CLINICAL STUDY PROTOCOL

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

Galderma Protocol Number:	RD.06.SPR.116912
EudraCT Number:	Not Applicable
CCI [redacted]	CCI [redacted]
Investigational Product:	Nemolizumab (CD14152)
IND Number:	CCI [redacted]
Phase:	2
Sponsor:	Galderma Research & Development, LLC 14501 North Freeway Fort Worth, TX 76177 United States
Contract Research Organization:	CCI [redacted] United States
Protocol Date:	21JUL2020
Protocol Version:	Version 6.0

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PPD


PPD

2 Study Personnel

Galderma Research & Development, LLC Personnel

Name: PPD

Title: PPD

Address: Galderma S.A.
Rue d'Entre-deux-Villes 10
1814 La Tour-de-Peliz
Switzerland

PPD

PPD

Name: PPD

Title: PPD

Address: PPD

Telephone No.: PPD

Mobile No.: PPD

Email: PPD

PPD

Name: PPD

Title: PPD

Address: PPD

Telephone No.: PPD

Mobile No.: PPD

Email: PPD

Coordinating Investigator

Name: PPD

Title: Coordinating Investigator

Address: PPD ,
PPD

Telephone No.: PPD

Email: PPD

3 Synopsis

Protocol Number:

116912

Title:

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

Investigational Product:

Nemolizumab (CD14152)

IND Number:

PPD

Study Centers:

Approximately 10 study centers across the United States

Phase:

2

Objectives:

Primary objective: To assess the pharmacokinetics (PK) and safety of nemolizumab in adolescent subjects with moderate-to-severe atopic dermatitis (AD) and associated pruritus not adequately controlled with topical treatments, when administered concomitantly with topical corticosteroids (TCS).

Secondary objective: To evaluate the efficacy of nemolizumab and to further characterize the relationship between nemolizumab concentrations and clinical efficacy endpoints.

Study Design:

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

Table 1: Clinical Trial Schematic

Screening ↓ Enrollment (~20 subjects)	
	Group 1 (n = ~20)
Treatment	Nemolizumab 30 mg (loading dose at the baseline visit: 60 mg)
Treatment Frequency	Every 4 weeks (Q4W)
Treatment Duration	16 weeks (last study drug injection at Week 12)
Duration of Follow-up Period	8 weeks (from Week 16 to Week 24)

Abbreviations: n = number of subjects; Q4W = every 4 weeks.

Eligible subjects must also have a documented history of inadequate response to topical AD medications. Subjects meeting the eligibility criteria at the screening visit will initiate (or continue) use of a moisturizer and authorized background TCS (including a medium potency TCS for the body, and low potency TCS for TCS-sensitive areas such as the face, neck, intertriginous areas, etc), and according to guidelines in Section 7.5.8.1 for use throughout the study. Use of authorized background therapy is required for at least 14 days before baseline/Day 1 as subjects complete daily assessments of pruritus, to confirm eligibility. Subjects who continue to meet the eligibility criteria at the baseline visit will be enrolled in the study. Subjects may be rescreened once unless the reason for screen failure is related to disease severity inclusion criteria (Investigator's Global Assessment [IGA], Eczema Area and Severity Index [EASI], body surface area [BSA], and Peak Pruritus Numeric Rating Scale [PP NRS]). The latter subjects are not permitted to rescreen.

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

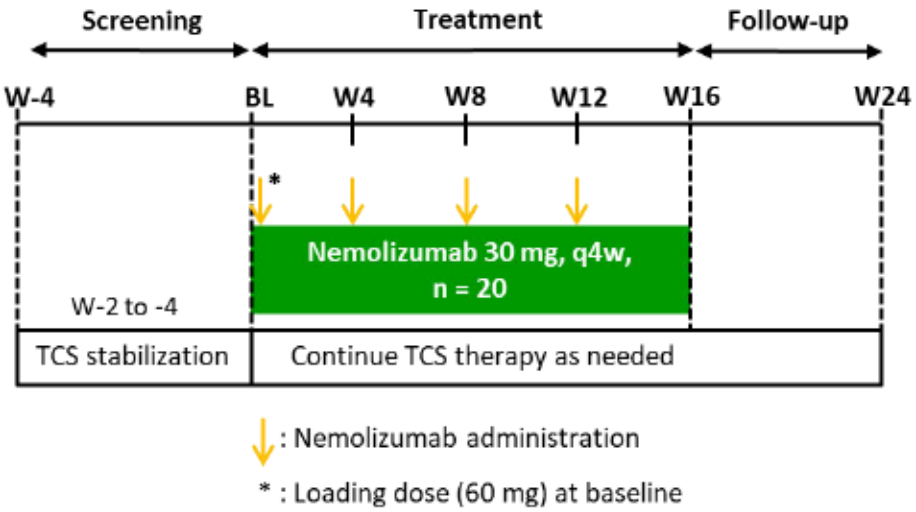
The schedule of assessments is summarized in Section 7.2. Assessments of PK, safety, and efficacy will be conducted throughout the study. Patient-reported assessments of pruritus, sleep disturbance and the use of topical AD medication for their eczema will be collected daily.

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

An Independent Data Monitoring Committee (IDMC) will review and monitor subject safety. The IDMC will provide recommendations on the safety of subjects. Details on the IDMC, including

the plan of analysis for IDMC outputs, the composition of the IDMC, the procedures, roles, responsibilities and their communications are provided in the IDMC charter.

Figure 1: Study Design (Synopsis)



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

Number of Planned Subjects:

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

Investigational Product Treatment:

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

Table 2: Dosing Scheme

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

Background Therapy:

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

Moisturizer: Subjects will apply a moisturizer 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 visit.

TCS therapy: Subjects will apply the authorized background TCS therapy to all AD lesions beginning within the screening period and ≥ 14 days before Day 1, and throughout the study as directed by the investigator.

Subjects will apply a medium potency TCS in areas of the body where use of medium potency TCS is considered safe (eg, trunk and extremities). A low potency TCS will be used on TCS-sensitive areas (eg, face, neck, intertriginous areas).

Subjects will apply a thin layer of authorized TCS 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. It should be noted that "as needed" (PRN) use of TCS is not permitted. Refer to Appendix 2 for authorized TCS and permitted daily use.

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

Rescue Therapy:

If deemed to be medically necessary by the investigator (eg, 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 (ie, Week 2 visit) 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. Some rescue therapies include:

- Topical calcineurin inhibitors (TCI)
- Higher potency of TCS (class I-II according to the US classification)
- 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 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:

Study participation may include a total of 28 weeks for subjects that complete the screening, treatment and follow-up periods. This study includes a 2 to 4-week run-in period followed by a 16-week treatment period. A follow-up visit (Week 24) is scheduled for subjects who will not

rollover into the nemolizumab long-term extension study. Subjects who prematurely discontinue the study before the Week 16 visit have to be followed for 12 weeks after their last dose of study drug.

Study Population:

Inclusion criteria:

1. Subjects ≥ 12 to < 17 years of age at the screening visit.
2. Chronic AD for at least 2 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria[2] (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:
   - [redacted]
   - [redacted]
7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). [redacted]

[redacted]

8. Agree to apply a moisturizer throughout the study from the screening visit daily, and liberally as needed; agree to apply an authorized TCS from the screening visit and throughout the study as determined appropriate by the investigator.

9. Women of childbearing potential must agree either to be strictly abstinent throughout the study and for 12 weeks after the last study drug injection or to use an effective and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. This criterion also applies to a prepubertal female subject who begins menses during the study.

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

   - Progestogen-only oral hormonal contraception
   - Male or female condom
   - Cap, diaphragm, or sponge with spermicide
   - Combination of male or female condom with cap, diaphragm, or sponge with spermicide
   - Combined (estrogen and progestogen containing-) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices

10. Subject and guardian willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.

11. Understand and sign an Informed Consent Form (ICF) and Assent Form before any investigational procedures being performed.

Exclusion criteria:

1. Body weight < 30 kg.

2. Subjects meeting one or more of the following criteria at screening or baseline:

   2a. Had an asthma exacerbation requiring hospitalization in the preceding 12 months.
   2b. Reporting asthma that has not been well-controlled (ie, symptoms > 2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the preceding 3 months.
   2c. Asthma Control Test ≤ 19 (applies only for subjects with a history of asthma).
   2d. Peak expiratory flow (PEF) < 80% of the predicted value.

3. Subjects with a current medical history of chronic obstructive pulmonary disease (COPD) and/or chronic bronchitis.

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

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical trial if hepatitis B surface antibody (HBsAb) is positive (considered immune after a natural infection).
7. Having received any of the following treatments in Table 3 within the specified timeframe before the baseline visit:

Table 3: Prior Treatments

Treatment(s):	Timeframe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Treatment(s):	Timeframe
[redacted]	[redacted]
[redacted]	[redacted]

Note: These treatments should not be discontinued for reasons related to this clinical study.

8. Subjects who failed to respond clinically to previous treatment with a biologic (eg, dupilumab) or a JAK inhibitor.
9. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical trial.
10. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, actinic keratoses or squamous cell carcinoma in situ (Bowen's disease) that have been treated and have no evidence of recurrence in the last 52 weeks before the baseline visit, or (2) carcinoma in situ of the cervix.
11. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
12. History of intolerance to low or mid potency TCS or for whom TCS is not advisable (eg, hypersensitivity to TCS, significant skin atrophy, etc).
13. Known active or latent tuberculosis (TB) infection.
14. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
15. History of or current confounding skin condition (eg, Netherton syndrome, psoriasis, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).
16. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), at the screening visit that may put the subject at significant risk according to the investigator's judgment if he/she participates in the clinical trial, or may interfere with study assessments (eg, poor venous access or needle-phobia).
17. Planned or expected major surgical procedure during the clinical trial.
18. Subjects unwilling to refrain from using prohibited medications during the clinical trial (see Section 7.5.8.2).

Currently participating in any other clinical trial of a drug or device, participated in a clinical trial within the past 3 months before the screening visit, or is in an exclusion period (if verifiable) from a previous clinical trial.

