 2.2, and 0.6 million US children, respectively (Silverberg 2014).

The clinical manifestations of AD vary with age (Wasserbauer 2009). The eczematous changes and its morphology are seen in different locations, depending on the age of the subject (child, adolescent, or adult).

Atopic dermatitis occurs in 3 main age-related stages (Rudikoff 1998) that may be separated by periods of remission or overlap: the first, the infantile stage up to age 2 years, is typified by highly pruritic, red, scaly, crusted, and sometimes weeping patches on both cheeks and on the extensor parts of the extremities. Eczematous changes of the scalp and wheal formation may also be seen. The diaper area is generally spared, and early infantile AD may be difficult to distinguish from seborrheic dermatitis on clinical grounds alone. The childhood stage from 2 years to 12 years shows papulation rather than exudation and

occurs in the flexural areas, especially the antecubital and popliteal fossae, the volar aspect of the wrists, ankles, and neck. Thickened plaques show lichenification and excoriation. In the adult stage, from puberty onward, subjects may have had few or no skin problems since infancy or may have suffered a chronic relapsing course with periods of remission. Lichenification occurring in the flexural areas and facial involvement is common, especially in the forehead and periorbital regions. The wrists, hands, ankles, feet, fingers, and toes are often involved.

The cause of AD, although still not completely understood, is probably multifactorial and involves complex interrelation between susceptibility genes, immunological factors, infections, and environmental factors to produce a skin barrier disturbance as well as immunologic dysregulation and inflammation (Rutkowski 2014). Abnormal protein (filaggrin and related proteins) and lipid (ceramide) metabolism may also play a key role. Upon stimulation with allergens, dendritic cells in the skin stimulate type 2 helper T cells (Th2) and cause the subsequent release of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5, and IL-13. High levels of Th2 cytokines in AD skin increase serine protease, which leads to further skin barrier dysfunction, and IL-31, which leads to pruritus and further inflammation and barrier dysfunction (Stott 2013), (Singh 2016). The pathophysiology also involves Th1 cells in the chronic phase of AD. Involvement of Th17 and Th22 cells in AD pathogenesis has been more recently reported (Gittler 2012). Of note, non-lesional skin already shows signs of subclinical inflammation with increased numbers of Th2 cells, Th22 cells, and to a lesser degree, Th17 cells, and a pro-inflammatory cytokine milieu (Suárez-Fariñas 2011).

The scratching behavior associated with pruritus is believed to exacerbate AD lesions by causing mechanical damage to the skin, allowing the penetration of foreign antigens, triggering inflammatory responses, and leading to further aggravation of dermatitis and itching. This vicious circle of scratching → exacerbation of dermatitis → aggravation of itching is known as the "itch-scratch cycle" (Wahlgren 1999).

IL-31 is involved in both primary AD pathophysiology and perpetuation of the itch-scratch cycle. IL-31 is preferentially produced by Th2 cells, following induction by IL-4, and its expression is consistently increased in the skin lesions of AD subjects (Stot 2013), (Szegedi 2012), (Neis 2006). Furthermore, the IL-31 receptor A (IL-31 RA) was found to be expressed in several tissues including the dorsal root spinal ganglia, which contain sensory nerve cells, (Sonkoly 2006) and keratinocytes (Kato 2014). Through interaction with its receptor, IL-31 promotes pruritus, Th2-driven inflammation, and keratinocyte proliferation and differentiation, which are crucial for skin barrier function (Stot 2013), (Singh 2016), (Saito 2017), (Hänel 2016). Together, these findings suggest that IL-31 is involved in the pathogenesis of pruritus and is implicated in the inflammation of AD.

Atopic dermatitis is currently managed with topical and systemic treatments, as well as phototherapy. Topical agents are the mainstay of AD therapy. Moisturizers are used to improve skin dryness and skin barrier dysfunction. Topical corticosteroids (TCS) are widely prescribed in adults and children for their anti-inflammatory effect, but their long-term use can lead to side effects, such as skin atrophy and risks associated with systematic

absorption (e.g., hypothalamic pituitary axis suppression and Cushing's syndrome). Topical calcineurin inhibitors (TCI) are effective for acute and chronic treatment in adults and children, particularly in selected anatomical areas. Stinging and burning are frequent local reactions, and both tacrolimus and pimecrolimus carry a warning in the US prescription information that long-term safety has not been established due to reports of (rare cases of) malignancy. Crisaborole ointment (Eucrisa®; Pfizer) is a topical phosphodiesterase (PDE)-4 inhibitor with an acceptable safety profile in adults and children but is most commonly used in the treatment of mild-to-moderate AD. Hypersensitivity reactions at or near the application site have also been observed (Eucrisa 2018).

Despite the demonstrated efficacy of topical treatments, they are not always sufficient to control moderate-to-severe AD in some subjects, who therefore require the addition of phototherapy or a systemic treatment to achieve sufficient control of AD (Sidbury 2014). There are various forms, doses, and treatment protocols of phototherapy, which lead to heterogeneous treatment outcomes, including common side effects such as actinic damage, local erythema and tenderness, pruritus, burning and stinging, as well as the long-term risk of skin cancer. Systemic corticosteroids, while effective at controlling disease temporarily, should be avoided due to an overall unfavorable risk-benefit safety profile, particularly in pediatric populations. Oral antihistamines (including both sedating and non-sedating medications) have been studied in the management of AD but there is insufficient evidence of treatment benefit. Cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil may be considered when systemic treatment is required (Sidbury 2014). Most of these systemic immunosuppressants, except cyclosporine, have not been approved for the treatment of AD and are used off-label in both adults and pediatric subjects. Cyclosporine is approved for treatment of severe AD in the European Union and in a few other countries (e.g., Japan), but not in the US. However, given the high response variability and the known secondary adverse effects of these drugs, there is a need for new drugs to better control the disease while decreasing the risk of secondary adverse effects.

Several biological agents are currently being used or developed for the treatment of AD. Dupilumab, a human monoclonal antibody that blocks the signaling pathway of both IL-4 and IL-13, is approved in pediatric populations and adults with moderate-to-severe AD not adequately controlled with topical medications (Simpson 2016). Two other anti-IL-13 therapies, lebrikizumab and tralokinumab, are also currently in development. Phase 3 studies with janus kinase (JAK) inhibitors are ongoing with pediatric populations.

Nemolizumab, a humanized anti-human IL-31 RA monoclonal antibody, inhibits the binding of IL-31 to IL-31 RA and subsequent signal transduction. Transgenic mice overexpressing IL-31 exhibited skin lesions resembling those of AD and scratching behavior, which could be suppressed by treatment with an anti-mouse IL-31 antibody (Dillon 2004), (Grimstad 2009). In dogs, lokivetmab, a caninized, anti-canine IL-31 antibody, has been shown to reduce pruritus in a dose-dependent manner with a rapid onset of effect and decrease in dermatitis score compared to placebo (Michels 2016). In cynomolgus monkeys, nemolizumab suppressed IL-31-induced scratching (Oyama 2018). In a phase 2a study (CIM003JG) in adult subjects with AD, nemolizumab improved both pruritus and lesional AD, while demonstrating an acceptable safety profile (Leshem 2015).

In a randomized, placebo-controlled, double-blind, parallel-group (10 mg, 30 mg, 90 mg, and placebo), phase 2b dose-finding study, the 30-mg dose was selected as the final dose for further evaluation in phase 3. A 16-week, open-label, phase 2 study (N = 20) evaluated the safety, efficacy, and pharmacokinetics (PK) of nemolizumab 30 mg every 4 weeks (Q4W), administered concomitantly with background TCS in adolescent subjects (12-17 years old) with moderate-to-severe AD who are not adequately controlled with topical treatments. Based on interim analysis (IA) results, it was concluded that nemolizumab PK in adolescents is similar to that in adults. No impact of age was observed. The independent data monitoring committee (IDMC) concluded that there were no safety concerns in the data presented and recommended to open enrollment in the intended nemolizumab studies to adolescents.

In conclusion, nemolizumab may present a new treatment option for AD in pediatric as well as adult subjects. Atopic dermatitis subjects with associated pruritus and an insufficient response to topical therapies could particularly benefit from such a therapy. The objective of this phase 2 study is to evaluate the PK, safety, and efficacy of nemolizumab in pediatric subjects (2-11 years) with moderate-to-severe AD who are not adequately controlled by topical therapies.

6.2 Clinical Studies

The Investigator's Brochure (IB) contains detailed information on clinical and non-clinical studies. A summary of the completed and ongoing clinical studies of nemolizumab in AD is included below.

6.2.1 Completed Clinical Studies

6.2.1.1 Phase 1 Single-Dose Safety Study

The safety, tolerability, and PK of a single subcutaneous (SC) dose of nemolizumab were evaluated in a randomized, double-blind, placebo-controlled phase 1 study including 80 healthy adult volunteers and 36 Japanese subjects with moderate-to-severe AD (Nemoto 2016). Doses ranged from 0.003 to 3.0 mg/kg in healthy volunteers and from 0.3 to 3.0 mg/kg in AD subjects. There were no deaths or serious adverse events (SAEs) reported in the study, and no dose-dependent increase in the incidence of adverse events (AEs) was observed.

Pharmacokinetic assessments following a single SC dose of nemolizumab showed a dose-dependent increase in serum nemolizumab concentration, AUC_{inf}, and maximum drug concentration. Peak serum concentrations were observed 4 to 6 days after nemolizumab administration, after which the drug gradually disappeared over a half-life of approximately 2 weeks.

6.2.1.2 Phase 2a Multi-Dose Safety and Efficacy Study

The safety, tolerability, and efficacy of nemolizumab monotherapy was evaluated in 264 moderate-to-severe AD subjects who were inadequately controlled by or intolerant to topical therapy in a phase 2a study (CIM003JG) (Ruzicka 2017), (CIM003JG Clinical

study report 2017). The study included a 12-Week, randomized, double-blind, placebo-controlled period (Part A) and a 52-Week extension (Part B). At Week 12, various doses of nemolizumab (0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg) administered SC Q4W were statistically significantly more effective than placebo in reducing pruritus visual analogue scale score, with 0.5 mg/kg and 2.0 mg/kg doses being more effective than 0.1 mg/kg. No additional benefit was observed with the 2.0 mg/kg Q4W or every 8 weeks (Q8W) doses compared to 0.5 mg/kg Q4W.

During the entire study (Parts A and B), AEs that occurred in 5% or more of the nemolizumab-treated subjects (all groups pooled) were nasopharyngitis, AD, increased blood creatine phosphokinase (CPK), upper respiratory tract infection, headache, peripheral edema, and impetigo. The majority of AEs were mild or moderate in intensity. No clinically relevant findings were observed during the study for laboratory tests, vital signs, physical examination, or electrocardiogram (ECG).

Pharmacokinetic assessments after SC injections of various doses showed a dose-proportional increase of nemolizumab serum concentrations after repeated injections. Limited accumulation was observed, with median actual accumulation index below 2, and steady state concentrations were achieved at Week 16 of treatment. The PK profile of nemolizumab is predictable: It is not affected by the number of administrations. This might be partly due to the low occurrence and minimal effect of serum anti-nemolizumab antibodies (ADA), with ADA-positive subjects representing 7.1% of all subjects treated with nemolizumab. In addition, in this study, 1 subject in the 0.1 mg/kg Q4W group with anti-nemolizumab antibodies from baseline developed neutralizing ADA at Week 64. Importantly, serum nemolizumab concentrations in ADA-positive subjects were not different from those in the ADA-negative subjects. Four subjects had treatment-emergent nemolizumab-specific immunoglobulin E (IgE) antibodies. No AEs possibly related to nemolizumab-specific IgE antibodies were observed.

6.2.1.3 Phase 2b Dose-Ranging Study

The phase 2b study was a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study (SPR.114322) to evaluate the efficacy and safety of various doses of nemolizumab in moderate-to-severe AD subjects with severe pruritus (peak pruritus numeric rating scale [PP NRS] ≥7).

A total of 226 adult subjects were randomized (1 subject in the placebo group was randomized but not treated): 57 subjects were randomized to placebo and 169 subjects were randomized to nemolizumab arms (55 subjects to 10 mg, 57 subjects to 30 mg, and 57 subjects to 90 mg). There were 176 subjects (77.9%) who completed the treatment and 44 subjects (19.5%) who discontinued the study. Overall, all demographic and baseline disease characteristics were similar in all treatment groups.

At the Week 24 visit, a greater percent change reduction in in Eczema Area and Severity Index (EASI) was observed with the nemolizumab 30-mg dose (least squares mean difference vs. placebo = 16.7%) and the difference was statistically significant (95% confidence interval [CI] = -30.2, -3.2; $p < 0.05$) compared to placebo. The nemolizumab 10-mg dose showed marginally significant difference versus placebo (least squares mean

difference = 13.6%; 95% CI = -27.3, 0.0; p = 0.05). However, the difference between the nemolizumab 90-mg dose and placebo did not achieve statistical significance.

The secondary endpoint of Investigator's Global Assessment (IGA) success (clear/almost clear and 2-point reduction) was not statistically significant at Week 24 (25.5% in nemolizumab 10 mg, 36.8% in 30 mg, 22.8% in 90 mg, and 21.1% in placebo). However, the difference was statistically different for the 30-mg dose compared to placebo at Week 16 (33.3% vs 12.3%; p = 0.008). The PP NRS responder (PP NRS improvement ≥4) rate was statistically significant ($p < 0.05$) for the nemolizumab 10-mg and 30-mg doses at Week 24, and all nemolizumab doses were statistically significantly superior to placebo at Week 16 ($p < 0.05$). Nemolizumab demonstrated an early onset of action in pruritus as early as Week 1. In addition, the proportion of EASI-75 responders was statistically significantly greater for nemolizumab 30 mg at Week 24 and for both the 30-mg and 90-mg doses at Week 16 compared to placebo ($p < 0.05$). The sleep disturbance NRS was highly statistically significant for all 3 nemolizumab doses at Week 24 ($p < 0.001$) vs placebo.

Among all nemolizumab doses, the 30-mg dose showed statistically significant and greater difference compared to placebo for all AD and pruritus endpoints at Week 16. Probably due to TCS background therapy, there was increasing placebo effect in the study, shrinking the deltas between active arms and placebo as the study progressed from Week 16 to Week 24. The dose-effect was closer to the maximum efficacy model, achieving the maximum efficacy at the 30-mg dose and lower efficacy with the 10-mg and 90-mg doses.

There was 1 non-related AE with a fatal outcome (82-year-old subject treated with the 10-mg dose died due to non–study drug related aspiration pneumonia and cardiopulmonary arrest). Three suspected unexpected serious adverse reactions (SUSARs) were recorded in the study: exacerbation of AD (10-mg dose, withdrawal from study), septic shock (90-mg dose, sepsis, Staphylococcus aureus–positive blood culture, recovered/resolved without sequelae), and phlegmon/cellulitis of the right cheek (30-mg dose, recovered/resolved without sequelae). All doses of nemolizumab were associated with a slightly higher incidence of serious treatment-emergent AEs (TEAEs) (1 [1.8%], 3 [5.5%], 2 [3.5%], and 2 ([3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) but not severe TEAEs (6 [10.7%], 3 [5.5%], 5 [8.8%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) when compared to placebo. There was a comparable percentage of subjects discontinuing treatment due to TEAE in the placebo and active treatment arms. All doses of nemolizumab were associated with a slightly higher incidence of TEAEs when compared to placebo. There was no increase in the incidence of skin infections in the nemolizumab compared to the placebo groups, although there was a higher incidence of non-skin infections with nemolizumab (mainly rhinopharyngitis and upper respiratory tract infections). There was a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) in subjects with pre-existing asthma. Events were mostly mild or moderate (1 severe event with highest dose), manageable, and reversible under treatment with study drug. Further, a higher incidence of AD exacerbation in the placebo arm compared to the nemolizumab treatment arms was observed. Local and systemic injection-related reactions (IRRs) occurred more frequently in the placebo compared to the active treatment groups. Finally,

there was a low incidence of peripheral edema, with no serious cases and no imbalance with the placebo arm.

The safety and efficacy data generated in the phase 2b dose-finding study supported the selection of the 30-mg dose as the treatment dose for the phase 3 studies.

Based on the safety data from the 3 completed studies, no additional risks for nemolizumab have been identified. Potential important risks to be monitored closely include newly diagnosed asthma or worsening of asthma and infections.

6.2.2 Ongoing Clinical Studies

6.2.2.1 Phase 2 Immunization Response Study in Adult and Adolescents

A randomized, double-blind, placebo-controlled study (SPR.118380) to assess immunization responses in adult and adolescent subjects with moderate-to-severe AD treated with nemolizumab is currently ongoing. At the baseline visit, subjects receive a loading dose of nemolizumab (60 mg) or placebo via 2 SC injections. Nemolizumab (30 mg) or placebo is administered via a single SC injection Q4W at Weeks 4, 8, and 12. At the Week 12 visit, subjects also receive single doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap; Adacel® [Sanofi Pasteur, Inc]) and quadrivalent meningococcal conjugate (MCV4; Menactra® [Sanofi Pasteur, Inc]) vaccines. The primary objective is to assess the effect of nemolizumab on humoral immune responses (IgG) to tetanus and meningococcal vaccination and the secondary objectives are to assess the safety and efficacy of nemolizumab (CD14152) after 16 weeks of treatment. Subjects who complete this study may be eligible to enter the planned phase 3 long-term extension study (SPR.118163).

