CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number:	RD.06.SPR.118161
EudraCT Number:	2019-001887-31
Syneos Health Study Number:	1008782
Investigational Product:	Nemolizumab (CD14152)
IND Number:	117122
Phase:	3
Sponsor:	Galderma S.A. Avenue Gratta-Paille 2 1018 Lausanne Switzerland Galderma Research & Development, LLC 14501 North Freeway Fort Worth, TX 76177 United States
Contract Research Organization:	Syneos Health 1030 Sync Street Morrisville, NC 27560 United States
Protocol Date:	4 Nov 2021
Protocol Version:	Version 8.0

CONFIDENTIAL

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number: RD.06.SPR.118161

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

Sponsor Signatory

Liliana Ulianov, MD, MSc
Senior Medical Expert
R&D Medical Advisory
Galderma S.A.

PPD
Signature

PPD
Date

2 STUDY PERSONNEL

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3 SYNOPSIS

Protocol Number:

RD.06.SPR.118161

Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Investigational Product:

Nemolizumab (CD14152)

IND Number:

117122

Study Centers:

Approximately 150 study centers are planned in Europe, Americas, and Asia-Pacific.

Phase:

3

Objectives:

Primary objective: The primary objective is to assess the efficacy and safety of nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe atopic dermatitis (AD) not adequately controlled with topical treatments.

Secondary objective: The secondary objective is to evaluate the efficacy and safety of maintenance treatment with nemolizumab (CD14152) for up to an additional 32 weeks.

Study Design:

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in adult and adolescent subjects with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s).

Approximately 750 total subjects will be randomized (2:1) to receive either nemolizumab (CD14152) or placebo, stratified by baseline disease severity (Investigator's Global Assessment [IGA]; moderate: IGA = 3; severe: IGA = 4) and peak pruritus numeric rating scale (PP NRS) severity (PP NRS $\geq$ 7; PP NRS < 7). A minimum of 250 subjects will be randomized in each PP NRS strata. Clinical responders at Week 16 (ie, the end of initial treatment/beginning of maintenance) will be re-randomized (1:1:1) to different treatment regimens (injections every 4 weeks [Q4W] or every 8 weeks [Q8W] of nemolizumab [CD14152] or placebo Q4W).

Subjects will apply a moisturizer at least once daily, beginning at screening. Subjects will also be provided or prescribed background topical therapy for AD (including a medium-potency topical corticosteroid [TCS] for the body and a low-potency TCS or topical calcineurin inhibitor (TCI) for sensitive areas such as the face, neck, intertriginous areas, etc for use throughout the study. If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects during the study, except during the run-in period (ie, at least 2 weeks [14 days] before Day 1/baseline).

The study consists of 4 periods over approximately 60 weeks: screening (including run-in), initial treatment, maintenance, and follow-up (unless the subject is a non-responder at Week 16, at which their participation could last up to 28 weeks). Refer to Figure 1 for an overview of the treatment/study design.

An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study. Details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities, and communications are provided in the respective IDMC and IAC charters.

Screening Period (Screening to Initial Randomization/Baseline)

The screening period (approximately 2-4 weeks before planned Day 1/baseline) will evaluate subject eligibility and introduce standardized background topical therapy over a run-in period of at least 2 weeks (ie, 14 days) before Day 1/baseline.

Initial Treatment Period (Baseline/Day 1 to Week 16 Pre-dose)

The initial treatment period is defined as Day 1/baseline through Week 16 (before the Week 16 dose, with last dose at Week 12). Eligible subjects will be randomized in a ratio of 2:1 at baseline to receive subcutaneous injections of nemolizumab (CD14152) or placebo Q4W.

Subjects will continue to use background topical therapy, which should be adjusted 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, based on investigator clinical judgment.

Table 1: Initial Treatment Period Randomized Group Assignments

Group	***Treatment***	***Loading dose (Day 1/Baseline)***	***Dose at Week 4, 8, 12***	***Route***	***Schedule***
1	Nemolizumab (CD14152)	60 mg (two 30-mg injections)	30 mg	sc	Q4W
2	Placebo	Placebo (two injections)	Placebo	sc	Q4W

Abbreviation(s): Q4W = every 4 weeks; sc = subcutaneous.

Clinical assessments will occur according to the schedule of assessments through the Week 16 visit (see Section 8.1.2). Subjects who are clinical responders at Week 16 will continue to the maintenance period. Subjects who are non-responders at Week 16 may be eligible to enroll into a long-term extension (LTE) study (Protocol 118163). Subjects who require rescue therapy for clinical worsening of AD before Week 16 may also be considered for the LTE study but will be required to continue with study visits until the Week 16 visit. The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after their last study drug injection.

Subjects who discontinue the initial treatment period prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection.

Initial treatment period results may be analyzed after all subjects have either completed the Week 16 visit or have withdrawn or been discontinued from the study before Week 16. To maintain the blind during the maintenance period, personnel directly involved with the ongoing

conduct of the study from the sponsor, contract research organization, or investigational study centers will not have access to any information that may lead to unblinding.

Maintenance Period (Re-Randomization: Week 16 to Week 48)

The maintenance period is defined as Week 16 (maintenance baseline) to Week 48. All nemolizumab (CD14152)-treated subjects (ie, group 1) who are clinical responders at Week 16 will be re-randomized (1:1:1) to study medication, as follows: group 1A, nemolizumab (CD14152) 30 mg Q4W; group 1B, nemolizumab 30 mg Q8W; or group 1C, placebo Q4W.

Clinical responders are defined as:

- IGA of 0 (clear) or 1 (almost clear) at Week 16
  OR
- Eczema Area and Severity Index (EASI)-75 at Week 16

All placebo-treated subjects (ie, subjects in group 2 from the initial treatment period) who responded to placebo during the initial treatment period will continue to receive placebo Q4W in the maintenance period.

Subjects who receive rescue therapy will be considered non-responders.

Based on the phase 2b results (Protocol 114322), it is estimated that 15% of subjects will drop out from the initial treatment period. Assuming a 45% responder rate in active treatment and 12% with placebo, approximately 216 subjects will participate in the maintenance period (190 nemolizumab and 26 placebo subjects).

Table 2: Maintenance Period Re-Randomized Group Assignments

Group	*Treatment*	*Dose*	*Week(s)*	*Route*	*Schedule*
1A	Nemolizumab (CD14152)	30 mg	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W
1B	Nemolizumab (CD14152)	30 mg	16, 20*, 24, 28*, 32, 36*, 40, 44*	sc	Q8W*
1C	Placebo	Placebo	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W

**with placebo Q4W at Week 20, 28, 36, and 44 to maintain blind*

Abbreviation(s): Q4W=every 4 weeks; Q8W=every 8 weeks; sc=subcutaneous.

Beginning at Week 16, subjects in group 1A will receive active (ie, nemolizumab [CD14152]) study drug injections Q4W up to Week 44. Subjects in group 1B will receive active study drug injections Q8W, with placebo at alternating visits to maintain the blind. Group 1B subjects will receive the last active study drug injection at Week 40 (final injection at Week 44 will be placebo). Group 1C subjects will receive placebo Q4W (ie, through Week 44).

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

Primary maintenance effect will be evaluated based on Week 48 assessments. All maintenance endpoints will be analyzed independently from each pivotal study and by using pooled data after the completion of both trials.

Subjects requiring rescue therapy before the Week 32 visit must undergo a required wait period (with continued study visits) until the Week 32 visit, at which time they may be considered for LTE eligibility/participation. Thereafter, no wait period is required.

Subjects who complete the Week 48 visit may be eligible to enroll into the LTE study (Protocol 118163). Subjects requiring rescue medication before the Week 48 visit may be considered for LTE eligibility. The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible for the LTE study will be asked to complete the follow-up visit.

Subjects who discontinue the maintenance period prematurely should complete an ET visit and a follow-up visit 12 weeks after the last study drug injection.

Follow-up

The follow-up visit will be conducted 12 weeks after the last study drug injection for subjects who decline or are not eligible to enter the LTE study. (Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously Q4W.) The follow-up visit is not required for subjects who participate in the LTE study.

Number of Subjects:

Approximately 750 total subjects are planned to be randomized, including a minimum of 130 adolescent subjects aged 12 to 17 years.

Treatment:

Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a single-use, pre-filled, dual-chamber syringe (DCS).

During the initial treatment period, eligible subjects will be randomized to receive either 30 mg of nemolizumab (CD14152) in group 1 or placebo in group 2, administered as a subcutaneous injection only after reconstitution Q4W for 16 weeks (last injection at Week 12), with a loading dose of 60 mg on Day 1/baseline.

Subjects (and/or their caregivers) will have the option to self-inject study drug while at the study center under staff supervision. Subjects (and/or their caregivers) will be trained on injecting the study drug at Day 1 and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject (and/or caregivers) is unwilling to perform the injections, study staff can administer study drug at each visit.

In the maintenance period, group 1 subjects who are clinical responders will be re-randomized to receive either 30 mg of nemolizumab (CD14152) or placebo for 32 weeks. Subjects in group 1A will receive a subcutaneous injection of nemolizumab Q4W (last injection at Week 44); group 1B will receive an injection of nemolizumab Q8W, with alternating placebo Q8W (last active injection at Week 40 and last placebo injection at Week 44); and group 1C will receive placebo Q4W. Subjects in group 2 who are clinical responders will continue to receive placebo Q4W.

Moisturizer

Subjects will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at screening, and throughout the study. The subjects' current moisturizer or a moisturizer recommended by the investigator may be used. To allow for accurate assessment of skin dryness, use should not occur within 8 hours before each clinic/office visit. Whenever possible, subjects should use the same moisturizer throughout the study.

Background topical therapies

Subjects will be provided or prescribed authorized background topical therapy for use during the study, beginning at screening:

- Medium-potency TCS therapy for non-sensitive areas: Subjects will apply the authorized medium-potency TCS background therapy in areas of the body where use of medium-potency TCS is considered safe (eg, trunk and extremities), beginning within the screening period and ≥ 14 days before Day 1 (ie, run-in). Refer to the current version of the pharmacy manual for a listing of permitted medium-potency TCS medications that are commercially available in planned countries.
- Low-potency TCS or TCI therapy for sensitive areas: Subjects will apply an authorized background therapy (ie, low-potency TCS or TCI) to areas of the body considered TCS-sensitive (eg, face, neck, intertriginous areas) or in cases where medium-potency TCS is not tolerated, beginning within the screening period and ≥ 14 days before Day 1 (ie, run-in). The investigator may select either low-potency TCS or TCI for each subject, per investigator discretion. The subject may only apply **one** medication to each affected area; concomitant use of low-potency TCS and TCI on the same lesion is not permitted. Refer to the current version of the pharmacy manual for a listing of permitted low-potency TCS and TCI medications that are commercially available in planned countries.

Subjects will apply a thin layer of authorized background topical therapy on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare but which does not exceed the daily frequency recommended in the product labeling. Refer to the current version of the pharmacy manual for the authorized topical medications and permitted daily frequency of use. "As needed" (PRN) use of TCS or TCI is not permitted. Only topical therapies specifically provided or prescribed for use in this study are permitted.

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

Rescue Therapies

If deemed to be medically necessary by the investigator (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) to allow a minimum time for study drug exposure in the presence of background therapy.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy.

Rescue treatments are only treatments that directly treat AD (mainly those that are approved or are standard of care) and include topical and systemic treatments as outlined. Rescue therapies include:

- Higher potency of TCS (equivalent to class I-II according to the United States classification)[2]
- 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:

The expected duration for each subject's participation in the study depends on the clinical response and may be:

- Up to 28 weeks (including a 4-week screening period, a 16-week initial treatment period and an 8-week follow-up period [12-weeks after the last study medication injection]) for subjects who are non-responders at the completion of the initial treatment period (Week 16)
- Up to 60 weeks (including a 4-week screening period, a 16-week initial treatment period, a 32-week maintenance period, and an 8-week follow-up period [12-weeks after the last study medication injection]) in subjects who are clinical responders at the completion of the initial treatment period (Week 16)

The 12-week follow-up visit is not required for subjects who will continue in the LTE study (Protocol 118163).

Study Population:

Inclusion Criteria: To be eligible for study entry, subjects must satisfy all of the following inclusion criteria.

1. Male or female subjects aged ≥ 12 years at the screening visit.

   Note: Enrollment of subjects aged 12 to 17 years has been opened after the IDMC has assessed interim safety data from the phase 2 study (Protocol 116912) and provided recommendations to the sponsor, who then determined the eligibility of this age group for enrollment in the study. The sponsor sent a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents could not be enrolled in the study until such communication was received.

2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1)[2] at the time of the screening visit.
3. EASI score ≥ 16 at both the 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 the screening and baseline visits.
5. AD involvement ≥ 10% of body surface area (BSA) at both the screening and baseline visits.
6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit.

   Screening PP NRS score will be determined by a single PP NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

   Baseline PP NRS score will be determined based on the average of daily PP NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.

7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit, or for whom TCI is selected as background therapy for sensitive areas, must also demonstrate inadequate response to TCI. Acceptable documentation includes patient records with information on TCS (with or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator.

   Inadequate response to TCS treatments (with or without TCI) is defined as:

   7a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency TCS (Class I-III according to the US classification)[2] (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;
   or
   7b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I-II according to the US classification)[2] (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);
   or
   7c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

   If documentation is inadequate, subjects may be re-screened after such documentation is obtained.

8. Agree to apply a moisturizer throughout the study from the screening visit; agree to apply authorized topical therapy from the screening visit and throughout the study as determined appropriate by the investigator.

9. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study and for 12 weeks after the last study drug injection, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate 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. *In Germany only, if a subject has reached Tanner stage 3 breast development, even if not having menarche, the subject will be considered a female of childbearing potential.

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

   - Progestogen-only oral hormonal contraception
   - Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are <u>not</u> considered a highly effective method of contraception)
     Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (eg, condom) together with a spermicide is not acceptable.
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices or intrauterine hormone-releasing system
   - Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study

- Bilateral vasectomy of partner at least 3 months before the study

10. Female subjects of non-childbearing potential must meet one of the following criteria:
    - Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle-stimulating hormone (FSH) level in the postmenopausal range
    - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before screening
      Note: Bilateral tubal ligation is not accepted as a reason for non-childbearing potential.
11. Subject (and guardian, when applicable) willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.
12. Understand and sign an informed consent form (and assent form, when applicable) before any investigational procedure(s) are performed.

Exclusion Criteria: Subjects will be excluded from the study if 1 or more of the following exclusion criteria are applicable.

1. Body weight < 30 kg.
2. Subjects meeting 1 or more of the following criteria at screening or baseline:

   2a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.

   2b. Reporting asthma that has not been well-controlled (ie, symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.

   2c. Asthma Control Test ≤ 19 (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 and/or chronic bronchitis.
4. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.3.4.2.
   Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this study.
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 (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, or human immunodeficiency virus antibody) at the screening visit.

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody 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***
Coal tar products	2 weeks
Topical PDE-4 inhibitor	2 weeks
Non-authorized TCS	2 weeks
Topical medications, including authorized TCS/TCI, with occlusive dressings (eg, wet wraps)	2 weeks
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors)	4 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (eg, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)
Dupilumab	10 weeks
Live attenuated vaccine	12 weeks
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening (Stable treatment with antihistamines with sedative effect is allowed at a dose that, based on previous experience, is well tolerated by the subject.)	1 week
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks
Cannabinoids	2 weeks
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks

Abbreviation(s): AD=atopic dermatitis; PDE-4=phosphodiesterase-4; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.
Note:
Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

8. Previous treatment with nemolizumab.
9. Subjects who, after a full treatment course of 16 weeks with dupilumab, experienced worsening of their AD or failed to achieve minimal improvement (eg, ≤ 10% reduction in EASI or no reduction in IGA).

10. 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 study.
11. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.
12. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
13. History of intolerance to TCS or for whom TCS is not advisable (eg, hypersensitivity, significant skin atrophy).
14. Known active or untreated latent tuberculosis infection.
    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.
15. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
16. Presence of confounding skin condition that may interfere with study assessments (eg, Netherton syndrome, psoriasis, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).
17. 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), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia).
18. Planned or expected major surgical procedure during the clinical study.
19. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.9.2).
20. Currently participating or participated in any other study of a drug or device, within the past 8 weeks before the screening visit, (or 5 half-lives of the investigational drug, whichever is longer), or is in an exclusion period (if verifiable) from a previous study.
21. History of alcohol or substance abuse within 6 months of the screening visit.