Primary Endpoint(s):

- Pharmacokinetics (PK):
  - Nemolizumab serum concentrations at baseline, Weeks 1-2, 4, 8, 12, 16, 24 and unscheduled visits for safety reasons
  - Nemolizumab serum PK parameters at steady state extrapolated with a population PK analysis (Cl/F, V_d/F, T_{lag}, k_a, C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, $AUC_{0\text{-}16w}$, and $t_{1/2}$)
- Immunogenicity:
  - Anti-drug antibody (ADA) assessments (screening, confirmatory, NAb), at baseline, Weeks 4, 8, 16, 24, and unscheduled visits for safety reasons
- Safety:
  - Incidence of adverse events, including treatment-emergent adverse events (TEAEs), adverse event of special interests (AESI) and serious adverse events (SAEs)
  - Asthma Control Test (ACT): Screening, baseline, Weeks 1-2, 4, 8, 12, 16, 24, and unscheduled visits
  - Physical examination: Change from baseline at all visits
  - Vital signs: Change from baseline at all visits
  - Clinical laboratory values: Change from baseline at Weeks 4, 8, 12, 16, 24 and unscheduled visits for safety reasons
  - Spirometry (PEF): Change from baseline at all visits
  - Electrocardiogram (ECG): Change from screening at Week 16 and unscheduled visits for safety reasons

Secondary Endpoint(s):

- Pharmacokinetics:
  - Nemolizumab serum PK parameters calculated with a non-compartmental analysis (NCA): $AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, and $AUC_{0\text{-}16w}$
- Pharmacodynamics (PD):
  - Blood biomarkers (eg, thymus and activation-regulated chemokine [TARC], IL-31 and/or other proteins) at baseline, Week 8, and Week 16
  - Stratum corneum biomarkers (eg, IL-31 and/or other proteins) at baseline and Week 16
- Efficacy:
  - Absolute and percent change in EASI score from baseline to Week 16
  - IGA success rate from baseline to Week 16
  - Change in BSA involvement of AD, reported as a percentage of all major body sections combined

- Absolute and percent change in weekly average of peak pruritus NRS score from baseline to Week 16
- Absolute and percent change in weekly average of average pruritus NRS score from baseline to Week 16
- Absolute and percent change in weekly sleep disturbance NRS score from baseline to Week 16
- Percent change in SCORing Atopic Dermatitis (SCORAD) score from baseline to Week 16
- Number of topical AD medication-free days

▪ Quality of Life (QoL) Assessment Results:

- Dermatology Life Quality Index (DLQI) for subjects > 16 years of age or children's DLQI for subjects 12-16 years of age at baseline and Week 16

Statistical Analysis:

The final statistical analysis will include all subjects who have completed the study. An interim analysis focused on PK and safety will be performed after approximately 10 subjects have completed the Week 8 visit as the basis to allow recruitment of adolescent subjects in the planned Phase 3 pivotal studies.

PK analysis:

- Population parameters at steady state (Cl/F, V_d/F, T_{lag}, k_a, C_{max}, T_{max}, C_{trough}, AUC_{0-4w}, AUC_{0-8w}, AUC_{0-12w}, AUC_{0-16w}, and $t_{1/2}$) will be extrapolated with a non-linear mixed effect modeling approach. The pre-specified population PK model based on existing information from previous studies in adults will be used to derive empirical Bayes estimates in the adolescent population based on their baseline characteristics, their dosing history and their measured concentrations.
- Some individual PK parameters (AUC_{0-4w}, AUC_{0-8w}, AUC_{0-12w}, AUC_{0-16w}) will also be derived using an NCA.
- Descriptive statistics on nemolizumab serum concentrations will be provided per time point.
- Descriptive statistics on individual NCA-derived PK parameters will be provided.
- A comparison of the average trough (C_{trough}) nemolizumab concentration between ADA+ samples and ADA- samples will be provided. Details will be defined in the SAP.

Safety analysis: Descriptive summaries of the frequency and severity of TEAEs, AESIs and SAEs.

Exposure-response (E/R) analysis: pharmacokinetic pharmacodynamics (PKPD) analysis will be done using the steady state C_{trough} nemolizumab predicted concentration as the exposure variable and efficacy secondary endpoints as confirmed by modeling (eg, change from baseline in EASI, IGA, peak and average pruritus NRS, etc)

Additionally, the following data will be summarized descriptively:

- Demographic and baseline characteristics
- Physical examination and vital signs

- Laboratory parameters
- Adverse events
- Efficacy and QoL parameters
- PD endpoints

Sample size assumption:

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

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

4 List of Abbreviations

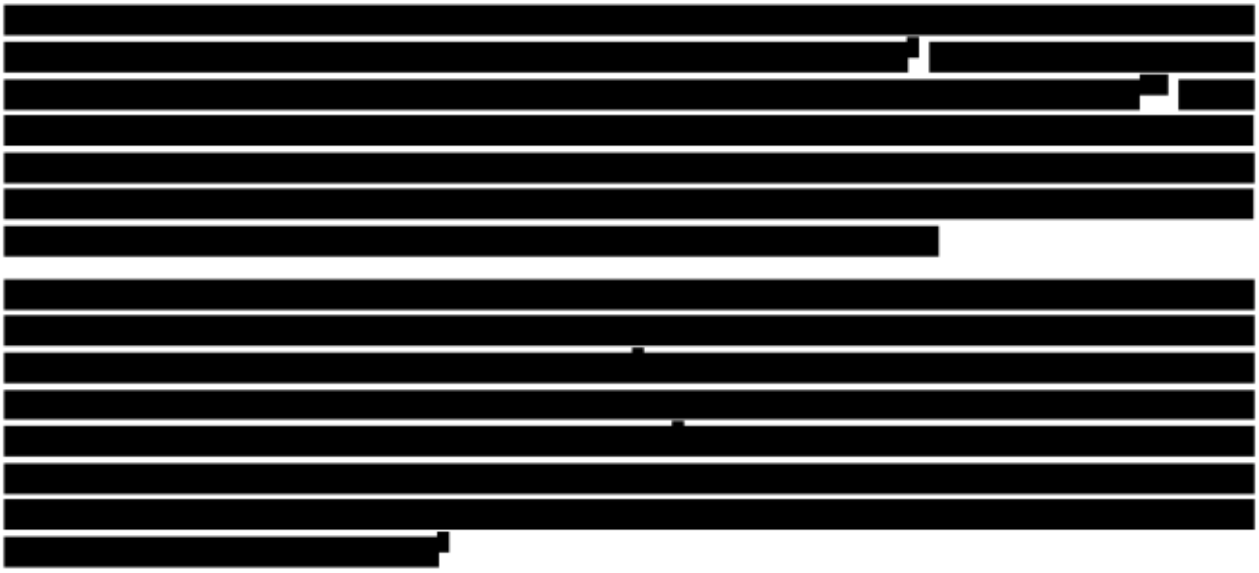
AAD	American Academy of Dermatology
ACT	asthma control test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCG	bacille Calmette-Guérin
BLQ	below the limit of quantification
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
cDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
C_{max}	maximum drug concentration
COPD	chronic obstructive pulmonary disease
CPK	creatinine phosphokinase
CRF	case report form
CRO	contract research organization
C_{trough}	concentration before dosing
CYP450	cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IgG	immunoglobulin G
IgE	immunoglobulin E
IL	interleukin
IRB	institutional review board
IRR	injection-related reaction

ISR	injection site reaction
ITT	intent-to-treat
JAK	Janus kinase
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward
LTE	long-term extension (study)
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
mRNA	messenger ribonucleic acid
n	number of subjects with an observation
N	number of subjects in the dataset or population
NAb	neutralizing antibody
NCA	non-compartmental analysis
NRS	numeric rating scale
OC	observe case
PD	pharmacodynamic
PEF	peak expiratory flow
PK	pharmacokinetic
PP NRS	peak pruritus numeric rating scale
PRN	pro re nata (when necessary or as needed)
Q4W	every 4 weeks
Q8W	every 8 weeks
QoL	quality of life
RA	Receptor A
RBC	red blood cell
RNA	ribonucleic acid
RSE	relative standard error
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	SCORing atopic dermatitis
SD	standard deviation
SIN	subject identification number
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
Th2	type 2 helper T cell
T_{max}	time to maximum concentration
ULN	upper limit of normal
UPT	urine pregnancy test
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

5 Introduction

5.1 Background & Rationale

Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population[1] and up to 25% of children.[2] 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 patients have another concomitant atopic condition (eg, 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 patients' quality of life (QoL), and depression and anxiety have been reported as comorbidities in AD patients.[3] Existing literature suggest that the prevalence of AD is highest in youngest children and gradually reduces with age. Prevalence is higher in developed countries.



The clinical manifestations of AD vary with age.[9] The eczematous changes and its morphology are seen in different locations, depending on the age of the patient (child, adolescent, or adult).

Atopic dermatitis occurs in 3 main age-related stages[10] 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 atopic dermatitis 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, patients 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 the forehead and periorbital regions. The wrists, hands, ankles, feet, fingers, and toes are often involved.

[redacted]

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. [redacted]

[redacted]

Atopic dermatitis is currently managed with topical and systemic treatments, as well as phototherapy. Topical agents are the mainstay of AD therapy. [redacted]

Despite the demonstrated efficacy of topical treatments, they are not always sufficient to control moderate-to-severe AD in some patients, who therefore require the addition of phototherapy or a systemic treatment to achieve sufficient control of AD.[24] [redacted]

[redacted]

Several biological agents are currently being used or developed for the treatment of AD. [redacted]

Nemolizumab, a humanized anti-human IL-31 receptor A (RA) monoclonal antibody, inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction. [redacted]

In conclusion, nemolizumab may present a new treatment option for AD in pediatric as well as adult patients. [redacted] The main objective of the study is to assess the PK profile and safety of nemolizumab, administered concomitantly with background TCS, in adolescent subjects with moderate-to-severe AD and associated pruritus who are not adequately controlled with topical treatments. A similar PK and safety profile compared to previous studies conducted in adults will support the enrollment of adolescent subjects in the planned nemolizumab Phase 3 studies.

5.2 Clinical Studies

The Investigator's Brochure (IB) contains detailed information on clinical and non-clinical studies. [redacted]

5.2.1 Phase 1 Single-Dose Safety Study

[redacted]

5.2.2 Phase 2a Multi-Dose Safety and Efficacy Study

[redacted]

5.2.3 Phase 2b Dose-Ranging Study

[redacted]

[redacted]

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. [redacted]

5.3 Risk/Benefit Assessment

Topical medications are the mainstay of AD therapy. Treatment options are, however, limited for patients 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. [redacted] Rescue therapy, including topical and systemic treatments or phototherapy, may be provided in the current study as judged appropriate by the investigator. [redacted]

[redacted]

b) The exclusion criteria of this clinical trial (ie, restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment) will prevent non-eligible patients from receiving nemolizumab. As no data are available in pregnant or breastfeeding women, these patients are not eligible for this study. [redacted]

[redacted]

d) As nemolizumab has not been evaluated in pediatric populations, including adolescents, safety will be evaluated closely throughout the study, [redacted].

e) 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 (ISR) (ie, lasting > 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
- 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.