6.2.2.2 Phase 2 PK and Safety Study in Adolescents

A 16-week, open-label, phase 2 study (SPR.116912) evaluated the safety, efficacy, and PK of nemolizumab 30 mg Q4W, administered concomitantly with background TCS, in adolescent subjects (N=20; 12-17 years old) with moderate-to-severe AD who are not adequately controlled with topical treatments.

The safety and PK profile of the 30-mg dose, selected for further development based on the results of the phase 2b study conducted in adult subjects, was investigated in adolescent subjects with moderate-to-severe AD.

A population-pharmacokinetic (PopPK) model developed from data in adult subjects was able to reliably predict individual nemolizumab concentration-time profiles in adolescents, fitting the actual data generated in the study. Based on these results, it was concluded that nemolizumab PK in adolescents is similar to that in adults. No impact of age was observed.

One subject presented with treatment-emergent ADA. No ADA-positive sample was identified after Week 4, and no ADA-positive sample had neutralizing antibodies (NAb), supporting the low immunogenicity potential of nemolizumab.

A safety data review meeting was held with the IDMC in March 2020. The IDMC concluded that there were no safety concerns in the data presented and recommended to open enrollment in the intended nemolizumab studies to adolescents. The Sponsor, after assessment of the interim safety data, concurred with the IDMC recommendation.

6.2.2.3 Phase 3 Efficacy and Safety Study in Adult and Adolescents

There are two phase 3 pivotal studies, with similar design that are currently ongoing: SPR.118161 and SPR.118169.

The two studies are randomized, double-blind, placebo-controlled phase 3 studies to assess the efficacy and safety of nemolizumab in adult and adolescent subjects with moderate-to-severe AD. Subjects are given SC injections of nemolizumab (30 mg) or placebo Q4W over a 16-week treatment period, with a loading dose of 60 mg (two 30-mg injections) on Day 1/Baseline. Clinical responders at Week 16 (i.e., the end of initial treatment/beginning of maintenance) are re-randomized (1:1:1) to different treatment regimens (injections every 4 weeks [Q4W] or every 8 weeks [Q8W] of nemolizumab [CD14152] or placebo Q4W) up to Week 48 (maintenance period). The study is being conducted in Europe, the Americas, and Asia-Pacific. Subjects who complete this study may be eligible to enter the planned phase 3 long-term extension study (SPR.118163).

6.2.2.4 Phase 3 Long Term Efficacy and Safety Study in Adult and Adolescents

RD.06.SPR.118163, a prospective, multicenter, long term study to assess the safety and efficacy of nemolizumab in subjects with moderate-to-severe AD who had been previously enrolled in the phase 2b dose-ranging study (SPR.114322), phase 2 adolescent PK/safety study (SPR.116912), phase 2 vaccination safety (SPR.118380) or phase 3 pivotal (SPR.118169, SPR.118161) studies is ongoing. The study is designed to evaluate long-term safety and efficacy of nemolizumab 30 mg Q4W when administered with background TCS, with or without TCI, over a 2-year treatment period (104 weeks).

For other studies refer to the Investigator Brochure.

6.3 Risks/Benefit Assessment

Topical medications are the mainstay of AD therapy. Treatment options are however, limited for subjects with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications.

Results of previous clinical studies in adults demonstrated that treatment with nemolizumab had a marked effect on AD, pruritus, and pruritus-related sleep loss. Improvements in the symptoms of AD were consistent with the observed improvement in sleep quality (evaluated subjectively) and QoL (evaluated using Dermatology Life Quality Index [DLQI]). Continuous treatment for up to 64 weeks led to improvements in overall AD severity, evaluated with various validated scales commonly used in dermatology clinical trials (i.e., EASI, SCORing Atopic Dermatitis [SCORAD], and IGA).

Nemolizumab was also well tolerated overall when used as monotherapy or concomitantly with a TCS.

Nemolizumab was also administered to 6-17 year-old pediatric subjects with AD.

- A Phase 1 PK, safety, and tolerability study (M525101-03) was sponsored by Maruho in pediatric Japanese subjects. Thirteen subjects aged 6 to 12 years with body weight ranging from 16 to 36 kg were enrolled into the study and received one single-dose administration of nemolizumab (7 subjects in Step 1 [0.5 mg/kg] and 6 subjects in Step 2 [1.0 mg/kg]). All 13 subjects completed the study as planned. The results of this study indicate that systemic exposure to nemolizumab increased proportionally to the administered SC dose in children. In addition, the nemolizumab PK in children was similar to that in adults. There appeared to be a trend towards improved pruritus of AD following a single SC administration of nemolizumab in pediatric subjects with AD. The time-course plots of efficacy variables indicated the absence of a dose-dependent response. In this study, single SC doses up to 1.0 mg/kg nemolizumab were safe and well tolerated in Japanese pediatric subjects with AD.

One Galderma-sponsored Phase 2 study (SPR.116912) is ongoing in adolescents aged 12 to 17 years with moderate-to-severe AD to investigate safety and PK of nemolizumab 30 mg q4W dose (with a loading dose of 60 mg on Day 1). Interim analysis of data from 10 subjects who had received at least 3 doses showed that the nemolizumab PK in adolescents is similar to that in adults. Based on the Sponsor's analysis of the interim PK/immunogenicity and safety data, and in concurrence with the recommendation of the independent data monitoring committee (IDMC), it was decided to allow recruitment of adolescent subjects into the ongoing nemolizumab Phase 3 studies (pivotal studies SPR.118161.SPR118169, SPR.118163) and in the Phase 2 immunization response study (study SPR.118380).

Based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the potential risks of nemolizumab treatment include local or systemic IRRs, newly diagnosed asthma or worsening of asthma, exacerbation of atopic dermatitis, and skin or non-skin infections. The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

a. In the phase 2b (SPR.114322) dose-ranging study, a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10-mg, 30-mg, and 90-mg treatment arms, respectively) in subjects with pre-existing asthma was observed. Events were mostly mild or moderate (1 severe event with highest dose), manageable, and reversible under treatment with study drug. The protocol will exclude subjects with asthma exacerbation requiring hospitalization in the preceding 12 months before screening, subjects whose asthma has not been well-controlled (i.e., daytime asthma symptoms >2 days per week, night-time awakenings with asthma symptoms >2 times per month, asthma exacerbation requiring oral corticosteroid use >2 times per year) during the last 3 months before the screening visit, Childhood Asthma Control Test (cACT) score ≤19, and

subjects with peak expiratory flow (PEF) below 80% of the predicted value. At all visits, all subjects will be asked about respiratory changes and a respiratory examination will be performed. PEF measurements and cACT will be performed only for Cohort 1 and Cohort 1.1 (aged 7 to 11 years) subjects, at screening, baseline, and regular intervals throughout the study. For subjects with a history of asthma, PEF measurements and cACT will be administered at all visits. Subjects diagnosed with de novo asthma will perform PEF and cACT assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects with a medical history of asthma will be referred to the physician managing their asthma if cACT ≤19, PEF <80% of the predicted value, and/or unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. An adjudication committee will review all asthma AEs reported during the course of the study.

b. The exclusion criteria of this clinical study (e.g., restricting entry of subjects with recent/current infections or known/suspected immunosuppression) will prevent non-eligible subjects from receiving nemolizumab. As no data are available in pregnant females, these subjects are not eligible for this study. Subjects who have recently received live attenuated or inactivated vaccines may be considered for enrolment after an appropriate time has elapsed before baseline/Day 1. Vaccinations during the study and follow-up period are not permitted, except for use of non-live seasonal vaccinations (e.g., influenza), Coronavirus Disease 2019 (COVID-19) and/or emergency vaccinations (e.g., rabies or tetanus). In the event of emergency vaccination during the study, the study drug administration should be discontinued until the immune response to vaccination is verified.

c. A slight trend of dose-dependent increase of peripheral edema was reported in the Chugai sponsored nemolizumab phase 2a study (CIM003JG). Most events were mild (11 of 21), no case was serious, and none resulted in premature treatment discontinuation; no case was associated with renal or cardiac AEs. The EASI values and thymus and activation-regulated chemokine levels were relatively higher in subjects with peripheral edema indicating that peripheral edema might be related to more severe AD. There were a few subjects reporting peripheral edema in the Galderma sponsored phase 2b (SPR.114322) study (2 [3.6%], 2 [3.6%], 4 [7%], and 2 [3.5%] in placebo, 10-mg, 30-mg, and 90-mg groups, respectively). Peripheral edema will be followed as an AE of special interest (AESI) in this study.

As nemolizumab has limited evaluation in pediatric populations, safety will be evaluated closely throughout the study. IA-1.1 will assess whether the observed safety and PK data in subjects in Cohort 1.1 (aged 7 to 11 years) are similar to the data obtained in adolescents and adults, which is the basis for allowing recruitment in the 2-6 year old cohort.

d. An IDMC will monitor the safety data regularly throughout the study, including AESIs, which were defined based on the currently available safety information on nemolizumab and the risks associated with biologic agents in general:

- IRRs
  - Anaphylactic reactions
  - Acute allergic reactions requiring treatment
  - Severe injection site reaction with a duration greater than 24 hours
- Newly diagnosed asthma or worsening of asthma
- Infections
  - Any severe infection or any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for >2 weeks
  - Any confirmed or suspected Coronavirus Disease (COVID)-19 infection
- Peripheral edema: limbs, bilateral
- Facial edema
- Elevated ALT or AST (>3 × ULN) in combination with elevated bilirubin (>2 × ULN)

In conclusion, when taking into consideration the currently available data of nemolizumab and the risk-minimization approaches to be implemented, the benefit/risk ratio of nemolizumab is considered to be favorable in this study.

6.4 Drug Profile

Nemolizumab (CD14152) is a humanized monoclonal modified immunoglobulin G 2 antibody comprising a structure of 2 H-chains (445 amino acid residues) and 2 L-chains (214 amino acid residues) connected by 16 disulfide bonds. Nemolizumab will be provided as a lyophilized powder for solution for SC injection in a vial or dual-chamber syringe (DCS) depending on body weight range. Injection will be performed after reconstitution with sterile water for injection. The dose to be used will provide a similar systemic exposure as in age 12 to 17 years subjects and in adults and will be a fixed dose per body weight range. Subjects will receive a dose of nemolizumab Q4W by SC injection and a loading dose at Baseline.

6.5 Dose Selection Rationale

Based on the outcome of the phase 2b dose-ranging study in adults, the 30-mg dose (with 60-mg loading dose), when administered Q4W, provided the best benefit/risk ratio of the 3 doses evaluated and is therefore selected as the final dose to be developed for the treatment of AD in adult and adolescents.

The proposed dose for subjects aged 2 to 11 years was initially selected based on a modeling and simulation approach, with the objective of achieving the same systemic exposure observed in adults and 12-17 year-old adolescents with 30-mg dosing (and 60-mg loading dose).

A popPK model was developed to describe the PK of nemolizumab and to identify any covariates that have significant impact on the nemolizumab PK profile. The popPK model was built based on data from 407 adult subjects included in three clinical trials (CIM001JP, CIM003JG and interim SPR.114322 data), assessing the exposure to SC nemolizumab over the dose range of 0.1 to 3 mg/kg and 10 to 90 mg for weight-based and flat dosing, respectively. The effect of several covariates was explored including age, body weight, serum creatinine, estimated glomerular filtration rate, bilirubin, serum albumin, total protein, immunoglobulin E, sex, and clinical study. The PK of nemolizumab was described with a 1-compartment model with linear elimination and first-order absorption with a lag time. Body weight was identified as the main source of variability in the PK profile of nemolizumab, with a decrease of body weight resulting in an increase of systemic exposure. Conversely age was not identified as a significant covariate in the popPK model.

The robustness of the PopPK model was confirmed by the data from the clinical trial SPR.116912 conducted in adolescents receiving multiple 30 mg flat doses (plus a 60 mg loading dose) of Nemolizumab. The model was able to accurately predict the observed nemolizumab PK profile in adolescents aged 12 to 17 years. In addition, the popPK model was validated versus the actual data collected in Japanese children aged 6 to 12 years receiving a single 0.5 or 1.0 mg/kg dose of nemolizumab (study M525101-03 sponsored by Maruho). The popPK model confirmed that the age does not impact the nemolizumab systemic exposure in adolescents and in children aged 6 to 12 years.

After this validation versus actual pediatric clinical data, the model was used to define the flat doses to be administrated in the 2 to <12 year-old children

Given the wide range in body weight encountered in the 2 to <12 year-old pediatric population, and the impact of body weight in nemolizumab systemic exposure, nemolizumab PK profiles were simulated for virtual subjects stratified by age and body weight (i.e., 500 subjects for each age and weight group). The pediatric body weight distributions in each age group were extracted from the NHANES 2017 database.

The popPK model was used to appropriately scale the dose so that nemolizumab exposure in children matches the exposure in adults and adolescents receiving the 30-mg dose (with 60-mg loading dose).

The PK interim analysis IA-1, performed on the first 18 subjects enrolled in Cohort 1 (7-11 years) that have completed the Week 16 visit, showed that, after receiving the doses planned for Cohort 1, the steady state systemic exposure in 7-11 children was approximately 2-fold higher than in adult and adolescent and 2-fold higher than the one predicted with the popPK model. The popPK model was derived from a population with a body weight above 40 kg (with very few subjects in the 40-50 kg range). Consequently, the popPK model was robust in predicting exposure for subjects with body weight above 40 kg, but should be refined with emerging data from the ongoing study to be predictive for lower body weight subjects. The popPK model parameters will be re-estimated once the complete data set of study SPR.118126 is available. Results of the modeling and simulation approach and observed data from IA-1 are summarized in Table 3 below:

Table 3. Nemolizumab trough concentrations predicted at Week 16 using PopPK model

Age Cohort	Body Weight cutoff	Dose (Q4W)	Week 16 C_{trough} [a] (ng/mL)	
			popPK predicted	Observed (IA-1), N=9
2-6 years	≥10 kg and <20 kg	20 mg LD + 10 mg	1420 [518 - 3390]	Not applicable
2-6 years	≥20 kg	40 mg LD + 20 mg	2170 [743 - 4840]	Not applicable
7-11 years	≥20 kg and <30 kg	40 mg LD + 20 mg	2080 [810 - 5220]	4025 [2719-5914]
7-11 years	≥30 kg	60 mg LD + 30 mg	2350 [799 - 5550]	5460 [922-8516]

a) Median [5th 95th percentile]
Median [min-max] C_{trough} at week 16 for adults (N=53, study SPR.114322): 1870 [273 - 4790] ng/mL
Median [min-max] C_{trough} at week 16 for 12-17 year-old adolescents (N=18, study SPR.116912): 2730 [1490 - 4890] ng/mL

The current study intends to select doses, for subjects aged 2 to 11 years that will provide a systemic exposure similar to the one observed in adults and 12-17 year-old adolescents. Therefore, doses 2-fold lower than initially planned in Cohort 1, will be tested in Cohort 1.1 and Cohort 2 as shown below.

- Children of all ages with a body weight ranging from 10 kg to below 20 kg, will receive a dose of 5 mg (with a 10 mg loading dose)

- Children of all ages with a body weight ranging from 20 kg to below 30 kg, will receive a dose of 10 mg (with a 20 mg loading dose)
- Children of all ages in the upper range of body weight (body weight from 30 kg and above) will receive a dose of 15 mg (with a 30 mg loading dose)

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.

The independent data monitoring committee (IDMC) concluded that there were no safety concerns in the data presented and recommended to continue the existing Cohort 1 as intended in 7-11 year old subjects and agreed to an additional Cohort (1.1) in 7-11 year old subjects with decreased doses to re-evaluate the PK.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Primary Objective

To assess the pharmacokinetics (PK), safety, and tolerability of nemolizumab administered concomitantly with topical corticosteroids (TCS) in pediatric subjects with moderate-to-severe AD not adequately controlled with topical treatments.

7.1.2 Secondary Objective

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

7.2 Study Endpoints

7.2.1 Primary Endpoints

The primary endpoints are as follows:

7.2.1.1 Pharmacokinetics:

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

7.2.1.2 Safety

- 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

7.2.2 Secondary Endpoints

7.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Absolute and percent change in 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 from baseline 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 Body Surface Area (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 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 Week 52
- Absolute and percent change in weekly average of sleep disturbance NRS score from baseline at each visit up to Week 16 and up to Week 52
- Proportion 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 Infants' Dermatitis Quality of Life Index (IDQOL) 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

7.2.2.2 PK/PD Analysis:

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

7.2.2.3 Immunogenicity:

- Anti-drug antibody (ADA) assessments (screening, confirmatory, NAb), at baseline, Weeks 16, 52, and unscheduled visits that are conducted for safety reasons if deemed necessary by the investigator

7.2.2.4 Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence of AEs, including TEAEs, AESI, AEs leading to discontinuation and SAEs through the study

8 INVESTIGATIONAL PLAN

8.1 Description of 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 AD, who are inadequately controlled by topical therapies. Approximately 45 study centers are planned in North America and the EU.

This protocol is part of a Pediatric Study Plan for IND 117122.

Eligible subjects must have a documented history of inadequate response to topical AD medications.

The study will enroll approximately 105 subjects in 3 cohorts of 35 subjects each:

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 include 2 parts; Part A will have a 16-Week treatment period and Part B will have a 36-week extension of treatment. The investigator should make every effort to enroll subjects who can stay within the age group cohort throughout the study.