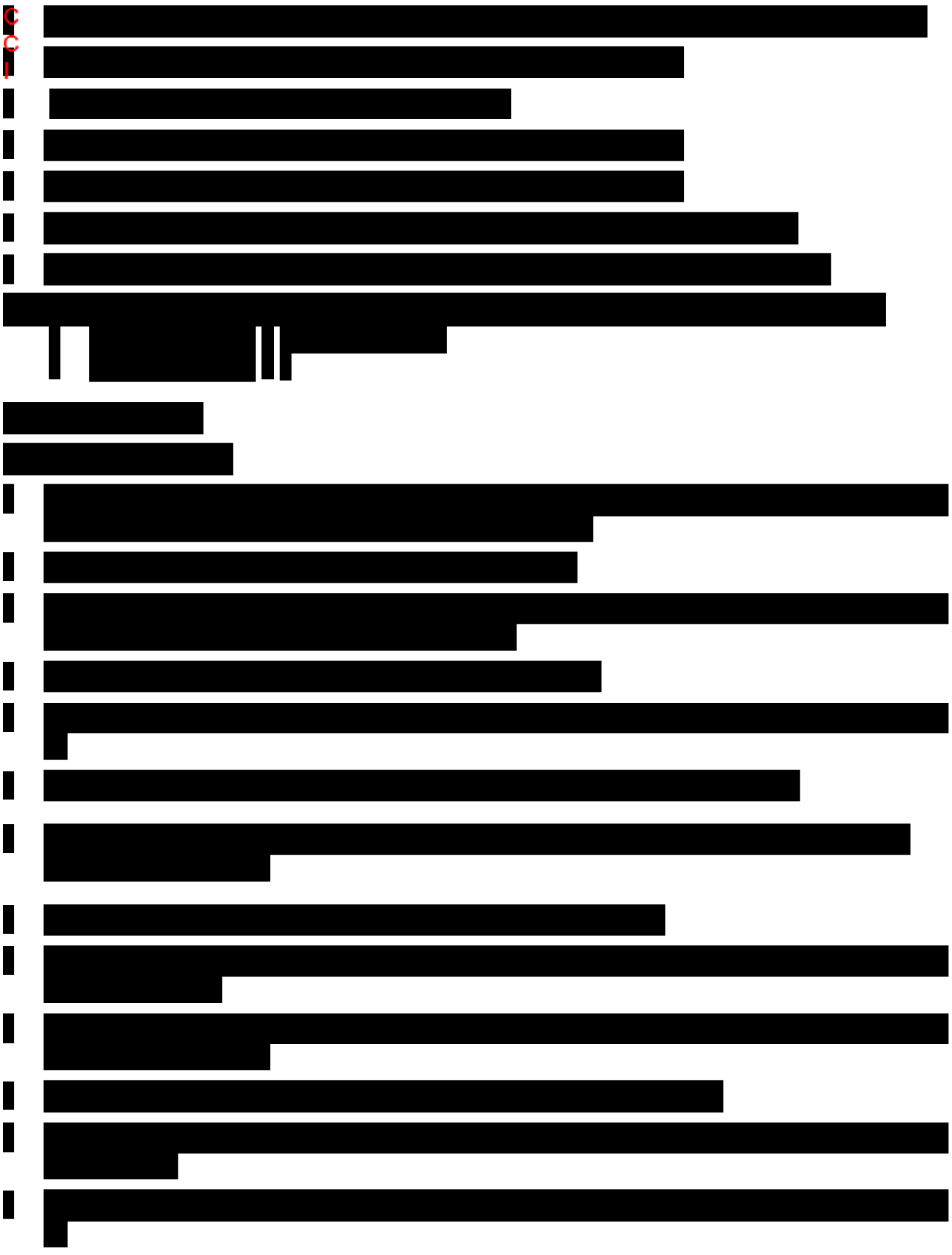
Endpoints:

Co-Primary Endpoints:

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16

Key Secondary Endpoints:

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with PP NRS < 2 at Week 16



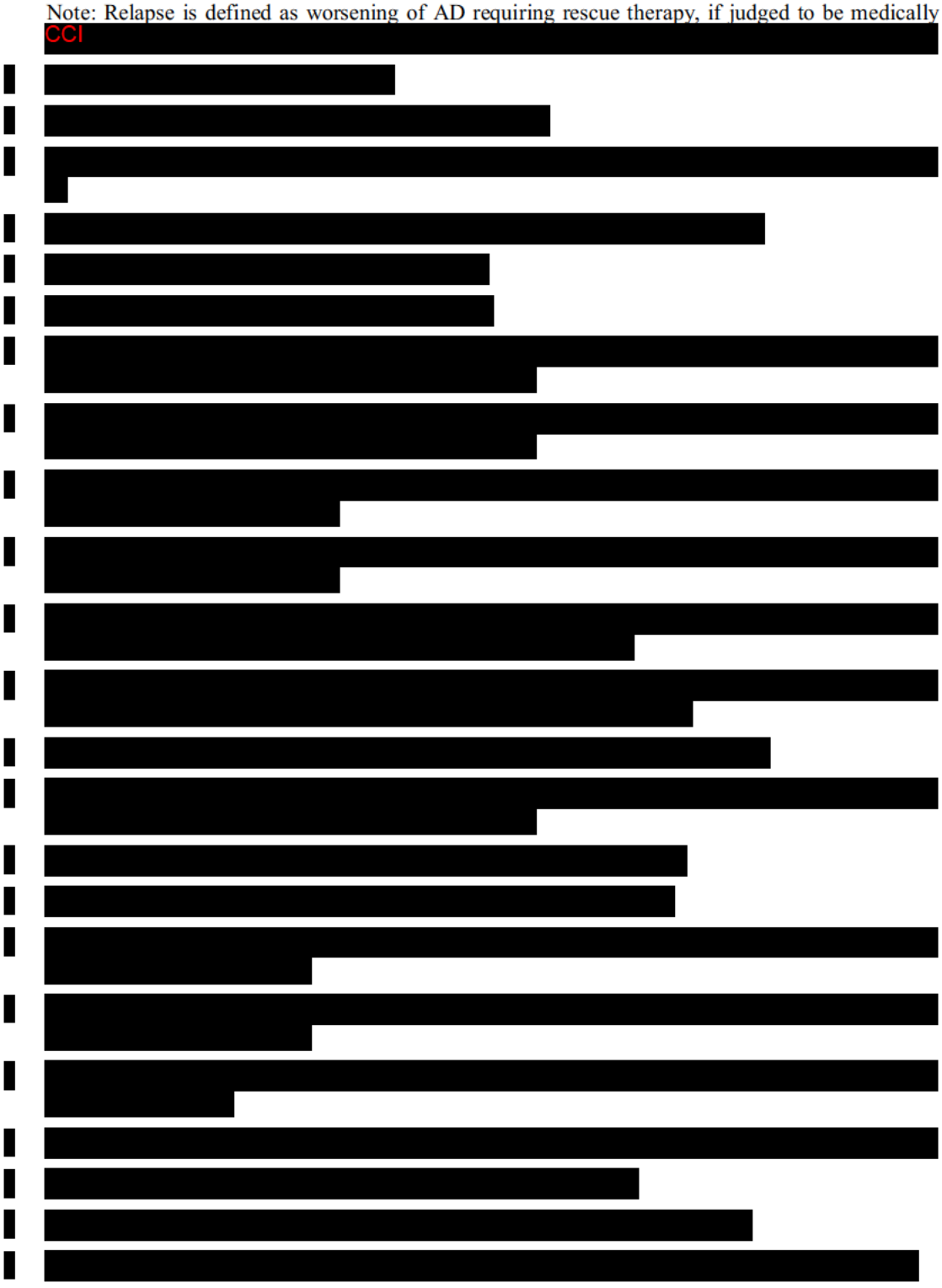
- Change from baseline in sleep metrics (sleep onset latency, wakefulness after sleep onset [WASO],

CCI

[redacted]

Note: Relapse is defined as worsening of AD requiring rescue therapy, if judged to be medically

CCI



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Statistical Analysis:

Principal Statistical Method

Populations: The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population will include all randomized subjects who receive at least 1 dose of study drug. The ITT population will be the primary population for all efficacy analyses, and all safety data will be summarized based on the safety population.

Primary Endpoint:

The 2 co-primary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for randomized stratification variables (IGA severity and PP NRS).

Key Secondary Endpoints:

All key secondary endpoints will be analyzed similar to the analysis of primary endpoint using a stratified Cochran-Mantel-Haenszel test.

Secondary Endpoints during Initial Period

Binary endpoints will be analysed with the same method as primary endpoint using non-responder imputation.

Continuous and QoL endpoints will be analyzed using an analysis of covariance (ANCOVA) including treatment group and randomization stratification factors as factors and appropriate baseline values as a covariate, if applicable. Missing values will be imputed using MI under MAR assumption. In addition, EASI, PP NRS, BSA and SCORAD will be analyzed using a mixed-effect model for repeated measures (MMRM) approach, including terms of treatment group, stratification factors, and appropriate baseline values. An unstructured covariance will be used to model the within-patient errors in the analysis. A linear contrast will be used, within the MMRM framework, to estimate difference between nemolizumab and placebo. Treatment difference between nemolizumab and placebo will be estimated along with associated 95% confidence intervals.

Secondary Endpoints during Maintenance Period

All secondary endpoints during the maintenance period will be descriptively summarized.

Multiplicity Adjustment:

The primary comparison of interest is nemolizumab 30 mg compared to placebo for the co-primary endpoints in both populations (baseline PP NRS ≥ 4; baseline PP NRS ≥ 7).

To control the type I error at 5% significance level, a serial gatekeeping approach will be implemented. The co-primary endpoints will be tested at 2.5% significance level for each population. If both co-primary endpoints are statistically significant at 2.5% significance level, the key secondary endpoints will be tested sequentially following hierarchical testing procedure using the pre-specified order of endpoints for each population. The comparisons for key secondary endpoints will be made sequentially, and the subsequent tests will be stopped when no statistical difference is found.

Other secondary endpoint comparisons will not be adjusted for multiplicity.

Sample Size

To achieve at least 90% power for both co-primary endpoints at 2.5% significance level, 150 subjects per group will be required to detect the following differences between treatment groups for 2 co-primary endpoints with 1:1 randomization ratio, assuming 15% dropout rate during the initial treatment period.

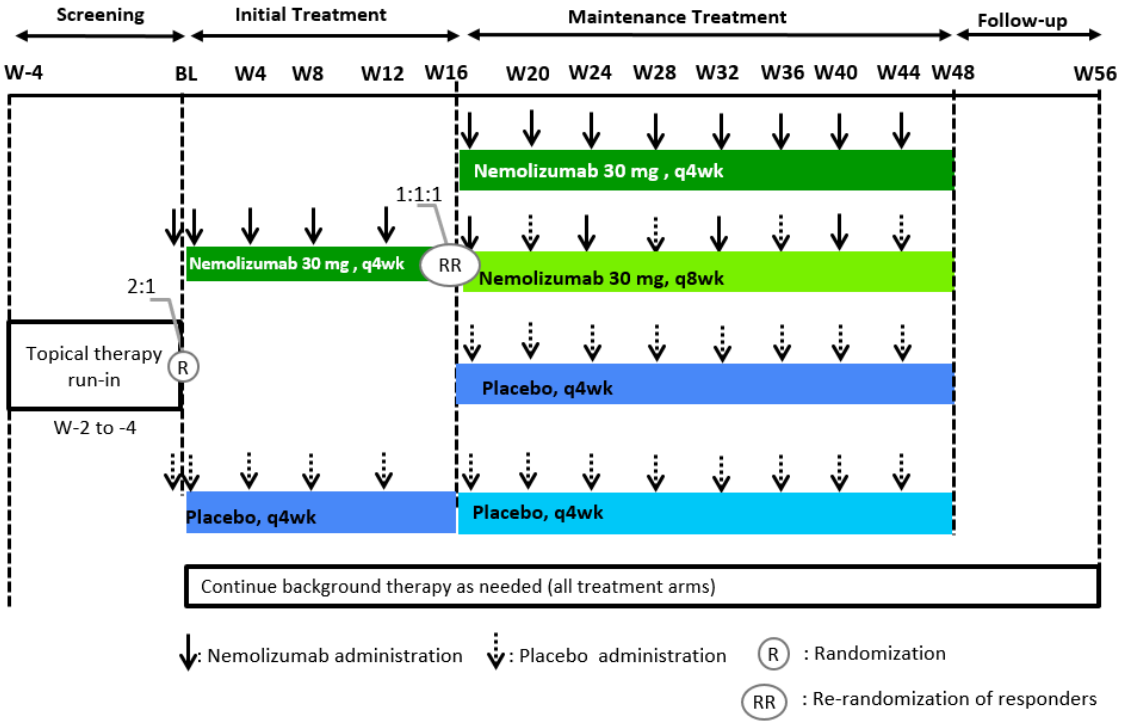
With a 2:1 randomization, 180 subjects in nemolizumab and 90 subjects in placebo will be required to detect the differences in both co-primary endpoints to achieve 90% power.

IGA Success: To detect a difference of 18%, assuming IGA response for nemolizumab 30% and placebo 12% at Week 16.

EASI-75 Response: To detect a difference of 30%, assuming EASI-75 response for nemolizumab 49% and placebo 19% at Week 16.

To ensure sufficient exposure with nemolizumab and to ensure sufficient size of the safety database, the sample size is increased to 750 subjects in total with randomization ratio 2:1. This sample size will provide more than 99% power to detect the treatment difference for both co-primary endpoints at 2.5% significance level.

Figure 1: Study Visit Schema (Synopsis)



Abbreviations: BL=baseline; q4wk=every 4 weeks; q8wk=every 8 weeks; W=week.

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5 LIST OF ABBREVIATIONS

ACT	Asthma Control Test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	Average pruritus
AST	aspartate aminotransferase
BL	baseline
BSA	body surface area
cDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
COVID-19	coronavirus disease-19
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CS	clinically significant
CYP450	cytochrome P450
DCS	dual chamber, single-use syringe
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQoL 5-Dimension
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAC	independent adjudication committee
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
IgE	immunoglobulin E
IL	interleukin
IRB	Institutional Review Board

IRR	injection-related reaction
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LTE	long-term extension
MI	multiple imputation
miRNA	micro ribonucleic acid
MMRM	mixed-effect model for repeated measures
mRNA	messenger ribonucleic acid
NAb	neutralizing antibody
NCA	non-compartmental analysis
NCS	not clinically significant
NRS	numeric rating scale
OC	observed case
PCS	Pruritus Categorical Scale
PD	pharmacodynamics
PDE	phosphodiesterase
PEF	peak expiratory flow
PGAD	Patient Global Assessment of Disease
PGAT	Patient Global Assessment of Treatment
PGIC-P	Patient Global Impression of Change - Pruritus
PGIC-SD	Patient Global Impression of Change - Sleep Disturbance
PGIS-P	Patient Global Impression of Severity - Pruritus
PGIS-SD	Patient Global Impression of Severity - Sleep Disturbance
PGx	pharmacogenomics
PIQ	PROMIS® Itch Questionnaire
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PP NRS	peak pruritus numeric rating scale
PRN	pro re nata (when necessary or as needed)
PRO	patient-reported outcome
PROMIS®	Patient-Reported Outcomes Measurement Information System
PTC	product technical complaint
Q4W (q4wk)	every 4 weeks
Q8W (q8wk)	every 8 weeks
QoL	quality of life
RA	receptor A
RNA	ribonucleic acid
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD NRS	sleep disturbance numeric rating scale

SIN	subject identification number
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
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]
TMF	Trial Master File
ULN	upper limit of normal
UPT	urine pregnancy test
US	United States
VAS	visual analogue scale
WASO	wakefulness after sleep onset
WOCBP	women of childbearing potential
WPAI:AD	Work Productivity and Activity Impairment: Atopic Dermatitis

6 INTRODUCTION

6.1 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 1 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 young children and gradually reduces with age. Prevalence is higher in developed countries.

The overall lifetime prevalence of AD has increased over the past 30 years.[2] In most countries, there has been an increase in AD prevalence over a 5- to 10-year period.[4] In the United States (US), the prevalence of AD in children has been reported between 10% and 13% in 2 studies.[5,6] Many environmental and geographic factors were shown to contribute to incidence rate and severity in both studies. These variables included urban living, household income, parental education level, and race.

The majority of AD cases can be regarded as "mild", with 10% to 20% of patients suffering from severe eczematous skin lesions, although the percentage of individuals experiencing severe disease appears to be higher in the adult AD population.[7] Whereas the prevalence of moderate-to-severe AD is up to 71% in adults suffering from AD, the prevalence of moderate and severe AD in children with AD was found to be 14% and 2%, respectively.[8] Evaluation of AD data collected through the US 2007 National Survey of Children's Health showed that 67% of pediatric AD patients had mild disease, 26% had moderate disease, and 7% had severe disease, which translates to approximately 5.6, 2.2, and 0.6 million US children, respectively.[6]

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 AD may be difficult to distinguish from seborrheic dermatitis on clinical grounds alone. The childhood stage from 2 years to 12 years shows papulation rather than exudation and occurs in the flexural areas, especially the antecubital and popliteal fossae, the volar aspect of the wrists, ankles, and neck. Thickened plaques show lichenification and excoriation. In the adult stage, from puberty onward, 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.

The cause of AD, although still not completely understood, is probably multifactorial and involves complex interrelation between susceptibility genes, immunological factors, infections, and environmental factors to produce a skin barrier disturbance as well as immunologic dysregulation and inflammation.[11] Abnormal protein (filaggrin and related proteins) and lipid (ceramide) metabolism may also play a key role. Upon stimulation with allergens, dendritic cells in the skin stimulate type 2 helper T cells (Th2) and cause the subsequent release of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5 and IL-13. High levels of Th2 cytokines in AD skin increase serine protease, which leads to further skin barrier dysfunction, and IL-31, which leads to pruritus and further inflammation and barrier dysfunction.[12,13] The pathophysiology also involves Th1 cells in the chronic phase of AD. Involvement of Th17 and Th22 cells in AD pathogenesis has been more recently reported.[14] Of note, non-lesional skin already shows signs of subclinical inflammation with increased numbers of Th2 cells, Th22 cells, and to a lesser degree, Th17 cells, and a pro-inflammatory cytokine milieu.[15]

The scratching behavior associated with pruritus is believed to exacerbate AD lesions by causing mechanical damage to the skin, allowing the penetration of foreign antigens, triggering inflammatory responses, and leading to further aggravation of dermatitis and itching. This vicious circle of scratching → exacerbation of dermatitis → aggravation of itching is known as the “itch-scratch cycle”.[16]

IL-31 is involved in both primary AD pathophysiology and perpetuation of the itch-scratch cycle. IL-31 is preferentially produced by Th2 cells, following induction by IL-4, and its expression is consistently increased in the skin lesions of AD patients.[12,17,18] Furthermore, the IL-31 receptor A (IL-31 RA) was found to be expressed in several tissues including the dorsal root spinal ganglia, which contain sensory nerve cells,[19] and keratinocytes.[20] Through interaction with its receptor, IL-31 promotes pruritus, Th2-driven inflammation, and keratinocyte proliferation and differentiation, which are crucial for skin barrier function.[12,13,21,22] Together, these findings suggest that IL-31 is involved in the pathogenesis of pruritus and is implicated in the inflammation of AD.