5.4 Drug Profile

Nemolizumab is a humanized monoclonal modified immunoglobulin G (IgG) 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. [redacted]

5.5 Dose Selection Rationale

Based on the outcome of the Phase 2b dose-ranging study, the 30-mg dose (with 60-mg loading dose) 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.

6 Study Objectives & Endpoints

6.1 Primary Objective

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

6.2 Primary Endpoints

6.2.1 Pharmacokinetics

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

6.2.2 Immunogenicity

- ADA assessments (screening, confirmatory, NAb), at baseline, Weeks 4, 8, 16, 24 and unscheduled visits for safety reasons

6.2.3 Safety

- Incidence of adverse events, including TEAEs, AESIs and SAEs
- Asthma Control Test: Screening, baseline, Weeks 1-2, 4, 8, 12, 16, 24, and unscheduled visits
- Physical examination: Change from baseline at all visits
- Vital signs: Change from baseline at all visits
- Clinical laboratory values: Change from baseline at Weeks 4, 8, 12, 16, 24 and unscheduled visits for safety reasons
- Spirometry (PEF): Change from baseline at all visits
- Electrocardiogram (ECG): Change from screening at Week 16 and unscheduled visits for safety reasons

6.3 Secondary Objective

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

6.4 Secondary Endpoints

6.4.1 Pharmacokinetics

- Nemolizumab serum PK parameters calculated with an NCA: $AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, and $AUC_{0\text{-}16w}$

6.4.2 Pharmacodynamics

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

6.4.3 Efficacy

- Absolute and percent change in EASI score from baseline to Week 16
- IGA success rate from baseline to Week 16
- Change in BSA involvement of AD, reported as a percentage of all major body sections combined
- Absolute and percent change in weekly average of peak pruritus NRS score from baseline to Week 16
- Absolute and percent change in weekly average of average pruritus NRS score from baseline to Week 16
- Absolute and percent change in weekly sleep disturbance NRS score from baseline to Week 16
- Percent change in SCORAD score from baseline to Week 16
- Number of topical AD medication-free days

6.4.4 Quality of Life Assessment

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

7 Investigational Plan

7.1 Overall Study Design and Plan: Description

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

Eligible subjects must also have a documented history of inadequate response to topical AD medications. Subjects meeting the eligibility criteria at the screening visit will initiate (or continue) use of a moisturizer and authorized background TCS (including a medium potency TCS for the body and low potency TCS for TCS-sensitive areas such as the face, neck, intertriginous areas, etc), and according to guidelines in Section 7.5.8.1 for use throughout the study. Use of authorized background therapy is required for at least 14 days before baseline/Day 1 as subjects complete daily assessments of pruritus, to confirm eligibility. Subjects who continue to meet the eligibility criteria at the baseline visit will be enrolled in the study. [redacted]

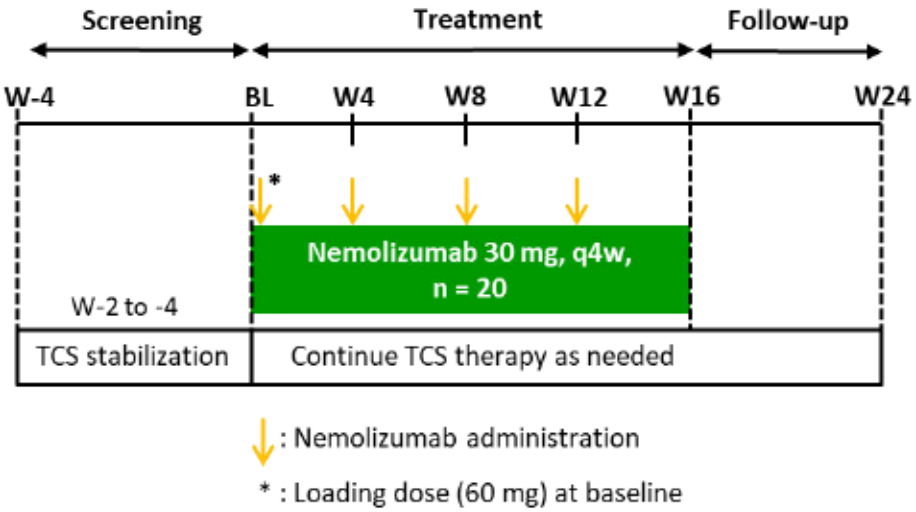
Figure 2 provides an overview of the open-label study design. Subjects will be screened and complete a run-in period of at least 14 days before the baseline visit. Eligible subjects will enter a 16-week treatment period with nemolizumab 30 mg administered subcutaneously every 4 weeks, with a loading dose of 60 mg at baseline/Day 1. The final dose of study drug will occur at Week 12 and subjects will complete the treatment period at the Week 16 visit. [redacted]

The schedule of assessments is summarized in Section 7.2. Assessments of PK, safety, and efficacy will be conducted throughout the study. Patient-reported assessments of pruritus, sleep disturbance and the use of topical AD medication for the subjects' eczema will be collected daily.

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

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

Figure 2: Study Design



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

7.2 Schedule of Assessments

	Screening	Treatment Period						Follow-up	Unscheduled Visit[a,e]	Early Termination Visit[a,f]
Visit	Visit 1/ **Run-in**	Visit 2[a]/ **Baseline**	Visit 3[b]	Visit 4[a]	Visit 5[a]	Visit 6[a]	Visit 7[a,c]	Visit 8[a,d]/ **Final**	(if applicable)	
Week	-4 to -2	(1)	1 to 2	4	8	12	16[c]	24		
Day(s)	-28 to -15	1	10 (± 3)	29 (± 3)	57 (± 3)	85 (± 5)	113 (± 5)	169 (± 5)		
Assessment(s)										
Informed consent and assent form	X									
Inclusion/exclusion criteria	X	X								
Demographic data	X									
Medical history, previous therapy	X	X								
EFFICACY/PATIENT-REPORTED OUTCOME ASSESSMENTS										
Peak pruritus NRS[h] (daily)	X----------X									
Average pruritus NRS[h] (daily)	X----------X									
Sleep disturbance NRS[i] (daily)	X----------X									
Topical AD medication used (daily)[j]	X----------X									
ACT[g,m]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	(X)[k]	X[k]
DLQI/cDLQI[g,l]		X					X			X
EASI	X	X	X	X	X	X	X	X	(X)	X
IGA	X	X	X	X	X	X	X	X	(X)	X
BSA	X	X	X	X	X	X	X	X	(X)	X
SCORAD	X	X	X	X	X	X	X	X	(X)	X

	Screening	Treatment Period						Follow-up	Unscheduled Visit[a,e]	Early Termination Visit[a,f]
Visit	Visit 1/ **Run-in**	Visit 2[a]/ **Baseline**	Visit 3[b]	Visit 4[a]	Visit 5[a]	Visit 6[a]	Visit 7[a,c]	Visit 8[a,d]/ **Final**	(if applicable)	
Week	-4 to -2	(1)	1 to 2	4	8	12	16[c]	24		
Day(s)	-28 to -15	1	10 (± 3)	29 (± 3)	57 (± 3)	85 (± 5)	113 (± 5)	169 (± 5)		
Assessment(s)										
SAFETY/LABORATORY ASSESSMENTS										
Physical examination (including respiratory examination)[m]	X	X	X	X	X	X	X	X	(X)	X
PEF Testing[m]	X	X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	(X)[m]	X[m]
Height	X				X		X	X	(X)	X
Weight	X	X	X	X	X	X	X	X	(X)	X
ECG[n]	X						X		(X)	X
Vital signs[o]	X	X	X	X	X	X	X	X	(X)	X
Urinalysis[p]	X	X[p]		X[p]	X[p]	X[p]	X	X	(X)	X
Hematology[p]	X	X[p]		X[p]	X[p]	X[p]	X	X	(X)	X
Clinical chemistry[p]	X	X[p]		X[p]	X[p]	X[p]	X	X	(X)	X
TB test[q]	X								(X)	
Hepatitis B and C test	X									
HIV test	X									
Pregnancy test[r]	X[r]	X		X	X	X	X	X	(X)	X
Contraceptive counseling	X									
Adverse event reporting	X	X	X	X	X	X	X	X	(X)	X
Concomitant therapy/medications	X	X	X	X	X	X	X	X	(X)	X

	Screening	Treatment Period						Follow-up	Unscheduled Visit[a,e]	Early Termination Visit[a,f]
Visit	Visit 1/ Run-in	Visit 2[a]/ Baseline	Visit 3[b]	Visit 4[a]	Visit 5[a]	Visit 6[a]	Visit 7[a,c]	Visit 8[a,d]/ Final	(if applicable)	
Week	-4 to -2	(1)	1 to 2	4	8	12	16[c]	24		
Day(s)	-28 to -15	1	10 (± 3)	29 (± 3)	57 (± 3)	85 (± 5)	113 (± 5)	169 (± 5)		
Assessment(s)										
PK[p,s,t], ADA[p,t], PD/BIOMARKER[t] ASSESSMENTS										
PK samples[p,s,t]		X	X	X	X	X	X	X	X	X
ADA samples[p,t]		X		X	X		X	X	X	X
Blood sample(s) for biomarkers[t]		X			X		X			X
Stratum corneum samples (using D-squames) for biomarkers[t]		X					X			X
STUDY DRUG AND BACKGROUND THERAPY										
Study drug injection		X[n,v]		X[v]	X	X				
Background therapy[w]	X[w]----------									----------X[w]

Abbreviations: ACT = Asthma Control Test; AD = atopic dermatitis; ADA = anti-drug antibody; BSA = Body Surface Area; cDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = Electrocardiogram; HIV = Human Immunodeficiency Virus; IGA = Investigator's Global Assessment; LTE = long-term extension; NRS = Numeric Rating Scale; PEF = peak expiratory flow; PK = Pharmacokinetics; SCORAD = SCORing Atopic Dermatitis; TB = Tuberculosis; TCS = topical corticosteroid; UPT = urine pregnancy test; WOCBP = women of childbearing potential.

Notes:

[a] Subjects are required to fast for at least 8 hours before the visit(s).

[b] Visit 3 is a single visit occurring between Week 1 to Week 2.

[c] For subjects that complete the Week 16 visit and will rollover to the nemolizumab LTE study, the Week 16 visit (Visit 7) will serve as the final study visit. See Section 7.6.1.

[d] A follow-up visit is required for subjects who discontinue after the Week 16 visit and will not rollover to the nemolizumab LTE study. The follow-up visit should occur 12 weeks after the last study drug injection. See Section 7.6.1.