There are three Interim Analyses (IAs) planned for this study, IA-1 for Cohort 1, IA-1.1 for Cohort 1.1 and IA-2 for Cohort 2. IA-1 will be performed after the first 18 subjects in Cohort 1 have completed the Week 16 visit. For subsequent Cohorts (1.1 and 2) the IA will be performed when approximately 18 subjects have completed the Week 16 visit. The recruitment will start with Cohort 1 (aged 7 to 11 years). 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.

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. During the interim analyses, enrollment will continue in each cohort. Note: as mentioned above, enrollment in Cohort 1.1 and Cohort 2 will only start after completion of the IA-1 and IA-1.1, respectively, and with the Sponsor's written approval. Once enrollment starts in Cohort 1.1 and in Cohort 2, enrollment in these Cohorts will continue during IA-1.1 and IA-2, respectively.

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 subjects will receive a flat dose of nemolizumab every 4 weeks (Q4W) with a loading dose at baseline on the basis of body weight. The planned nemolizumab doses (see Table 4a and Table 4b below) will be confirmed by the IA-1, IA-1.1, and IA-2.

Table 4a. Selected Pediatric Dose for Cohort 1

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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 4b. Selected Pediatric Dose for Cohort 1.1 and Cohort 2

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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

Subjects meeting the eligibility criteria will initiate (or continue) use of a moisturizer beginning at screening. Subjects will also be provided or prescribed background topical therapy for AD (including a medium-potency TCS for the body, and low-potency TCS or TCI for sensitive areas such as the face, neck, intertriginous areas, etc.), for use throughout the study. Use of authorized background therapy is required for at least 14 days before baseline/Day 1. Subjects who continue to meet the eligibility criteria at the baseline visit will be enrolled in the study. Subjects may be rescreened once.

Figure 2 provides an overview of the study visit schema. Subjects will be screened and complete a run-in period of at least 14 days before the baseline visit. At baseline, eligible subjects will enter a 16-week initial treatment period with nemolizumab administered SC Q4W, with a loading dose at baseline/Day 1 for each cohort. The administered dose will be selected based on subject body weight as defined in Table 4a and Table 4b.

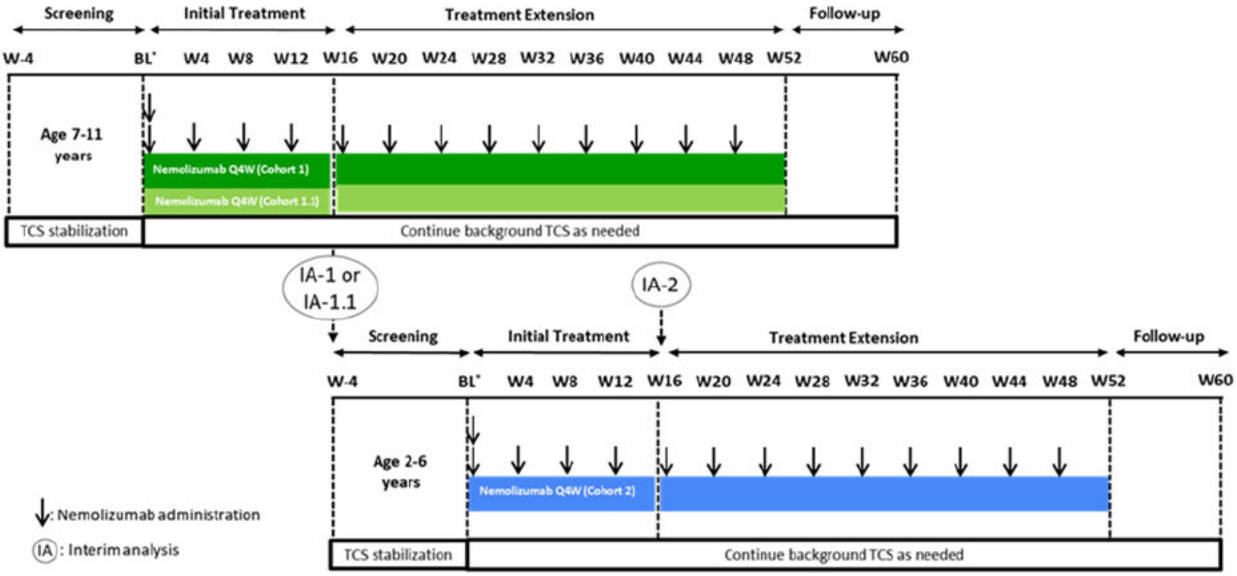
Subjects will continue to receive treatment for an additional 36 weeks in the treatment extension period. Following the treatment extension period, subjects will enter an 8-week follow-up period. Subjects who prematurely discontinue the study before the Week 48 visit will be followed for 12 weeks after their last dose of study drug.

The Schedule of Assessments is summarized in Table 5. Assessments of PK, safety, and efficacy will be conducted throughout the study. Subject-reported assessments of pruritus, sleep disturbance and the use of topical AD medication for their eczema will be collected daily.

The IDMC will review and monitor subject safety. The IDMC will provide recommendations on the safety of subjects. 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.

8.1.1 Study Visit Schema

Figure 2. Study Visit Schema



* See Tables 4a and 4b 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

8.1.2 Schedule of Assessments

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 5).


CCI


CCI


CCI

8.2 Discussion of Study Design

8.2.1 Study Design

This study will evaluate the PK, safety, and efficacy (change from baseline) of nemolizumab in pediatric subjects (aged 2 to 11 years) with moderate-to-severe AD, who are inadequately controlled by topical therapies.

The study is proposed to have an open label design because the study is being conducted primarily to assess safety and PK in children aged 2 to <12 years. This is in accordance with the agreed PSP, where the proposed pediatric study design was driven by the concept of extrapolation of efficacy from adequate and well-controlled studies in adults/adolescents to children.

Efficacy will be assessed as change from baseline to verify the response and treatment benefit. Efficacy data will also be used to verify the adequacy of exposure–response relationship (PK/PD models) between nemolizumab systemic exposure and clinical efficacy endpoints

The study population is consistent with the anticipated clinical use and proposed labeling for nemolizumab. The study population is selected based on the current unmet need in the management of AD in pediatric populations, the mode of action of nemolizumab (CD14152), and the need to understand the safety and long-term exposure of nemolizumab (CD14152) in the pediatric population.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately 105 subjects are planned to be enrolled in this study across 3 age cohorts. Each cohort will enroll approximately 35 subjects.

8.3.2 Inclusion Criteria

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

2. Chronic AD that has been documented for at least 6 months for subjects aged 2-6 years and at least 1 year for subjects aged 7 to 11 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria (Appendix 1) at the time of the screening visit.
3. EASI score ≥16 at both screening and baseline visits.
4. 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 BSA at both screening and baseline visits.
6. Peak (maximum) Pruritus NRS score of at least 4.0 at both screening and baseline visits:

CCI

8. Agree to apply a moisturizer throughout the study from the screening visit daily, and liberally as needed; agree to apply an authorized TCS, with or without TCI, from the screening visit and throughout the study as determined appropriate by the investigator.

CCI

10. Subject and caregiver willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.
11. CCI [redacted]

8.3.3 Exclusion Criteria

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

1. Body weight <10 kg.
2. Child in Care: a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government, or a government body, acting in accordance with powers conferred on them by law or regulation.

CCI [redacted]

4. Subjects with a current medical history of chronic bronchitis.
5. CCI [redacted]

CCI [redacted]

6. Requiring rescue therapy for AD during the run-in period or expected to require rescue therapy within 2 weeks following the baseline visit.
7. Positive serology results for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), hepatitis C (HCV) antibody with positive confirmatory test for HCV (e.g., polymerase chain reaction [PCR]), or human immunodeficiency virus (HIV) antibody at the screening visit.

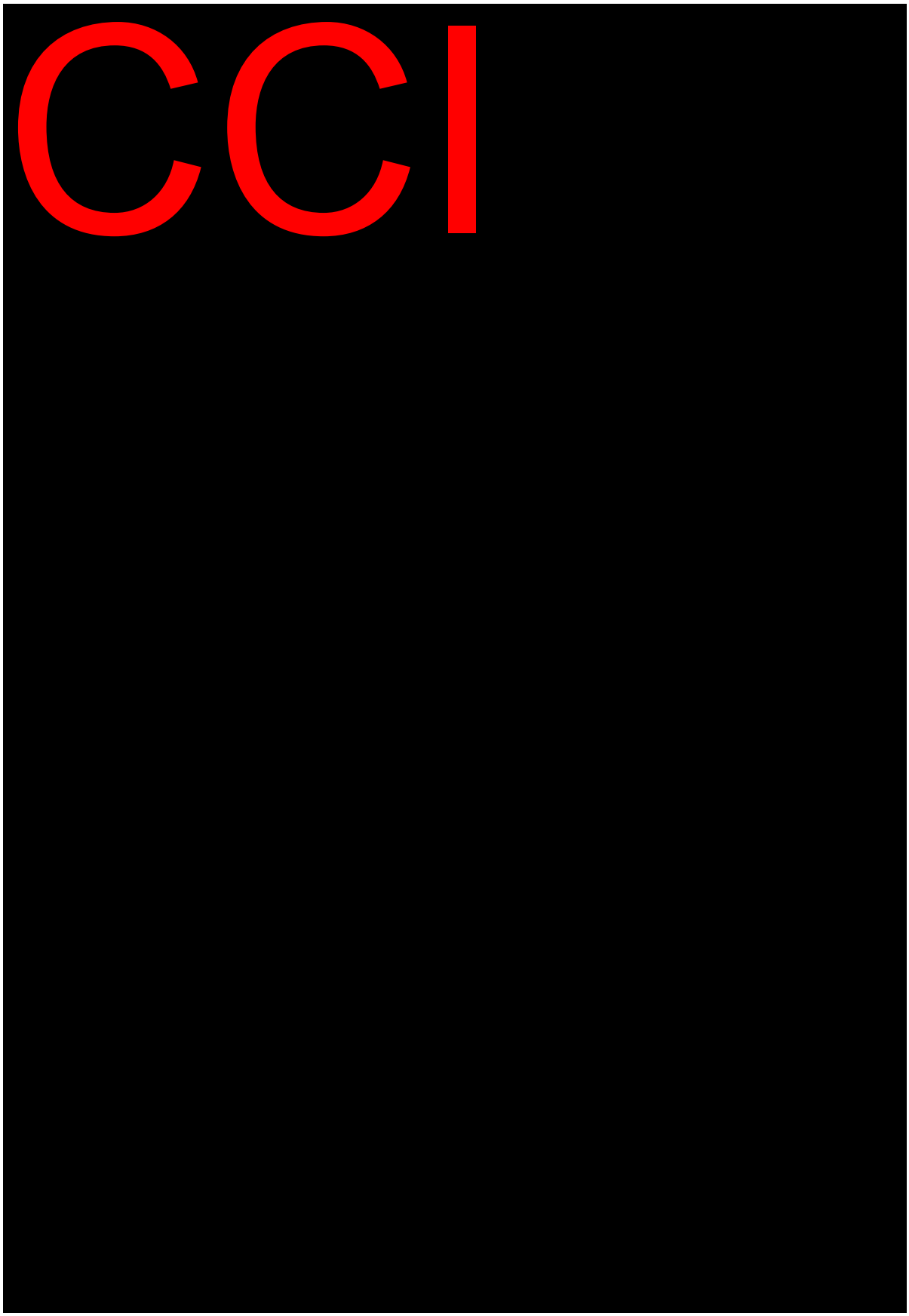
CCI [redacted]

9. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years or since birth for subjects <5 years of age.

CCI [redacted]

12. Known or suspected immunosuppression.

CCI [redacted]



CCI [redacted]

CCI [redacted]

[redacted]

19. Subjects unwilling to refrain from using prohibited medications during the clinical trial.

CCI [redacted]

8.3.4 Removal of Subjects from Therapy or Assessments

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Investigators or the Sponsor can also withdraw subjects from the clinical study if deemed to be necessary.

Reasons for discontinuing study drug include:

- Subject/caregiver request (i.e., consent withdrawal)
- Non-compliance with the study drug or study schedule
- Lost to follow-up

- Occurrence of AEs, including laboratory abnormalities, not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue, including but not limited to the following:
  - Serious immediate-type allergic manifestations including anaphylactic reaction
  - Serious worsening of asthma considered related to study drug administration
  - Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma [Bowen's disease] or basal cell carcinoma)
  - Opportunistic infections such as but not limited to active TB and other infections whose nature or course suggest an immune-compromised or immune-suppressed status
  - Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for >2 weeks considered related to study drug administration
  - Confirmed or suspected COVID-19 infection (temporary discontinuation may be acceptable; for instructions on resuming study drug administration, see Section 8.3.4.2).
- Pregnancy
- Use of non-permitted concurrent therapy (unless discussed and agreed upon with the investigator and medical monitor)
- Use of systemic rescue therapy, as specified in Table 9 of Section 8.4.7.2 and Section 8.4.7.1.3
- Treatment failure
- Investigator request
- Sponsor request, including any of the above criteria

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

Subjects who prematurely discontinue study drug will be encouraged to complete the scheduled study visits.

When a subject discontinues study drug, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 8.5.1 (Early Termination Visit).

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

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making

further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.3.4.1 Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not receive any further injection(s) of the study drug.**

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 9.2.1.5) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 9.2.1.5).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (pediatrician) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide tri-monthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 9.2.1.3).

The investigator should also be notified of pregnancy occurring during the study (and within 12 weeks [± 5 days] after the last dose of study drug) but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 9.2.1.5.

8.3.4.2 COVID-19 Infection

Study drug administration will be discontinued in a subject in whom a COVID-19 infection is confirmed or suspected. COVID-19 must be specified as the reason for study drug discontinuation.

Study drug administration may resume in subjects with confirmed or suspected COVID-19 infection based on investigator judgment after discussion with the medical monitor or Sponsor and only if the following minimum conditions are met:

- For symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- For asymptomatic subjects: At least 21 days have passed since the positive PCR test and no symptoms.

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

See Appendix 2 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

8.4 Investigational Products

"Study drug" or "study medication" refers to nemolizumab (CD14152). The list of excipients is detailed in the IB.

8.4.1 Investigational Products Administered

Subjects will receive a flat dose of nemolizumab Q4W for 52 weeks, with a loading dose at Baseline (2x dose). The flat dose will be defined for a range of body weight (see Table 7a and Table 7b).

For subjects with body weight <30 kg at baseline, nemolizumab will be provided as a lyophilized powder in a single dose vial. Injection will be performed after reconstitution with sterile water for injection.

For subjects with body weight ≥30 kg, nemolizumab will be provided as a lyophilized powder and water for injection for solution for injection for SC use after reconstitution in a single dose, pre-filled dual chamber syringe or in a single dose vial.

8.4.1.1 Study Drug Dosing – Initial Treatment Period/ Treatment Extension Period

Eligible subjects will enter a 16-week initial treatment period with nemolizumab administered SC Q4W, with a loading dose at baseline/Day 1 for each cohort, the administered dose will be selected based on subject body weight as defined in Table 7a and Table 7b.

Table 7a. Selected Pediatric Dose for Cohort 1

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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 7b. Selected Pediatric Dose for Cohort 1.1 and Cohort 2

Body Weight[a]	Q4W - dose			Baseline - loading dose		
	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

Subjects will continue to receive treatment for an additional 36 weeks in the treatment extension period.

8.4.1.2 Investigational Product Preparation and Injection

Dosage utilizes open-label study drug.

The study center staff will prepare and perform all injections according to instructions provided in the current version of the pharmacy manual and the instructions for use. Good hygiene practices and clean techniques must apply at all times.

The study drug does not contain preservatives. From a microbiological point of view, the preparation of the study drug has to be done as close to subject administration as possible, and the study drug should be used immediately after reconstitution. If not used immediately, the study drug has to be used within 1 hour maximum after reconstitution stored at room temperature (below 30°C).

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

After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. Subjects should remain at the study center for at least 30 minutes after the first 2 injections during the study (i.e., at Baseline and Week 4 study visits).

8.4.2 Identity of Investigational Products

Table 8 provides a description and overview of study medication usage.

Table 8. Description and Usage of Investigational Product

Investigational Product	***Treatment BW<30 kg***	***Treatment Treatment BW≥30 kg***
Name (internal code)	Nemolizumab (CD14152)	Nemolizumab (CD14152)
Pharmaceutical form	Lyophilized powder in a single dose vial	Lyophilized powder in a single dose vial And for the loading dose: Lyophilized powder and water for injection for solution for injection in a single dose pre-filled dual chamber syringe
Dosage	5, 10 mg (with a loading dose of 10 or 20 mg at baseline) based on range of body weight	15 mg (with a loading dose of 30 mg at baseline)
Dose regimen	Q4W	Q4W
Route*	Subcutaneous use by clinic staff after reconstitution with water for injection	Subcutaneous use by clinic staff after reconstitution with water for injection

Abbreviation(s): Q4W=every 4 weeks; SC = subcutaneous
Note(s):
*All injections are performed at the study center clinic office.

8.4.3 Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products in the local language, national regulations/guidelines, and the relevant regulatory requirements, specifying that the drug is for use in a clinical study.

Each vial will be packaged in an individual carton.

Each DCS will be packaged in an individual carton, including a 27G 1/2” needle and a plunger rod (not assembled).