Atopic dermatitis is currently managed with topical and systemic treatments, as well as phototherapy. Topical agents are the mainstay of AD therapy. Moisturizers are used to improve skin dryness and skin barrier dysfunction. Topical corticosteroids (TCS) are widely prescribed in adults and children for their anti-inflammatory effect, but their long-term use can lead to side effects, such as skin atrophy and risks associated with systematic absorption (eg, hypothalamic pituitary axis suppression and Cushing's syndrome). Topical calcineurin inhibitors (TCI) are effective for acute and chronic treatment in adults and children, particularly in selected anatomical areas. Stinging and burning are frequent local reactions, and both tacrolimus and pimecrolimus carry a warning in the US prescription information that long-term safety has not been established due to reports of (rare cases of) malignancy. Crisaborole (Eucrisa®; Pfizer) is a topical phosphodiesterase (PDE)-4 inhibitor with an acceptable safety profile in adults and children but is most commonly used in the treatment of mild-to-moderate AD. Hypersensitivity reactions at or near the application site have also been observed.[23]

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] There are various forms, doses, and treatment protocols of phototherapy, which lead to heterogeneous treatment outcomes, including common side effects such as actinic damage, local erythema and tenderness, pruritus, burning and stinging, as well as the long-term risk of skin cancer. Systemic corticosteroids, while effective at controlling disease temporarily, should be avoided due to an overall unfavorable risk-benefit safety profile, particularly in pediatric populations. Oral antihistamines (including both sedating and non-sedating medications) have been studied in the management of AD but there is insufficient evidence of treatment benefit. Cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil may be considered when systemic treatment is required.[24] Most of these systemic immunosuppressants, except cyclosporine, have not been approved for the treatment of AD and are used off-label in both adults and pediatric patients. Cyclosporine is approved for treatment of severe AD in the European Union and in a few other countries (eg, Japan), but not in the US. However, given the high response variability and the known secondary adverse effects of these drugs, there is a need for new drugs to better control the disease while decreasing the risk of secondary adverse effects.

Several biological agents are currently being used or developed for the treatment of AD. Dupilumab, a human monoclonal antibody that blocks the signaling pathway of both IL-4 and IL-13, is approved in adults with moderate-to-severe AD not adequately controlled with topical medications[25] and is being developed for use in

pediatric populations. Two other anti-IL-13 therapies, lebrikizumab and tralokinumab, are also currently in development.

Nemolizumab, a humanized anti-human IL-31 RA monoclonal antibody, inhibits the binding of IL-31 to IL-31 RA and subsequent signal transduction. Transgenic mice overexpressing IL-31 exhibited skin lesions resembling those of AD and scratching behavior, which could be suppressed by treatment with an anti-mouse IL-31 antibody.[26,27] In dogs, lokivetmab, a caninized, anti-canine IL-31 antibody, has been shown to reduce pruritus in a dose-dependent manner with a rapid onset of effect and decrease in dermatitis score compared to placebo.[28] In cynomolgus monkeys, nemolizumab suppressed IL-31-induced scratching.[29] In a phase 2a study (CIM003JG) in adult subjects with AD, nemolizumab improved both pruritus and lesional AD, while demonstrating an acceptable safety profile.[30] In a randomized, placebo-controlled, double-blind, parallel-group (10 mg, 30 mg, 90 mg, and placebo), phase 2b dose-finding study, the 30-mg dose was selected as the final dose for further evaluation in phase 3. Nemolizumab has not been previously studied in subjects under the age of 18 years. The safety and pharmacokinetic (PK) profile of the 30-mg dose, selected for further development based on the results of the phase 2b study conducted in adult subjects, will be investigated in adolescent subjects with moderate-to-severe AD.

In conclusion, nemolizumab may present a new treatment option for AD in pediatric as well as adult patients. Atopic dermatitis patients with associated pruritus and an insufficient response to topical therapies could particularly benefit from such a therapy. The objective of this phase 3 pivotal study is to evaluate the safety and efficacy of nemolizumab administered concomitantly with background topical therapy in adult and adolescent subjects with moderate-to-severe AD who are not adequately controlled with topical treatments.

6.2 Clinical Studies

The Investigator's Brochure (IB) contains detailed information on clinical and non-clinical studies. Results of 3 completed clinical studies of nemolizumab in AD are summarized below.

6.2.1 Phase 1 Single-Dose Safety Study

The safety, tolerability, and PK of a single subcutaneous dose of nemolizumab were evaluated in a randomized, double-blind, placebo-controlled phase 1 study including 80 healthy adult volunteers and 36 Japanese subjects with moderate-to-severe AD.[31] Doses ranged from 0.003 to 3.0 mg/kg in healthy volunteers and from 0.3 to 3.0 mg/kg in AD subjects. There were no deaths or serious adverse events (SAEs)

reported in the study, and no dose-dependent increase in the incidence of adverse events (AEs) was observed.

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

6.2.2 Phase 2a Multi-Dose Safety and Efficacy Study

The safety, tolerability, and efficacy of nemolizumab monotherapy was evaluated in 264 moderate-to-severe AD subjects who were inadequately controlled by or intolerant to topical therapy in a phase 2a study (CIM003JG).[30,32] The study included a 12-week, randomized, double-blind, placebo-controlled period (Part A) and a 52-week extension (Part B). At Week 12, various doses of nemolizumab (0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg) administered subcutaneously every 4 weeks (Q4W) were statistically significantly more effective than placebo in reducing pruritus visual analogue scale (VAS) score, with 0.5 mg/kg and 2.0 mg/kg doses being more effective than 0.1 mg/kg. No additional benefit was observed with the 2.0 mg/kg Q4W or every 8 weeks (Q8W) doses compared to 0.5 mg/kg Q4W.

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

Pharmacokinetic assessments after subcutaneous injections of various doses showed a dose-proportional increase of nemolizumab serum concentrations after repeated injections. Limited accumulation was observed, with median actual accumulation index below 2, and steady-state concentrations were achieved at Week 16 of treatment. The PK profile of nemolizumab is predictable: It is not affected by the number of administrations. This might be partly due to the low occurrence and minimal effect of serum anti-nemolizumab antibodies (ADA), with ADA-positive subjects representing 7.1% of all subjects treated with nemolizumab. In addition, in this study, 1 subject in the 0.1 mg/kg Q4W group with anti-nemolizumab antibodies from baseline developed neutralizing ADA at Week 64. Importantly, serum nemolizumab concentrations in ADA-positive subjects were not different from those in the ADA-negative subjects. Four subjects had treatment-emergent nemolizumab-

specific immunoglobulin E (IgE) antibodies. No AEs possibly related to nemolizumab-specific IgE antibodies were observed.

6.2.3 Phase 2b Dose-Ranging Study

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

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

At the Week 24 visit, a greater percent change reduction in Eczema Area and Severity Index (EASI) was observed with the nemolizumab 30-mg dose (least squares mean difference vs placebo = 16.7%) and the difference was statistically significant (95% confidence interval [CI] = -30.2, -3.2; $p < 0.05$) compared to placebo. The nemolizumab 10-mg dose showed marginally significant difference vs placebo (least squares mean difference = 13.6%; 95% CI = -27.3, 0.0; $p = 0.05$). However, the difference between the nemolizumab 90-mg dose and placebo did not achieve statistical significance.

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

Among all nemolizumab doses, the 30-mg dose showed statistically significant and greater difference compared to placebo for all AD and pruritus endpoints at Week 16.

Probably due to TCS background therapy, there was increasing placebo effect in the study, shrinking the deltas between active arms and placebo as the study progressed from Week 16 to Week 24. The dose-effect was closer to the maximum efficacy model, achieving the maximum efficacy at the 30-mg dose and lower efficacy with the 10-mg and 90-mg doses.

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

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

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

6.2.4 Phase 2 Safety Study in Adolescents

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

Nemolizumab has not been previously studied in subjects under the age of 18 years. The safety and PK profile of the 30-mg dose, selected for further development based on the results of the phase 2b study conducted in adult subjects, will be investigated in adolescent subjects with moderate-to-severe AD.

An interim analysis is planned to support enrollment of adolescent subjects in the current phase 3 pivotal study for AD.

6.3 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. Improvements in the symptoms of AD were consistent with the observed improvement in sleep quality (evaluated subjectively) and QoL (evaluated using Dermatology Life Quality Index [DLQI]). Continuous treatment for up to 64 weeks led to improvements in overall AD severity, evaluated with various validated scales commonly used in dermatology clinical trials (ie, EASI, SCORing Atopic Dermatitis [SCORAD], and IGA). Nemolizumab was also well tolerated overall when used as monotherapy or concomitantly with a TCS.

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

a. In the phase 2b (114322) dose-ranging study, a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10-mg, 30-mg, and 90-mg treatment arms, respectively) in subjects with pre-existing asthma was observed. Events were mostly mild or moderate (1 severe event with highest dose), manageable, and reversible under treatment with study drug. The protocol

will exclude subjects with asthma exacerbation requiring hospitalization in the preceding 12 months before screening, subjects whose asthma has not been well controlled (ie, symptoms > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the last 3 months before the screening visit, Asthma Control Test (ACT) score ≤ 19, and subjects with peak expiratory flow (PEF) below 80% of the predicted value. At all visits, all subjects will be asked about respiratory changes and a respiratory examination will be performed. Peak expiratory flow measurements will be performed for all subjects at screening, baseline, and regular intervals throughout the study. For subjects with a history of asthma, PEF measurements and ACT will be administered at all visits. Subjects diagnosed with de novo asthma will perform PEF and ACT assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects with a medical history of asthma will be referred to the physician managing their asthma if ACT ≤ 19, PEF < 80% of the predicted value, and/or unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. An independent adjudication committee (IAC) will review all asthma adverse events reported during the course of the study.

b. The exclusion criteria of this clinical study (ie, restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections) 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. Patients who have recently received live vaccines may be considered for enrollment after an appropriate time has elapsed before baseline/Day 1. Administration of live vaccines is prohibited during the study. Administration of non-live vaccines is permitted including coronavirus disease 2019 (COVID-19) vaccination.

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

d. Based on the Sponsor's and IDMC analysis of the data in 12 to 17-year-old adolescents obtained in the PK/safety study (SPR.116912), it was decided to allow recruitment of adolescent subjects.

e. An independent data monitoring committee (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. AESIs for this study are:
    - IRRs
        - Anaphylactic reactions
        - Acute allergic reactions requiring treatment
        - Severe injection site reactions with a duration greater than 24 hours
    - Newly diagnosed asthma or worsening of asthma
    - Infections
        - Any severe infection or any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for > 2 weeks
        - Any confirmed or suspected coronavirus disease (COVID-19) infection
    - Peripheral edema: limbs, bilateral
    - Facial edema
    - Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

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

6.4 Drug Profile

Nemolizumab is a humanized monoclonal modified immunoglobulin G 2 antibody comprising a structure of 2 H-chains (445 amino acid residues) and 2 L-chains (214 amino acid residues) connected by 16 disulfide bonds. Study drug will be supplied as a lyophilized powder for solution in a pre-filled, dual chamber, single-use syringe (DCS). The lyophilized CD14152 powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30-mg dose of CD14152. The placebo will be supplied as a lyophilized powder for solution in a pre-filled, single-use DCS.

6.5 Dose Selection Rationale

Based on the outcome of the phase 2b dose-ranging study in adults, the 30-mg dose (with 60-mg loading dose), when administered Q4W, provided the best benefit/risk ratio of the 3 doses evaluated and is therefore selected as the final dose to be developed for the treatment of AD. Across the full range of subject body weights in the phase 2b study, the 30-mg dose (with 60-mg loading dose) provided a comparable observed exposure with respect to the body weight-based dose of 0.5 mg/kg tested during the phase 2a study.

Adolescent subjects will be enrolled after the sponsor confirms the safety of the 30-mg Q4W dose in adolescents in a separate clinical study (Protocol 116912).

The current study includes a 32-week maintenance period whereby clinical responders on nemolizumab 30 mg Q4W at Week 16 will be re-randomized (1:1:1) to 30 mg Q4W, 30 mg Q8W, or placebo to evaluate maintenance of effect. The nemolizumab 30 mg Q8W regimen is proposed to evaluate whether a clinical response can be maintained with a lower dosing frequency.

PK/pharmacodynamic (PD) modeling was performed on three clinical endpoints (EASI, IGA, and PP NRS) to support selection of the additional Q8W dose regimen for Phase 3 maintenance. The medians of the active treatment arms were not contained within the range of the placebo for all clinical endpoints, indicating a benefit with active treatment over placebo in both dose regimens (Q4W and Q8W). While higher efficacy on all clinical endpoints was observed with the Q4W dose regimen, it was evidenced that subcutaneous nemolizumab Q8W for 16 weeks will maintain clinical benefit compared to placebo.

PK/PD modeling provides the rationale to evaluate and compare the safety and efficacy of Q4W and Q8W dosing of 30 mg nemolizumab in the maintenance phase of the pivotal studies.

7 STUDY OBJECTIVES & ENDPOINTS

7.1 Primary Objective

The primary objective is to assess the efficacy and safety of nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe AD not adequately controlled with topical treatments.

7.2 Co-Primary Endpoints

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16

7.3 Secondary Objective

The secondary objective is to evaluate the efficacy and safety of maintenance treatment with nemolizumab (CD14152) for up to 32 weeks.

7.4 Key Secondary Endpoints:

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with PP NRS < 2 at Week 16

[redacted]

CCI

[redacted]

- Proportion of subjects with an improvement of SD NRS ≥4 at each visit up to [redacted]

[redacted]

- Change from baseline up to Week 16 in Hospital Anxiety and Depression Scale (HADS) for each subscale (ie, depression and anxiety)

- Change from baseline up to Week 16 in Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI:AD) for each subscale (ie, work productivity and activity impairment)

- CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.6 Safety Endpoints

- Incidence and severity of AEs, including AESIs, TEAEs, and SAEs

7.7 Other Endpoints

7.7.1 Pharmacokinetics

- Nemolizumab (CD14152) serum concentrations

7.7.2 Immunogenicity

- ADA concentrations

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in adult and adolescent subjects with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medications. Approximately 150 study centers are planned in Europe, Americas, and Asia-Pacific.

Beginning at screening, subjects will apply a moisturizer at least once daily and an authorized background topical therapy (including a medium-potency TCS for the body and a low-potency TCS or a TCI for sensitive areas such as the face, neck, intertriginous areas, etc) for use throughout the study. If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects during the study, except during the run-in period (ie, at least 2 weeks [14 days] before Day 1/baseline).

The study consists of 4 periods over approximately 60 weeks: screening (including run-in), initial treatment, maintenance, and follow-up (unless the subject is a non-responder at Week 16, at which their participation could last up to 28 weeks). Refer to Figure 2 for an overview of the treatment/study design.

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

Screening Period (Screening to Initial Randomization/Baseline)

The screening period (approximately 2-4 weeks before planned Day 1/baseline) will evaluate subject eligibility and introduce standardized background topical therapy over a run-in period of at least 2 weeks (ie, 14 days) before Day 1/baseline.

Subjects may be rescreened once unless the reason for screen failure is related to disease severity inclusion criteria (IGA, EASI, BSA, and PP NRS). The latter subjects are not permitted to rescreen.

Initial Treatment Period (Baseline/Day 1 to Week 16 Pre-dose)

The initial treatment period is defined as Day 1/baseline through Week 16 (before the Week 16 dose, with last dose at Week 12). Approximately 750 total subjects will be randomized (2:1) to receive either nemolizumab (CD14152) or placebo, stratified by baseline disease severity (IGA; moderate: IGA = 3; severe: IGA = 4) and PP NRS severity [PP NRS $\geq$ 7; PP NRS < 7). A minimum of 250 subjects will be randomized in each PP NRS strata. Table 4 summarizes study drug dosing during the initial treatment period.

Subjects will continue to use background topical therapy, which should be adjusted 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, based on investigator clinical judgment. Any adjustments to background topical therapy are to be recorded in the appropriate case report form (CRF).

Table 4: Initial Treatment Period Randomized Group Assignments

Group	*Treatment*	*Loading dose (Day 1/Baseline)*	*Dose at Week 4, 8, 12*	*Route*	*Schedule*
1	Nemolizumab(CD14152)	60 mg (two 30-mg injections)	30 mg	sc	Q4W
2	Placebo	Placebo (two injections)	Placebo	sc	Q4W

Abbreviation(s): Q4W=every 4 weeks; sc=subcutaneous.

A pharmacist (or other qualified personnel) will prepare study drug for injection throughout the study, including confirmation of complete reconstitution, prior to delivery of study medication for injection. The pharmacist (or other qualified personnel) preparing study medication should not discuss any aspects of study drug preparation with the subject/caregivers or study staff involved in subject interviews or study assessments.

Subjects (and/or their caregivers) will have the option to self-inject study drug while at the study center under staff supervision. Subjects (and/or their caregivers) will be trained on injecting the study drug at Day 1 and will be allowed to inject study drug at all subsequent visits. If the subject (and/or caregiver) is unwilling to perform injections, study staff can administer study drug at each visit.

Clinical assessments will occur according to the schedule of assessments through the Week 16 visit (see Section 8.1.2). Subjects who are clinical responders at Week 16 will continue to the maintenance period. Subjects who are non-responders at Week 16 may be eligible to enroll into the LTE study (Protocol 118163). Subjects who require rescue therapy for clinical worsening of AD before Week 16 may also be considered for LTE study participation but will be required to continue with study visits until the Week 16 visit is due. The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after their last study drug injection.

Subjects who discontinue the initial treatment period prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection.

Initial treatment period results may be analyzed after all subjects have either completed the Week 16 visit or have withdrawn or been discontinued from the study before Week 16. To maintain the blind during the maintenance period, personnel directly involved with the ongoing conduct of the study from the sponsor, contract research organization (CRO), or investigational study centers will not have access to any information that may lead to unblinding.

Maintenance Period (Re-Randomization: Week 16 to Week 48)

The maintenance period is defined as Week 16 (maintenance baseline) to Week 48. All nemolizumab (CD14152)-treated subjects (ie, group 1) who are clinical responders at Week 16 will be re-randomized (1:1:1) to study medication, as follows: group 1A, nemolizumab (CD14152) 30 mg Q4W; group 1B, nemolizumab (CD14152) 30 mg Q8W; or group 1C, placebo Q4W (Table 5).

Clinical responders are defined as:

- IGA of 0 (clear) or 1 (almost clear) at Week 16
  OR
- EASI-75 at Week 16

All placebo-treated subjects (ie, subjects in group 2 from the initial treatment period) who responded to placebo during the initial treatment period will continue to receive placebo Q4W in the maintenance period.

Subjects who receive rescue therapy will be considered non-responders.

Based on the phase 2b results (Protocol 114322), it is estimated that 15% of subjects will drop out from the initial treatment period. Assuming a 45% responder rate with active treatment and 12% with placebo, approximately 216 subjects will participate in the maintenance period (190 nemolizumab and 26 placebo subjects).

Table 5: Maintenance Period Re-Randomized Group Assignments

Group	*Treatment*	*Dose*	*Week(s)*	*Route*	*Schedule*
1A	Nemolizumab (CD14152)	30 mg	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W
1B	Nemolizumab (CD14152)	30 mg	16, 20*, 24, 28*, 32, 36*, 40, 44*	sc	Q8W*
1C	Placebo	Placebo	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W

**with placebo Q4W at Week 20, 28, 36, and 44 to maintain blind*

Abbreviation(s): Q4W=every 4 weeks; Q8W=every 8 weeks; sc=subcutaneous.