[e] Assessments to be conducted at the unscheduled visit(s) depend on the reason for the visit. See Section 7.6.2.

[f] Subjects who discontinue before the Week 16 visit should attend an early termination visit and a follow-up/final study visit 12 weeks after the last study drug injection. See Section 7.6.1.

[g] Patient-reported efficacy measurements (ACT and DLQI/cDLQI) should occur before investigator (efficacy and safety) assessments, blood sample collections, and study drug administration.
[h] Peak and average pruritus NRS should be recorded by subjects once daily in the evening, beginning ≥ 2 weeks before Day 1.
[i] Sleep disturbance NRS should be recorded by subjects once daily in the morning, beginning ≥ 2 weeks before Day 1.
[j] Subjects will be asked to record the response (yes/no) to the following question each evening, "Did you apply the eczema medication your doctor gave you, to your skin today?", beginning ≥ 2 weeks before Day 1. See Section 7.5.8.1.1.
[k] Subjects with a history of asthma will complete the ACT at each study visit before physical examination and other investigator assessments. Subjects with de novo diagnosed asthma will complete the ACT beginning at the first visit of de novo diagnosis and at all follow-up study visits.
[l] Subjects aged 17 years or older will complete the DLQI, while subjects aged 12-16 years old will complete the cDLQI.
[m] Complete PE should be performed at each visit. See Section 8.6.8 for PE details. At all visits, all subjects should be asked about respiratory changes and a respiratory examination should also be done during the PE. In addition, PEF measurements will be performed for **all** subjects at screening and baseline. For subjects reporting a medical history of asthma, PEF measurements **and ACT** will be performed at all visits during the clinical trial. Subjects with a medical history of asthma will be referred to the physician managing their asthma if ACT ≤ 19, PEF < 80% of the predicted value, and/or unexpected worsening of asthma is observed or reported. For subjects diagnosed with de novo asthma, PEF measurements **and ACT** will be performed at all visits starting with the visit in which the diagnosis was confirmed. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. PEF measurements will be done under the supervision of qualified study personnel and should occur at approximately the same time of day for all visits, when possible. Attempts should be made 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. See Section 8.6.9 for details on the respiratory examination assessment.
[n] ECGs should be performed before any scheduled vital sign measurements and blood draws. See Section 8.6.10.
[o] 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.
[p] At study drug injection visits, laboratory (hematology, clinical chemistry, and urinalysis), PK, and ADA samples are to be collected ≤ 30 minutes before study drug injection(s). See Sections 8.6.2.1 and 8.6.2.2 for hematology and clinical chemistry testing details, respectively.
[q] TB screening: QuantiFERON-TB Gold test for all subjects. See Section 8.6.5 for details.
[r] Only for WOCBP. **Serum pregnancy test to be performed at the screening visit and urine pregnancy test (UPT) for all other visits**. 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 WOCBP.
[s] See Section 8.2 for details on PK assessments. At the study drug injection visits (baseline, Weeks 4, 8 and 12), PK samples will be collected within 30 minutes before study drug injection (pre-dose samples). At Weeks 1-2, 16 and 24, attempts should be made to collect PK samples at approximately the same time of the day, to the extent possible.
[t] See Section 8.3 and Section 8.4 for details on ADA and PD/Biomarker assessments, respectively.
[u] Subjects will receive a loading dose of 60 mg on Day 1.
[v] Subjects are required to remain at the study center for at least 30 minutes post-injection, following the first 2 injections, to monitor for possible hypersensitivity reaction.
[w] Background therapy (ie, moisturizer and authorized TCS) beginning ≥ 2 weeks before Day 1. Moisturizer should NOT be used *for at least 8 hours before* each clinical visit. See Section 7.5.8.1.1. **The investigator should adjust background TCS use during the study, according to the disease activity and tolerability, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur.**

7.3 Discussion of Study Design

7.3.1 Study Design

This study will evaluate the safety and PK in adolescent AD subjects. The rationale for the general study design is detailed in this section, and is based upon the prior Phase 2b design conducted in adult subjects with AD. The rationale for dose/dose regimen are provided in Section 5.5.

Based on the results of the prior Phase 1, 2a, and 2b and simulation from the pop-PK model, the fixed dose of 30 mg (with a loading dose of 60 mg) was chosen to be administered Q4W in this clinical trial. The selected dose provided the best risk/benefits ratio in adults and is expected to provide similar efficacy and safety in adolescent subjects.

Eligible subjects for this clinical trial will be adolescents with moderate-to-severe AD and associated pruritus whose disease is not adequately controlled by topical treatments. 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, and the need to understand the PK and safety of nemolizumab in the adolescent population for dose verification before initiating planned Phase 3 studies, which will also enroll adolescent subjects. The inclusion criteria for IGA, BSA and EASI are consistent with the disease severity targeted in the Phase 3 studies, enrolling adolescents and adults: An IGA of 3 or 4 corresponds to moderate or severe AD, respectively; BSA of at least 10% is usually observed in these more severe AD patients; an EASI threshold of 16 is generally recognized to be representative of moderate-to-severe AD, and is consistent with the published analyses correlating IGA and EASI assessments in patients with AD.[33,34] Finally, subjects with associated pruritus are targeted because of prior studies with nemolizumab and its marked effect on pruritus.

The study includes a 16-week treatment period and an 8-week follow-up period for safety (ie, 12 weeks after last study drug administration at Week 12) for subjects who will not rollover to the nemolizumab long-term extension study. A 16-week treatment period is considered adequate to evaluate the safety and efficacy of nemolizumab based on the results of the Phase 2b study (114322). As steady state in adults can be achieved in 4 weeks, a trial duration of 16 weeks in adolescents was deemed sufficient to assess all study outcomes.

The duration of the follow-up period (ie, 12 weeks after the last study drug administration), corresponds to 5 half-lives of nemolizumab: the drug plasma level is expected to be lower than the Limit of Quantification at the end of the study, and the follow-up period is therefore considered adequate to ensure the safety of subjects.

Background therapy including moisturizer and authorized TCS will be used throughout this study. This is in line with the current practice to use topical agents in conjunction with systemic treatment in more severe cases.[2] Background TCS will be started from the screening visit, to ensure disease stability and avoid flares. The potency of TCS selected for this study is clinically justified. A medium potency TCS will be used on the body where considered safe (eg, trunk and extremities), and a low potency TCS will be used in TCS-sensitive areas (eg, face, neck, intertriginous areas). The prescribed background TCS use should be within daily frequency limits according to the product labeling. Background TCS use includes guidelines to adjust usage to 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.

Rescue therapy including topical and systemic treatment or phototherapy may be provided if judged to be necessary by the investigator.

This study will assess the PK and safety profile of nemolizumab in the adolescent population, in order to allow their subsequent enrolment in planned Phase 3 studies.

Nemolizumab serum concentration will be assessed at baseline, Weeks 1-2, 4, 8, 12, 16 and Week 24 and at any unscheduled visit for safety reasons. Given that the nemolizumab drug supply configuration and preparation are similar to that used in the Phase 2b study involving adult AD subjects, no change is anticipated in the absorption phase (ka). Thus, limited PK assessment will be done during the absorption phase and serial pre-dose PK samples will be collected at steady state.

PK data from the Phase 1 and Phase 2a studies were used to develop a population PK model that allows an accurate simulation of nemolizumab serum concentrations with different doses and dosing regimens. The population PK model was used to simulate systemic exposure using several fixed doses for the Phase 2b study. The Phase 2b results confirm the predictability of the pop-PK model for the 30 mg dose (Table 4).

Table 4: Nemolizumab Predicted Average Serum Concentrations (µg/mL) Compared to Actual C_{trough} Level for the 30 mg Dose in Adults

C_{trough} (µg/mL) Mean ± SD	Predicted serum concentrations[a]	Actual serum concentration[b]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] N represents the number of observations. Concentrations are the individual predictions derived from the model.

[b] n represents the number of adult subjects that provide PK data for the interim PK analysis of study 114322.

The PK profile in adolescents will be extrapolated from the pop-PK population model developed with the data obtained in adults. As the simulation in adults was performed on a body weight range of 30 to 150 kg, a minimum body weight of 30 kg is required for adolescent participation in the present study. Body weight in patients aged between 12 and 17 years is expected to be between 40 and 70 kg (50th percentile).

Only adolescents with a body weight ≥ 30 kg will be allowed to participate in this study, therefore, the possible maximal doses/kg will be 2.0 mg/kg for the 60-mg loading dose. Pharmacokinetic data for multiple doses up to 2.0 mg/kg have already been collected in the Phase 2a study (Study CIM003JG) in adults, and up to 90 mg in the Phase 2b study, and have been considered as

safe. The proposed dose appears to be below the highest doses studied previously; therefore, the proposed doses are supported by the available clinical safety data.

7.4 Selection of Study Population

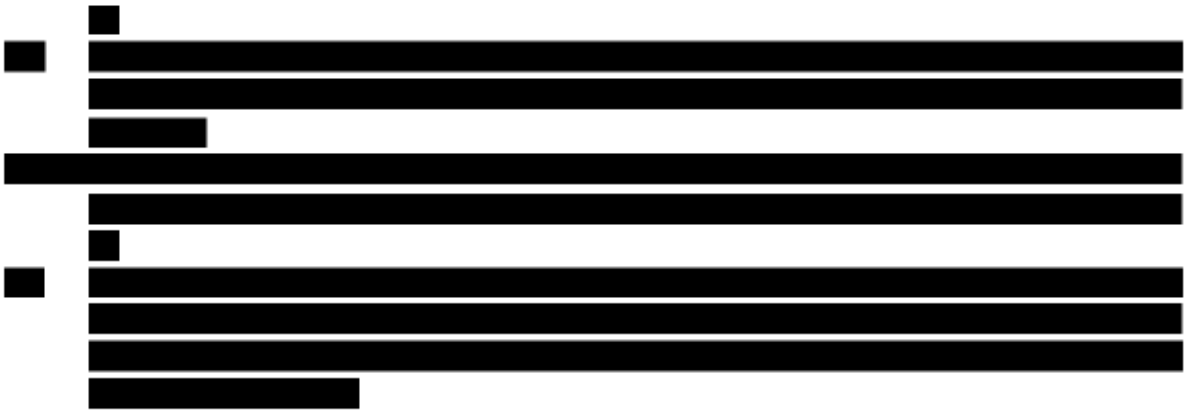
7.4.1 Number of Planned Subjects

It is anticipated that approximately 30 subjects will be screened, with approximately 20 eligible subjects enrolled in approximately 10 study centers across the United States. Refer to the statistical considerations on which the numbers are based in Section 9.5.