8.4.4 Study Drug Management

8.4.4.1 Storage of Study Drug

All units must be stored together in a safe and secure area with restricted access. Upon receipt, the units must be removed from the shipping cooler, kept in the outer carton until use, and stored in a refrigerator between 2°C to 8°C (36°F to 46°F), protected from light and protected from freezing.

The refrigerator must be monitored daily, and if a temperature excursion occurs, the designated personnel should promptly inform the study monitor, as specified in the current version of the pharmacy manual.

8.4.4.2 Study Drug Accountability

Study drug will be provided to the investigational site and site personnel will acknowledge receipt of the study drug using interactive response technology to confirm the shipment condition and content. If a damaged shipment is received and/or a temperature excursion has been experienced, he/she will notify the Sponsor/contract research organization (CRO) and follow the guidelines according to the current version of the pharmacy manual.

The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered and received units, and the return/destruction of unused study drug as specified in the current version of the pharmacy manual. No unauthorized use is permitted. Used units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected or an event occurs before, during, or just after the injection, the used units can be disposed of in an appropriate sharps container and according to waste regulation(s) in the country. A unit involved in a malfunction, or an investigator or subject complaint must be retained on site and designated personnel must proceed as defined in the current version of the pharmacy manual. Refer to Section 8.4.7.3 for product technical complaints.

The study monitor may check the study supplies at each study center at any time during the study. It is the responsibility of the study monitor to ensure that the investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned/destroyed on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of any unused study drug not destroyed by the site. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

8.4.4.3 Dispensing and Return of Study Drug

All drug preparation must be appropriately performed and documented by the designated personnel. Any error in the preparation of dosing solution must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/return process for all unused study drug will be conducted according to the sites' SOPs, local regulations, and best practices, as described in the current version of the

pharmacy manual. The unused study drug will be returned to the CRO/drug depot for destruction.

8.4.4.4 Treatment Compliance

Treatment compliance will be assessed through the treatment records and drug dispensation logs.

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, dose, injector (caregiver, or site staff), and site of injection should be accurately recorded to confirm that each dose of study treatment was properly administered.

8.4.5 Selection of Doses in the Study

The doses (Q4W) proposed for this study are supported by the results of the nemolizumab phase 2b study (SPR.114322) and other supportive data. Refer also to Section 6.5 for further details.

8.4.6 Dosage Modification

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 1a and Table 1b. 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 1a and Table 1b. After the body weight assessment at week 32, the dose will remain unchanged until the end of the study.

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

In the event of a missed dose (i.e., temporary discontinuation of the study drug), it will be documented in the CRF that the drug has not been administered at the study visit, together with the reason (e.g., for safety). Subjects will be asked to return to the study centers for all remaining visits and complete all study assessments and procedures as described in Section 8.1.2.

Dosing frequency is scheduled for Q4W, 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.

8.4.7 Prior and Concomitant Therapy

Prior therapies are defined as therapies that have been stopped or vaccinations received within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, all prior therapies for AD should be documented.

Concomitant therapies/medications are defined as follows:

- Any existing therapies ongoing at the time of the screening visit,
- Any changes to existing therapies (such as changes in dose, formulation or application frequency) during the course of the study, or
- Any new therapies received by the subject since the screening visit.

The following 2 categories are to be considered for prior and concomitant therapies:

- Drugs/therapies include but are not limited to prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures (e.g., phototherapy, etc.). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

Prior and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate CRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

At each visit, investigators should also confirm concomitant therapies for contraception. When applicable, contraceptive counselling should occur at screening (or at applicable visits when prepubertal subjects begin menses).

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE form should be completed to account for the new therapy or change in therapy, except in some cases such as dose modification for a chronic condition (see Section 8.4.6), in which case the medication will be linked to an item in the subject's medical history.

8.4.7.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 8.4.7.2), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, topical anaesthetics, and antihistamines without a sedative effect.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10) during chronic inflammation. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab (CD14152) on such enzymes has not been studied. Therefore, investigators should consider observing for clinical or laboratory signs that might indicate a potential effect of nemolizumab (CD14152) in subjects using concomitant therapies that are CYP450 substrates, particularly those with a narrow therapeutic index. Typical examples of substrates with a narrow therapeutic range include warfarin, drugs that may cause torsade de pointes, almost all cytotoxic antineoplastic drugs,

and aminoglycoside antibiotics. A list of representative CYP450 substrates with narrow therapeutic index can be found in Appendix 3.

8.4.7.1.1 Moisturizer

Subject/Caregivers will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at screening, and throughout the study. The subject's current moisturizer or a moisturizer recommended by the investigator may be used. Use should not occur within 8 hours before each clinic/office visit. Whenever possible, subjects should use the same moisturizer throughout the study. Moisturizer use and any adjustments should be documented in the CRF.

8.4.7.1.2 Background Topical Therapy

Subjects/caregivers will apply the authorized background topical therapy to all AD lesions beginning within the screening period and ≥14 days before Day 1 (i.e., run-in).

Medium-potency TCS Therapy for Non-Sensitive Areas: Subjects/caregivers will apply a medium-potency TCS in areas of the body where use of medium-potency TCS is considered safe (e.g., trunk and extremities) beginning within the screening period and ≥14 days before Day 1 (i.e., run-in). TCS medications will be commercially available products.

Low-potency TCS or TCI Therapy for Sensitive Areas: A low-potency TCS or a TCI will be used in sensitive areas considered unsafe for medium-potency TCS (e.g., face, neck, intertriginous areas) or in cases where medium-potency TCS is not tolerated, beginning within the screening period and ≥14 days before Day 1 (i.e., run-in). The investigator may select either low-potency TCS or TCI for each subject, per investigator discretion. The subject/caregiver may only apply **1** medication to each affected area; concomitant use of low-potency TCS and TCI on the same lesion is not permitted. Refer to the current pharmacy materials for authorized TCS and topical calcineurin inhibitors and permitted daily frequency of use. "As needed" (PRN) use of topical therapy is not permitted. Only topical therapies specifically provided or prescribed for use in this study are permitted.

The prescribed use of background therapies and any adjustments should be documented in the CRF. Subjects/caregivers will apply a thin layer of authorized topical therapy on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare, but which does not exceed the daily frequency recommended in the product labelling. "As needed" (PRN) use of TCS or TCI is not permitted. Only topical therapies specifically dispensed or prescribed for use in this study are permitted.

The investigator should adjust background therapy use during the study, according to the disease activity and tolerability of the subject, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur.

In transitioning to the treatment extension period, subjects should generally continue the same pharmacy therapy used in the initial treatment period leading up to the Week 16 visit, including tapering or complete cessation (no use), if applicable. Throughout the treatment extension period, adjustments to background topical therapy, as determined by the investigator, are permitted based on the subject's clinical response.

8.4.7.1.3 Rescue Therapy

If deemed to be medically necessary by the investigator (e.g., to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects at any time during the study, except during the run-in period. Subjects receiving rescue therapies during the run-in period are not eligible to participate in the study.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks after baseline to allow a minimum time for study drug exposure in the presence of background therapy.

Rescue treatments are only treatments that directly treat AD (mainly those that are approved or are standard of care) 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
- Phototherapy

Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams are **not** considered to be rescue therapy because they do not directly treat AD.

Whenever possible, investigators should first use topical medication as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy for AD, the study drug administration must be permanently discontinued.

For the purpose of efficacy analysis, 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. Further, the use of any rescue therapies should be documented in the CRF.

8.4.7.2 Prohibited Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study unless otherwise specified in Table 9. "As needed" (PRN) use of TCS or TCI is not permitted.

Table 9. Prohibited Medication/Therapy

Treatment(s)	*Timeframe*	
	Before Baseline/Day 1	**Day 1 – Week 60**
Coal tar products	2 weeks	Prohibited
Topical PDE-4 inhibitor	2 weeks	Prohibited
Non-authorized TCS	2 weeks	Prohibited
Topical medications with occlusive dressings (e.g., wet wraps)	2 weeks	Prohibited
Systemic corticosteroids (corticosteroid inhalers and intraocular corticosteroids are permitted)	4 weeks	Prohibited*
Phototherapy or tanning beds	4 weeks	Prohibited*
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors)	4 weeks or 5 half-lives (whichever is longer)	Prohibited*
Biologics and their biosimilars (e.g., etanercept, adalimumab, infliximab, omalizumab, etc.)	8 weeks or 5 half-lives (whichever is longer)	Prohibited*
Dupilumab	10 weeks	Prohibited*
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (e.g., amitriptyline), SSRIs (e.g., paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening (Stable treatment with antihistamines with sedative effect is allowed.)	1 week	Prohibited
Alternative medicine for AD (e.g., traditional Chinese medicine)	2 weeks	Prohibited
Vaccines (live (attenuated) or non-live)	4 weeks	Prohibited**

Abbreviation(s): AD=atopic dermatitis; PDE-4=phosphodiesterase-4; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

* Unless used as rescue therapy during the study.

** Except for use of non-live seasonal vaccinations (e.g., influenza), Coronavirus Disease 2019 (COVID-19) or emergency vaccinations (e.g., rabies or tetanus). These vaccines are allowed during the study.

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the medical monitor and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical study (e.g., inadvertent short-term use), the investigator should also notify the medical monitor and discuss whether or not it is acceptable for the subject to continue receiving the study drug.

Specifically, the use of systemic corticosteroids during the study is prohibited except when used as rescue therapy for AD (in accordance with the instructions in Section 8.4.7.1.3). If the use of systemic corticosteroids becomes necessary for the safety of the subject to treat conditions other than AD, the study drug should be temporarily discontinued for the duration of treatment with systemic corticosteroids plus 5 half-lives.

Immunization with non-live COVID-19 vaccine is permitted during the study if in accordance with local regulations. Wherever possible, it is recommended to avoid administration of COVID-19 vaccinations within 1 week of study drug dosing. A different anatomical location should be used for study drug administration and vaccine administration.

8.4.7.3 Product Technical Complaints

All units must be inspected prior to preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to a product technical complaint. In case of doubt, the unit should not be used, and the deficiency must be reported as defined in the pharmacy manual.

All PTCs should be reported to the Sponsor/designee by filing the relevant forms available in the Investigator Site File and the pharmacy manual and as required by local regulations. A PTC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, durability, effectiveness, or performance of a drug or delivery system. Examples may include but are not limited to appearance issues, discoloration, odor, broken/cracked vials or syringe, missing parts, damaged stoppers, and foreign matter in lyophilized powder or diluent. These complaints may or may not represent a potential risk to the subject. For these types of events, a form must be completed as per the specific instruction by the site personnel, pictures of the defective units must be attached, and forwarded to the Sponsor/designee at the latest on the next working day. Reporting to health authorities will be in accordance with local regulations. The defective units must be kept in case of investigation need as defined in the pharmacy manual and may be requested to be sent to the Sponsor/designee in accordance with regulations.

Refer to the current version of the pharmacy manual for further details.

8.5 Duration of Subject Participation

The expected duration of each subject's participation in the study is up to 64 weeks, including a 4-week screening period, a 16-week initial treatment period, a 36-week treatment extension period, and an 8-week follow-up period (12-weeks after the last study medication injection).

8.5.1 Early Termination Visit

Subjects may discontinue from the study or discontinue the study treatment only and continue to participate in the study.

Subjects who prematurely discontinue from the study should attend an ET visit to undergo final study assessments. A follow-up/final visit is required 12 weeks after the last study drug administration.

Subjects who prematurely discontinue the study drug will be asked to continue participation in the study and return for all remaining visits and assessments (including daily assessment of pruritus, sleep disturbance, etc.). Participation will continue until the subject completes the final study visit or otherwise discontinues study participation.

8.5.2 Unscheduled Visit

The subject's caregiver should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results, for follow-up of AEs, or to conduct efficacy assessments for subjects requiring rescue medication between regularly scheduled study visits. Visits occurring outside of the visit window are not considered unscheduled visits.

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit: Any of the procedures/assessments listed in Section 8.1.2 may be conducted, but not all are required. Blood sample collection for PK and ADA analyses are only required during unscheduled visits that are conducted for safety reasons if deemed necessary by the investigator.

9 STUDY ASSESSMENTS

A written, signed ICF, assent form, and Health Insurance Portability and Accountability Act (HIPAA) authorization is required before any study-related procedures are performed.

Upon provision of the signed ICF/assent form, each subject will be assigned a unique subject identification number. For the duration of the entire clinical study, the subject will be identified using the subject identification number in all documentations and discussion.

The planned study assessments are in Section 8.1.2. At each visit, assessments/procedures should be performed in the following order:

1. Patient-reported efficacy and safety measurements
2. Investigator assessments (including efficacy and safety)
    - ECG should be done before vital signs measurements (and blood draws). See Section 9.2.10
3. Sample collections for laboratory assessments
4. Sample collections for correlative assessments (PK, ADA)
5. Administration of study drug injections

9.1 Efficacy Assessments

Efficacy measurements should be conducted by the investigators (or trained designees) and subjects' caregiver (for subject-reported efficacy measurements) according to Section 8.1.2. Whenever possible, the same evaluator should make the assessment throughout the study. Refer to Section 7.2.2.1 for efficacy endpoints.

9.1.1 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 2-point improvement from baseline (see Appendix 4) (Paller 2016).

9.1.2 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 (see Appendix 5) (Hanifin 2001). 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.

9.1.3 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 (see Appendix 6) Two measures of the pruritus NRS will be assessed (average and peak/maximum itch intensity). The PP NRS has been validated in other AD clinical trials in adults, and the minimum clinically important difference was shown to be 4 (Simpson 2016). The average pruritus (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 will be determined by a single assessment using the PP NRS (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. The baseline PP NRS will be determined based on the average of daily PP NRS (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).

9.1.4 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 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).

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?" (see Appendix 7).

9.1.5 Body Surface Area

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.

9.1.6 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, as described in Section 9.1.5), intensity (signs), and subject-reported symptoms of pruritus and sleep loss (see Appendix 8) (European Task Force on Atopic Dermatitis 1993). 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.

9.2 Safety Assessments

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit.

9.2.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments.

Note(s):

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms, or abnormal laboratory values.
- Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 9.2.1.5.

- Each worsening of a chronic disease from the screening visit should be reported as a new AE.

The investigator or designee will report all AEs that occur from the time the ICF is signed until the end of the study. The Sponsor/CRO should be informed if the investigator becomes aware of any safety information that appears to be drug related, even after the subject has completed the clinical study.

At each post-enrollment visit, the investigator (or sub-investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs (for example, "Have you noticed any change in your health since the last visit?"). Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug(s) or not, will be recorded immediately in the source document and described on the Adverse Event Form ("AE Form") along with the date of onset, severity, relationship to the study drug(s), and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

Adverse events assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug (i.e., nemolizumab or placebo) and/or study procedure (e.g., injection, topical background therapy, blood sample

collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E2A, Section IIIA 1).

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

Reasonable Possibility:

According to the reporting investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered:

- Between the study drug (nemolizumab) and the AE, and/or
- Between the clinical study protocol procedure (e.g., injection, 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.

Action Taken

The investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None
- Drug withdrawn
- Study drug temporarily interrupted
- Concomitant medication (any additions or discontinuations)
- Other, specify

Follow-up of Adverse Events

All investigators should follow-up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Subjects should be followed up for 12 weeks (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2.1.1 Adverse Events of Special Interest

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. See Section 9.2.1.4 for reporting procedure. An AESI can be either serious or non-serious.

Based on the potential risks of nemolizumab (CD14152) and the risks associated with biologics (and their biosimilar equivalents) in general (i.e., class effects), the following AEs will be considered AESIs:

- Injection-related reactions (IRRs)
    - Anaphylactic reactions
    - Acute allergic reactions requiring treatment
    - Severe injection site reaction with a duration greater than 24 hours
    - Newly diagnosed asthma or worsening of asthma
    - More specifically, subjects with a medical history of asthma will be referred to the physician who manages their asthma when:

        - cACT score ≤19: An cACT score ≤19 conveys asthma that may not be adequately controlled. An AESI is reported based on the investigator's clinical judgment, including consideration of the managing physician's report. cACT will only be performed on Cohort 1 and Cohort 1.1 (7-11 year-old).
        - PEF <80% of the predicted value: An AESI should be reported.
        - Unexpected worsening of asthma is observed or reported. An AESI is reported based on the investigator's clinical judgment.
    - Subjects without a medical history of asthma will be referred to an appropriate respiratory physician/specialist when:
        - Signs and/or symptoms suggestive of asthma have been observed or reported. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
        - Respiratory assessments (e.g., examination, PEF) suggest a decline in the subject's respiratory health. An AESI is reported based on the investigator's clinical judgment of the specialist's report.

- Infections
    - Any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for >2 weeks
    - Any confirmed or suspected COVID-19 infection
- Peripheral edema: limbs, bilateral
- Facial edema
- Elevated ALT or AST (>3 × ULN) in combination with elevated bilirubin (>2 × ULN)

9.2.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and SAEs if they cause prolongation of the current hospitalization. Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for

the purpose of diagnostic tests [even if related to an AE], elective hospitalization for an intervention that was already planned before subject enrolment in the clinical study, admission to a day care facility, social admission [e.g., if the subject has no place to sleep], or administrative admission [e.g., for a yearly examination]. The details of such hospitalizations must be recorded on the medical history or physical examination CRF.)

- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Results in a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent 1 of the outcomes listed above in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

9.2.1.3 Procedure for Reporting a Serious Adverse Event

For any SAE occurring during the clinical study, regardless of whether or not related to the study drug and/or procedure, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.
2. Ensure that the event is evaluated as an SAE. Immediately notify (within 24 hours of receipt of the event) the PPD Safety and Pharmacovigilance group of an SAE report, by phone or fax:

   Safety Fax Number: +44 122 337 4102

   Safety Hotline Number: +44 1223 374 240

   Note: Immediate SAE reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in CRF, at that time.
3. Send any relevant information or anonymized medical records (e.g., laboratory test results) to the PPD Safety and Pharmacovigilance group (see contact details above), within 24 hours of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, complete an updated SAE report **within 24 hours** of receipt of the updated information.
5. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
6. When the outcome of the event is known, complete an updated SAE report, if appropriate.
7. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor or its delegate (i.e., the CRO) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and are forwarded to investigators as necessary.

   An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or its delegate (i.e., the CRO) will file it accordingly (i.e., within the Trial Master File [TMF]), and will notify the IRB/IEC, if appropriate according to local requirements.
8. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

9.2.1.4 Procedure for Reporting an Adverse Event of Special Interest

For any AESI occurring during the clinical study, regardless of whether or not related to the treatment, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Ensure that the event is evaluated as an AESI. Notify (**within 3 days of receipt of the event)** the PPD Safety and Pharmacovigilance group of an AESI report, by phone or fax. Refer to Section 9.2.1.3.

   Note: AESI reporting is required by the investigator if it occurs during the clinical study following the first dose of study drug or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in CRF, at that time.

3. Send any relevant information or medical records (e.g., laboratory test results) to the PPD Safety and Pharmacovigilance group within 3 days of receipt of this relevant information.
4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AESI form within 3 days of receipt of the updated information.
5. Obtain and maintain in the files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
6. When the outcome of the event is known, update the AESI form, if appropriate.

9.2.1.5 Procedure for Reporting Pregnancies

Any pregnancy occurring during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome in order to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Withdraw the subject from the clinical study. The subject must not receive any further injection of the study drug.
2. Complete as fully as possible the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy. Send by phone or fax along with the exit form within 24 hours of receipt of the information, to the PPD Safety and Pharmacovigilance group. Refer to Section 9.2.1.3.

   Note: Immediate pregnancy reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.
3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, send the form by phone or fax to the PPD Safety and Pharmacovigilance group within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., lost to follow up), documentation of the

non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete as fully as possible the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. Print and send the form by phone or fax to the PPD Safety and Pharmacovigilance group within 24 hours of receipt of the information.
6. If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 9.2.1.3).

9.2.1.6 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose, the nature or severity of which is not consistent with the applicable product information (e.g., reference safety information in the IB for nemolizumab, study protocol, etc.).

The Sponsor or its delegate will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, IRB/IEC, and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and Sponsor policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or its delegate will file it accordingly (i.e., with the TMF), and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.2 Clinical Laboratory Evaluation

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

The investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the investigator or designee will evaluate whether

he/she considers it to be clinically significant, defined as meeting at least 1 of the following conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management (e.g., discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation).

If the investigator observes a clinically significant laboratory result, the test will be repeated as soon as possible, and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that which may impact the safety of the subject or the interpretation of the trial results; only after discussion with medical monitor.

All clinically significant out-of-range laboratory values at the screening visit will be recorded in the medical history form (report a diagnosis rather than the laboratory value whenever possible). All clinically significant out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the scre8ening visit (i.e., changed significantly from the screening visit). Whenever possible, the investigator should provide a diagnosis of an AE when reporting the abnormal laboratory value.

Subjects should be reminded to be well hydrated before all visits for phlebotomy purposes. The screening visit laboratory values must be available before the baseline visit.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual and in Appendix 9. Additional samples may be required if medically indicated (e.g., at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test). The total and by visit amount of blood could change due to bio-analytical constraints and will be detailed in the Laboratory Manual and in the Informed Consent.

The total blood sample volume at a single time for this study and over four- or eight-week period (see Appendix 9) is below the maximum blood draw volume in pediatric subjects as determined in the National Institutes of Health Policy for Blood Drawn for Research Purposes in the Clinical Center (NIH, 2009) which clarify that for pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

For blood sampling, three attempts at most should be performed. If the physician is not successful after the third attempt, he/she will make no further attempt at that visit. According to local practices, the Study Personnel in charge of the blood draw may recommend the use of special patch or cream containing local anesthesia to decrease the pain when a blood sample is taken.

See Sections 9.2.3, 9.2.4, and 9.2.5 for details regarding pregnancy testing, virology, and TB testing samples, respectively. (See Sections 9.3 and 9.4, for details regarding PK and ADA sampling, respectively.)

The following laboratory safety tests will be performed as specified in Table 5:

9.2.2.1 Hematology

Tests for hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, and mean cell volume will be performed.

9.2.2.2 Clinical Chemistry

Tests for creatinine, AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), and creatine phosphokinase (CPK) will be performed. CPK isoenzyme test will be performed only if CPK is elevated to >2.5 × ULN. The investigator should also contact the medical monitor in such situations.

9.2.2.3 Urinalysis

Tests for urine pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity will be performed.

9.2.3 Pregnancy Testing

All female subjects of childbearing potential (i.e., a female subject who has started menstruating) 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 Section 8.1.2. Pregnancy test results must be available prior to the administration of the study drug.

For prepubertal subjects, reconfirm pre-menses status at every visit and, in case of status change, collect information on contraceptive measures and perform a UPT according to the schedule for FOCBP.

Subjects with a positive serum pregnancy test result at screening must not be enrolled.

Urine pregnancy tests with a sensitivity <25 IU/L will be provided to the study centers for use in the trial.

UPTs will be performed at the study centers, and all other samples will be sent to central laboratory for analysis.

If the result of a UPT is positive, it must be confirmed with a serum pregnancy test, and no study drug should be administered pending the serum pregnancy test result. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

9.2.4 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).

9.2.5 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.

9.2.5.1 Definitions

Active TB is a disease caused by *Mycobacterium tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or by radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with *M tuberculosis*, as evidenced by a positive Interferon Gamma Release Assay, (Centers for Disease Control and Prevention 2010) such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

9.2.5.2 Tuberculosis Screening

Ideally, as part of the medical history, the caregiver should be asked if the subject has presented with active or latent TB in the past and whether they have received a bacillus Calmette-Guérin (or BCG) vaccination. They should also be asked if they have been in contact with any individuals known to have active TB or been placed in any circumstances that may have exposed them to an increased risk of TB infection, such as travel to TB endemic regions, close contact with persons with active TB, or workplace risk (e.g., prison, hospitals).

A subject who tests positive for latent TB (with a positive QuantiFERON-TB Gold test) should be referred to the subject's treating physician for appropriate follow-up. If the result is indeterminate, the test may be repeated once. If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

9.2.6 Vital Signs

Vital signs will be evaluated at the screening visit and at each subsequent visit according to Section 8.1.2. Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least 5 minutes), and body temperature. All abnormal values at the screening visit identified as clinically significant by the investigator will be recorded in the medical history form. Any clinically significant changes from the screening visit will be recorded as an AE.

9.2.7 Height and Weight

Height and weight will be measured, according to Section 8.1.2.

Subjects must be >10 kg at both screening and baseline visits in order to be enrolled into this clinical study. Additionally, if the body weight is <10 kg after baseline, subject should not receive the dose.

9.2.8 Physical Examination

Complete physical examination should be performed at all visits, according to Section 8.1.2. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (for additional respiratory assessments, see Section 9.2.9), gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

The investigator should assess all abnormal findings for clinical significance. All clinically significant abnormal findings at the screening visit will be recorded in the medical history form. Any clinically significant changes from the screening visit will be recorded as an AE.

9.2.9 Respiratory Assessments

At screening, the investigator should specifically question caregivers on behalf of all subjects about any *medical history* of asthma and their respiratory health (e.g., wheezing, coughing, allergies, infections). Subjects with a history of asthma will be questioned about the seasonality of their asthma and known triggers, such as allergens. Newly diagnosed asthma or worsening of asthma during the study will be reported as an AESI.

9.2.9.1 Childhood Asthma Control Test (cACT)

Subjects in Cohort 1 and Cohort 1.1 (aged 7-11 years only) with a medical history of asthma will take the cACT at all visits according to Section 8.1.2 before questioning and physical examination by the investigator. Subjects with a new (de novo) diagnosis of asthma will take the cACT beginning at the visit the diagnosis was first confirmed and at all subsequent study visits thereafter. Subjects with an cACT score ≤19 will be referred to the physician managing their asthma.

The cACT is an assessment to determine if a subject's asthma symptoms are well-controlled and will be completed by the subject and the subject's parent/legal guardian/caregiver (as applicable) at the investigational center. The first 4 items of the test are completed by the subject, while the last 3 items are completed by the patient's parents/legal guardians/caregivers. The first 4 questions are scored on a 3-point scale (0 to 3) and the last 3 questions are scored on a 5-point scale (0 to 5), with summation of all items providing scores ranging from 0 to 27. A higher score indicates better asthma control while a score of 19 or less indicates the subject's asthma may not be under control. See Appendix 10.

9.2.9.2 Respiratory Examination

A respiratory examination will be required to be performed for all subjects at all scheduled visits, according to Section 8.1.2. The cACT will aid the investigator's questioning of subjects with a medical history of asthma and should be completed before the clinical questioning. After the screening visit, all subjects will be asked non-leading questions about any respiratory changes. The investigator or designee will then perform a respiratory examination of all subjects at all visits.

Subjects with a medical history of asthma will be referred to the physician managing their asthma if unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma who experience respiratory changes (examination findings or newly reported signs and/or symptoms suggestive of asthma) will be referred to a respiratory specialist.

9.2.9.3 Peak Expiratory Flow

Subjects in Cohort 1 and Cohort 1.1 (aged 7-11 years) only will undergo PEF testing at screening, baseline, and specified visits according to Section 8.1.2. For subjects reporting a medical history of asthma, PEF testing will be conducted at all visits.

Subjects with a new (de novo) diagnosis of asthma will undergo PEF testing at all visits after the diagnosis is first made according to Section 8.1.2.

PEF testing during the clinical study will be performed under the supervision of qualified study personnel. PEF measurements should consist of 3 good efforts, with the best result documented. It is preferable that the PEF measurement be performed before noon or at the same time during each study visit whenever possible. Obtained PEF values will be compared to predicted values based on the subject's age, sex, and height (Quanjer 1993), (Polgar 1979).

Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject, to avoid interference with PEF measurements.

Subjects with a medical history of asthma will be referred to the physician managing their asthma if PEF <80% of the predicted value.

9.2.9.4 Respiratory Referrals

Subjects with a medical history of asthma will be referred to the physician who manages their asthma when:

- PEF <80% of the predicted value.
- cACT score ≤19 (an cACT score ≤19 conveys asthma that may not be adequately controlled).
- Unexpected worsening of asthma is observed or reported at any time during the study.

At any study visit, subjects without a medical history of asthma will be referred to an appropriate specialist physician whenever:

- Signs and/or symptoms suggestive of asthma are newly observed or reported.
- Respiratory assessments (e.g., examination, PEF) suggests a decline in the subject's respiratory health.

9.2.10 Electrocardiogram

A 12-lead ECG will be performed and read centrally according to visits specified in Section 8.1.2 using the ECG machine provided. ECGs for each subject should be obtained using the same electrocardiograph machine whenever possible. ECGs will be performed in the supine position and before any scheduled vital sign measurements and blood draws. Subjects should be monitored for potentially clinically significant ECG results (refer to the current version of the central laboratory manual). Tests with abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. ECG abnormalities present at screening should be recorded in the medical history form. Any abnormalities considered by the investigator to be clinically significant after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

9.3 Pharmacokinetics

9.3.1 Blood Sampling

Blood samples will be collected according to Section 8.1.2, Appendix 9, and the clinical laboratory manual to determine the PK profile of nemolizumab. At each sampling time point for PK assessment, the collected blood will be placed to clot at room temperature (no more than 60 minutes after collection) and then centrifuged at room temperature. The serum will be collected into storage tubes.

As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples). The date and the time of each sample collection will be recorded in the CRF, together with the time of study drug injection at the same visit (or missed injection if applicable).

9.3.2 CD14152 Quantification in Biological Sampling

Concentration of nemolizumab (CD14152) in the serum will be determined using a validated enzyme linked immunosorbent assay (ELISA) method by a dedicated bioanalytical CRO. Details related to the processing of serum samples and the assessments of nemolizumab will be described in the bioanalytical plan, which will be finalized before the beginning of sample analysis. Results will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

9.3.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using a non-linear mixed effect modeling approach by a dedicated PK CRO. A pre-specified population PK model, based on existing information from studies in adults and adolescents (first-order absorption and a 1-compartment distribution model) and re-estimated once all emerging pediatric data will be available, 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 (Cl/F, V_d/F, k_a), including inter-individual variability, covariate effects, residual error, and their relative standard error (RSE), will be obtained using the popPK model.

Individual nemolizumab PK parameters will be derived at the end of the study using the same popPK model (Cl/F, V_d/F, k_a, AUC_{inf}, $t_{1/2}$, and predicted C_{trough}). No individual PK parameter will be included in the 3 Interim Analyses.

Results will be described in a separate PK modeling report, which will be included as an appendix in the final clinical study report.

Observed C_{trough} level will be also reported.

9.4 Immunogenicity

Blood samples will be collected according to Section 8.1.2, Appendix 9, and the clinical laboratory manual to assess anti-nemolizumab ADA. The ADA will be determined by the designated bioanalytical CRO using a validated electrochemiluminescence immunoassay (ECLIA) method.

Details related to the processing of serum samples and the assessments of ADA will be described in the bioanalytical plan, which will be finalized before the beginning of sample analysis. Results will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

If serum circulating ADA is detected, presence will be confirmed and characterized (e.g., for neutralizing potential, NAb) using a validated assay. Incidence of positive treatment-related ADA results will be summarized (absolute occurrence and percent of subjects).

9.5 Patient-Reported Outcome Assessments

9.5.1 Dermatology Life Quality Index

9.5.1.1 Children's Dermatology Life Quality Index

According to the Schedule of Assessments (Table 5), cDLQI, a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment, will be assessed at baseline, Week 8, Week 16, Week 32 and Week 52 for subjects ≥4 years of age. The subject will rate each question ranging from 0 (not at all) to 3 (very much). A higher total score indicates a poorer QoL (see Appendix 11) (Lewis-Jones 1995).

9.5.1.2 Infants' Dermatitis Quality of Life Index

According to the Schedule of Assessments (Table 5), Infants' Dermatitis Quality of Life Index, a validated 10-item questionnaire covering domains including symptoms/feelings, daily activities, leisure, and treatment, 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 (see Appendix 12) (Lewis-Jones 2001).

9.5.2 Patient-Oriented Eczema Measure

Patient-Oriented Eczema Measure will be assessed at baseline, Week 8, Week 16, Week 32, and Week 52. 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). See Appendix 13 (Charman 2004).

9.6 Independent Data Monitoring Committee

An IDMC will review and monitor subject safety throughout the study. The IDMC will provide recommendations on the safety of subjects. 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.

9.7 Independent Adjudication Committee

An IAC will review all asthma-related adverse events throughout the study. Details on the IAC, including the plan of analysis for IAC outputs, the composition of the IAC, and the procedures, roles, responsibilities, and their communications are provided in the IAC charter.

10 STATISTICAL METHODS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

10.1 Statistical and Analytical Plans

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. No hypothesis testing will be performed. Summary statistics will be presented by age group and overall. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, maximum, 25% and 75% quartiles. For categorical variables, data will be tabulated with the number and proportion of subjects for each category.

There are three Interim Analyses (IAs) planned for this study, IA-1 for Cohort 1, IA-1.1 for Cohort 1.1 and IA-2 for Cohort 2. IA-1 will be performed after the first 18 subjects in cohort 1 have completed the Week 16 visit. For subsequent Cohorts (1.1 and 2) the IA will be performed when approximately 18 subjects have completed the Week 16 visit. The recruitment will start with Cohort 1 (aged 7 to 11 years). 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.

IA-1, IA-1.1, and IA-2 will focus on PK and safety. Additional efficacy analysis may be performed at IA-1.1 and IA-2.

Additional interim data summaries may be produced to support the regulatory submissions/interactions and to support the program development.

10.1.1 Analysis Populations

The analysis populations will consist of the following:

10.1.1.1 Enrolled Population

The enrolled population will include all individuals who met the inclusion/exclusion criteria and signed the ICF. It will be used for the subject listings.

10.1.1.2 Safety Population

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

10.1.1.3 Pharmacokinetic Population:

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

10.1.1.4 Intent-to-treat (ITT) Population

The Intent-to-treat population will include all enrolled subjects. This set of population will be used for the analysis of efficacy.

10.1.2 Demographic and Other Baseline Characteristics

Subject disposition, demographics, baseline characteristics, medical history, prior and concomitant therapies/medications will be summarized by descriptive statistics.

10.1.3 Efficacy Variables

All efficacy endpoints (as listed in Section 7.2.2.1) will be summarized by age cohorts and overall on the ITT population as follows:

Continuous efficacy endpoints and data, including QoL scores, will be summarized using descriptive statistics for actual values, change from baseline and percent change from baseline (if relevant) at each visit. Data will be summarized based on Observed Cases (OC) and using Last Observation Carry Forward (LOCF).