Beginning at Week 16, subjects in group 1A will receive active (ie, nemolizumab [CD14152]) study drug injections Q4W up to Week 44. Subjects in group 1B will receive active (ie, nemolizumab [CD14152]) study drug injections Q8W, with placebo at alternating visits to maintain the blind. Group 1B subjects will receive the last active study drug injection at Week 40 (final injection at Week 44 will be placebo). Group 1C subjects will receive placebo Q4W (ie, through Week 44).

Clinical assessments will occur according to the schedule of assessments through the Week 48 visit (see Section 8.1.2). Subjects should continue the same background topical therapy used in the initial treatment period leading up to the Week 16 visit, including tapering or complete cessation (no use), if applicable. Throughout the maintenance period, adjustments to background topical therapy, as determined by the investigator, are permitted based on the subject's clinical response.

Primary maintenance effect will be evaluated based on Week 48 assessments. All maintenance endpoints will be analyzed independently from each pivotal study and by using pooled data after the completion of both trials.

Subjects requiring rescue before the Week 32 must undergo a required wait period (with continued study visits) until Week 32, at which time they may be considered for LTE eligibility/participation. Thereafter, no wait period is required. See Section 8.5.1 for details.

Subjects who complete the Week 48 visit may be eligible to enroll into the LTE study (Protocol 118163). The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible for the LTE study will be asked to complete the follow-up visit.

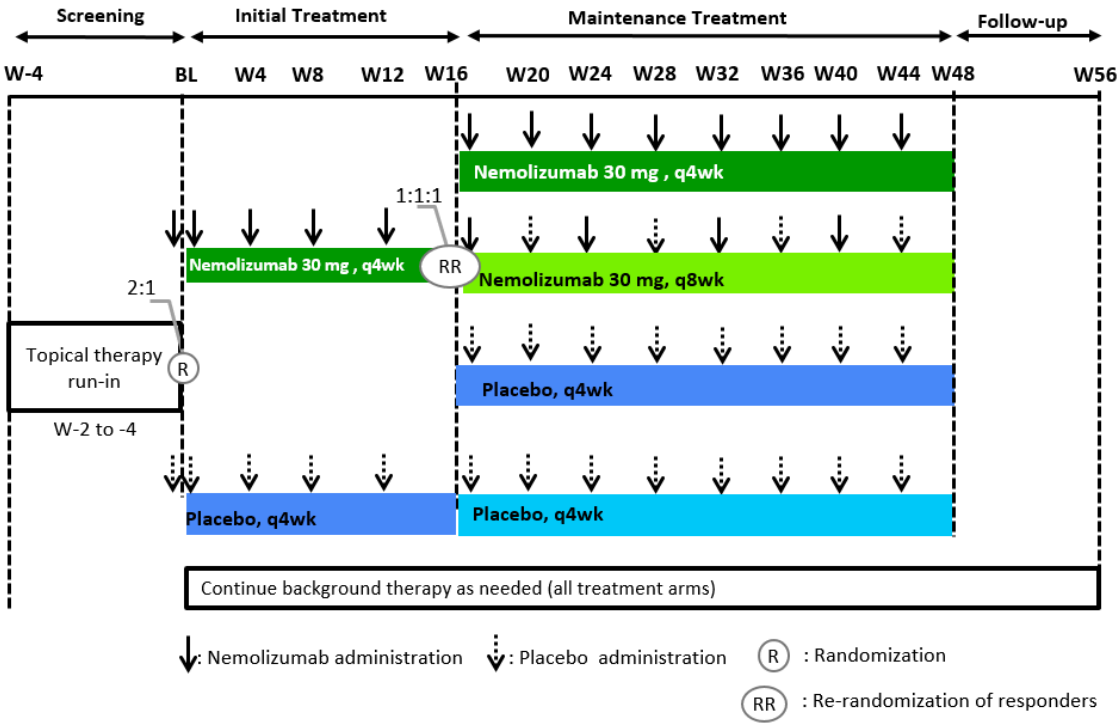
Subjects who discontinue the maintenance period prematurely should complete an ET visit and a follow-up visit 12 weeks after the last study drug injection.

Follow-up

The follow-up visit will be conducted 12 weeks after the last study drug injection for subjects who decline or are not eligible to enter the LTE study. The follow-up visit is not required for subjects who participate in the LTE study. (Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously Q4W.)

8.1.1 Study Visit Schema

Figure 2: Study Visit Schema



Abbreviations: BL=baseline; q4wk=every 4 weeks; q8wk=every 8 weeks; W=week.

8.1.2 Schedule of Assessments

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
Informed consent and assent form	X															(X)	
PGx, subject interview, photography consent form(s) (if applicable)	X															(X)	
Inclusion/exclusion criteria	X	X														(X)	
Demographic data	X															(X)	
Medical history, previous therapy, smoking status	X															(X)	
PATIENT-REPORTED OUTCOME ASSESSMENTS																	
DLQI (≥ 17 years) or cDLQI (12-16 years) [g]		X		X			X				X				X	(X)	
CCI [redacted]		X		X			X				X				X	(X)	
CCI [redacted]		X		X			X									(X)	

Periods	**Screening**	**Initial Treatment**						**Maintenance**								*Unscheduled Visit* [a,b]	**Follow-up** [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ **(ET)**[d]	7	8	9	10[a,d]	11	12	13	14[a]/ **(ET)**[d]	(as applicable)	
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		(12 weeks after last injection)
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
AD-associated pain intensity and frequency [g]		X		X			X				X				X	(X)	
CCI		X		X			X				X				X	(X)	
CCI				X			X				X				X	(X)	
CCI	X[i] ---------- X[i]								X[k]		X[k]		X[k]		X[k]	(X)	
CC		X		X		X[c]	X									(X)	
CCI		X		X		X[c]	X									(X)	
				X		X[c]	X									(X)	
Topical AD medication used (daily) [i]	X---------- X															(X)	
Subject interview (optional) [l]							X									(X)	
CLINICAL PHOTOGRAPHS																	
Clinical photographs (optional) [m]		X					X								X	(X)	
EFFICACY ASSESSMENTS																	
EASI	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	
IGA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	
BSA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	

Periods	**Screening**	**Initial Treatment**						**Maintenance**								*Unscheduled Visit* [a,b]	**Follow-up** [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ **(ET)**[d]	7	8	9	10[a,d]	11	12	13	14[a]/ **(ET)**[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
SCORAD	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	
SAFETY ASSESSMENTS																	
ACT [g,n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	(X)[n]	X[n]
Respiratory examination [o]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
PEF testing [p]	X	X	X[p]	X	X[p]	X		X[p]	X[p]	X[p]	X	X[p]	X[p]	X[p]	X	X	(X)	X
Physical examination [q]	X	X		X		X			X		X		X		X	X	(X)	X
Contraceptive counseling [r]	X																(X)	
Height [s]	X			X[s]			X[s]		X[s]		X[s]		X[s]		X[s]	(X)[s]	X[s]	
Weight	X	X					X				X				X	X	(X)	X
12-lead ECG [t]	X						X								X	X	(X)	X
Vital signs [u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Adverse event reporting [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Concomitant therapy (including contraception)/ medications [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
LABORATORY ASSESSMENTS																		
Urinalysis [v]	X	X		X			X				X				X	X	(X)	X

Periods	**Screening**	**Initial Treatment**						**Maintenance**								*Unsched-uled Visit* [a,b]	**Follow-up** [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ **(ET)**[d]	7	8	9	10[a,d]	11	12	13	14[a]/ **(ET)**[d]	(as applicable)	
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		(12 weeks after last injection)
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
Hematology [v]	X	X		X			X				X				X	(X)	X
Blood chemistry [v]	X	X		X			X				X				X	(X)	X
TB test [w]	X															(X)	
Hepatitis B and C test	X															(X)	
HIV test	X															(X)	
Pregnancy test [x]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
FSH [y]	X															(X)	
PK, ADA, PD/BIOMARKERS, and OPTIONAL PGx ASSESSMENTS																	
PK samples [v,z]		X	X	X	X		X	X	X		X		X		X	(X)	X
ADA samples [v,aa]		X	X	X			X		X		X				X	(X)	X
PD samples (blood) for biomarker assessments [aa]		X		X			X									(X)	
D-Squames samples [aa]		X					X									(X)	
PGx samples (optional) [bb]		X														(X)	
STUDY DRUG ADMINISTRATION																	
Randomization		X					X[cc]									(X)	
Study drug injection and training [dd,ee]		X[ff]	X	X	X		X	X	X	X	X	X	X	X		(X)	

Periods	**Screening**	**Initial Treatment**						**Maintenance**								*Unsched-uled Visit* [a,b]	**Follow-up** [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ **(ET)**[d]	7	8	9	10[a,d]	11	12	13	14[a]/ **(ET)**[d]	(as applicable)	
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		(12 weeks after last injection)
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
CONCOMITANT THERAPY																	
Moisturizer use	X[gg] ----------																X[gg]
Background topical therapy use	X[hh] ----------																X[hh]
TCS ± TCI accountability [ii,jj]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X[ij]

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; EQ-5D = EuroQoL 5-Dimension; ET = early termination; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IRR = injection-related reaction; LTE = long-term extension; PCS = pruritus categorical scale; PD = pharmacodynamics; PGAD = Patient Global Assessment of Disease; PGAT = Patient Global Assessment of Treatment; CCI [redacted] CCI [redacted] Disturbance; PGx = pharmacogenomics; PIQs = PROMIS® Itch Questionnaires; PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; PP NRS = peak pruritus numeric rating scale; PRO = patient-reported outcome; CCI [redacted]

Notes:

[a] Subjects should fast for at least 8 hours before the visit(s) when blood chemistry testing is planned, except for the screening visit.

[b] Assessments to be conducted at the unscheduled visit depend on the reason for the visit. PK and ADA analyses are obligatory at unscheduled visits that are conducted for safety reasons when safety labs are collected for the management/monitoring of an AE. When series of unscheduled visits is needed for the monitoring of the same safety event, PK and ADA collection is not required if already done at the first unscheduled visit of the series. Additional collection of samples for PK and ADA analysis should

be performed per investigator's judgement.. Subjects requiring rescue therapy between scheduled visits should return to the clinic for an unscheduled visit for investigator assessments of efficacy before starting rescue therapy.

[c] CCI [redacted]

[d] Subjects discontinued prematurely should complete ET assessments according to: Visit 6/Week 16 if during the initial treatment period **or** Visit 14/Week 48 if during the maintenance period **and** a final/follow-up visit 12 weeks after the last study drug injection (for subjects not participating in the LTE study). Subjects who require rescue therapy (with or without study medication discontinuation) must continue with study visits until: Visit 6/Week 16 if during the initial treatment period **or** until Visit 10/Week 32 if during the maintenance period to be considered for LTE eligibility. (If during the maintenance period, rescue is needed after the Week 32 visit, no wait period is required.) See Section 8.5.1 for details.

[e] The follow-up visit will be conducted for subjects who decline or are not eligible to enter the LTE study and should be conducted 12 weeks after the last study drug injection. (The follow-up visit is not required for subjects who will rollover to the LTE study.)

[f] The run-in period begins at least 2 weeks (ie, 14 days) before Day 1/baseline. Subjects receiving rescue therapies during the run-in period are not eligible to participate in the study.

[g] Patient-reported outcome assessments and designated safety measurements should occur before investigator assessments, laboratory sample collections, and study drug administration.

[h] CCI [redacted]

[k] Assessments to be completed by subjects for 7 consecutive days before the designated target visit dates during study treatment.

[l] Optional subject interviews will be conducted at the end of the initial treatment period between Week 16 and Week 18. See Section 9.7.15 for details.

[m] Optional photographs of AD lesions will be performed only for consenting subjects at selected sites. See Section 9.8 for details.

[n] Subjects with a history of asthma will complete the ACT (and PEF testing) at each scheduled visit. Subjects with de novo asthma will complete the ACT (and PEF testing) beginning from de novo diagnosis and at all subsequent scheduled visits. See Section 9.2.9.1 for details.

[o] At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, coughing, allergies, infections). A respiratory examination will be required for all subjects at all scheduled visits. See Section 9.2.9.2 for details.

[p] PEF testing will be performed for all subjects at screening, baseline, Week 8, 16, 32, 48, and follow up visits. For subjects reporting a medical history of asthma, PEF testing (and ACT) will be performed at all visits during the clinical study. For subjects diagnosed with de novo asthma, PEF testing (and ACT) will be performed at all visits, starting with the visit in which the diagnosis was confirmed. Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject. See Section 9.2.9.3 for details.

[q] Complete PE should be performed at designated visits. See Section 9.2.8 for PE details.

[r] Contraceptive counseling should occur at screening or at applicable visits when pre-pubertal subjects begin menses.

[s] Height collection will be performed for all subjects at screening. Height collection is only required for adolescents (ages 12-17) at designated post-screening visits.

[t] 12-lead ECGs should be performed in the supine position, before any scheduled vital sign measurements and blood draws. See Section 9.2.10 .

[u] 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. See Section 9.2.6 .

[v] At scheduled visits with laboratory, PK, and ADA assessments, samples are to be collected before study drug injection(s). See Section 9.2.2.1, 9.2.2.2, and 9.2.2.3 for hematology, clinical chemistry (including FSH for postmenopausal subjects), and urinalysis testing details, respectively.

[w] TB screening: QuantiFERON-TB Gold test for all subjects. See Section 9.2.5 for details.

[x] Only for WOCBP. Pregnancy test results must be available prior to the administration of the study drug. **Serum pregnancy test to be performed at the screening visit; UPT at 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.

[y] For postmenopausal subjects (ie, no menses for 12 consecutive months), confirm status with a high FSH level in the postmenopausal range. Blood chemistry sample at the screening visit (V1) will also be used for an FSH test for the confirmation of postmenopausal status.

[z] See Section 9.3 for details on PK assessments. As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples).

[aa] See Section 9.4 and Section 9.5 for details on ADA and PD/biomarker assessments, respectively.

[bb] Optional PGx sample collection is only for subjects who provide additional consent. See Section 9.5.1 for details.

[cc] All nemolizumab (CD14152)-treated subjects who are clinical responders at Week 16 (defined as 1. IGA of 0 [clear] or 1 [almost clear]; **OR** 2. EASI-75) will be **re-randomized** (1:1:1) to receive nemolizumab (CD14152) Q4W, Q8W, or placebo Q4W.

[dd] Study drug reconstitution will be performed by the pharmacist (or other qualified personnel) throughout the study, and complete reconstitution confirmed, prior to delivery for injection. Study center staff will provide study drug injection training for subjects willing and able to self-inject (or have their caregiver inject) study medication. Subjects and/or caregivers will then be allowed to inject medication at subsequent visits. Based on the subject's preference, study center staff can also perform all injections.

[ee] After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. Subjects should remain at the study center for at least 30 minutes after the first 2 injections during the study. *In Germany only, subjects must undergo a 60 minute observation period after the first 3 injections and a 30 minute observation period after all subsequent doses.

[ff] Subjects will receive a loading dose on Day 1 (ie, 2 injections of nemolizumab 30 mg or placebo).

[gg] 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 clinic/office visits.

[hh] Authorized topical therapy use beginning ≥ 14 days before Day 1. See Section 8.4.9.1.2. **The investigator should adjust background topical therapy 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, based on investigator clinical judgment.**

[ii] Appropriate amounts of TCS and/or TCI should be dispensed or prescribed at each visit, according to investigator judgement. Containers of previously dispensed/prescribed TCS and/or TCI should be collected at each visit. Collected containers with remaining medication may be re-dispensed back to the subject, when applicable.

[jj] No dispensation of TCS and/or TCI should occur at the final study visit. Collection only.

8.2 Discussion of Study Design

8.2.1 Study Design

This study will evaluate the safety and efficacy of nemolizumab (CD14152) in adolescent and adult subjects with AD. The rationale for the general study design is based upon the prior phase 2b design conducted in adult subjects with AD, with background TCS therapy. The rationale for the nemolizumab dose/dose regimen is provided in Section 6.5.

Eligible subjects for this clinical study will be adolescents and adults with moderate-to-severe AD 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 (CD14152), and the need to understand the safety and long-term exposure of nemolizumab (CD14152) in the adolescent and adult population. The inclusion criteria for IGA, BSA, and EASI are consistent with the disease severity targeted in the study and in nemolizumab (CD14152) studies in 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 (CD14152) and its marked effect on pruritus. Specifically, subjects with a PP NRS score of ≥ 7 were included based on the population evaluated in the phase 2b study; a lower PP NRS threshold of ≥ 4 was selected for this study based on anticipated benefits for subjects with less severe pruritus as well.

The study includes a 16-week initial treatment period, a 32-week maintenance period, and an 8-week follow-up period (ie, 12 weeks after last study drug administration) for subjects who decline or are not eligible to enter the LTE study. A 16-week treatment is considered adequate to evaluate the safety and efficacy of nemolizumab based on the results of the phase 2b study (114322) and other registrational studies for the treatment of AD. The maintenance period will compare the maintenance of effect of 2 nemolizumab dosing regimens (30 mg Q4W and 30 mg Q8W) compared to placebo. The nemolizumab 30 mg Q8W regimen is proposed to evaluate whether a clinical response can be maintained with a lower dosing frequency. Subjects who are clinical responders at Week 16 will be re-randomized (1:1:1) to 1 of 3 maintenance treatment groups.

Clinical responders are defined as:

- IGA of 0 (clear) or 1 (almost clear) at Week 16
  OR
- EASI-75 at Week 16

Subjects who are non-responders at the Week 16 visit can be considered for LTE study eligibility. All subjects who complete the maintenance period (Week 48 visit) can be considered for LTE study eligibility.

The selected endpoints for assessing the PK and safety of nemolizumab (CD14152) are in accordance with current standards, as are the safety endpoints of the trial. Blinding subjects and the designated study team to the treatment assignment(s) ensures objectivity and minimizes bias. Randomization through the interactive response technology (IRT) guards against selection bias.

A follow-up visit is scheduled for subjects who decline participation in the LTE study or are not eligible to participate. The duration of the follow-up period from the final nemolizumab dose (12 weeks) corresponds to approximately 5 half-lives of nemolizumab, which is considered adequate to ensure subject safety. The follow-up visit is not required for subjects who participate in the LTE study as its primary objective is long-term evaluation of safety.