7.4.2 Inclusion Criteria

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

1. Subjects ≥ 12 to < 17 years of age at the screening visit.
2. Chronic AD for at least 2 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria[2] (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 Body Surface Area (BSA) at both screening and baseline visits.
6. Peak (maximum) pruritus NRS score of at least 4.0 at both screening and baseline visits:
   - [redacted]
   - [redacted]
7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). [redacted]



8. Agree to apply a moisturizer throughout the study from the screening visit daily, and liberally as needed; agree to apply an authorized TCS from the screening visit and throughout the study as determined appropriate by the investigator.

9. Women of childbearing potential must agree either to be strictly abstinent throughout the study and for 12 weeks after the last study drug injection or to use an effective and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. This criterion also applies to a prepubertal female subject who begins menses during the study.

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

   - Progestogen-only oral hormonal contraception
   - Male or female condom
   - Cap, diaphragm or sponge with spermicide
   - Combination of male or female condom with cap, diaphragm or sponge with spermicide
   - Combined (estrogen and progestogen containing-) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices

10. Subject and guardian willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.

11. Understand and sign an Informed Consent Form (ICF) and Assent Form before any investigational procedures being performed.

7.4.3 Exclusion Criteria

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

1. Body weight < 30 kg.
2. Subjects meeting one or more of the following criteria at screening or baseline:
   - 2a. Had an asthma exacerbation requiring hospitalization in the preceding 12 months.
   - 2b. Reporting asthma that has been not well-controlled (ie, symptoms > 2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the preceding 3 months.
   - 2c. Asthma Control Test ≤ 19 (applies only for subjects with a history of asthma).
   - 2d. Peak expiratory flow < 80% of the predicted value.
3. Subjects with a current medical history of chronic obstructive pulmonary disease (COPD) and/or chronic bronchitis.
4. Cutaneous infection within 1 week before the screening visit or any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 1 week before the screening visit. Subjects may be rescreened once the infection has resolved.
5. Requiring rescue therapy for AD during the run-in period, or expected to require rescue therapy within 2 weeks following the baseline visit.
6. Positive serology results for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, or human immunodeficiency virus [HIV] antibody at the screening visit;

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical trial if hepatitis B surface antibody (HBsAb) is positive (considered immune after a natural infection).
7. Having received any of the following treatments in Table 5 within the specified timeframe before the baseline visit:

Table 5: Prior Treatments

Treatment(s):	Timeframe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Treatment(s):	Timeframe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Note: These treatments should not be discontinued for reasons related to this clinical study.

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

17. Planned or expected major surgical procedure during the clinical trial.
18. Subjects unwilling to refrain from using prohibited medications during the clinical trial (see Section 7.5.8.2).
19. Currently participating in any other clinical trial of a drug or device, participated in a clinical trial within the past 3 months before the screening visit, or is in an exclusion period (if verifiable) from a previous clinical trial.

7.4.4 Removal of Subjects From Therapy or Assessments

Although the importance of completing the entire clinical trial 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 trial if deemed to be necessary.

Subjects may stop study drug for any of the following reasons:

- Subject consent withdrawal
- Use of non-permitted concurrent therapy
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue
- Serious immediate-type allergic manifestations including anaphylactic reaction
- Pregnancy
- Use of systemic rescue therapy during the run-in period through the Week 12 visit (last study drug injection), unless otherwise specified in Table 8 of Section 7.5.8.2.
- Investigator request
- Intercurrent illness
- Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma or basal cell carcinoma)
- Any opportunistic infection (such as active TB and other infections whose nature or course suggest an immune-compromised status)
- Sponsor request
- Treatment failure

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. Subjects discontinuing study drug before the Week 16 visit should attend an early termination visit and a follow-up/final visit 12 weeks after the last study drug injection for safety follow-up.

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.

7.4.4.1 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 8.6.1.2) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Form(s) (see Section 8.6.1.2).
- 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.
- 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 (voluntary abortion, spontaneous abortion or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for reporting an SAE (Section 8.6.1.2).

The investigator should also be notified of pregnancy occurring during the study 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 (the Exit Form) of the CRF, or an SAE report will be completed if the subject has completed the study.

7.5 Investigational Product: Nemolizumab

"Study drug" or "study medication" refers to nemolizumab (CD14152) drug product for purposes of this open-label study. The list of excipients are detailed in the IB.

7.5.1 Investigational Product Administered

Nemolizumab drug supply configuration and preparation are similar to that used in the Phase 2b study involving adult AD subjects, to minimize exposure variability when comparing adolescent results to adults.

Nemolizumab will be supplied in single-use vials in the form of 153 mg lyophilized powder. The drug product is to be reconstituted by adding 1.3 mL of sterile water for injection. A vial of nemolizumab placebo will be used for dilution, to achieve desired dose level. (Syringes, needles, and sterile water for injection will be provided to the study centers for use in the trial.)

[redacted]

All study drug doses will be administered by trained and qualified personnel at study centers. Qualified personnel will prepare the dosing solution by mixing appropriate amounts of reconstituted nemolizumab, according to the provided "instruction(s) for use" in the pharmacy manual.

Table 6: Dosing Scheme

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

Once the dosing solution is prepared, 1.0 mL of it will be drawn into a syringe, which will be administered subcutaneously in the abdomen of the subjects. Other sites of injection may be permitted (ie, for safety reasons) after discussion with the medical monitor. The site of injection should be recorded in the subject's treatment record at each time point.

[redacted]

7.5.2 Identity of Investigational Product

Table 7: Description of Nemolizumab

Name	Nemolizumab
Internal code	CD14152
Pharmaceutical form	Lyophilized powder
Formula number	N/A
Packaging	Vial
Dosage	30 mg (with a loading dose of 60 mg at baseline)
Route	Subcutaneous injection
Dose regimen	Every 4 weeks (Q4W)
Treatment duration	16 weeks (last injection at Week 12)

7.5.3 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 trial.

7.5.4 Study Drug Management

CCI

[redacted]

7.5.4.2 Study Drug Accountability

Study drug at the study center will be accounted for and no unauthorized use is permitted. The designated personnel will acknowledge receipt of the study drug to confirm the shipment condition and content. If a damaged shipment is received, he/she will notify the sponsor/clinical research organization (CRO), quarantine the shipment in a specific storage area, and document the event as specified in the pharmacy manual.

The designated personnel will also maintain accurate records of the study drug throughout the clinical trial, including the inventory delivered to the study center, the use by each subject,

the reconciliation of all delivered and received vials of study drug, and the return of used and unused study drug as specified in the pharmacy manual.

[redacted]

7.5.4.3 Dispensing and Return of Study Drug

All drug preparation must be appropriately performed and documented by the designated personnel. [redacted]

7.5.4.4 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). [redacted]

7.5.5 Method of Assigning Subjects to Treatment

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

[redacted]

7.5.6 Selection of Doses in the Study

The 30 mg dose proposed for this study is supported by the results of the nemolizumab Phase 2b study (114322). Refer to Section 5.5 for further details.

7.5.7 Dose Modification

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

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

In the event of a missed dose (ie, temporary discontinuation of the study drug), it will be documented in the CRF that the drug has not been administered at the study visit, together with the reason (eg, for safety). Subjects will be asked to return to the study centers for all remaining visits and complete all study assessments and procedures as described in Section 7.2.

Dosing frequency is scheduled for every 4 weeks, based on the baseline/Day 1 visit date. [redacted]

7.5.8 Prior and Concomitant Therapy

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

Concomitant therapies 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 (eg, phototherapy, exodontia, 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. (Contraceptive counseling should occur at screening). Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form should be completed to account for the change in therapy, except in some cases such as dose modification for a chronic condition, in which case the medication will be linked to an item in the subject's medical history.

7.5.8.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 7.5.8.2), all therapies are authorized including basic skin care (cleansing and bathing), emollients, bleach baths, topical anesthetics and antihistamines without a sedative effect.

[redacted]

7.5.8.1.1 *Background Therapy*

The prescribed use of background therapies should be documented in the CRF. Background therapies are used throughout the study (screening through the follow-up visit), as described below.

Moisturizer: Subjects will apply a moisturizer 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. [redacted]

TCS therapy: Subjects will apply the authorized background TCS therapy to all AD lesions beginning within the screening period and ≥ 14 days before Day 1, and throughout the study as directed by the investigator.

Subjects will apply a medium potency TCS in areas of the body where use of medium potency TCS is considered safe (eg, trunk and extremities). A low potency TCS will be used on TCS-sensitive areas (eg, face, neck, intertriginous areas).

[redacted]

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

7.5.8.1.2 *Rescue Therapy*

If deemed to be medically necessary by the investigator (eg, 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. As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks from baseline (ie, Week 2 visit) 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. Some rescue therapies include:

- Topical calcineurin inhibitors
- Higher potency of TCS (class I-II according to the US classification)
- Oral corticosteroids
- Biologics (including their biosimilars)
- Systemic nonsteroidal immunosuppressants/immunomodulators

- Phototherapy

[redacted]

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, 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. [redacted]

Further, the use of any rescue therapies should be documented in the CRF.

7.5.8.2 Prohibited Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study, unless otherwise specified in Table 8:

Table 8: Prohibited Medication/Therapy

Treatment(s)	Timeframe	
	Before Baseline/Day 1	Day 1 – Week 24
Non-live vaccine	2 weeks	Prohibited
Coal tar products	2 weeks	Prohibited
Topical calcineurin inhibitors	2 weeks	Prohibited *
Non-authorized medium or low potency TCS	2 weeks	Prohibited
Higher potency TCS (US classification I-II)	2 weeks	Prohibited *
Topical medications, including authorized TCS, with occlusive dressings (eg, wet wraps)	2 weeks	Prohibited
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks	Prohibited *
Phototherapy	4 weeks	Prohibited *
Tanning bed use	4 weeks	Prohibited
Live or attenuated vaccine (eg, measles, mumps, rubella, live attenuated influenza, chicken pox, smallpox, oral polio (Sabin), rotavirus, yellow fever)	12 weeks	Prohibited
Biologics and their biosimilars (eg, dupilumab, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)	Prohibited *

Treatment(s)	Timeframe	
	Before Baseline/Day 1	Day 1 – Week 24
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil)	4 weeks or 5 half-lives (whichever is longer)	Prohibited *
Investigational topical and systemic medication (other than nemolizumab) (eg, topical or oral JAK inhibitors)	16 weeks	Prohibited
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, or sedative anti-depressants (eg, amitryptiline). (Note: Stable treatment with antihistamines with or without sedative effect is allowed.)	1 week	Prohibited
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks	Prohibited
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks	Prohibited

* unless used as rescue therapy during the study

Note: These treatments should not be discontinued for reasons related to this clinical 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 trial, the investigator should also notify the medical monitor and discuss whether or not it is acceptable for the subject to continue the study treatment.