Categorical and/or binary efficacy endpoints (including outcomes in proportion such as response/success/achievement rate) will be presented by number and percentage of subjects in the respective category for each visit. Data will be summarized based on Observed Cases (OC) and using the Non-Responder Imputation (NRI). For NRI, all missing values or data collected after use of rescue medication will be treated as a non-responder.

10.1.4 Safety Variables

Summaries and analyses of safety endpoints will be presented by age cohorts and overall on the Safety population.

10.1.4.1 Extent of Exposure

The duration of exposure, the total dose received, and dose compliance will be summarized by visit.

10.1.4.2 Adverse Events

Treatment-emergent adverse events (a TEAE is defined as an AE that starts on or after the first administration of study medication) reported during the study will be tabulated and listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term. Tables will display number and percentage of subjects experiencing the event for the following categories: all TEAEs, TEAEs related to study

drug, TEAEs by severity, serious TEAEs, treatment-emergent AESI, and AEs leading to study/treatment discontinuation.

10.1.4.3 Clinical Laboratory

Laboratory results will be summarized by visit using descriptive statistics. Shift from baseline will be presented using reference ranges. Subjects with potentially clinically significant laboratory abnormalities will be summarized.

10.1.4.4 Vital Signs

All vital signs and weight data (absolute values and change from baseline) will be summarized by visit. Shift table presenting the number and percent of subjects with normal and abnormal values will be summarized. In addition, the number, and percent of subjects with clinically significant abnormal values (of clinical concern as identified by the investigator) will be summarized by treatment group.

10.1.4.5 Asthma Control Test and Peak Expiratory Flow

All cACT and PEF (absolute values and change from baseline) will be summarized by visit.

10.1.4.6 Physical Examination and Respiratory Examination

All physical examination and respiratory examination will be summarized by visit.

10.1.4.7 Electrocardiogram

All ECG results will be summarized by visit.

10.1.5 Pharmacokinetic Parameters and ADA Analyses

10.1.5.1 Pharmacokinetic Analysis and Modeling

The PK parameters derived from the popPK model will be regarded as primary endpoints for the PK analyses (see details in Section 9.3.3). Primary inference for all the PK parameters will be based on the pharmacokinetic analysis population.

The PK/PD relationship between nemolizumab 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.

The popPK and PK/PD models will be detailed in a separate PK Modeling Analysis Plan.

The observed C_{trough} concentrations at each time point will be summarized as arithmetic mean, standard deviation, Coefficient of Variation (CV)% geometric mean, median, minimum, maximum, and number of samples below the limit of quantification.

Descriptive statistics (n, arithmetic mean, standard deviation, Coefficient of Variation (CV)%, geometric mean, minimum, median, maximum) will be calculated for all individual popPK-derived parameters.

10.1.5.2 Immunogenicity Analysis

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 age cohort groups and overall.

10.1.6 Interim Analyses

There are three Interim Analyses (IAs) planned for this study, IA-1 for Cohort 1, IA-1.1 for Cohort 1.1 and IA-2 for Cohort 2. IA-1 will be performed after the first 18 subjects in cohort 1 have completed the Week 16 visit. For subsequent Cohorts (1.1 and 2) the IA will be performed when approximately 18 subjects have completed the Week 16 visit. The recruitment will start with Cohort 1 (aged 7 to 11 years). 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.

IA-1, IA-1.1, and IA-2 will focus on PK and safety. Additional efficacy analysis may be performed at IA-1.1 and IA-2. The IAs will assess whether the observed safety and PK data from each cohort are similar to the data obtained in adolescent and adult subjects. During the interim analyses, enrollment will continue in each Cohort. Note: as mentioned above, enrollment in Cohort 1.1 and Cohort 2 will only start after completion of the IA-1 and IA-1.1, respectively, and Sponsor's written approval. Once enrollment starts in Cohort 1.1 and in Cohort 2, enrollment in these Cohorts will continue during IA-1.1 and IA-2, respectively.

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

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.

Drug exposure and dose confirmation using a population PK analysis by the Sponsor.

Additional interim data summaries may be produced to support the regulatory submissions/interactions and to support the program development.

Further details will be provided in the SAP.

10.2 Determination of 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 aged 7 to 11 years in two cohorts (1 and 1.1) of 35 subjects, and

35 subjects aged 2 to 6 years in cohort (2). Based on the variability of nemolizumab serum concentrations, a sample size of approximately 35 in each cohort was considered sufficient to calculate PK parameters with adequate precision and to ensure adequate representation across the pediatric age range.

10.3 Protocol Deviations

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be described in the clinical study report. Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded as a COVID-19 deviation. Further details of protocol deviations will be provided in the Protocol Deviation and Non-Compliance Management Plan.

Summary of protocol deviations (major and minor) will be provided by age cohort and overall.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on CRFs. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with current Good Clinical Practice (GCP) and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

11.3 Personnel Training

Study monitors and all relevant personnel will be trained before study initiation on the condition to be treated, the standard operating procedures to be used in this clinical study, the protocol, and all study-specific procedures. Team organization, communication, and operational issues will also be discussed and agreed upon.

Investigators, evaluators, study coordinators, pharmacists, and other applicable personnel are recommended to attend an investigator meeting. During the meeting, participants will be trained on the protocol, ICH/GCP, study-specific procedures (including efficacy assessment scales and instruction for use of the study drug), interactive response technology, and CRF completion.

All personnel involved in the study conduct will receive training before participating in any procedure and/or evaluation. Each study center will have a training record as part of the site file and TMF.

11.4 Data Management

The designated CRO will be responsible for activities associated with the data management of this study. This will include, but is not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. All data management activities will be detailed in the data management plan.

Study centers will enter data directly into an electronic data capture system by completing the CRF via a secure internet connection. Data entered into the CRF must be verifiable against source documents at the study center. Data to be recorded directly on the CRF will be identified and the CRF will be considered the source document. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail.

11.5 Clinical Study Conduct

With the exception of avoiding an immediate risk to a subject, the investigator should not deviate from the clinical study protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The investigator should document and explain any deviation from the clinical study protocol.

11.6 Amendments

The Sponsor may modify the clinical study protocol at any time for ethical, medical, or scientific reasons. Any amendments will be handled according to applicable local regulations.

The Sponsor does not have to notify non-substantial amendments to the competent authorities or IRB/IEC. However, non-substantial amendments will be recorded and detailed in subsequent submissions (e.g., in the subsequent notification of a substantial amendment).

11.7 Quality Management and Risk Evaluation

Details will be provided in a separate Integrated Quality Risk Management Plan.

12 ETHICS

12.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

12.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

12.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

12.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

All minor subjects who participate in this clinical study must be accompanied by a caregiver/guardian. Subjects and caregivers are required to be fully informed about the clinical study in accordance with GCP guidelines, federal regulations (for the US, HIPAA) (US Department of Health and Human Services 1996) and guidelines and in accordance with local requirements.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points she/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

12.5 Subject Confidentiality

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

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations (HIPAA for the US) (US Department of Health and Human Services 1996) on personal data protection.

12.6 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the designated CRO and the Sponsor.

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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15 APPENDICES

Appendix 1. American Academy of Dermatology Consensus Criteria for AD Diagnosis

Features to be considered in diagnosis of patients with atopic dermatitis:

ESSENTIAL FEATURES; must be present:
- Pruritus
- Eczema (acute, subacute, chronic):
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

**Patterns include*:*
- *Facial, neck, and extensor involvement in infants and children;*
- *Current or prior flexural lesions in any age group;*
- *Sparing of groin and axillary regions.*

IMPORTANT FEATURES; seen in most cases, adding support to the diagnosis:
- Early age of onset
- Atopy
  - Personal and/or family history
  - IgE reactivity
- Xerosis

ASSOCIATED FEATURES; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
- Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
- Ocular / periorbital changes
- Other regional findings (e.g., perioral changes / periauricular lesions)
- Perifollicular accentuation / lichenification / prurigo lesions

EXCLUSIONARY CONDITIONS; it should be noted that a diagnosis of AD depends on excluding conditions such as:
- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Appendix 2. Specific Guidance for Study Conduct and Subject Safety during the COVID-19 Pandemic

This guidance applies during the COVID-19 pandemic, as defined by regional and/or local authorities. The information summarized below is relevant to the referenced sections of the protocol.

Section 6.3 Risk/Benefit Assessment

During the COVID-19 pandemic, additional risks to participants may exist, including general environmental risks (e.g., being outside the home, possible contact with unsanitized surfaces) and study-related activities (e.g., interaction with study staff). Potential new subjects with known or suspected COVID-19 infection are ineligible for study enrolment until the infection has resolved. Risk mitigation measures to be implemented for enrolled subjects and for new subjects during the COVID-19 pandemic are detailed in **Additional Measures for Subjects Amidst COVID-19 Pandemic** below. Subjects with a known or suspected COVID-19 infection will immediately discontinue study drug; instructions for resuming treatment are described in Section 8.3.4.2 and below in Guidance for Existing Subjects. Known or suspected COVID-19 infection will also be followed as an AESI.

Subsection to Section 8.1, Overall Study Design and Plan:
Additional Measures for Subjects Amidst COVID-19 Pandemic

All investigational sites should act according to applicable site regulations, to guidelines and restrictions implemented by local authorities, and to best practices for conducting clinical research during the COVID-19 pandemic.

- Guidance for New Subjects:

Best practices currently in place must be followed when evaluating eligibility of subjects to participate in the study during the COVID-19 pandemic.

If at the time of screening, in the opinion of the Investigator, the subject or caregiver will not be willing and able to reach the investigational site and comply with all of the time commitments and requirements of the clinical study protocol, the subject should not be considered for enrolment. The subject may be rescreened at a later time.

Pre-screening phone calls should be conducted to exclude potential candidates/subjects who display possible symptoms of COVID-19 or are at high risk of having been exposed to COVID-19.

- Guidance for Enrolled Subjects:

If the local situation allows for subjects to reach the clinical investigational site and complete all study procedures, the following measures should be taken:

- Implement and document in the subject records regular communication with the subject/caregiver between visits to attempt to ensure early detection of potential signs/symptoms of COVID-19 infection, and provide adequate advice, as per local medical practice and public health guidelines for suspected COVID-19 infection. Please refer to the Centers for Disease Control (CDC;
- https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. /European CDC (https://www.ecdc.europa.eu/en/covid-19/questions-answers)/local disease prevention agency and applicable local guidelines for assessment of subjects' COVID-19 status.
- Following the same guidelines, implement and document in the subject records an additional communication to the subject/caregiver just before the scheduled visit.
- Discontinue study drug administration in case of confirmed or suspected COVID-19 infection until the infection is resolved. See Section 8.3.4.2.

  Study drug administration may resume in subjects with confirmed or suspected COVID-19 infection based on investigator judgement after discussion with the medical monitor or Sponsor and only if the following minimum conditions are met:

  - For symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g. cough, shortness of breath)

  - For asymptomatic subjects: At least 21 days have passed since the positive PCR test and no symptoms.

  Note: The above should be considered minimum criteria. Where the local guidelines are more stringent for infection resolution criteria, those must be applied.
- Report any COVID-19 infection (confirmed or suspected) as an AE:
  - if any seriousness criterion is met, also report as an SAE (see Section 9.2.1.3).

  - If it occurs during the clinical study following the first dose of study drug administration, also report as AESI (see Section 9.2.1.4).

- Implement preventive infection control measures against COVID-19 infection following local guidelines (e.g. good hygiene practice, clean techniques, and use of personal protective equipment such as gloves, goggles, and masks).
- Implement preventive measures in handling all subject-facing study-mandated assessment devices and parts:
  - PEF meter device body is to be cleaned after each use, with recommended wipes, as per user manual
  - PEF meter flow sensor is to be disposed of after each set of measurements is taken
  - Approved bacterial/virus filters may be used; if used, they must be disposed of after each set of measurements is taken
  - Offer protective gloves to subjects/caregivers for use while filling out assessments on a tablet and provide training on hygienic removal and disposal of gloves

If the local situation allows for subjects to reach the investigational site and complete only some study procedures where visit duration needs to be limited, the above measures also apply. All assessments should be conducted if possible.

Subjects **can be dosed only if**, taking into account the local situation and risk of exposure to COVID-19, the site considers that:

- The study drug subcutaneous injection can be performed at the investigational site according to the instructions in the protocol, pharmacy manual and instruction for use, including preparation of study drug by an independent pharmacist or other qualified personnel.
- cACT (applies only for subjects aged 7 to 11 years; c**ACT will not be performed for subjects aged 2 to 6 years**; for subjects with a medical history of asthma), and PEF (applies only for subjects aged 7 to 11 years; **PEF will not be performed for subjects aged 2 to 6 years**) can be performed according to the protocol.
- All other safety assessments are to be performed as per protocol: physical exam, vital signs, ECG, laboratory assessments, pregnancy test, monitoring of AEs and concomitant medications.
- All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

If the local situation does not allow for subjects to reach the investigational site:

- See Subsection to Section 8.4.7, Dose Modification: **Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic** (below) for guidance on further dosing of subjects.
- Remote collection of data by Investigator or delegate are still to be done for the following assessments at the regularly scheduled visit time, by phone or video call:
  - AE collection
  - Concomitant therapies used

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

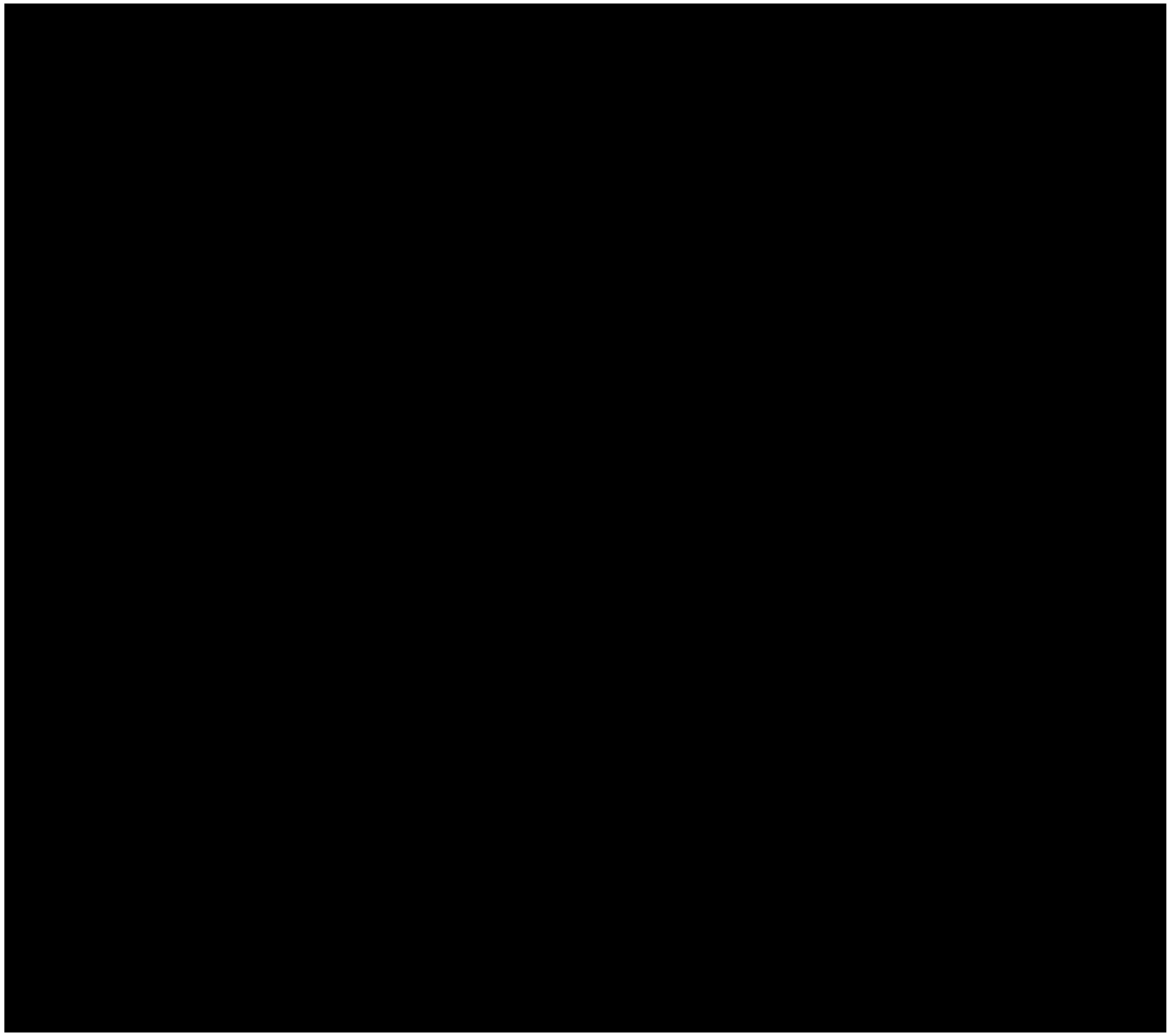
Subsection to Section 8.4.7, Dose Modification:
Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic

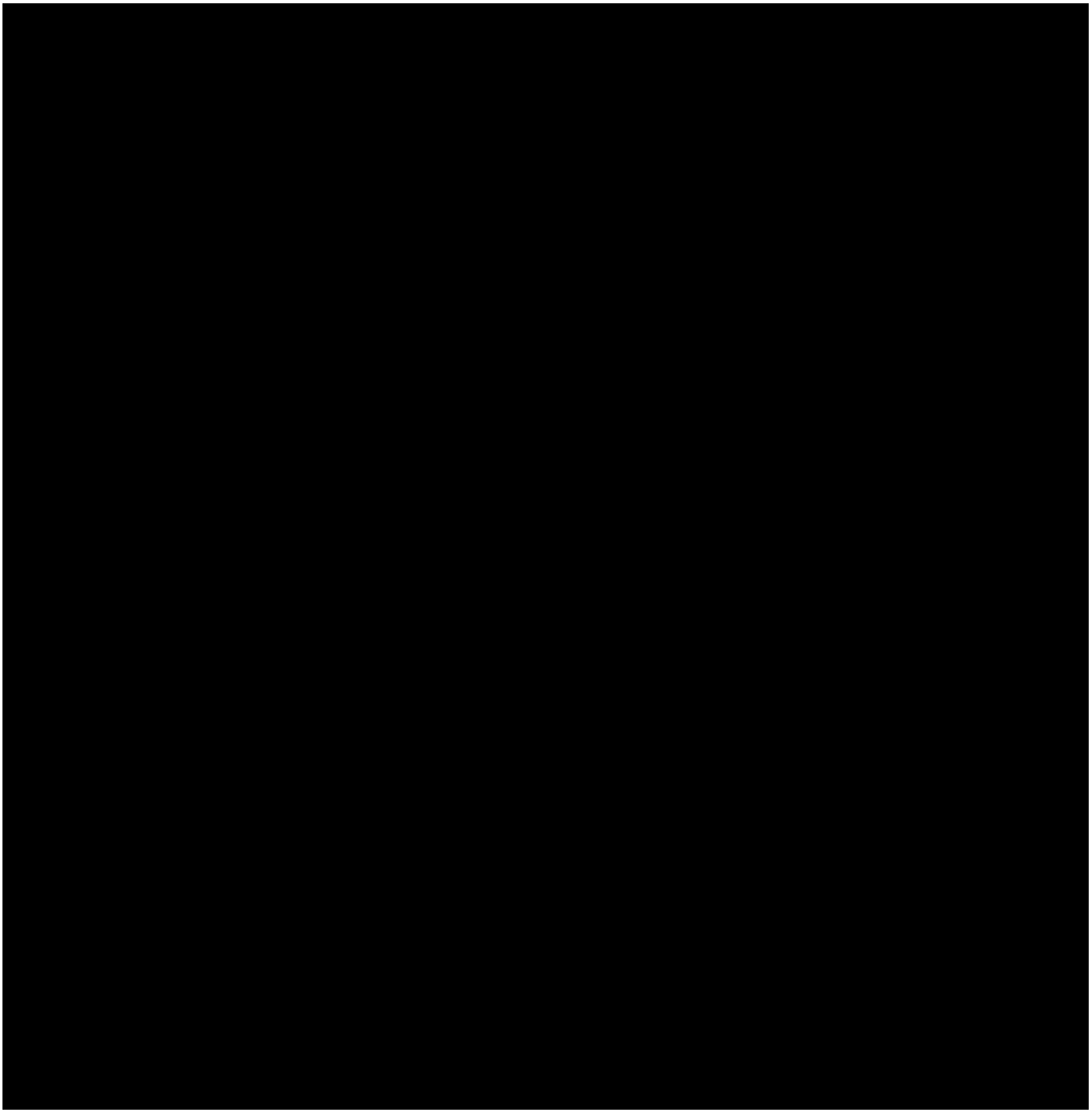
If a subject misses a dose of study drug due to the COVID-19 pandemic, study drug administration may be continued. The following conditions apply:

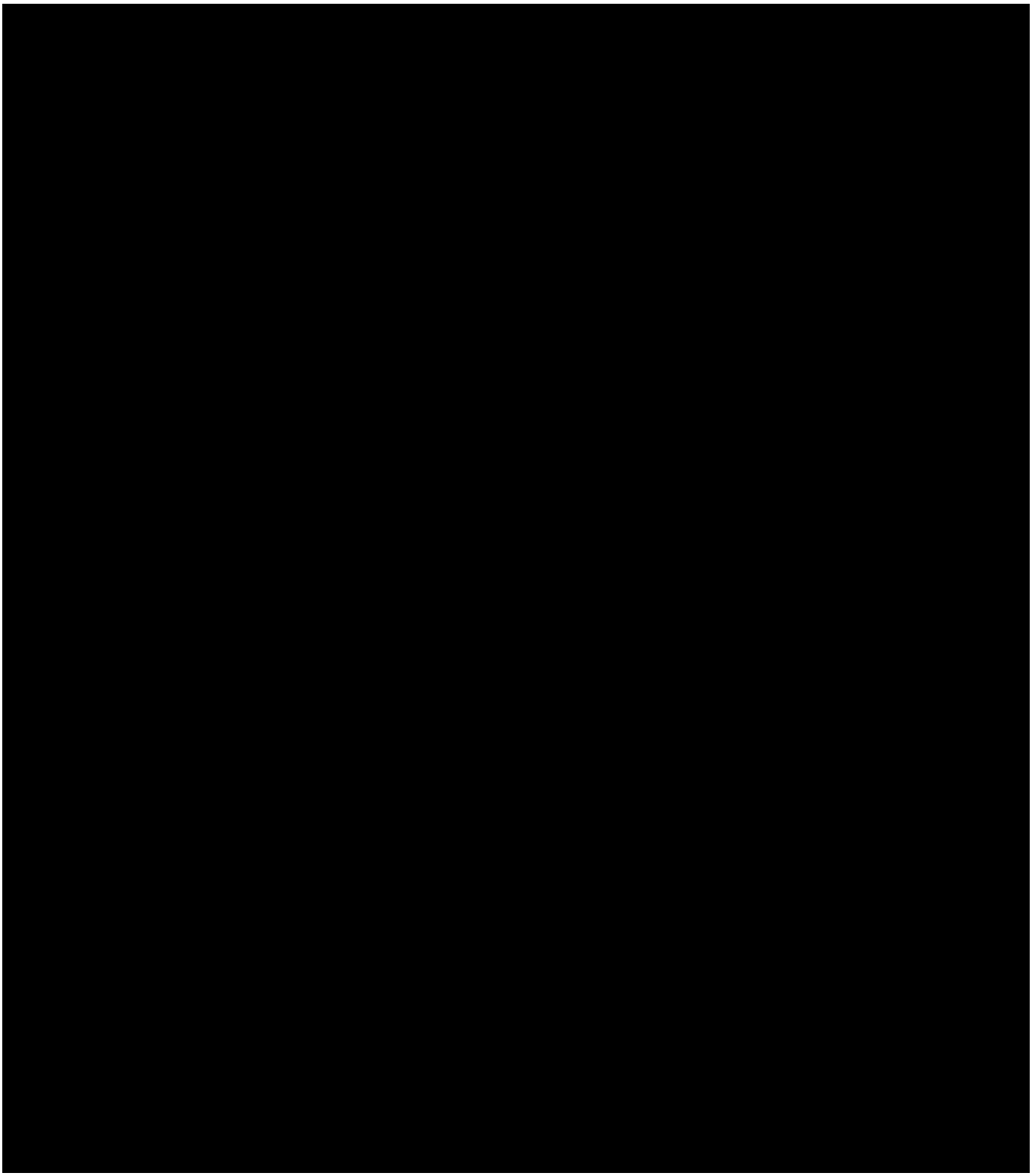
- There is a minimum 3-week interval between injections
- If a subject cannot come to a planned visit due to COVID-19, the visit should be conducted remotely according to the above guidance
- If there are more than 2 doses missed (e.g. 12 weeks or more interval between injections), the investigator must contact the Sponsor for further guidance.
- Instructions for resuming treatment are described in Section 8.3.4.2.

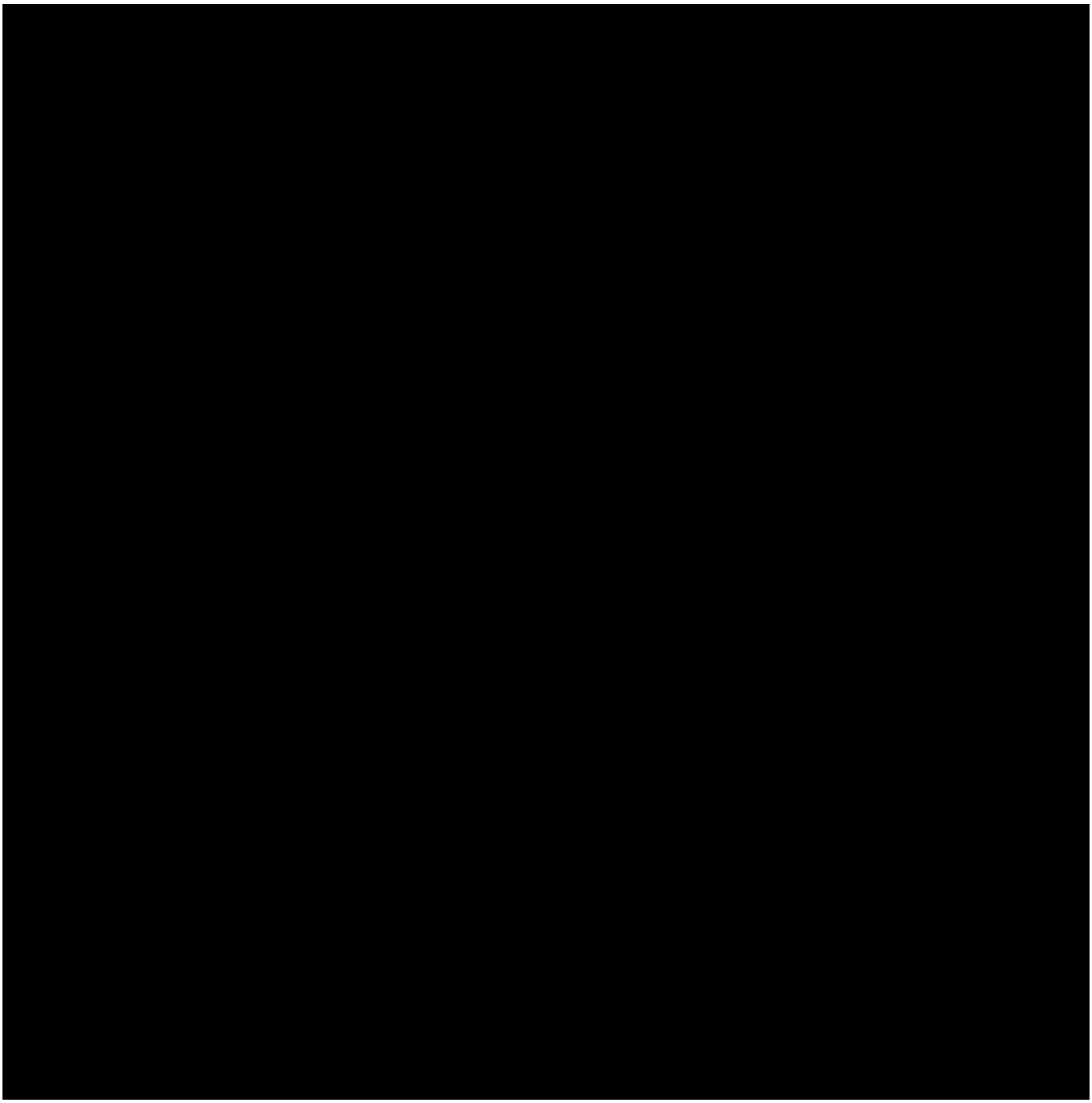
11.2 Monitoring

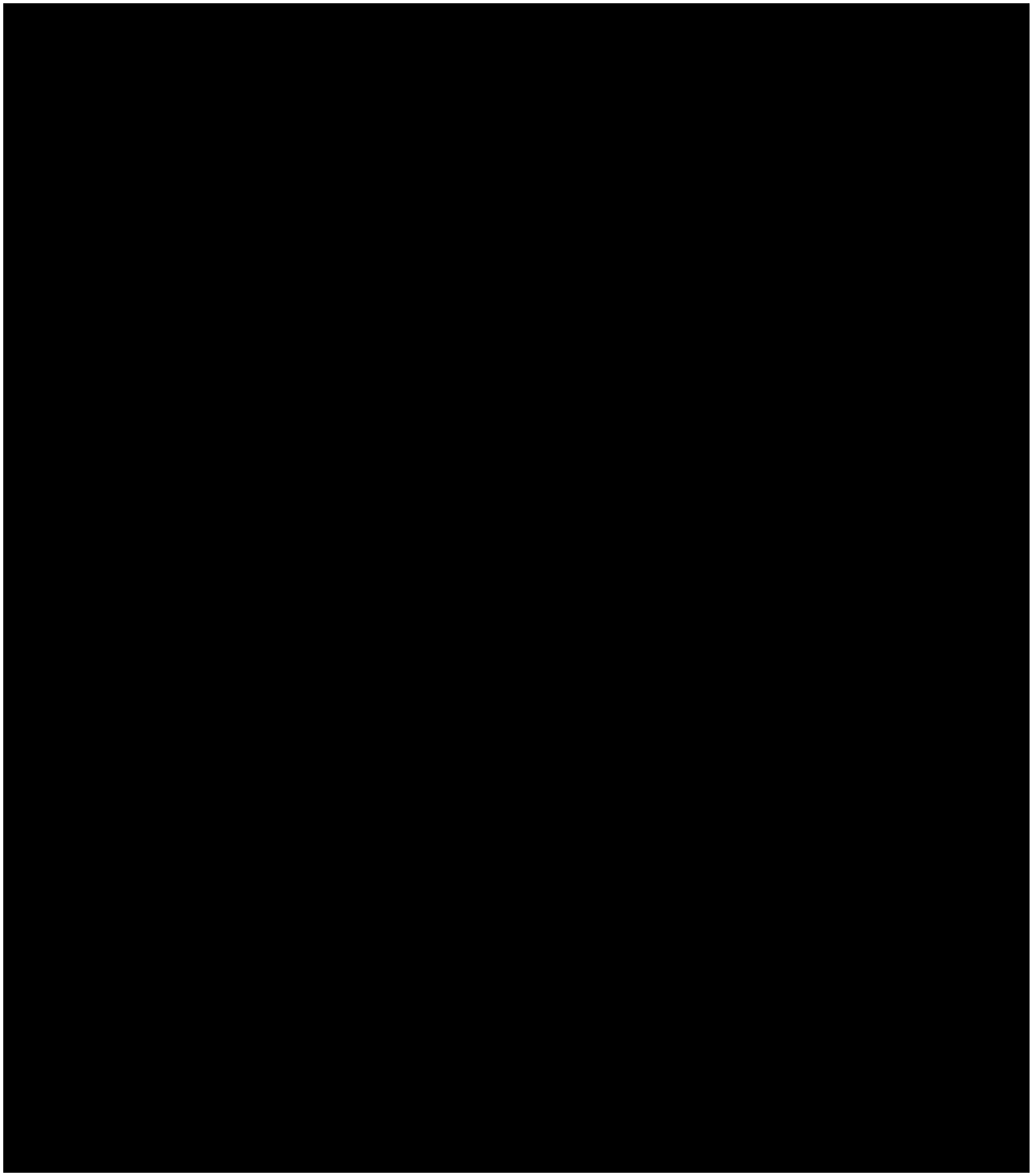
On-site interim monitoring visits may not be feasible during COVID-19 restrictions; therefore, remote monitoring will be completed until on-site monitoring can be conducted again. Site monitoring activity will comply with the processes documented within the COVID-19 Site Management Risk Assessment Form.