Differences may be detectable during the study drug reconstitution process between active study drug and placebo but appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study medication for injection, including confirmation of complete reconstitution, prior to delivery of study medication for injection. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

Background topical therapy includes the use of authorized TCS ± TCI 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 topical therapy 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). A low-potency TCS or a TCI will be used in

sensitive areas considered unsafe for medium-potency TCS (eg, face, neck, intertriginous areas) or where medium-potency TCS is not tolerated. The prescribed background therapy use should be within daily limits according to the product labeling. The protocol includes guidelines to adjust background therapy usage according 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, based on investigator clinical judgment.

The placebo-control design includes a provision for rescue therapy for clinical worsening of AD or lack of improvement in AD based on investigator clinical judgment. Subjects requiring rescue therapy may be eligible for the LTE study but will be required to continue scheduled study visits until the Visit 6/Week 16 visit during the initial treatment period or the Week 32 visit for those participating in the maintenance period before LTE eligibility will be assessed. After Week 32, no wait period is required. The required wait periods for considering LTE study eligibility are intended to discourage inappropriate use of rescue medication for the sole purpose of accessing open-label, active study medication.

Initial treatment period results may be analyzed after all subjects have either completed the Visit 6/Week 16 visit or have withdrawn or been discontinued from the study before Visit 6/Week 16.

To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the sponsor, CRO, or other investigational study centers will not have access to any information that may lead to unblinding.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately 750 total subjects are planned to be randomized, including a minimum of 130 adolescent subjects aged 12 to 17 years.

Refer to Section 10.2 for the statistical considerations on which the sample size is based.

8.3.2 Inclusion Criteria

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

1. Male or female subjects aged ≥ 12 years at the screening visit.

Note: Enrollment of subjects aged 12 to 17 years has been opened after the IDMC has assessed interim safety data from the phase 2 study (Protocol 116912) and provided recommendations to the sponsor, who then determined the eligibility of this age group for enrollment in the study. The sponsor sent a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents could not be enrolled in the study until such communication was received.

2. Chronic AD for at least 2 years before the screening visit and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1)[2] at the time of the screening visit.
3. EASI score ≥ 16 at both the 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 the screening and baseline visits.
5. AD involvement ≥ 10% of BSA at both the screening and baseline visits.
6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit.

   Screening PP NRS score will be determined by a single PP NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

   Baseline PP NRS score will be determined based on the average of daily PP NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.
7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit, or for whom TCI is selected as background therapy for sensitive areas, must also demonstrate inadequate response to TCI. Acceptable documentation includes patient records with information on TCS (with or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator. If documentation is inadequate, subjects may be re-screened after such documentation is obtained.

   Inadequate response to TCS treatments (with or without TCI) is defined as:

   7a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency

TCS (Class I-III according to the US classification)[2] (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;

or

7b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I-II according to the US classification)[2] (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);

or

7c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

8. Agree to apply a moisturizer throughout the study from the screening visit; agree to apply authorized topical therapy from the screening visit and throughout the study as determined appropriate by the investigator.

9. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study and for 12 weeks after the last study drug injection, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate 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. *In Germany only, if a subject has reached Tanner stage 3 breast development, even if not having menarche, the subject will be considered a female of childbearing potential.

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

   - Progestogen-only oral hormonal contraception
   - Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception)
     Note: “Double barrier methods” refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (eg, condom) together with a spermicide is not acceptable.
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices or intrauterine hormone-releasing system

- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Bilateral vasectomy of partner at least 3 months before the study

10. Female subjects of non-childbearing potential must meet one of the following criteria:
    - Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle-stimulating hormone (FSH) level in the postmenopausal range
    - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before screening
      Note: Bilateral tubal ligation is not accepted as a reason for non-childbearing potential
11. Subject (and guardian, when applicable) willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.
12. Understand and sign an informed consent form (ICF) (and assent form, when applicable) before any investigational procedure(s) are performed.

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Body weight < 30 kg.
2. Subjects meeting 1 or more of the following criteria at screening or baseline:

   2a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.

   2b. Reporting asthma that has not been well-controlled (ie, symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.

   2c. ACT ≤ 19 (only for subjects with a history of asthma).

   2d. PEF < 80% of the predicted value.

3. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.
4. Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected COVID-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.3.4.2.
   Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this study.
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 (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 study if hepatitis B surface antibody is positive (considered immune after a natural infection).
7. Having received any of the following treatments in Table 6 within the specified timeframe before the baseline visit:

Table 6: Prior Treatments

Treatment(s)	***Timeframe***
Coal tar products	2 weeks
Topical PDE-4 inhibitor	2 weeks
Non-authorized TCS	2 weeks
Topical medications, including authorized TCS/TCI, with occlusive dressings (eg, wet wraps)	2 weeks
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Phototherapy or tanning beds	4 weeks

Treatment(s)	***Timeframe***
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors)	4 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (eg, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)
Dupilumab	10 weeks
Live attenuated vaccine	12 weeks
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening (Stable treatment with antihistamines with sedative effect is allowed at a dose that, based on previous experience, is well tolerated by the subject.)	1 week
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks
Cannabinoids	2 weeks
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks

Abbreviation(s): AD=atopic dermatitis; PDE-4=phosphodiesterase-4; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.
Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

8. Previous treatment with nemolizumab.
9. Subjects who, after a full treatment course of 16 weeks with dupilumab, experienced worsening of their AD or failed to achieve minimal improvement (eg, ≤ 10% reduction in EASI or no reduction in IGA).

10. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test [UPT] at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study.
11. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.
12. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
13. History of intolerance to TCS or for whom TCS is not advisable (eg, hypersensitivity, significant skin atrophy).
14. Known active or untreated latent tuberculosis (TB) infection.
    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.
15. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
16. Presence of confounding skin condition that may interfere with study assessments (eg, Netherton syndrome, psoriasis, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).
17. 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), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia).
18. Planned or expected major surgical procedure during the clinical study.
19. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.9.2).

20. Currently participating or participated in any other study of a drug or device, within the past 8 weeks before the screening visit, (or 5 half-lives of the investigational drug, whichever is longer), or is in an exclusion period (if verifiable) from a previous study.
21. History of alcohol or substance abuse within 6 months of the screening visit.

8.3.4 Removal of Subjects From Therapy or Assessments

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

Reasons for discontinuing study drug include:

- Subject request (ie, consent withdrawal)
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs, including laboratory abnormalities, not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue, including but not limited to the following:
    - Serious immediate-type allergic manifestations including anaphylactic reaction
    - Serious worsening of asthma considered related to study drug administration
    - Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma [Bowen's disease] or basal cell carcinoma)
    - Opportunistic infections such as but not limited to active TB and other infections whose nature or course suggest an immune-compromised or immune-suppressed status
    - Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks considered related to study drug administration
    - Confirmed or suspected COVID-19 infection (temporary discontinuation may be acceptable; for instructions on resuming study drug administration, see Section 8.3.4.2).

- Pregnancy
- Use of non-permitted concurrent therapy (unless discussed and agreed upon with the investigator and medical monitor)
- Use of systemic rescue therapy, as specified in Table 10 of Section 8.4.9.2 and Section 8.4.9.1.3
- Treatment failure
- Investigator request
- Sponsor request, including any of the above criteria

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

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

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

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

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.3.4.1 Pregnancy

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

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 9.2.1.5) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 9.2.1.5).

- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (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 (ie, voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 9.2.1.3).

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

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

8.3.4.2 COVID-19 Infection

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

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

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

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

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

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

8.4 Investigational Products

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

8.4.1 Investigational Products Administered

Study drug will be supplied as a lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a pre-filled, single-use DCS. The lyophilized nemolizumab (CD14152) powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30-mg dose of nemolizumab (CD14152) after reconstitution.

8.4.1.1 Study Drug Dosing – Initial Treatment Period

Table 7 summarizes study drug dosing for the initial treatment period, which includes Day 1/baseline to Visit 6/Week 16.

Table 7: Initial Treatment Period Dosing By Treatment Group

Group	*Treatment*	*Loading Dose (Day 1/Baseline)*	*Dose at Week 4, 8, 12*	*Route*	*Schedule*
1	Nemolizumab (CD14152)	60 mg (two 30-mg injections)	30 mg	sc	Q4W
2	Placebo	Placebo (2 placebo injections)	Placebo	sc	Q4W

Abbreviation(s): Q4W=every 4 weeks; sc=subcutaneous.

At Visit 6/Week 16, subjects who are clinical responders to nemolizumab (CD14152) treatment will be re-randomized (1:1:1) for participation in the maintenance period, and assigned by IRT to nemolizumab (CD14152) 30 mg Q4W, nemolizumab (CD14152) 30

mg Q8W, or placebo Q4W. The Q8W group will receive alternating injections of placebo to maintain the blind. Refer to the study design in Section 8.1 for the definition of clinical responders. Subjects responding to placebo treatment will be assigned by IRT to receive placebo Q4W in the maintenance period.

Subjects who are non-responders at the Visit 6/Week 16 visit can be considered for LTE study eligibility. Similarly, subjects who require rescue therapy for clinical worsening of AD or lack of improvement in AD may be considered for LTE study eligibility but must continue study visits until the Visit 6/Week 16 visit is due.

8.4.1.2 Study Drug Dosing – Maintenance Treatment Period

Table 8 summarizes study drug dosing for the maintenance period, which spans the Week 16 to Week 48 visits.

Table 8: Maintenance Period Dosing By Treatment Group

Group	*Treatment*	*Dose*	*Week(s)*	*Route*	*Schedule*
1A	Nemolizumab (CD14152)	30 mg	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W
1B	Nemolizumab (CD14152)	30 mg	16, 20*, 24, 28*, 32, 36*, 40, 44*	sc	Q8W*
1C	Placebo	Placebo	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W

**with placebo injections at Week 20, 28, 36, and 44 to maintain blind*

Abbreviation(s): Q4W=every 4 weeks; Q8W=every 8 weeks; sc=subcutaneous.

Subjects who complete the Week 48 visit can be considered for LTE study eligibility. Similarly, subjects requiring rescue therapy prior to the Week 48 visit may be considered for LTE eligibility. A wait period with continued study visits is required if rescue occurs before the Week 32 visit. Thereafter, no wait period is required. Subjects must complete the final study/ET visit prior to rollover to the LTE study.

8.4.1.3 Study Drug Preparation

A pharmacist (or other qualified personnel) will prepare study medication for injection according to instructions provided in the current version of the pharmacy manual and the instructions for use. Study medication preparation should be conducted in a secured and

clean area with limited access to only designated personnel at the time of the preparation. Good hygiene practices and clean techniques must apply at all times.

Differences may be detectable during the study drug reconstitution process between active and placebo, but active and placebo appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study medication for injection, including confirmation of complete reconstitution, prior to delivery of study medication for injection. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

The study drug does not contain preservatives. From a microbiological point of view, the preparation of the study drug has to be done as close to subject administration as possible, and the study drug should be used immediately (less than 1 hour) after reconstitution. If not used immediately, the study drug has to be used within 4 hours maximum after reconstitution stored at room temperature (below 30°C) and only if the preparation has taken place applying strictly good hygiene practices and clean techniques to ensure controlled aseptic conditions.

8.4.1.4 Study Drug Injection

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

For subjects willing and able to self-inject, or to have their caregiver inject study medication, study center staff will provide training on study medication injections. Subjects or caregivers will be allowed to inject medication at subsequent visits under supervision by study center clinic staff (with DCS preparation including reconstitution performed by the pharmacist or other qualified personnel and delivered for injection after reconstitution is complete). Study center/clinic staff can perform all injections if the subject (or caregiver) is unwilling or unable to perform injections. The CRF will record who performed study drug injection at each visit.

After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. Subjects should remain at the study center for at least 30 minutes after the first 2 injections during the study. *In Germany only, subjects must undergo a 60 minute observation period after the first 3 injections and a 30 minute observation period after all subsequent doses.

8.4.2 Identity of Investigational Products

Table 9 provides a description and overview of study medication usage.

Table 9: Description and Usage of Investigational Product

Investigational Product	***Initial Treatment***	***Maintenance***
Name (internal code)	Nemolizumab (CD14152)	Nemolizumab (CD14152)
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Dosage	30 mg (with a loading dose of 60 mg at baseline)	30 mg
Dose regimen	Q4W	Q4W or Q8W
Route*	Subcutaneous use by subjects, caregivers, or clinic staff after reconstitution	Subcutaneous use by subjects, caregivers, or clinic staff after reconstitution
Duration of treatment	16 weeks: baseline to Week 16	32 Weeks: Week 16 to Week 48
Comparator	***Initial Treatment***	***Maintenance***
Name (internal code)	CD14152 placebo (N/A)	CD14152 placebo (N/A)
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Dosage	N/A (2 injections at baseline, to maintain the blind)	N/A
Dose regimen	Q4W	Q4W (Note: CD14152 Q8W dose regimen uses placebo injections to maintain the blind)
Route*	Subcutaneous use by subjects, caregivers, or clinic staff after reconstitution	Subcutaneous use by subjects, caregivers, or clinic staff after reconstitution
Duration of treatment	16 weeks: baseline to Week 16	32 Weeks: Week 16 to Week 48

Abbreviation(s): DCS=dual-chamber, single-use syringe; N/A=not applicable; Q4W=every 4 weeks; Q8W=every 8 weeks.
Note(s):
* All injections are performed at the study center clinic office. Injections by subjects or caregivers are performed under supervision by clinic staff, after appropriate training.

8.4.3 Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products in the local language, national regulations/guidelines, and the relevant regulatory requirements, specifying that the drug is for use in a clinical study. Each DCS will be packaged in an individual carton, including a 27G 1/2" needle and a plunger rod (not assembled). Local adaptation of the kit design may be required; specific details for each country are provided in the pharmacy manual.

8.4.4 Study Drug Management

8.4.4.1 Storage of Study Drug

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

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

8.4.4.2 Study Drug Accountability

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

The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered and received DCS units, and the return/destruction of unused study drug as specified in the current version of the pharmacy manual. No unauthorized use is permitted. Used DCS units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected or an event occurs before, during, or just after the injection, the used DCS can be disposed in

an appropriate sharps container and according to waste regulation(s) in the country. A DCS involved in a malfunction or an investigator or subject complaint must be retained on site and designated personnel must proceed as defined in the current version of the pharmacy manual. Refer to Section 8.4.10 for product technical complaints.

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

8.4.4.3 Dispensing and Return of Study Drug

All drug preparation must be appropriately performed and documented by the designated personnel. Any error in the preparation of dosing solution must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/return/destruction process for all unused study drug will be conducted according to the sites' SOPs, local regulations, and best practices, as described in the current version of the pharmacy manual. If the site does not have the capability to destroy drug, then the unused study drug will be returned to the CRO/drug depot for destruction.

8.4.4.4 Treatment Compliance

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

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

8.4.5 Method of Assigning Subjects to Treatment Groups: Randomization and Re-Randomization

Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number will be assigned to that subject via IRT at the baseline visit. Subjects will be randomized (2:1) to receive treatment of nemolizumab (CD14152) Q4W or placebo. Randomization will be stratified by disease severity (IGA=3, IGA=4) and pruritus severity (PP NRS ≥ 7, PP NRS < 7).

Subjects who were randomized to nemolizumab in the initial period and achieved clinical response (EASI-75 or IGA 0/1) at Week 16 will be re-randomized (1:1:1) to receive nemolizumab Q4W, nemolizumab Q8W, or placebo via IRT in the maintenance period.

8.4.6 Selection of Doses in the Study

The 30-mg dose (Q4W or Q8W) proposed for this study is supported by the results of the nemolizumab phase 2b study (114322) and other supportive data. Refer also to Section 6.5 for further details.

8.4.7 Dose Modification

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

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 8.1.2 .

Dosing frequency is scheduled for Q4W, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window, study drug can be administered provided there is a minimum of 3 weeks since the last injection. Future visits should be scheduled within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between 2 injections.

8.4.8 Blinding

All attempts will be made to keep the study center staff and subjects blinded throughout the study. Members of the study center staff, including those responsible for DCS preparation, will not have access to the randomized treatment assignment.

To ensure double-blind administration of study drug the study center pharmacist(s) or other qualified personnel will prepare all nemolizumab (CD14152) or placebo treatments, according to the current versions of the pharmacy manual and Instruction for Use and assigned DCS provided by the IRT system.

As there may be detectable differences between active and placebo during the reconstitution process, the DCS is delivered for injection after the reconstitution is complete. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

To maintain the integrity of the study blinding, the bioanalytical laboratory staff who process/analyze the PK/PD/PGx samples will not provide any information to sponsor, CRO, or investigational study center personnel directly involved with the ongoing conduct of the study that may lead to unblinding.

Unblinding of a subject's individual treatment code should occur only in case of a medical emergency or in the event of a serious medical condition that necessitates identification of the study drug for the welfare of that subject, as judged by the investigator. The emergency unblinding process utilizes IRT to allow the investigator to have unrestricted, immediate, and direct access to the subject's individual study treatment. When possible (ie, when the health of the subject is not immediately at risk), the investigator or sub-investigator is encouraged to consult with the medical monitor and the sponsor before breaking the blind.

If emergency unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected subject will be unblinded.
- The IRT system will provide the treatment assignment to the investigator.

Refer to the Randomization and Trial Supply Management (RTSM) User Guide for information on the steps for breaking the blind in the IRT system.

When the blinding code is broken, the reason must be fully documented. If the code is broken by the investigator, the subject must be withdrawn from the study and must also be appropriately followed for a minimum of 12 weeks after the last dose of study drug.

The reporting requirements for unblinding are the same for reporting an SAE. See also Section 9.2.1.3.

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked. Although initial treatment period results may be analyzed after all subjects have either completed the Week 16 visit, or have withdrawn or been discontinued from the study before Week 16, personnel from sponsor, CRO, and investigational sites directly involved with the ongoing conduct of the study will not have access to any information that may lead to unblinding for the ongoing maintenance evaluation.

The IDMC will review data at periodic intervals throughout the study as defined in the IDMC charter. The IDMC charter will specify the procedures for unblinding to ensure that treatment assignment remains undisclosed to all individuals involved in the direct execution and management of the study until the final database is locked.

8.4.9 Prior and Concomitant Therapy

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

Concomitant therapies/medications are defined as follows:

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

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

- Drugs/Therapies include but are not limited to prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.