7.6 Duration of Subject Participation

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

7.6.1 Early Termination Visit

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

[redacted]

- [redacted]

7.6.2 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results or for follow-up of AEs. Visits occurring outside of the visit window are not considered as unscheduled visits.

[redacted] blood sample collection for PK and ADA analyses are mandatory during unscheduled visits for safety reasons.

8 Study Assessments

A written, signed ICF, assent form and 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 SIN. For the duration of the entire clinical trial, the subject will be identified using the SIN in all documentations and discussion.

The planned schedule of assessments is described in Section 7.2. At each visit, assessments/ procedures should be performed in the following order:

1. Patient-reported efficacy measurements
2. Investigator assessments (including efficacy and safety)
   - ECG should be done before vital signs measurements (and blood draws). See Section 8.6.10.
3. Blood sample collection for laboratory assessments
4. Administration of study drug

8.1 Efficacy Assessments

Efficacy measurements should be conducted by the investigators (or trained designees) and subjects (for patient-reported efficacy measurements) according to Section 7.2 and Section 8.1. Whenever possible, the same evaluator should make the assessment throughout the study.

8.1.1 Eczema Area and Severity Index

Eczema Area and Severity Index is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs. EASI is a composite score ranging from 0 to 72 (see Appendix 3).[36] 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) [redacted] The EASI score will be calculated in the CRF.

8.1.2 Investigator 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 0 (clear) or 1 (almost clear) and a 2 grade change from baseline (see Appendix 4).[37]

8.1.3 Body Surface Area

The BSA involvement of AD will be assessed by the investigator or trained designee for each part of the body [redacted]

8.1.4 SCORing Atopic Dermatitis

SCORing Atopic Dermatitis is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs and symptoms. SCORAD ranges from 0 to 103 and has 3 components: extent (BSA, as described in Section 8.1.3), signs, and symptoms of AD and subject-reported symptoms of pruritus and sleep loss (see Appendix 5).[38]

Investigator or designee will assess the severity of 6 signs of AD (erythema/darkening, edema/papulation, oozing/crusting, excoriation, lichenification/prurigo and dryness), each on a scale ranging from 0 (none) to 3 (severe). Investigator or 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 VAS from 0 to 10. The SCORAD score will be calculated in the CRF.

8.1.5 Pruritus Numeric Rating Scale

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). Pruritus NRS has been validated in other AD clinical trials in adults and the minimum clinically important difference was shown to be 3 to 4.

The screening PP NRS score, measuring maximal pruritus intensity, will be determined by a single PP NRS assessment (score ranging from 0 to 10) [redacted]

Subjects will receive instructions on how to use and record their pruritus NRS scores on an electronic device, and will complete the assessment once daily in the evening throughout the clinical trial (including the run-in and the follow-up period).

Subjects will be asked the following questions in their local language:

- For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch [redacted]?"
- For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment [redacted]?"

8.1.6 Sleep Disturbance Numeric Rating Scale

Sleep disturbance NRS is a scale to be used by the subjects to report the degree of their sleep loss related to AD (see Appendix 7). Subjects will receive instructions on how to use and record their sleep disturbance NRS scores on an electronic device, and will complete the assessment once daily in the morning throughout the clinical trial (including the run-in and the follow-up period).

Subjects will be asked the following questions in their local language:

- On a scale of 0 to 10, with 0 being 'no sleep loss related to signs/symptoms of AD' and 10 being 'I cannot sleep at all due to the signs/symptoms of AD', how would you rate your sleep last night?"

8.1.7 Application of Topical Medication for AD: Diary

Subjects will be instructed to use the authorized background TCS as prescribed by the investigator. Each evening, subjects will be asked to record the response (yes/no) to the following question, "Did you apply the eczema medication your doctor gave you, to your skin today?", on an electronic device (ie, diary), throughout the clinical trial (including the run-in and the follow-up period).

8.1.8 Dermatology Life Quality Index (DLQI)/Children's DLQI (cDLQI)

Dermatology Life Quality Index is a validated 10-item questionnaire for subjects aged > 16 years, covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment (see Appendix 8).[39]

Children's DLQI (cDLQI) is a comparable validated 10-item questionnaire designed for pediatric subjects aged 16 years or less (see Appendix 8).[40]

Subject will rate each question ranging from 0 (not at all) to 3 (very much). A higher total score indicates a poorer QoL.The DLQI/cDLQI will be administered according to the schedule of assessments (Section 7.2).

8.2 Pharmacokinetics

8.2.1 Blood Sampling

Blood samples will be collected according to Section 7.2 to determine the PK profile of nemolizumab. The serum concentration of nemolizumab will be assessed at baseline, Weeks 1-2, 4, 8, 12, 16, 24 and at any unscheduled visit for safety reasons.

[redacted] 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).

8.2.2 PK Parameters

PK parameters of nemolizumab in the serum will be calculated by the designated CRO using 2 analyses:

PK parameters will be derived using a non-linear mixed effect modeling approach with NONMEM. A pre-specified population PK model based on existing information from previous studies in adults (first-order absorption and a 1-compartment distribution model) will be used to derive empirical Bayes estimates in the adolescent population based on their baseline characteristics, their dosing history and their measured concentrations. The adequacy of the model to properly describe the adolescent data will be based on the model diagnostic tools described in a in a dedicated PK modeling plan.Estimates of main population PK parameters (Cl/F, V_d/F, T_{lag}, k_a), including inter-individual variability, covariate effects, residual error and their relative standard error [RSE]), will be obtained using the popPK model.

- Other individual nemolizumab PK parameters will be derived using the same popPK model (C_{max}, T_{max}, C_{trough}, $AUC_{0\text{-}4w}$, $AUC_{0\text{-}8w}$, $AUC_{0\text{-}12w}$, $AUC_{0\text{-}16w}$, and $t_{1/2}$).
- In addition, a static analysis based on pre-dose (C_{trough}) serum concentration will be performed using an NCA. Data from subjects with missing concentration values (missing samples) may be used if PK parameters can be estimated using the remaining data points.

  For the NCA analysis, the following PK parameters will be determined for each subject based on C_{trough} concentration:

From baseline to Week 4:

- $AUC_{0\text{-}4w}$: Area under the concentration time curve from pre-dose through 4 weeks post dosing. $AUC_{0\text{-}8w}$ includes the serum drug concentration up to Week 4 (ie, the serum concentration collected at baseline, Week 1-2, and 4).

From baseline to Week 8:

- $AUC_{0\text{-}8w}$: Area under the concentration time curve from pre-dose through 8 weeks post dosing. $AUC_{0\text{-}8w}$ includes the serum drug concentration up to Week 8 (ie, the serum concentration collected at baseline, Week 1-2 , 4 and 8).

From baseline to Week 12:

- $AUC_{0\text{-}12w}$: Area under the concentration time curve from pre-dose through 12 weeks post dosing. $AUC_{0\text{-}12w}$ includes the serum drug concentration up to Week 12 (ie, the serum concentration collected at baseline, Week 1-2, 4, 8 and 12).

From baseline to Week 16:

- $AUC_{0\text{-}16w}$: Area under the concentration time curve from pre-dose through 16 weeks post dosing. $AUC_{0\text{-}16w}$ includes the serum drug concentration up to Week 16 (ie, the serum concentration collected at baseline, Week 1-2, 4, 8, 12 and 16).

8.3 Immunogenicity

Blood samples will be collected according to Section 7.2 to assess anti-drug (anti-nemolizumab) antibodies (ADA). Serum samples will be assessed for ADA at baseline, Weeks 4, 8, 16, 24 and at any unscheduled visit for safety reasons. ADA will be determined at these time points by the designated CRO using a validated enzyme-linked immunosorbent assay (ELISA) screening assay. The serum concentration will be assessed using a multi-tiered approach.

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

[redacted] Results will be [redacted] included as an appendix in the final CSR.

8.4 Pharmacodynamics

Blood and stratum corneum samples will be collected to investigate the effect of nemolizumab on selected biomarkers. [redacted]

Blood samples will be collected for assessment of TARC and IgE by the central laboratory. [redacted]

[redacted]

8.5 CD14152 Quantification in Biological Sampling

Concentration of nemolizumab in the serum will be determined by the designated CRO using a validated ELISA method. [redacted] Results will be [redacted] included as an appendix in the final CSR.

8.6 Safety Assessments

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

8.6.1 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 case report form (CRF) under specific efficacy assessments.

Notes:

- 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 as an AE; however, it must be monitored and reported as described in Section 8.6.1.2.
- Each new episode of a chronic disease (eg, hay fever, allergy, etc) 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 trial.

[redacted]

[redacted]

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 (ie, nemolizumab) and/or study procedure (eg, injection, TCS, blood sample collection). [redacted]

[redacted]

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

Reasonable Possibility:

According to the reporting investigator, there is a reasonable possibility (ie, 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 trial protocol procedure (eg, injection, TCS, 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 trial protocol procedure and the AE.

Action Taken

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

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication
- Other, specify.

Follow-up of Adverse Events

All investigators should follow up 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]).

8.6.1.1 Adverse Events of Special Interest

An AESI is a noteworthy event for the study drug that should be monitored closely and reported immediately. See Section 8.6.1.4 for reporting procedure. An AESI can be either serious or non-serious.

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

- Injection-related reactions
  - Anaphylactic reactions
  - Acute allergic reactions requiring treatment
  - Severe ISR (ie, lasting > 24 hours)
- Newly-diagnosed asthma or worsening of asthma
  - More specifically, subjects *with* a medical history of asthma must be referred to the physician who manages their asthma when:
    - ACT score ≤ 19; an ACT score ≤ 19 conveys asthma which may not be adequately controlled. An AESI is reported based on the investigator's clinical judgment of the managing physician's report.
    - 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 must 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 assessment suggests 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
- Peripheral edema: limbs, bilateral
- Facial edema

- Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

8.6.1.2 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, ie, 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 enrollment in the clinical trial, admission to a day-care facility, social admission [eg, if the subject has no place to sleep], or administrative admission [eg, 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 one 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.

8.6.1.3 Procedure for Reporting a Serious Adverse Event

For any SAE occurring during the clinical trial, 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 CCI Safety and Pharmacovigilance group of an SAE report, by email or fax:

   Fax No.: PPD

   Safety email: PPD

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 (eg, laboratory test results) to the CCI [redacted] 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 form **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 form, 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 (ie, 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 Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements, and are forwarded to investigators as necessary.