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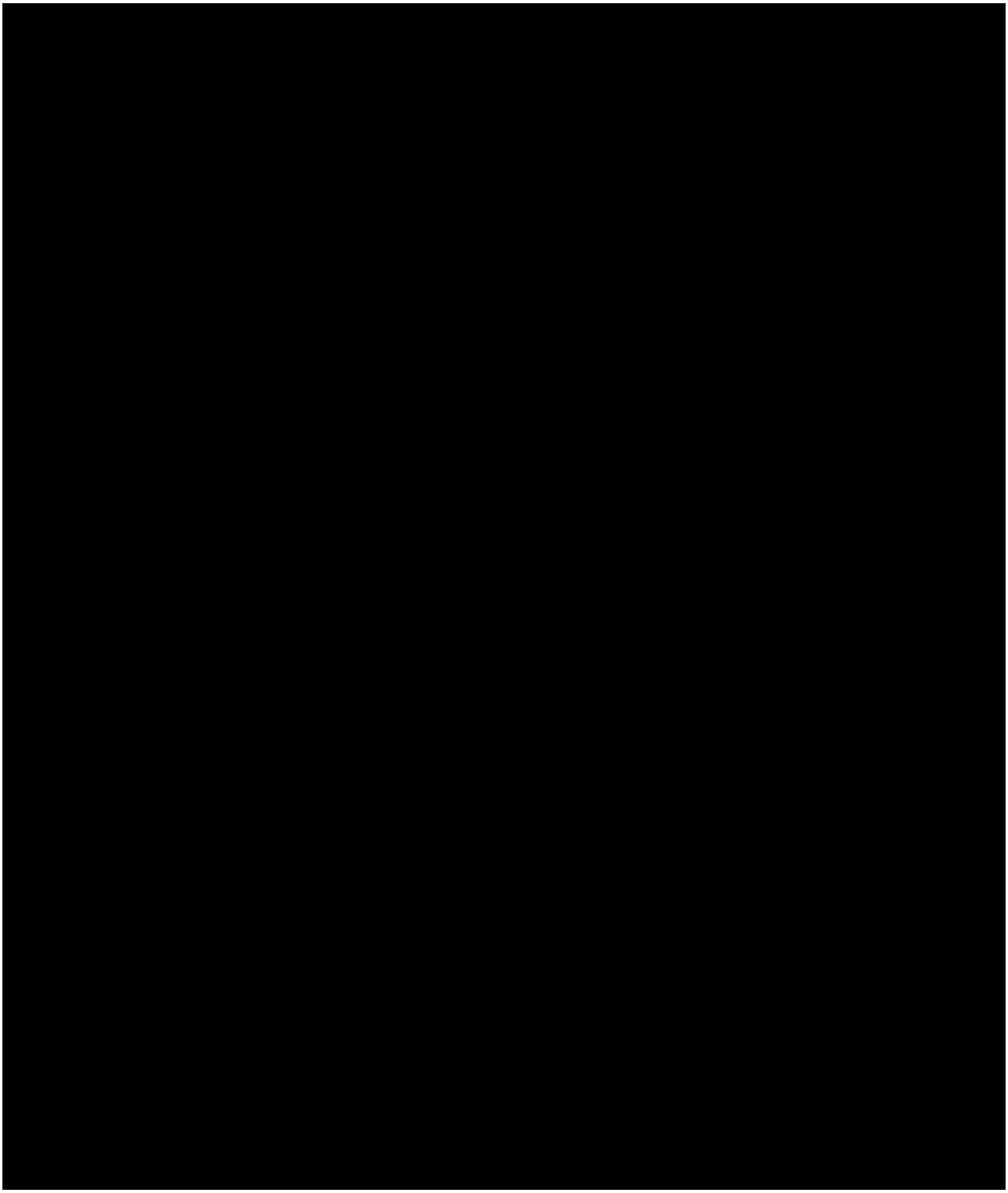

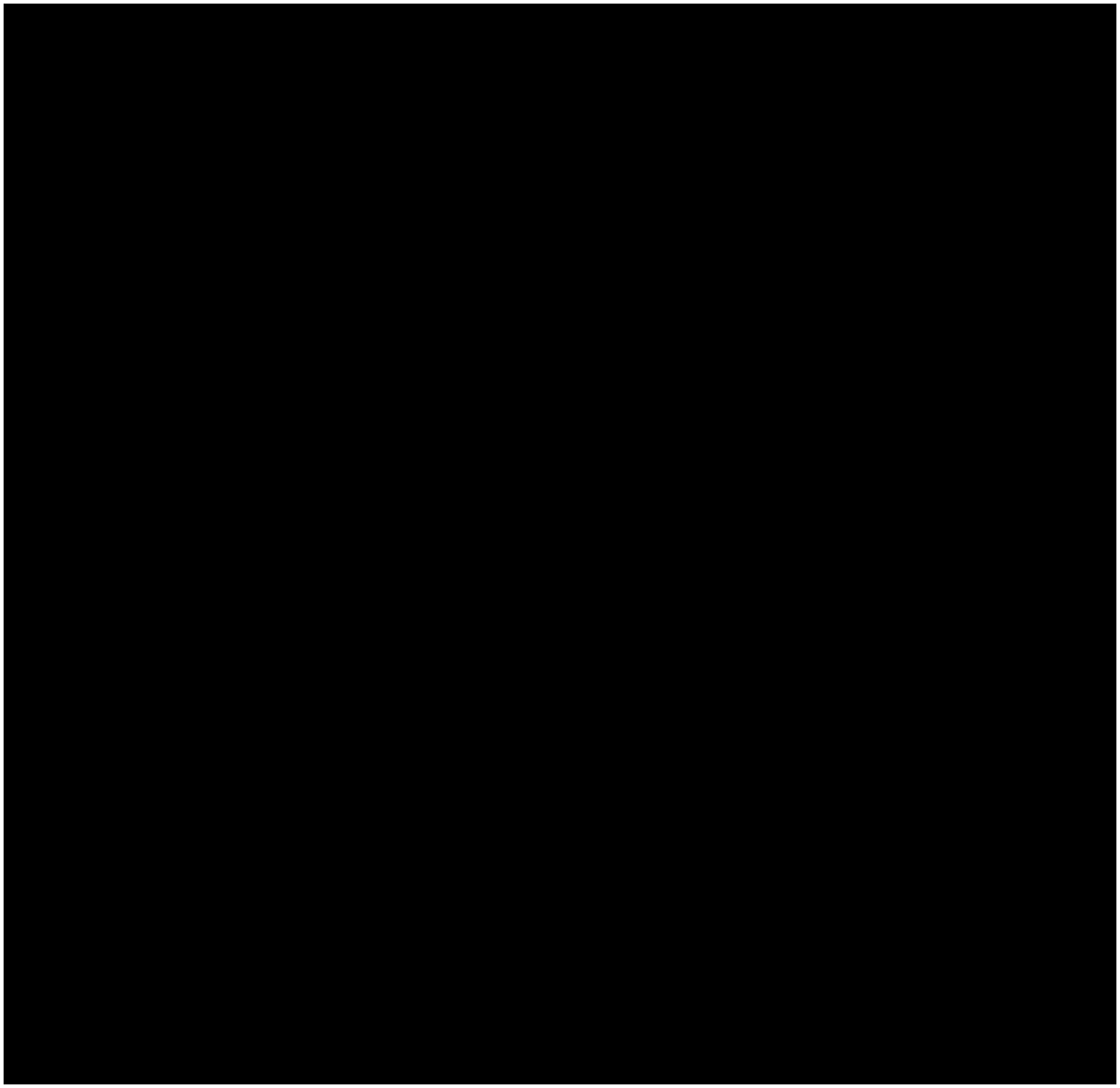

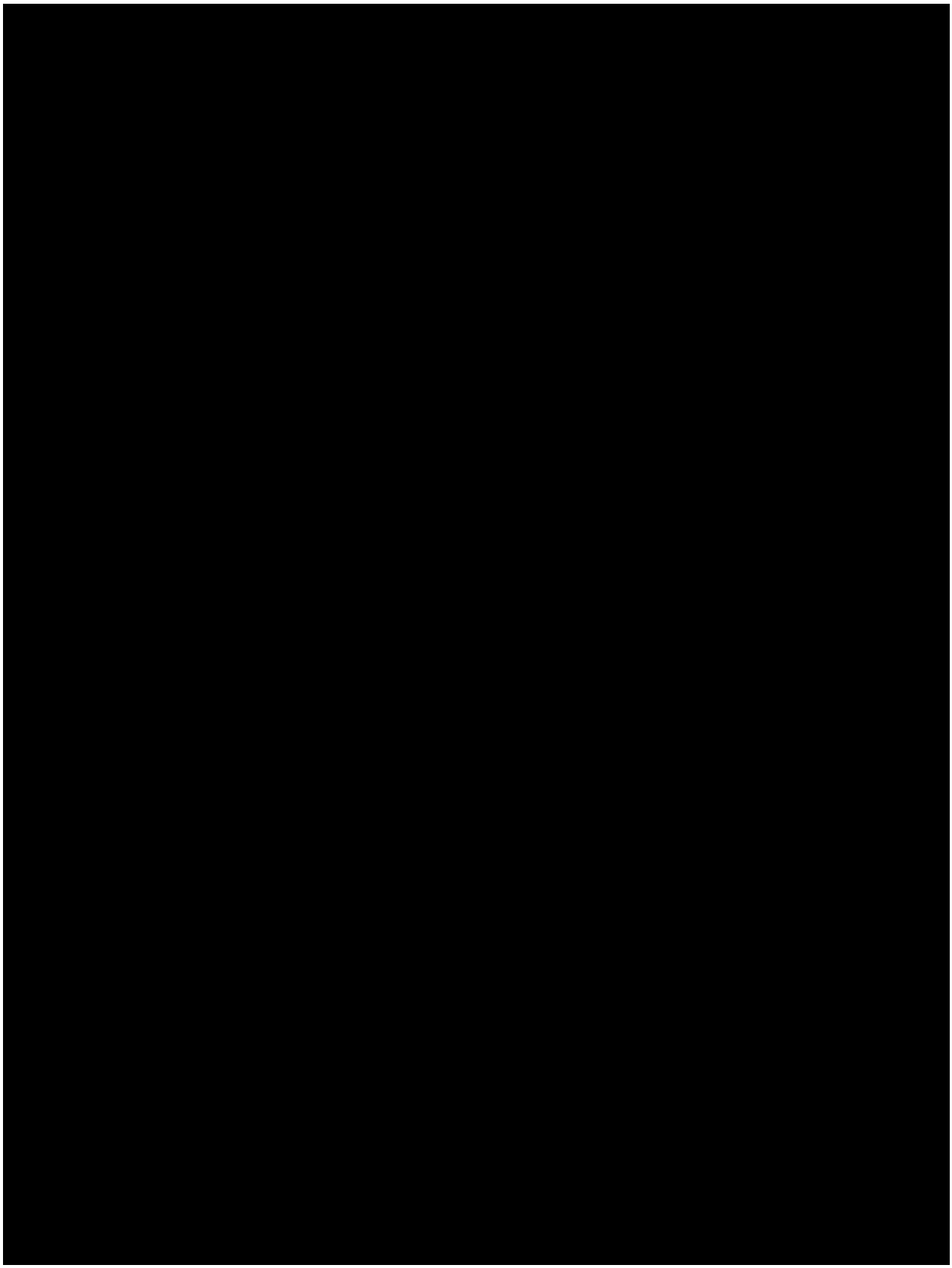

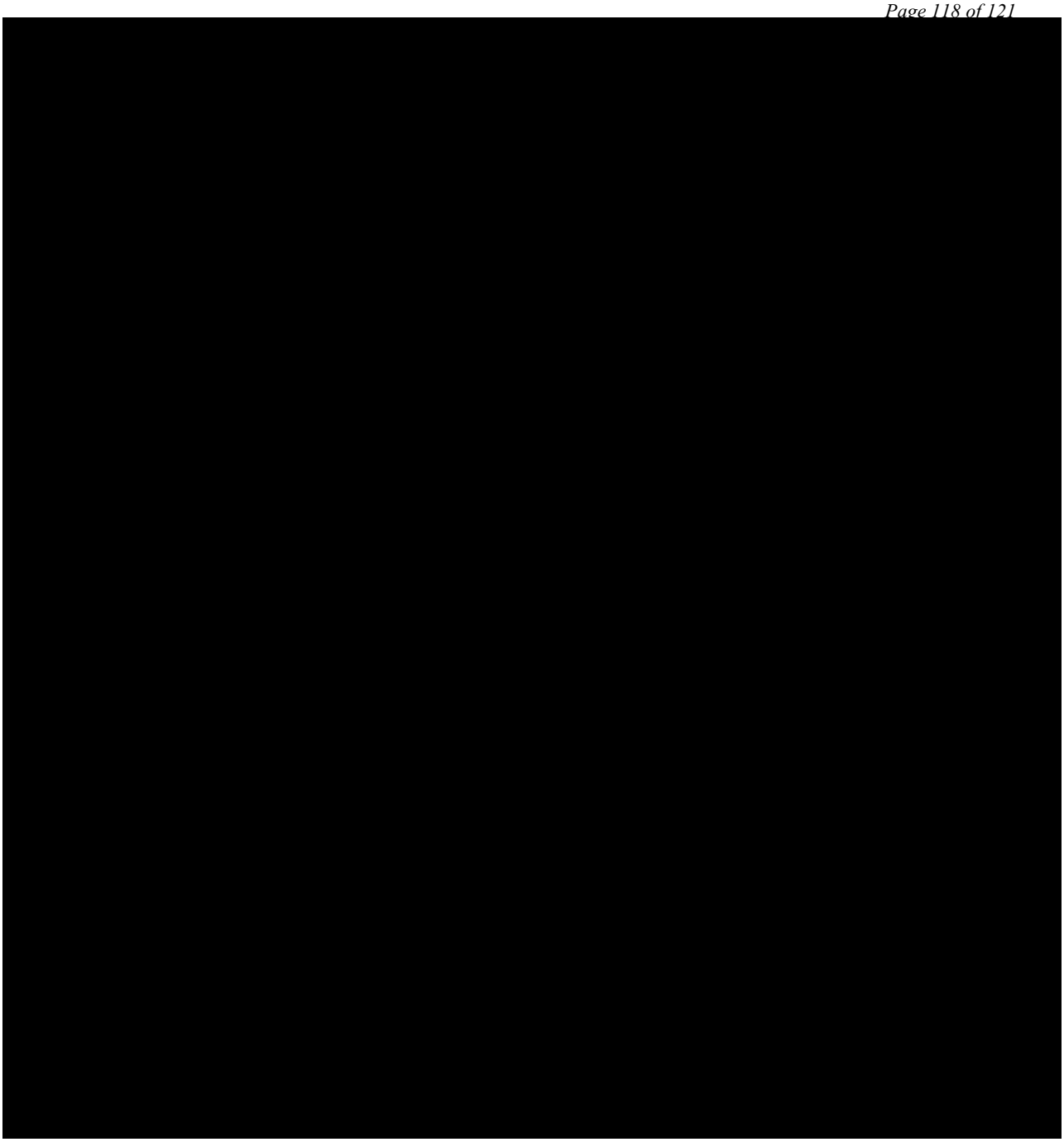

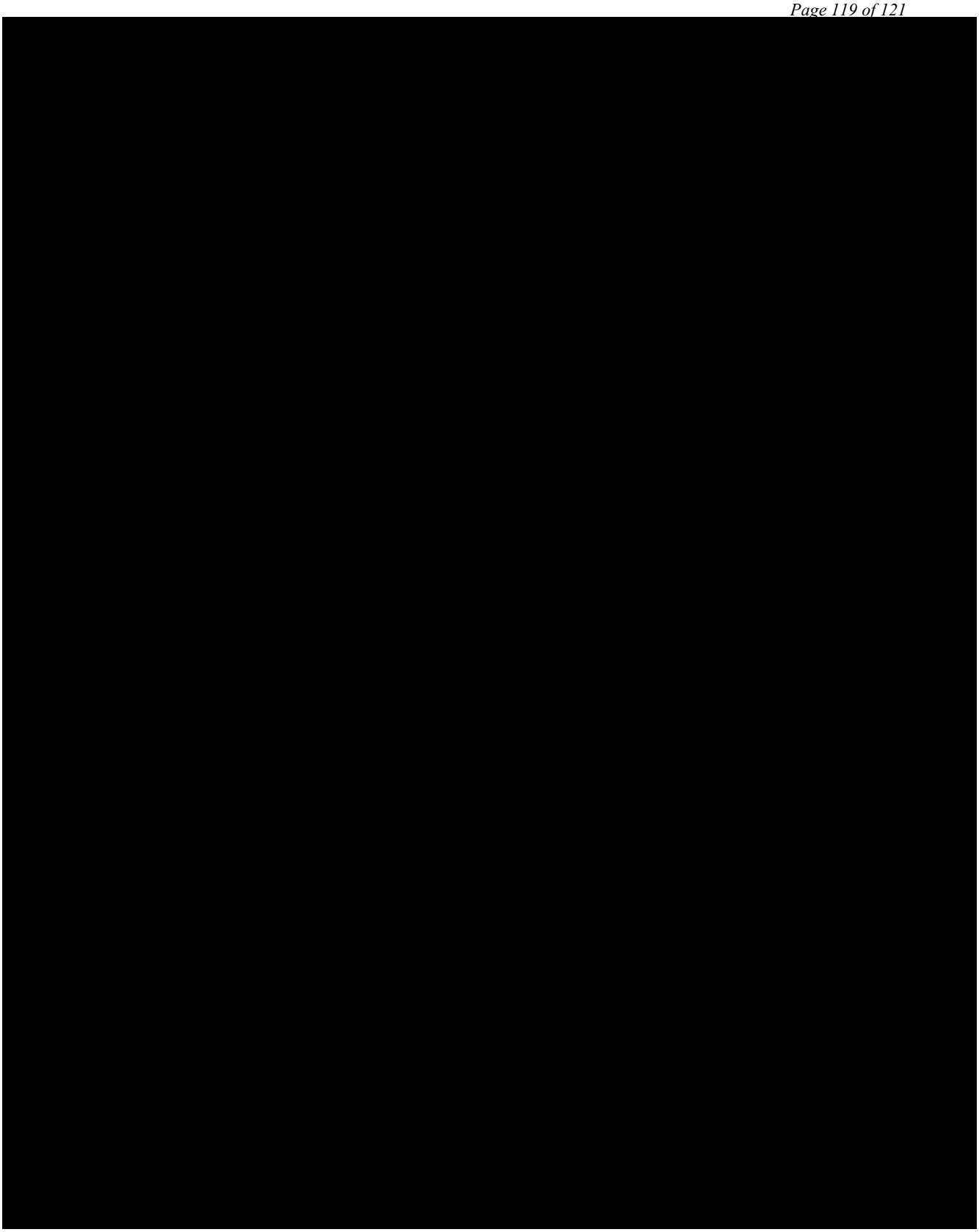

INVESTIGATOR SIGNATURE PAGE

Protocol Title: 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

Protocol Number: RD.06.SPR.118126

Confidentiality and Current Good Clinical Practice (GCP) Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Galderma S.A. and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Galderma S.A. and the IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Galderma S.A. to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature	Date
Printed Name	Title
Institution	Study Center Number