- Medical and surgical procedures (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 (or at applicable visits when pre-pubertal subjects begin menses).

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE form should be completed to account for the new therapy or change in therapy, except in some cases such as dose modification for a chronic condition (see Section 8.4.7), in which case the medication will be linked to an item in the subject's medical history.

8.4.9.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 8.4.9.2), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, topical anesthetics, and antihistamines without a sedative effect.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, IL-10) during chronic inflammation. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab (CD14152) on such enzymes has not been studied. Therefore, investigators should consider observing for clinical or laboratory signs that might indicate a potential effect of nemolizumab (CD14152) in subjects using concomitant therapies that are CYP450 substrates, particularly those with a narrow therapeutic index. Typical examples of substrates with a narrow therapeutic range include warfarin, drugs that may cause torsade de pointes, almost all cytotoxic antineoplastic drugs, and aminoglycoside antibiotics. A list of representative CYP450 substrates with narrow therapeutic index can be found in Appendix 3.

8.4.9.1.1 Moisturizer

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

8.4.9.1.2 Background Topical Therapy

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

Medium-potency TCS Therapy for Non-Sensitive Areas: 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).

Low-potency TCS or TCI Therapy for Sensitive Areas: A low-potency TCS or a TCI will be used in sensitive areas considered unsafe for medium-potency TCS (eg, face, neck, intertriginous areas) or in cases where medium-potency TCS is not tolerated. The investigator may select either low-potency TCS or TCI for each subject, per investigator discretion. The subject may only apply **1** medication to each affected area; concomitant use of low-potency TCS and TCI on the same lesion is not permitted.

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

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

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

8.4.9.1.3 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) to allow a minimum time for study drug exposure in the presence of background therapy.

Rescue treatments are only treatments that directly treat AD (mainly those that are approved or are standard of care) and include topical and systemic treatments as outlined. Rescue therapies include:

- Higher potency of TCS (equivalent to class I-II according to the US classification)[2]
- Oral corticosteroids
- Biologics (including their biosimilars)
- Systemic nonsteroidal immunosuppressants/immunomodulators
- Phototherapy

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

Whenever possible, investigators should first use topical medication as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy, 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 (ie, non-responders). Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. Further, the use of any rescue therapies should be documented in the CRF.

8.4.9.2 Prohibited Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study unless otherwise specified in Table 10. "As needed" (PRN) use of TCS or TCI is not permitted.

Table 10: Prohibited Medication/Therapy

Treatment(s)	***Timeframe***	
	Before Baseline/Day 1	**Day 1 – Week 56**
Coal tar products	2 weeks	Prohibited
Topical PDE-4 inhibitor	2 weeks	Prohibited
Non-authorized medium- or low-potency TCS	2 weeks	Prohibited
Higher-potency TCS (US classification I-II or equivalents)[2]	2 weeks	Prohibited*
Topical medications, including authorized TCS/TCI, 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
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors)	4 weeks or 5 half-lives (whichever is longer)	Prohibited*
Biologics and their biosimilars (eg, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)	Prohibited*
Dupilumab	10 weeks	Prohibited*

Treatment(s)	***Timeframe***	
	Before Baseline/Day 1	**Day 1 – Week 56**
Live attenuated vaccine	12 weeks	Prohibited
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (eg, amitriptyline), SSRIs (eg, paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening (Stable treatment with antihistamines with sedative effect is allowed at a dose that, based on previous experience, is well tolerated by the subject.)	1 week	Prohibited
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks	Prohibited
Cannabinoids	2 weeks	Prohibited
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks	Prohibited

Abbreviation(s): AD=atopic dermatitis; PDE-4=phosphodiesterase-4; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid; US=United States.
Note:
Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.
* Unless used as rescue therapy during the study.

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

Specifically, the use of systemic corticosteroids during the study is prohibited except when used as rescue therapy for AD (in accordance with the instructions in Section 8.4.9.1.3). If the use of systemic corticosteroids becomes necessary for the safety of the subject to treat conditions other than AD, the study drug should be temporarily discontinued for the duration of treatment with systemic corticosteroids plus 5 half-lives.

Immunization with non-live COVID-19 vaccine is permitted during the study if in accordance with local regulations. Wherever possible, it is recommended to avoid

administration of COVID-19 vaccinations within 1 week of study drug dosing. A different anatomical location should be used for study drug administration and vaccine administration.

8.4.10 Product Technical Complaints

All DCS units must be inspected prior to preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to a DCS PTC. This also includes the needle and plunger rod. In case of doubt, the DCS should not be used, and the deficiency must be reported as defined in the pharmacy manual.

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

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

8.5 Duration of Subject Participation

The expected duration for each subject's participation in the study depends on the clinical response and may be:

- Up to 28 weeks (including a 4-week screening period, a 16-week initial treatment period, and an 8-week follow-up period [12-weeks after the last study medication injection]) for subjects who are non-responders at the completion of the initial treatment period (Week 16)

- Up to 60 weeks (including a 4-week screening period, a 16-week initial treatment period, a 32-week maintenance period, and an 8-week follow-up period [12-weeks after the last study medication injection]) in subjects who are clinical responders at the completion of the initial treatment period (Week 16)

The 12-week follow-up visit is not required for subjects who will continue in the LTE study (Protocol 118163).

8.5.1 Early Termination Visit

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

Subjects who prematurely discontinue from the study should undergo final study assessments according to the following guidelines:

- Subjects discontinued from the study during the initial treatment period on/before the Week 16 visit should attend an ET visit. A follow-up/final visit is required 12 weeks after the last study drug administration.
- Subjects discontinued from the study during the maintenance period should attend an ET visit.

A follow-up/final visit is required 12 weeks after the last study drug administration.

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

Subjects requiring rescue medication (with or without study medication discontinuation) may be eligible for LTE study participation:

- Subjects requiring rescue medication during the initial treatment period should continue with study visits including the Visit 6/Week 16. A follow-up/final visit is not required for subjects participating in the LTE study.
- During the maintenance period, for subjects requiring rescue medication before the Week 32 visit, a wait period with continuing study visits until the Week 32 visit is due is required. Thereafter, no wait period is required. Subjects must complete the final study/ET assessments prior to rollover to the LTE study.

A follow-up visit is not required for subjects who will participate in the LTE.

8.5.2 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, for follow-up of AEs, or to conduct efficacy assessments for subjects requiring rescue medication between regularly scheduled study visits. Visits occurring outside of the visit window are not considered unscheduled visits.

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

9 STUDY ASSESSMENTS

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

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

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

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

9.1 Efficacy Assessments

Efficacy measurements should be conducted by the investigators (or trained designees) and subjects (for patient-reported efficacy measurements) according to Section 8.1.2 . Whenever possible, the same evaluator should make the assessment throughout the study. Refer to Section 7.2 and Section 7.3 for efficacy endpoints.

9.1.1 Investigator's Global Assessment

The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the investigator or trained designee to evaluate the global severity of AD and the clinical response to a treatment. Treatment success is defined as 0 (clear) or 1 (almost clear) and a 2-point improvement from baseline (see Appendix 4).[35]

9.1.2 Eczema Area and Severity Index

The EASI is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs. The EASI score is a composite score

ranging from 0 to 72 (see Appendix 5).[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) for each of the 4 body areas: head/neck, trunk, upper limbs, and lower limbs, with half points allowed. In addition, the extent of AD involvement in each of the 4 body areas will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. The EASI score will be calculated in the CRF.

9.1.3 Pruritus Numeric Rating Scale

The Pruritus NRS is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours (see Appendix 6). Two measures of Pruritus NRS will be assessed (average and peak/maximum itch intensity). The PP NRS has been validated in other AD clinical trials in adults, and the minimum clinically important difference was shown to be 4.[25]

The average pruritus NRS (AP NRS) provides a measure of overall pruritus intensity over a given period and has clinical relevance to both subjects and physicians because peak pruritus may show higher intensity but short duration.

Subjects will be asked the following questions:

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

The screening PP NRS will be determined by a single assessment using the PP NRS (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. The baseline PP NRS will be determined based on the average of daily PP NRS (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation. Subjects will receive instructions on how to record their pruritus NRS scores and will complete the assessment once daily in the evening throughout the clinical study (including the run-in and the follow-up period).

The proportion of "itch-free days" will be calculated from the number of subject-reported PP NRS and AP NRS scores of 0 or 1 during the treatment period.

9.1.4 Sleep Disturbance Numeric Rating Scale

The SD 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 record their SD NRS scores and will complete the assessment once daily in the morning throughout the clinical study (including the run-in and the follow-up period).

Subjects will be asked the following question:

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

CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.1.9 Application of Topical Medication for Atopic Dermatitis

Subjects will be instructed to use the authorized background topical therapy 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 atopic dermatitis medication your doctor gave you to your skin today?" throughout the clinical study (including the run-in and the follow-up period).

9.2 Safety Assessments

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

9.2.1 Adverse Events

Adverse Event Definition

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

Note(s):

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

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

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

During optional subjects interviews, the subject will be queried on changes in his or her condition and perceived effects of the study treatment. Any unfavorable changes reported by the subjects will be reported to the Investigator or designee by the designated CRO responsible for the interviews. The Investigator will be responsible for reporting all AEs,

including those reported during the interviews following the process described in the protocol.

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

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

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

Assessment of Severity

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

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

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

Assessment of Causality

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug (ie, nemolizumab or placebo) and/or study procedure (eg, injection, topical background therapy, blood sample collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

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

Reasonable possibility:

According to the reporting investigator, there is a reasonable possibility (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 study protocol procedure (eg, injection, topical background therapy, blood sample collection) and the AE

No Reasonable Possibility:

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

Action Taken

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

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

Follow-up of Adverse Events

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

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

Documentation and Reporting of Adverse Events

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

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

9.2.1.1 Adverse Events of Special Interest

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

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

- Injection-related reactions (IRRs)
    - Anaphylactic reactions
    - Acute allergic reactions requiring treatment
    - Severe injection site reactions with a duration greater than 24 hours
- Newly diagnosed asthma or worsening of asthma
    - More specifically, subjects *with* a medical history of asthma will be referred to the physician who manages their asthma when:
        - ACT score ≤ 19: An ACT score ≤ 19 conveys asthma that may not be adequately controlled. An AESI is reported based on the

investigator's clinical judgment, including consideration of the managing physician's report.
        - PEF < 80% of the predicted value: An AESI should be reported.
        - Unexpected worsening of asthma is observed or reported. An AESI is reported based on the investigator's clinical judgment.
    - Subjects *without* a medical history of asthma will be referred to an appropriate respiratory physician/specialist when:
        - Signs and/or symptoms suggestive of asthma have been observed or reported. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
        - Respiratory assessments (eg, examination, PEF) suggest a decline in the subject's respiratory health. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
- Infections
    - Any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks
    - Any confirmed or suspected COVID-19 infection
- Peripheral edema: limbs, bilateral
- Facial edema
- Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

9.2.1.2 Serious Adverse Events

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

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, 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

study, 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 1 of the outcomes listed above in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

9.2.1.3 Procedure for Reporting a Serious Adverse Event

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

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.

2. Ensure that the event is evaluated as an SAE. Immediately notify (**within 24 hours of receipt of the event**) the Syneos Health Safety and Pharmacovigilance group of an SAE report, by email or fax:

   Fax Number: 001-877-464-7787
   Safety email: SafetyReporting@SyneosHealth.com

   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 Syneos Health Safety and Pharmacovigilance group (see contact details above), within 24 hours of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, complete an updated SAE report **within 24 hours** of receipt of the updated information.

5. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, complete an updated SAE report, if appropriate.

7. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor or its delegate (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 SUSARs according to local regulatory requirements, and are forwarded to investigators as necessary.

   An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or its delegate (ie, the CRO) will file it accordingly (ie, within the Trial Master File [TMF]), and will notify the IRB/IEC, if appropriate according to local requirements.

8. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

9.2.1.4 Procedure for Reporting an Adverse Event of Special Interest

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

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.

2. Ensure that the event is evaluated as an AESI. Notify (**within 3 days of receipt of the event)** the Syneos Health Safety and Pharmacovigilance group of an AESI report, by email or fax. Refer to Section 9.2.1.3.

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

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

3. Send any relevant information or medical records (eg, laboratory test results) to the Syneos Health Safety and Pharmacovigilance group within 3 days of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AESI form within 3 days of receipt of the updated information.

5. Obtain and maintain in the files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, update the AESI form, if appropriate.

9.2.1.5 Procedure for Reporting Pregnancies

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

1. Withdraw the subject from the clinical study. The subject must not receive any further injection of the study drug.

2. Complete as fully as possible the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy. Send by email or fax along with the exit form within 24 hours of receipt of the information, to the Syneos Health Safety and Pharmacovigilance group. Refer to Section 9.2.1.3.

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

3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.

4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, send the form by email or fax to the Syneos Health 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 Syneos Health 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/reporting an SAE (see Section 9.2.1.3).

9.2.1.6 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose, the nature or severity of which is not

consistent with the applicable product information (eg, reference safety information in the investigator's brochure for nemolizumab, study protocol, etc).

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

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

9.2.2 Clinical Laboratory Evaluation

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

The investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the investigator or designee will evaluate whether he/she considers it to be clinically significant, defined as meeting at least 1 of the following conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management, 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.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that which may impact

the safety of the subject or the interpretation of the trial results; only after discussion with medical monitor.

All clinically significant out-of-range laboratory values at the screening visit will be recorded in the medical history form (report a diagnosis rather than the laboratory value whenever possible). All clinically significant out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the 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 should 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. Laboratory testing conducted in a nonfasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual and in Appendix 11. 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).

See Sections 9.2.3 , 9.2.4 , and 9.2.5 for details regarding pregnancy testing, virology, and TB testing samples, respectively. (See Sections 9.3, 9.4, 9.5, and 9.6, for details regarding PK, ADA, PD/biomarkers, and optional PGx sampling, respectively.)

The following laboratory safety tests will be performed as specified in Section 8.1.2 :

9.2.2.1 Hematology

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

9.2.2.2 Clinical Chemistry

Creatinine, AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), creatine 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.

For postmenopausal subjects (ie, no menses for 12 consecutive months), postmenopausal status will be confirmed with a high follicle-stimulating hormone level in the postmenopausal range.

9.2.2.3 Urinalysis

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

9.2.3 Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and UPTs at subsequent visits according to Section 8.1.2 . Pregnancy test results must be available prior to the administration of the study drug.

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

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

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

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

9.2.4 Virology

Virology including HBsAg, HBcAb, hepatitis C, HIV-1, and HIV-2 antibody will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody.

9.2.5 Tuberculosis Testing

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

9.2.5.1 Definitions

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

Latent TB is said to exist when an individual is infected with *M tuberculosis*, as evidenced by a positive Interferon Gamma Release Assay,[39] such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

9.2.5.2 Tuberculosis Screening

Ideally, as part of the medical history, the 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-TB gold test) should be referred to the subject's treating physician for appropriate follow-up. If the result is indeterminate, the test may be repeated once. If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

9.2.6 Vital Signs

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

9.2.7 Height and Weight

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

Subjects must be at least 30 kg at both screening and baseline visits in order to be enrolled into this clinical study.

After the screening visit, additional height assessments will only be conducted for adolescent subjects (age 12-17).

9.2.8 Physical Examination

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

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

9.2.9 Respiratory Assessments

At screening, the investigator should specifically question all subjects about any *medical history* of asthma and their respiratory health (eg, wheezing, coughing, allergies, infections). Subjects with a history of asthma will be questioned about the seasonality of

their asthma and known triggers, such as allergens. Newly diagnosed asthma or worsening of asthma during the study will be reported as an AESI.

9.2.9.1 Asthma Control Test

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

The ACT is an assessment to determine if a subject's asthma symptoms are well controlled. The ACT is designed for adults and adolescents 12 years or older, and is composed of 5 questions. For each question, the subject will choose the best answer out of 5 possible answers. The test provides a numerical score ranging from 5 to 25 to assess asthma control; a higher score indicates better asthma control while a score of 19 or less indicates the subject's asthma may not be under control. See Appendix 12.

9.2.9.2 Respiratory Examination

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

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

9.2.9.3 Peak Expiratory Flow

All subjects will undergo PEF testing at screening, baseline, and specified visits according to Section 8.1.2 . For subjects reporting a medical history of asthma, PEF testing will be conducted at all visits.

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

PEF testing during the clinical study will be performed under the supervision of qualified study personnel. PEF measurements should consist of 3 good efforts, with the best result documented. It is preferable that the PEF measurement be performed before noon or at the same time during each study visit whenever possible. Obtained PEF values will be compared to predicted values based on the subject's age, sex and height.[40,41]

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

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

9.2.9.4 Respiratory Referrals

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

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

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

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

9.2.10 Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed and read centrally according to visits specified in Section 8.1.2 using the ECG machine provided. ECGs for each subject

should be obtained using the same electrocardiograph machine whenever possible. ECGs will be performed in the supine position at the time points described in the schedule of assessments and before any scheduled vital sign measurements and blood draws. Subjects should be monitored for potentially clinically significant ECG results (refer to the current version of the central laboratory manual). Tests with abnormal results that are deemed clinically significant should be repeated to ensure reproducibility of the abnormality. ECG abnormalities present at screening should be recorded in the medical history form. Any abnormalities considered by the investigator to be clinically significant after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

9.3 Pharmacokinetics

9.3.1 Blood Sampling

Blood samples will be collected according to Section 8.1.2 , Appendix 11, and the clinical laboratory manual to determine the PK profile of nemolizumab. At each sampling time point for PK assessment, the collected blood will be placed to clot at room temperature (no more than 60 minutes after collection) and then centrifuged. The serum will be collected into storage tubes.

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

9.3.2 CD14152 Quantification in Biological Sampling

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

9.3.3 Pharmacokinetic Parameters

Pharmacokinetic parameters of nemolizumab (CD14152) in the serum may be calculated, if needed, by a designated CRO using 2 analyses:

- PK parameters may be derived, if needed, 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 and adolescents (first-order absorption and a 1-compartment distribution model) will be updated with the nemolizumab serum concentrations obtained in this study.
- In addition, a static analysis based on serum concentration may be performed, if needed, using a noncompartmental analysis, for each subject based on concentration before dosing, to obtain areas under the curve. Data from subjects with missing concentration values (missing samples) may be used if PK parameters can be estimated using the remaining data points.