   An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or its delegate (ie, the CRO) will file it with the IB 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.

8.6.1.4 Procedure for Reporting an Adverse Event of Special Interest

For any AESI occurring during the clinical trial, 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 and recorded as an AESI in the CRF **within 24 hours of receipt of the event**. The CCI [redacted] Safety and Pharmacovigilance group will receive automated notification of an AESI by email.

Note: Immediate AESI 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 medical records (eg, laboratory test results) to the CCI Safety and Pharmacovigilance group 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, update the AESI form within 24 hours 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.

8.6.1.5 Procedure for Reporting Pregnancies

Any pregnancy occurring during clinical trials, 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 trial. 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 email or fax along with the exit form within 24 hours of receipt of the information, to the CCI Safety and Pharmacovigilance group. Refer to Section 8.6.1.3.

   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 email or fax to the CCI Safety and Pharmacovigilance group within 24 hours of receipt of the information. If the subject can no longer be reached (ie, 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 email or fax to the CCI Safety and Pharmacovigilance group within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (ie, voluntary abortion, spontaneous abortion or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 8.6.1.3).

8.6.1.6 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 (eg, reference safety information in the investigators brochure for nemolizumab, study protocol, etc).

The sponsor or its delegate (ie, CCI) 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 an SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or its delegate (ie, CCI CCI will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.6.2 Clinical Laboratory Evaluations

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

The investigator or medically qualified co-investigator must review and evaluate laboratory values for each subject in a timely manner. 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 one 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, eg, 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.

All clinically significant out-of-range laboratory values at the screening visit will be recorded (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 screening visit (ie, 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. Subjects will be required to fast for at least 8 hours before the visits when blood chemistry testing is planned, except for the screening visit. 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. Additional samples may be required if medically indicated (eg, at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

The following laboratory safety tests will be performed as specified in Section 7.2:

8.6.2.1 Hematology

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

8.6.2.2 Clinical Chemistry

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

8.6.2.3 Urinalysis

pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

8.6.3 Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs) at subsequent visits according to Section 7.2.

UPTs 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.

8.6.4 Virology

Virology including HBsAg, HBcAb, hepatitis C, HIV-1 and -2 antibody will be assessed at the screening visit.

8.6.5 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.

8.6.5.1 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 (or IGRA)[35], 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.

8.6.5.2 Tuberculosis Screening

Ideally, as part of the medical history, the subject should be asked if they have 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 (eg, prison, hospitals).

A subject who tests positive for latent TB (with a positive QuantiFERON 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 they have a positive test result.

8.6.6 Vital Signs

Vital signs will be evaluated at the screening visit and at each subsequent visit according to Section 7.2. 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. Any clinically significant changes from the screening visit will be recorded as an AE.

8.6.7 Height and Weight

Height will be measured at screening and designated visits; weight will be measured at all visits. Subject must be at least 30 kg at both screening and baseline visits in order to be enrolled into this clinical trial.

Any clinically significant weight changes from the screening visit will be recorded as an AE.

8.6.8 Physical Examination

Complete physical examination (PE) should be performed at all scheduled visits and any unscheduled visits for safety reasons, according to Section 7.2. A complete PE will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (with respiratory assessment; see Section 8.6.9), gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system.

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.

8.6.9 Respiratory Assessments

At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, 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.

8.6.9.1 Asthma Control Test

Subjects with a medical history of asthma will take the Asthma Control Test (ACT) at each study visit before questioning and physical examination by the investigator. Subjects with a new (de novo) diagnosis of asthma will take the ACT beginning at the visit the diagnosis was first confirmed and thereafter, at all subsequent study visits. Subjects with an ACT score ≤ 19 should be referred to the physician managing their asthma.

8.6.9.2 Respiratory Examination

The ACT will aid the investigator's questioning of subjects with a medical history of asthma and should be completed before the clinical questioning. 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

should 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 (exam findings or newly-reported signs and/or symptoms suggestive of asthma) should be referred to a respiratory specialist.

8.6.9.3 Spirometry/Peak Expiratory Flow

All subjects will have spirometry (PEF) performed at screening and baseline. For subjects reporting a medical history of asthma, spirometry (PEF) will be performed at each visit during the clinical trial under the supervision of qualified study personnel. Subjects with a new (de novo) diagnosis of asthma will be evaluated by spirometry (PEF) at all visits after the diagnosis is first made.

Peak expiratory flow 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. Attempts should be made 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 PEF < 80% of the predicted value should be referred to a respiratory specialist.

8.6.9.4 Respiratory Referrals

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

- PEF < 80% of the predicted value.
- ACT score ≤ 19. As an ACT score ≤ 19 conveys asthma that may not be adequately controlled.
- Unexpected worsening of asthma is observed or reported.

Subjects without a medical history of asthma must be referred to an appropriate specialist physician when:

- Signs and/or symptoms suggestive of asthma are newly-observed or reported.
- Respiratory assessment suggests a decline in the subject's respiratory health.

8.6.10 Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed according to Section 7.2. ECGs for each subject should be obtained using the same electrocardiograph machine whenever possible. To minimize variability, subjects must remain in a resting position for at least 10 minutes before each ECG recording. Environmental distraction should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed before any scheduled vital sign measurements and blood draws. For safety monitoring, the investigator or qualified designee must review, sign and date all ECG tracings. Paper ECG recordings will be kept as part of the subject file at the study center. All abnormal ECG findings considered to be clinically significant by the

investigator at the screening visit will be recorded. Any clinically significant changes from the screening visit will be reported as AEs in the CRF.

8.7 Independent Data Monitoring Committee

An IDMC consisting of independent experts will review and monitor the accumulating safety data for the study on an ongoing basis.

The specific responsibilities and composition of the IDMC are outlined in a separate document, the IDMC Charter. The details of outputs provided for the meetings are also referenced in this separate IDMC Charter.

9 Statistical Methods

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain detailed and technical descriptions of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the protocol below. Any changes made to the analysis after finalization of the SAP will be documented in the clinical study report.

The final statistical analysis will include all subjects who have completed the study. An interim analysis focused on PK and safety will be performed after approximately 10 subjects have completed the Week 8 visit as the basis to allow recruitment of adolescent subjects in the planned Phase 3 pivotal studies.

9.1 Data Transformations

Details of any data transformation for endpoints will be provided in the SAP.

9.2 Analysis Populations

The following populations and evaluability criteria will be used to analyze the pharmacokinetic-pharmacodynamic (PK/PD), safety, efficacy, and QoL endpoints.

9.2.1 PK Analysis Population

The PK analysis population will include all subjects in the safety population who provide at least one post-baseline evaluable drug concentration value. All PK and PK/PD endpoints will be analysed using the PK population.

9.2.1.1 Safety Population

The safety population will comprise all subjects in the ITT population who receive at least one dose of study drug. Subjects will only be excluded if there is clear documented evidence that the subject did not receive any study drug injection. All safety data will be summarized based on the safety population.

9.2.2 Intent-to-Treat (ITT) Population

The ITT population will consist of all enrolled subjects. All efficacy endpoints will be analyzed based on the ITT population.

9.3 Imputation of Missing Data

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

Continuous Endpoints: To impute the missing values for efficacy continuous endpoints, Last Observation Carried Forward (LOCF) approach will be used. In addition, Observed Case (OC) will be carried out as sensitivity analysis.

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

Use of Rescue Therapy: All Efficacy Data, Except OC, Will Be Set To Missing After Rescue Medication Is Used. In OC Analysis, No Observed Data After Subject Has Received Rescue Treatment Will Be Excluded.

There will be no imputations for PK, missing laboratory, and vital sign data. Further details on imputation of missing data will be provided in the SAP.

9.4 Descriptive and Inferential Statistical Analyses

9.4.1 Demography and Baseline Characteristics

Subject disposition, demographics, baseline characteristics, previous therapies, concomitant therapies, and physical examinations will be summarized by descriptive statistics. Pre- and post-treatment therapies and procedures will be summarized separately.

9.4.2 PK Parameters and ADA Analyses

The PK parameters obtained using modelling techniques will be regarded as primary endpoints for the PK analyses (see details in Section 6.4.1). Primary inference for all the PK parameters will be based on the pharmacokinetic analysis population.

The 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.

The pop-PK and PKPD models will be detailed in a separate Modeling Analysis Plan.

The concentration at each time point will be summarized as arithmetic mean, standard deviation, median, minimum, and maximum, number of BLQs (Below the Limit of Quantification).

Descriptive statistics (n, arithmetic mean, standard deviation [SD], minimum, median, maximum) will be calculated for all PK parameters obtained using NCA.

For ADA analyses, the incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, treatment-related ADA). A presentation of ADA results will be detailed in the SAP.

9.4.3 Safety Analyses

All safety analyses will be based on the safety population. Summary of all safety endpoints will be presented.

9.4.3.1 Extent of Exposure

The duration of exposure and the number of subjects exposed to study drug will be summarized by visit. The number of subjects exposed will be presented by study periods (treatment period and follow-up period).

9.4.3.2 Adverse Events

Treatment-emergent adverse events (TEAEs), defined as those AEs occurring after the first administration of study treatment until the last study visit, will be tabulated in frequency tables by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (MedDRA) for each study phase. Additional summary tables will be provided for SAEs, AEs related to the study drug and/or study procedure, AESIs, and AEs leading to treatment discontinuation and study withdrawal. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

Pre-treatment AEs will be listed separately.

9.4.3.3 Electrocardiogram

All ECG changes from screening at Week 16 and unscheduled visits will be summarized for safety reasons.

9.4.3.4 Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized. In addition, the number and percent of subjects below, within, and above the laboratory reference ranges will be summarized by visit. Shift tables will be generated using the reference ranges.

Abnormal laboratory values from tests performed on the baseline visit will not be considered as TEAEs, because the sample collection will be conducted before study drug administration.

9.4.3.5 Vital Signs

All vital signs and weight data (absolute values and change from baseline) will be summarized by visit. In addition, the number and percent of subjects with clinically significant abnormal values of clinical concern will be summarized.

9.4.3.6 Asthma Control Test

Total ACT scores will be summarized by visit.

9.4.3.7 Peak Expiratory Flow

Peak expiratory flow measurements (absolute values and change from baseline) will be summarized by visit.

Further details on the safety analyses will be provided in the SAP.

9.4.4 Efficacy Analyses

Primary inference for all the efficacy analyses will be based on the ITT population at the Week 16 endpoint.

All efficacy variables will be summarized by visit. The categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using mean, median, minimum, maximum, and standard deviations for the data collected at each visit. Further details on efficacy analyses will be provided in the SAP.

9.4.5 Biomarker Analyses

Primary inference for all biomarker analyses (including eosinophil, TARC, IgE, etc) will be based on the observed cases. All biomarker variables (eg, absolute and change from baseline) will be summarized descriptively at each time point. If the variable is not Gaussian distributed then it will be log transformed. In addition, a box-plot will be produced at each time point. Biomarker analysis will be conducted by the designated CRO based on a separate biomarker analysis plan.

9.4.6 Quality of Life Analyses

Primary study population for all QoL analyses will be based on ITT population. The DLQI/cDLQI data will be summarized descriptively by analysis visit. Details of the analyses will be provided in the SAP.

9.5 Sample Size Assumption

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

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

9.6 Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessments will be identified, evaluated, and resolved (if applicable) before the respective database lock (interim or final analysis), and will be described in the final SAP / clinical study report.

10 Quality Assurance and Quality Control

10.1 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.

10.2 Monitoring

Data for each subject will be recorded on CRFs. Data collection must be completed for each subject who signs an informed consent form (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.

10.3 Personnel Training

Study monitors and all relevant personnel will be trained before study initiation on the condition to be treated, the Standard Operating Procedures (SOPs) to be used in this clinical trial, 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), IRT 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 Trial Master File.

10.4 Data Management and Coding

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 (DMP).

Study centers will enter data directly into an electronic data capture (EDC) 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 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 EDC system will be recorded in the audit trail.

10.5 Clinical Trial Conduct

With the exception of avoiding an immediate risk to a subject, the investigator should not deviate from the clinical trial 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 trial protocol are authorized. The investigator should document and explain any deviation from the clinical trial protocol.

10.6 Amendments

The sponsor may modify the clinical trial 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 (eg, in the subsequent notification of a substantial amendment).

10.7 Quality Management and Risk Evaluation

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

11 Ethics

11.1 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 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.

11.2 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.

11.3 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.

11.4 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 trial must be accompanied by a parent/guardian. Subjects and guardians are required to be fully informed about the clinical trial in accordance with GCP guidelines, federal regulations, (for the United States, the Health Insurance Portability and Accountability Act [HIPAA])[41], 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 s/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 their 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.

11.5 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 United States (US) FDA, as well as that of any other applicable regulatory 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' identity 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 United States) on personal data protection.

11.6 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between CCI CCI and the sponsor.

12 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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14 APPENDICES

14.1 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 (eg,, facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
- Ocular / periorbital changes
- Other regional findings (eg,, 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

14.2 Appendix 2 - Authorized Background Topical Corticosteroids

The following medium and low potency TCS are authorized for background therapy with prescribed use not to exceed daily limits according to the product labeling.

Medium Potency TCS		Low Potency TCS	
Type	**Daily Use Limit**	**Type**	**Daily Use Limit**
Mometasone furoate, 0.1% cream	x1 QD	Hydrocortisone, 1% cream (OTC)	x3-4 QD
Hydrocortisone butyrate, 0.1% cream	x2 QD		

Abbreviations: OTC = over-the-counter; QD = daily.

Subjects will apply the authorized background TCS therapy beginning within the screening period and ≥ 14 days before Day 1 and throughout the study as directed by the investigator.

Subjects will apply a medium potency TCS in areas of the body where use of medium potency TCS is considered safe (eg, trunk and extremities). A low potency TCS will be used on TCS-sensitive areas (eg, face, neck, and intertriginous areas).

Subjects will apply a thin layer of authorized TCS on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare, but which does not exceed the frequency recommended in the product labeling. It should be noted that "as needed" (PRN) use of TCS is not permitted.

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

If a subject requires additional treatment beyond the authorized TCS usage, a rescue medication may be prescribed (see Section 7.5.8.1.2).

14.3 Appendix 3 - Eczema Area and Severity Index (EASI)

Body region	EASI score
Head/Neck (H)	(E + I + Ex + L) x Area x 0.1
Upper limbs (UL)	(E + I + Ex + L) x Area x 0.2
Trunk (T)	(E + I + Ex + L) x Area x 0.3
Lower limbs (LL)	(E + I + Ex + L) x Area x 0.4
EASI =	Sum of the above 4 body region scores

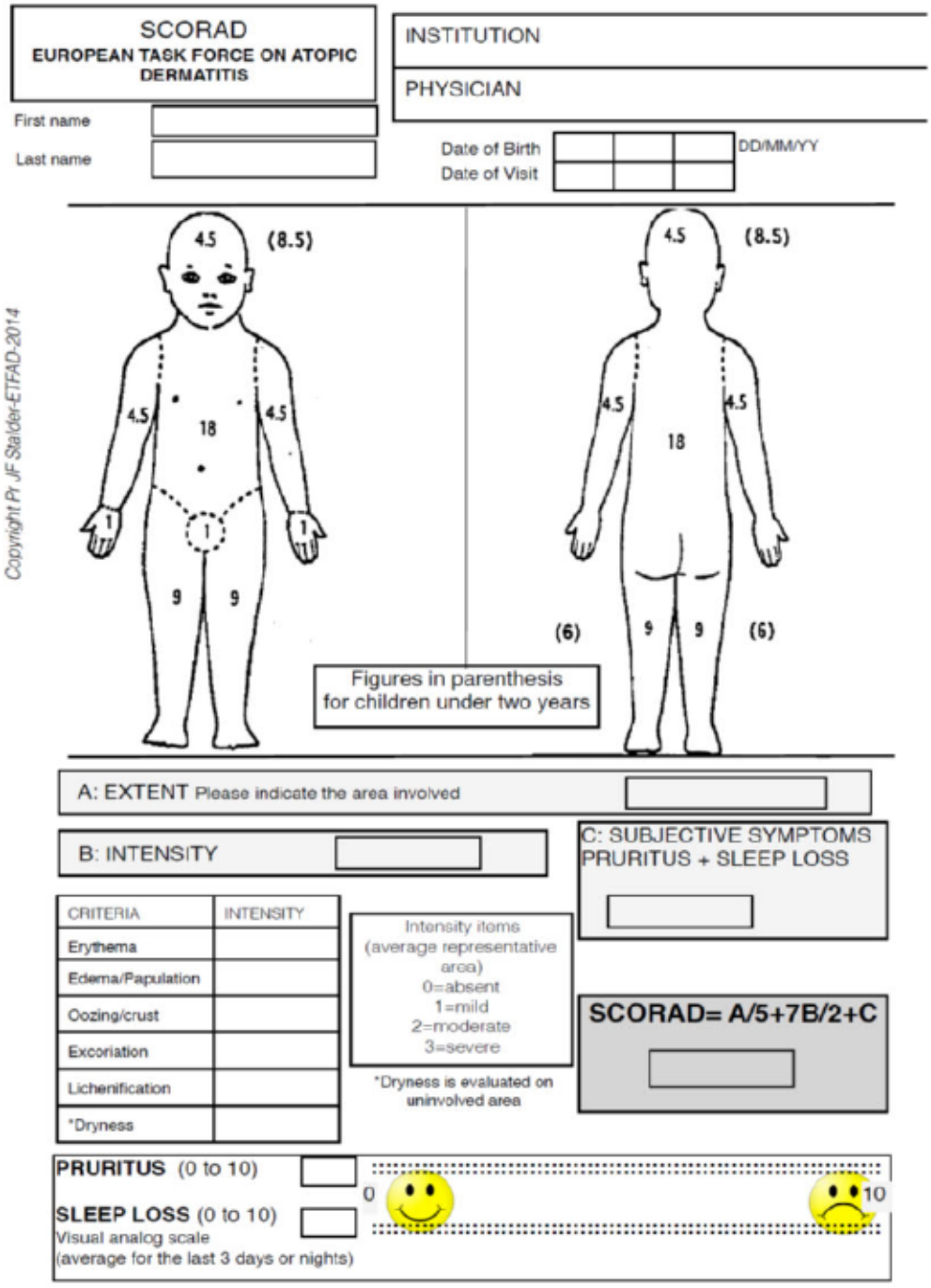
The degree of severity of each sign (E=erythema, I=induration/papulation, Ex=excoriation, L=lichenification) in each of the 4 body regions is evaluated based on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe), with half points allowed.

Area (the affected body area) is defined as follows: 0= 0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Among the 4 zones, trunk includes the genital area, and lower limbs include the buttocks (Hanifin 2001).[36]

14.4 Appendix 4 - Investigator's Global Assessment (IGA)

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

14.5 Appendix 5 - SCORing Atopic Dermatitis (SCORAD)



Extent: The extent of body area affected by atopic dermatitis

Intensity: To determine the intensity, select a representative area and assess the intensity of each as 0 (absence), 1 (mild), 2 (moderate), or 3 (severe). Dryness should be assessed in an area without inflammation or application of moisturizer within 8 hours prior to the assessment.

Subject symptoms: Subject evaluation of pruritus (itch) and sleep loss during the last 3 days prior to the visit.

14.6 Appendix 6 - Pruritus Numeric Rating Scale (NRS)

For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch overall during the previous 24 hours?"

0	1	2	3	4	5	6	7	8	9	10

No itch worst itch imaginable

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

0	1	2	3	4	5	6	7	8	9	10

No itch worst itch imaginable

14.7 Appendix 7 - Sleep Disturbance Numeric Rating Scale (NRS)

On a scale of 0 to 10, with 0 being 'no sleep loss related to symptoms of AD' and 10 being 'I cannot sleep at all due to the symptoms of AD', how would you rate your sleep last night?"

No sleep loss I cannot sleep at all

14.8 Appendix 8 - Dermatology Life Quality Index (DLQI) and Children's DLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	 Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.

Instructions for DLQI scoring:

'Very much' = 3

'A lot' = 2

'A little' = 1

'Not at all' = 0

'Not relevant' = 0

Question 7, 'prevented work or studying' = 3

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

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No:
Name: Diagnosis: CDLQI
Age: SCORE: ☐
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** ⇒ **If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **holiday time?** ⇒ **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

Instructions for cDLQI scoring:

'Very much' = 3

'A lot' = 2

'A little' = 1

'Not at all' = 0

'Not relevant' = 0

Question 7, 'prevented school' = 3

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

14.9 Appendix 9 - Asthma Control Test

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. During the *past 4 weeks*, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. During the *past 4 weeks*, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. How would you rate your asthma control during the *past 4 weeks*?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

14.10 Investigator Signature Page

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

Protocol Number: 116912

Confidentiality and cGCP 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 Research & Development, LLC and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Galderma Research & Development, LLC and 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 Research & Development, LLC, 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