If the population PK and non-compartmental analyses will be performed, details will be specified in an ad hoc Modeling Analysis Plan and PK Analysis Plan, respectively.

9.4 Immunogenicity

Blood samples will be collected according to Section 8.1.2 , Appendix 11, and the clinical laboratory manual to assess anti-nemolizumab ADA. The ADA will be determined by the designated CRO using a validated ELISA screening assay. The serum concentration will be assessed using a multi-tiered approach.

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

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

9.5 Pharmacodynamic Biomarkers

Blood and stratum corneum (D-Squames) samples will be collected at selected sites to investigate the effect of nemolizumab (CD14152) on RNA and protein biomarkers, including but not limited to TARC, IgE, and IL-31. Samples will be collected according to Section 8.1.2 . The recruitment of subjects for this part of the study will continue until the end of recruitment period of the study.

The details of the procedures for PD samples and storage conditions are further described in the clinical laboratory manual. Samples will be shipped to the designated CRO for biomarker assessment, unless otherwise specified. Samples will be stored by the sponsor or designated CRO for up to 15 years after the end of the study.

9.5.1 Blood Samples for PD

Blood samples will be collected for assessment of TARC and IgE by the central laboratory. Additional blood samples will be collected and shipped to the designated CRO for RNA and protein biomarkers assessment. Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual and in Appendix 11.

9.5.2 D-Squames Samples

Stratum corneum samples will be collected using D-Squames (ie, tape strips) to evaluate biomarker expression levels.[42,43,44] As much as possible, skin sampling should be performed in similar body areas (eg, upper arms) for all samples in all subjects, with a selected area at baseline, and recorded in the CRF.

At baseline prior to administration of study drug, 1 lesional and 1 non-lesional area will be identified, and 20 consecutive D-squames will be collected from each area, making 40 D-squames in total (20 from lesional skin and 20 from non-lesional skin). At week 16, 20 consecutive D-squames will be collected from the exact anatomical location of the lesional area identified at baseline, regardless if the lesion has regressed (20 D-squames in total). The samples will be shipped to the designated CRO for analysis of protein and RNA biomarkers.

9.6 Optional Pharmacogenomic Testing

Pharmacogenomic testing (deoxyribonucleic acid [DNA] analysis) is optional for this study, and will apply to subjects who provide written consent for this procedure. Subjects

are not required to participate in the DNA analysis sub-study in order to enroll in the main study.

DNA analysis will be performed using a blood sample collected at baseline (see Appendix 11 for total blood volume). If inadvertently not collected at baseline, the sample may be collected at a post-baseline visit.

Samples will be stored by the sponsor or designated CRO for up to 15 years after the end of the study. Candidate sequences in DNA analysis may include but are not limited to genes that encode IL-31 and its receptor (IL-31 RA). DNA analysis will be conducted for the purpose of understanding inter-individual variability in nemolizumab (CD14152) efficacy, safety, and PK. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence variation or single nucleotide polymorphism identification within candidate genes and surrounding genomic regions. Genome-wide studies may also be performed.

It is the intent of the sponsor to assure that PGx information obtained remains confidential. The sponsor maintains rigorous confidentiality standards for clinical studies by “coding” (ie, assigning a unique patient ID number at the investigational study center) for all subjects enrolled in the study. All samples taken for DNA analysis will undergo a second level of “coding” (each sample will receive a double-coded ID), according to ICH15 standards. Records will exist to trace double-coded samples to individual subjects for destruction if a subject provides a written request to withdraw their sample for DNA analysis. The data from samples that have already been analyzed will not be destroyed.

Blood samples for DNA analysis will be destroyed after 15 years have elapsed from the completion of this study.

9.7 Patient Reported Outcome Assessments

9.7.1 Asthma Control Test

For this study, the ACT will be completed as part of the respiratory assessments. See Section 9.2.9.1 and Appendix 12 for details.

9.7.2 Patient Global Assessment of Disease

For the PGAD, subjects will be asked to rate their overall impression of their AD severity using a 5-point scale from "clear" to "severe" (Appendix 13). Subjects will be asked the following question:

- "Overall, how would you describe your atopic dermatitis right now?"

9.7.3 Patient Global Assessment of Treatment

The PGAT utilizes a 5-point Likert scale for subjects to rate the way they feel their AD is responding to the study treatment. See Appendix 14.

9.7.4 Pruritus Categorical Scale

The 4-point PCS will be provided for the subjects to report the intensity of their itch during the last 24 hours (Appendix 15). Subjects will record their PCS score in the evening after completing the Pruritus NRS. If a subject does not complete the PCS in the evening before a scheduled visit, the subject will be allowed to complete the assessment the following day at the clinic visit before investigator assessments, laboratory sample collections, and study drug administration. The PCS will serve as an anchor for the patient-reported outcome (PRO) psychometric validation.

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

9.7.15 Optional Subject Interviews

Subject interviews are optional and will be conducted with approximately 75 consenting subjects, including adolescents. Subjects are not required to participate in the interview sub-study to enroll in the main study. Interviews will be conducted by the designated CRO in English-speaking countries (the US, the United Kingdom [UK], Canada, and Australia).

Subjects will be invited to participate in the subject interviews by the study investigators during the screening process. A patient information brochure that explains participation in the interview process will be given to the subjects (see Appendix 27). Acceptance to participate in the interviews will be documented on the ICF. Upon acceptance, the subject will be asked to complete a subject contact form (Appendix 27). This form will be sent to the designated CRO by the study staff. The designated CRO will be responsible for managing the interviews, scheduling, and interviewing the subjects.

Qualitative telephone interviews will be scheduled to take place between week 16 and week 18. The interview will last approximately 60-90 minutes and will collect subjects' current and past experience with their disease and their experience of participating in the trial. Perceived treatment effects and perceived changes in daily life since baseline will also be explored. Interviewers will follow a semi-structured interview guide specifically designed for the current trial (see Appendix 27). The interviews will be audio recorded and serve as source documents for archiving in the TMF. The audio recordings will be transcribed for analysis purposes. The details of the interview analysis are further described in a subject interview analysis plan.

9.8 Optional Clinical Photographs

Clinical photographs are optional for this study and will apply only to subjects who provide written consent at selected sites. Photographs of AD lesions will be captured from approximately 50 subjects using standardized photographic methods. Subjects are not required to provide photographs to enroll in the main study. Additional details will be provided in the photographic manual.

9.9 Independent Data Monitoring Committee

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

9.10 Independent Adjudication Committee

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

10 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 statistical procedures for executing the analyses that are specified in the sections of the clinical study protocol below.

10.1 Statistical and Analytical Plans

10.1.1 Datasets or Populations Analyzed

For initial and maintenance period, the following populations will be defined for analysis. Only subjects who are re-randomized after initial period will be included for the analysis of maintenance period.

10.1.1.1 Intent-to-Treat Population

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

10.1.1.2 Safety Population

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

10.1.1.3 PK Analysis Population

The PK analysis population will include all subjects in the safety population who provide at least 1 post-baseline evaluable drug concentration value. All PK and ADA endpoints will be analyzed using the PK analysis population under the treatment group ‘as treated’.

10.1.1.4 Per-Protocol Population

The per-protocol population will comprise all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. Only primary and key secondary endpoints will be analyzed using the per-protocol population.

10.1.1.5 PD Analysis Population

The PD analysis population(s) will be described in a separate pharmacodynamic plan.

10.1.2 Demographic and Other Baseline Characteristics

Subject disposition, demographics, baseline characteristics, previous therapies, and concomitant therapies by treatment will be summarized by descriptive statistics.

10.1.3 Efficacy Variables

Both primary and key secondary endpoints will be evaluated for the following populations:

- Baseline PP NRS ≥ 4 (full population)
- Baseline PP NRS ≥ 7

Primary inference for all the efficacy analyses will be based on the ITT population at the Week 16 endpoint. The per-protocol analysis will be carried out as supportive analyses for the primary and key secondary endpoints.

All efficacy variables will be summarized by treatment at each visit.

The categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using means, medians, minimum, maximum, and standard deviations for the data collected at each visit.

Primary Efficacy Endpoint

Primary efficacy endpoint consists of 2 co-primary endpoints. Both co-primary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for the randomized stratification variables (IGA severity and PP NRS) for both populations (baseline PP NRS ≥ 4; baseline PP NRS ≥ 7) to compare the proportion of subjects achieving success between treatment groups. The estimate of treatment difference, the corresponding 2-sided 95% confidence interval, and p-values will be presented.

Any subjects with missing data at Week 16 will be regarded as a non-responder. If a subject received any rescue therapy, the data after receipt of rescue therapy will be set to missing and subsequently regarded as a non-responder for the respective primary endpoint.

Key Secondary Efficacy Endpoints

All key secondary endpoints will be analyzed similar to the analysis of primary endpoint using a stratified Cochran-Mantel-Haenszel test.

Multiplicity Adjustment for Two Co-Primary and Key Secondary Efficacy Endpoints

The primary comparison of interest is nemolizumab 30 mg compared to placebo for the co-primary endpoints in both populations (baseline PP NRS ≥ 4; baseline PP NRS ≥ 7).

To control the type I error at 5% significance level, a serial gatekeeping approach will be implemented. The co-primary endpoints will be tested at 2.5% significance level for each population. If both co-primary endpoints are statistically significant at 2.5% significance level, the key secondary endpoints will be tested sequentially following hierarchical testing procedure using the pre-specified order of endpoints in Section 7.4 for each population. The comparisons for key secondary endpoints will be made sequentially, and the subsequent tests will stop when no statistical difference is found.

Other secondary endpoint comparisons will not be adjusted for multiplicity.

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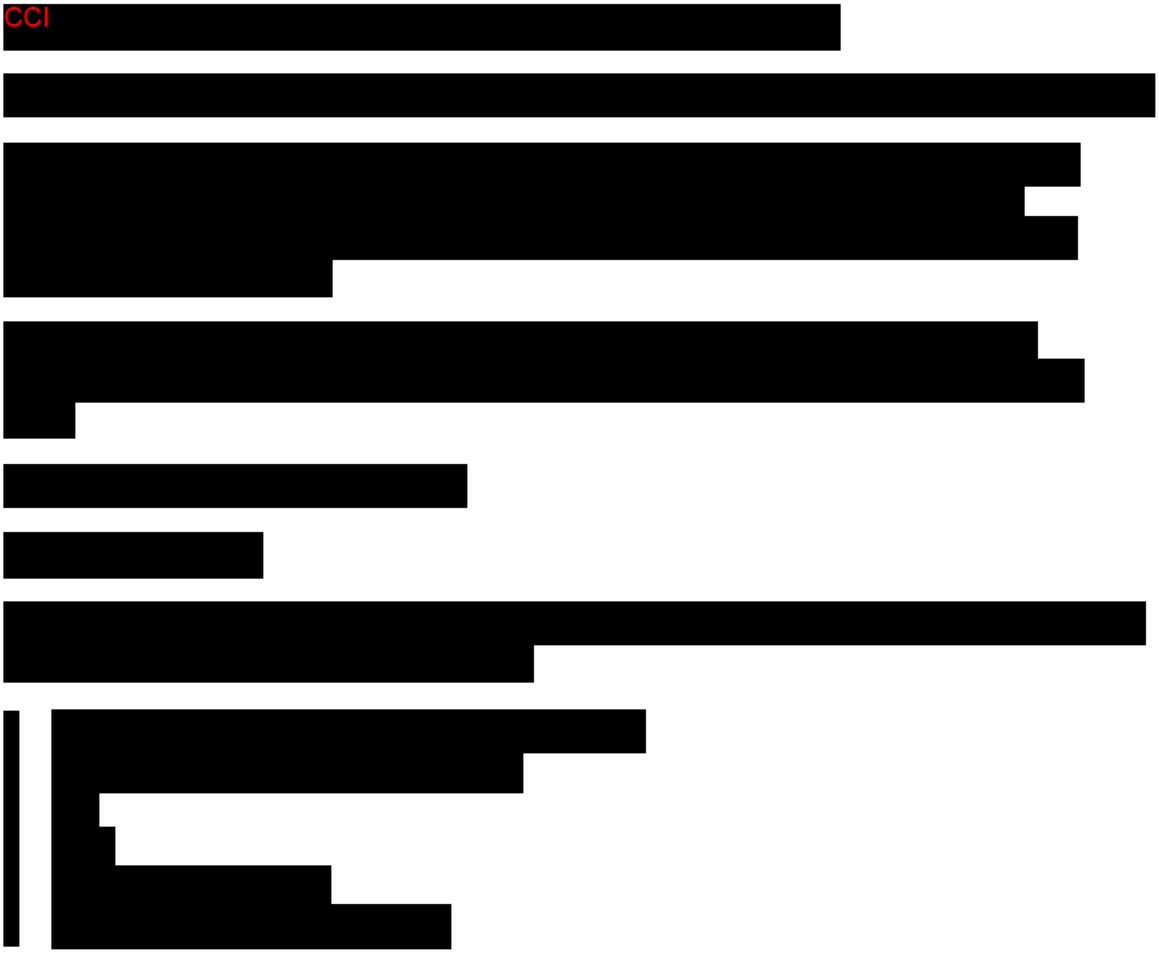

10.1.4 Safety Variables

All safety analyses will be based on the safety population.

Summary of all safety endpoints will be presented by study period (initial treatment period, maintenance period, and follow-up period) for each treatment group.

10.1.4.1 Extent of Exposure

The duration of exposure and the number of subjects exposed to study medication will be summarized by treatment group and visit. The number of subjects exposed will be presented by study periods (initial treatment period and maintenance period).

10.1.4.2 Adverse Events

Treatment-emergent AEs, 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 for each study phase. Additional summary tables will be provided for SAEs, AEs related to the study drug(s) (reasonable possibility, no reasonable possibility), AEs related to the 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.

Pretreatment AEs will be listed separately.

10.1.4.3 Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized by visit and treatment group for each study phase. In addition, the number and percentage of subjects below, within, and above the laboratory reference ranges and the number and percentage of subjects who met criteria of potential clinically significant value will be summarized by treatment group. Shift tables will be generated using the reference ranges. Reference ranges will be provided in the laboratory manual.

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

10.1.4.4 Vital Signs

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

10.1.4.5 Peak Expiratory Flow

The PEF measurements (absolute values and change from baseline) will be summarized by visit, treatment group, and medical history of asthma.

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

10.1.4.6 Physical Examination

The number and percentage of subjects who are normal, abnormal (clinically significant [CS]), and abnormal (not clinically significant [NCS]) will be displayed by treatment at each visit.

10.1.4.7 Electrocardiogram

The number and percentage of subjects who have ECGs that are abnormal/CS and normal/NCS will be displayed by treatment at each visit.

10.1.5 Pharmacokinetic Parameters and Anti-Drug Antibody Analyses

Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) by treatment group will be calculated for all derived PK endpoints.

The concentration at each time point will be summarized as arithmetic mean, standard deviation, median, minimum, maximum, and number below the limit of quantification.

Incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, and treatment-related ADA). The ADA results presentation will be detailed in the SAP.

The population PK and PKPD modeling will be detailed in a separate Modeling Analysis Plan.

10.1.6 Biomarker Analyses

Biomarker analysis will be conducted by the designated CRO based on a separate pharmacodynamic plan.

10.1.7 Subject Interview Analysis

De-identified transcripts of subject interviews will be analyzed by the designated CRO using a qualitative thematic analysis using ATLAS.ti version 7.0 software. Qualitative data (eg, subjects' perceptions of the nature, magnitude, and impact of symptom changes) and quantitative data (eg, the actual changes experienced by the subjects on relevant PROs) will be combined to help interpret clinically meaningful within-patient score

changes. Further details of the analysis of subject interviews will be provided in a separate subject interview analysis plan.

10.1.8 Psychometric Validation Analyses

Psychometric analyses will be conducted on the Phase 3 data for the evaluation of the PP NRS, SD NRS, and Subject Sleep Diary in both adult and adolescent subjects. These blinded analyses will be performed by the designated CRO after approximately half of adult and adolescent subjects complete the initial treatment period, on the basis of a separate psychometric validation statistical analysis plan.

10.1.9 Interim Analyses

No interim analysis is planned.

Week 16 Analysis: Primary analysis may be carried out once all subjects have completed the Week 16 visit or have withdrawn from the study. No personnel directly involved with the conduct of the study shall have access to the unblinded data before the completion of the trial in order to avoid introducing bias to the remaining study data.

10.1.10 Handling of Missing Data

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

Continuous Endpoints: For continuous endpoints during initial period, the MI under MAR assumption approach and the MMRM approach will be used to handle the missing data for the selected secondary endpoints. QoL endpoints (eg, DLQI/cDLQI, EQ-5D, PIQ) may be imputed using last observation carried forward (LOCF), where applicable.

Binary Endpoints: All missing values will be treated as a non-responder for the binary endpoints. To assess the robustness of non-responder analysis, a tipping point analysis will be performed. The MI under MAR assumption, LOCF, and OC will be used as sensitivity analysis to impute the missing values for the primary and key secondary endpoints.

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 missing data.

10.1.11 Sensitivity Analyses for Primary and Key Secondary Endpoints

The following sensitivity analyses will be conducted for the robustness of the analyses.

- Same analysis on Per-protocol population
- **Tipping point analysis** will be performed by converting non-responders due to missing data to responders in successive increments (Δ) for both treatment groups to assess the robustness of analysis. The value of Δ that overturns (ie, non-significant) the primary results will represent the tipping point. A graphic display of all possible combination of the number of responders among both treatment groups will be presented.
- **Multiple imputation (MI) methods** for missing data: The MI imputation will be carried out as follows.
  1. Imputation Phase
     a. A 50 imputed datasets with a monotone missing pattern will be created using SAS MI procedure based on the observed data (Markov-Chain-Monte-Carlo method, MCMC). The seed to be used is 118161 (the Protocol number). Pattern of missing data will be evaluated and it is expected that the pattern of missing data will be monotonic. For non-monotone missing data patterns, MCMC method of MI procedure will be used to impute enough data so that the remaining missing data is monotone.
     b. Each of the imputed datasets will be used to generate 50 complete datasets, using the following approaches:
        i. *Ordinal data (eg, IGA score):* A logistic regression method to impute the ordinal missing data, including treatment, randomization strata, and assessments from earlier time points as covariates. Response or total score of the subjects will be derived using these imputed data.
        ii. *Continuous data (eg, EASI score):* A linear regression model including treatment, randomization strata, and assessments from earlier time points as covariates will be used to impute the score. Response or total score of the subjects will be derived using these imputed data.
  2. Analysis Phase: The analysis will be conducted using the complete datasets.
     a. *Binary endpoint:* The complete datasets will be modelled for the endpoint using CMH method as per analysis described in Section 10.1.3 .

Proportion of responders in each treatment arm, difference and standard error will be calculated.

b. *Continuous endpoint:* The complete datasets will be analysed using ANCOVA including treatment group and randomization stratification factors as factors and appropriate baseline values as a covariate, if applicable. LSMeans in each treatment arm, difference and standard errors will be calculated.

3. Pooling Phase: The results from the analysis phase will be combined as follows.
   a. *Binary endpoint:* The results from the CMH analysis of the multiple imputed datasets will be combined using the Rubin (1987) and Li et al (1991) approach to produce pooled CMH statistics and p-value. Proportion of responders in each treatment arm, difference and standard error will be combined using the MIANALYZE procedure in SAS.
   b. *Continuous endpoint:* The LSMeans in each treatment arm, difference and standard errors from the ANCOVA of the multiple imputed datasets will be combined using the MIANALYZE procedure in SAS.

- **Last Observation Carried Forward (LOCF)** imputation method for missing data (or where rescue medication is received)
- **Observed Case (OC)** - No data will be imputed. For this analysis, if any rescue medication is received, and data are collected post rescue receipt, data post-rescue will be analyzed as observed (ie, not set to missing).

Sensitivity analyses may be performed to evaluate the impact COVID-19 deviations. Further details will be provided in SAP.

10.2 Determination of Sample Size

To achieve at least 90% power for each co-primary endpoint at 2.5% significance level, 150 subjects per group will be required to detect the following differences between treatment groups for 2 co-primary endpoints with 2:1 randomization ratio, assuming 15% dropout rate during the initial treatment period.

With 2:1 randomization, 180 subjects in nemolizumab and 90 subjects in placebo will be required to detect the differences in both co-primaries to achieve 90% power.

IGA Success: To detect a difference of 18%, assuming IGA response for nemolizumab 30% and placebo 12% at Week 16.

EASI-75 Response: To detect a difference of 30%, assuming EASI-75 response for nemolizumab 49% and placebo 19% at Week 16.

To ensure sufficient exposure with nemolizumab and to ensure sufficient size of safety database, sample size is increased to 750 subjects in total with a randomization ratio of 2:1. This sample size will provide more than 99% power to detect the treatment difference for both co-primary endpoints at 2.5% significance level.

10.3 Protocol Deviations

Major deviations are categorized into the following categories:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study medication
- Noncompliance with study medication per the investigator's discretion
- Noncompliance with study procedures if the consequence of noncompliance would compromise either the subject's safety and/or the study integrity, primary endpoint, and/or is not in line with Good Clinical Practice (GCP)/ICH guidelines
- Use of prohibited concomitant therapies

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

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

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

11.2 Monitoring

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

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

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

11.3 Personnel Training

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

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

11.4 Data Management

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

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

11.5 Clinical Study Conduct

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

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

11.6 Amendments

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

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

11.7 Quality Management and Risk Evaluation

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

12 ETHICS

12.1 Independent Ethics Committee or Institutional Review Board

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

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

12.2 Regulatory Authorities

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

12.3 Ethical Conduct of the Study

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

12.4 Informed Consent

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

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

All minor subjects who participate in this clinical study must be accompanied by a parent/guardian. Subjects and parent/guardians are required to be fully informed about the clinical study in accordance with GCP guidelines, federal regulations (for the US, HIPAA),[52] and guidelines and in accordance with local requirements.

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

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

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

12.5 Subject Confidentiality

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

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations (HIPAA for the US) [52] on personal data protection.

For subjects participating in the qualitative interviews, audio files of the interviews will be transcribed and de-identified (any identifying information such as names and locations will be removed). The de-identified transcripts will be delivered for analysis, and a single audio file will be kept as a source document in the TMF. Any copies of the audio file will be destroyed immediately upon confirmation of receipt of the transcript.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject contact details and data. Subjects will be informed accordingly and will be requested to give their consent on contact details data handling procedures in accordance with national regulations. Patient contact details will be sent to the designated CRO using a secure server, independently from study sponsor, monitor, data management and data analysis structures, and other study stakeholders. The subject contact form will not include health data and will be destroyed after completion of the interview.

12.6 Financing and Insurance

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

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

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

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

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15 APPENDICES

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

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

ESSENTIAL FEATURES; must be present:

- Pruritus
- Eczema (acute, subacute, chronic):
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

**Patterns include*:*

1) *Facial, neck, and extensor involvement in infants and children;*
2) *Current or prior flexural lesions in any age group;*
3) *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

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

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

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

Section 6.3 Risk/Benefit Assessment

During the COVID-19 pandemic, additional risks to participants may exist, including general environmental risks (eg, being outside the home, possible contact with unsanitized surfaces) and study-related activities (eg, interaction with study staff). Potential new subjects with known or suspected COVID-19 infection are ineligible for study enrollment until the infection has resolved. Furthermore, potential new subjects in a high-risk population for COVID-19 (e.g. 60 years and older or with comorbidities), should be temporarily deferred until the COVID-19 risk has subsided at the location of the enrolling site, according to investigator judgement. Risk mitigation measures to be implemented for enrolled subjects and for new subjects during the COVID-19 pandemic are detailed in **Additional Measures for Subjects Amidst COVID-19 Pandemic** below. Subjects with a known or suspected COVID-19 infection will immediately discontinue study drug; instructions for resuming treatment are described in Section 8.3.4.2 and below in Guidance for Existing Subjects. Known or suspected COVID-19 infection will also be followed as an AESI.

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

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

- Guidance for New Subjects:

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

For potential subjects in a high-risk population for COVID-19 as defined by the American Academy of Dermatology (AAD) (e.g. 60 years and older or with

comorbidities) or local guidelines, deferring participation in the study should be considered. Deferment of enrollment is based on the potential risk posed by general environmental risks (e.g. being outside home, possible contact with unsanitized surfaces) and study-related activities (e.g. interaction with study staff).

For potential subjects in the low-risk population for COVID-19 (e.g. less than 60 years of age and without comorbidities), the risks and benefits of participation in the study should be assessed on a case by case basis.

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

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

- Guidance for Enrolled Subjects:

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

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

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

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

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

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

- Report any COVID-19 infection (confirmed or suspected) as an AE
  - if any seriousness criterion is met, also report as an SAE (see Section 9.2.1.3).
  - if it occurs during the clinical study following the first dose of study drug administration, also report as AESI (see Section 9.2.1.4).
- Implement preventive infection control measures against COVID-19 infection following local guidelines (e.g. good hygiene practice, clean techniques, and use of personal protective equipment such as gloves, goggles, and masks).
- Implement preventive measures in handling all subject-facing study-mandated assessment devices and parts:
  - PEF meter device body is to be cleaned after each use, with recommended wipes, as per user manual
  - PEF meter flow sensor is to be disposed of after each set of measurements is taken
  - Approved bacterial/virus filters may be used; if used, they must be disposed of after each set of measurements taken

- Offer protective gloves to subjects for use while filling out assessments on a tablet and provide training on hygienic removal and disposal of gloves

If the local situation allows for subjects to reach the investigational site and complete only some study procedures where visit duration needs to be limited, the above measures also apply. All assessments should be conducted if possible. Subject-reported assessments that would usually be collected on the site tablet (e.g. ACT, PGAD, PGAT, EQ-5D, DLQI, AD-associated pain intensity and frequency) may be collected remotely (e.g. completed over the phone), as available.

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

- The study drug subcutaneous injection can be performed at the investigational site according to the instructions in the protocol, pharmacy manual and instruction for use, including preparation of study drug by an independent pharmacist or other qualified personnel.
- ACT (for subjects with medical history of asthma) and PEF (all subjects) can be performed according to the protocol.
    - Exceptionally, if sites cannot perform PEF safely on site, the subjects should perform it at home prior to the onsite visit, on the same day. See section below for remote PEF testing instructions.
- All other safety assessments are to be performed as per protocol: physical exam, vital signs, ECG, laboratory assessments, pregnancy test, monitoring of AEs and concomitant medications.
- All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

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

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

- AE collection,
- ACT (for subjects with history of asthma),
- Concomitant therapies used,
- Moisturizer use/background topical therapy,
- UPT results (for WOCBP),
- PEF results,

Note: For remote PEF measurements the following should be done:

- To prepare subjects to do remote PEF measurement at home in case it is needed during the course of the study, all subjects should be previously trained onsite
- During the remote visits, subjects can receive additional support (if needed) over the phone or video call by site staff when performing PEF
- If a subject has a PEF <80% of the predicted value:
  - Site staff can try to evaluate whether this is due to poor technique and ask the subject to repeat the set of measurements
  - If the subject's best PEF measurement is still <80% of the predicted value or if there are other concerns regarding the subject's respiratory health, refer to appropriate physician and report an AESI (see Section 9.2.1.4)

- All laboratory samples should be collected at the site and analyzed at the central lab. Only in exceptional situations when subject safety cannot be assured otherwise and subject cannot reach the site, a local laboratory test (i.e. hematology, blood chemistry, urinalysis) can be performed and reported, based on investigator judgement.
- Subject-reported assessments that would usually be collected on the site tablet (e.g., ACT, PGAD, PGAT, EQ-5D, DLQI, AD-associated pain frequency and intensity), may be completed over the phone, as available.

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

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

If a subject misses a dose of study drug due to the COVID-19 pandemic, study drug administration may be continued. The following dosing schedules apply.
For subjects with a missed dose(s) during the initial treatment period (Baseline to Week 16), study drug administration can be continued based on one of the following scenarios (see also **Diagram 1**, below):

1) Subject has missed one or more doses between Baseline and Week 16 but can come to the clinical site at Week 16 (see also **Diagram 2a**)**:**

- Subjects who are clinical responders (IGA of 0/1 or EASI-75) at Week 16 can continue into the maintenance period.
- Subjects who are non-responders at Week 16 may be eligible to enroll in the long-term extension (LTE) study RD.06.SPR.118163.
- Subjects who required rescue therapy before Week 16 may be considered for the LTE study but will be required to continue with study visits until Week 16 visit is due.

2) Subject has no missed doses through Week 12 but cannot reach the clinical site at Week 16 (see also **Diagram 2b**)**:**

- The Week 16 visit can be delayed by up to 8 weeks from the originally planned date. A remote Unscheduled visit should be planned between Week 12 and the delayed Week 16 visit for safety follow-up.
    - Subjects who are clinical responders (IGA of 0/1 or EASI-75) at the rescheduled Week 16 visit can continue into the maintenance period.
    - Subjects who are non-responders at the rescheduled Week 16 visit may be eligible to enroll in the LTE study.
- If the subject still cannot come to the delayed Week 16 visit within 8 weeks of the originally planned date, the delayed Week 16 visit should be performed remotely at the rescheduled date. A remote Unscheduled visit

should be planned between Week 12 and the delayed Week 16 visit for safety follow-up. The subject may be considered for rollover into the LTE study after the delayed Week 16 visit is complete.

3) Subject has missed one or more doses between Baseline and Week 16 and cannot reach the clinical site at Week 16:

- For subjects who cannot come to the clinical site at week 12 but with an administered dose at Week 8 (with or without Week 4), the Week 12 visit can be delayed up to 3 weeks, and the Week 16 visit can be delayed up to 4 weeks from the rescheduled Week 12 visit (see also **Diagram 2c**).
- For subjects with an administered dose at week 12 but with a missed dose at Week 4 and/or Week 8, the Week 16 visit can be delayed by up to 4 weeks from the originally planned date (see also Diagram 2d).
    - Subjects who are clinical responders (IGA of 0/1 or EASI-75) at the rescheduled Week 16 visit can continue into the maintenance period.
    - Subjects who are non-responders at the rescheduled Week 16 visit may be eligible to enroll in LTE study.
- For subjects with a missed dose at week 12, the Week 16 visit will be performed remotely at Week 16 (cannot be delayed) and the subject may be considered for rollover into the LTE study (see also **Diagram 2d**).

For subjects with a missed dose(s) during the maintenance treatment period (Week 16 to Week 48), study drug administration can be continued. Any visits where the subject cannot reach the site should be done remotely. If a subject misses three doses, the investigator must contact the Sponsor for further guidance.

- Subjects may be eligible to enroll in the LTE study at Week 48.
- Subjects who required rescue therapy may be considered for the LTE study but will be required to continue with study visits until the Week 32 visit is due.

In all scenarios, study drug can be administered provided that there is a minimum 3 week interval between injections. If a subject cannot come to a planned visit due to COVID-19, the visit should be conducted remotely according to **Additional Measures for Subjects Amidst COVID-19 Pandemic**. Enrolment of subjects into the LTE study must be done in accordance with the LTE study protocol. Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after the last study drug injection.

11.2 Monitoring

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

Diagram 1. Flow Chart of Management of Subjects with Missed Visits Before Week 16 due to COVID-19

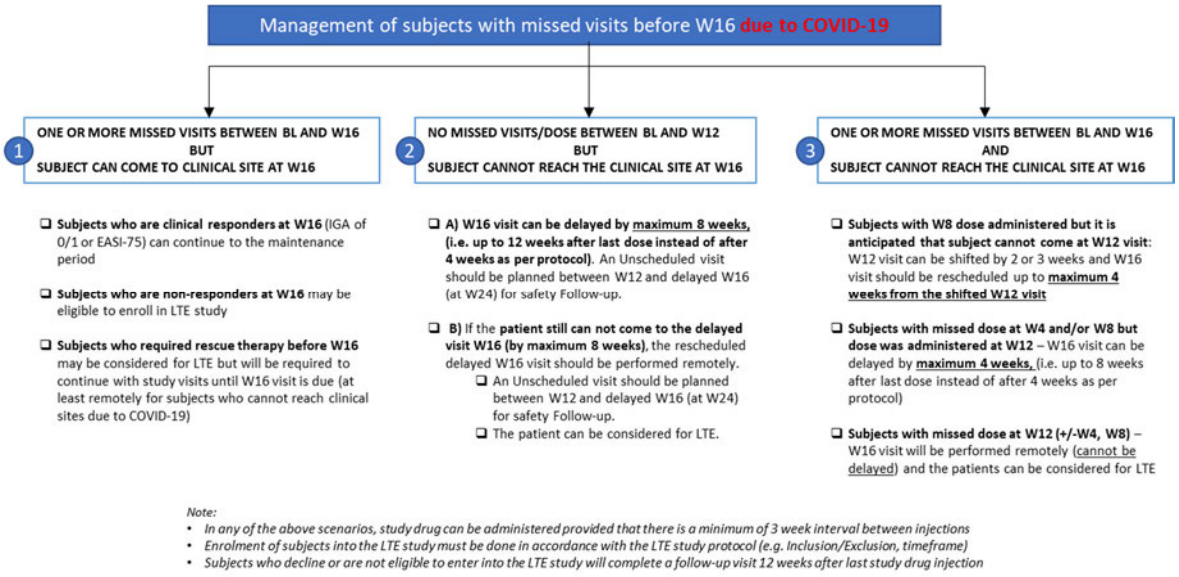
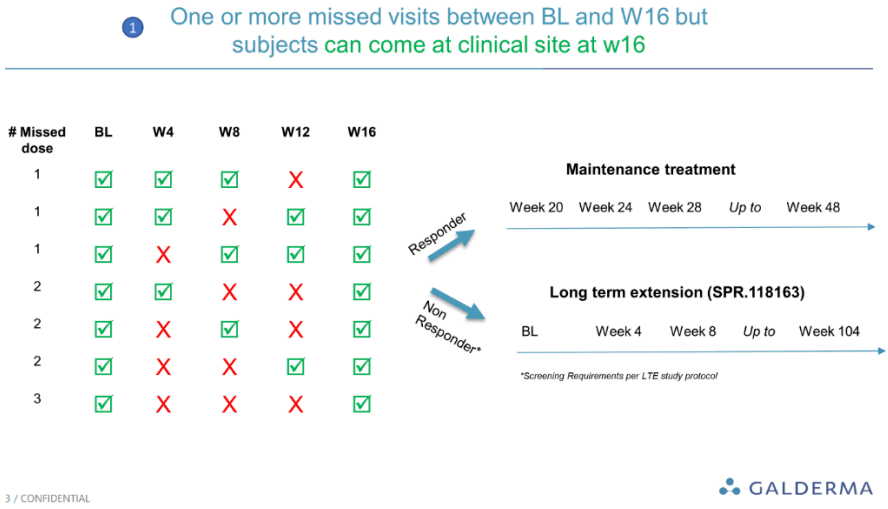
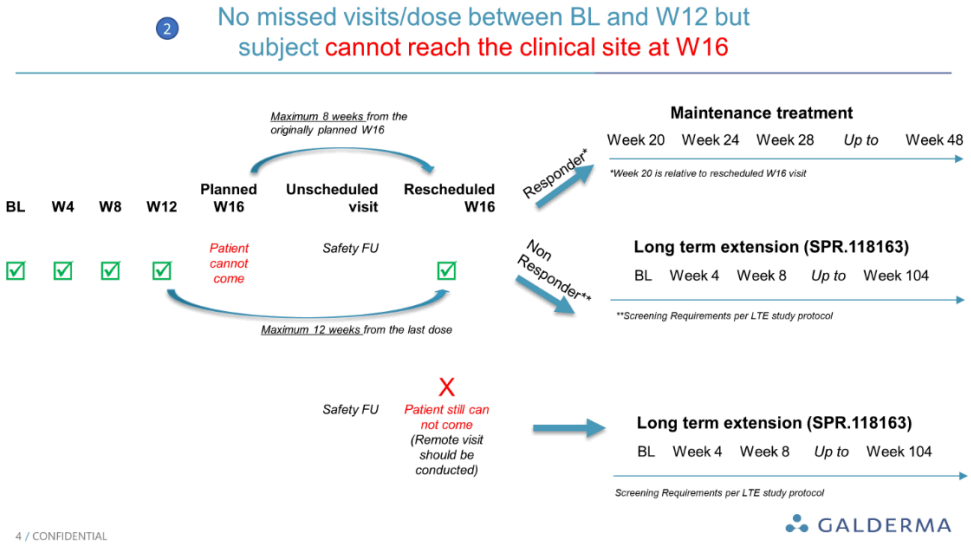


Diagram 2. Management of Subjects Based on Missed Dosing Scenarios

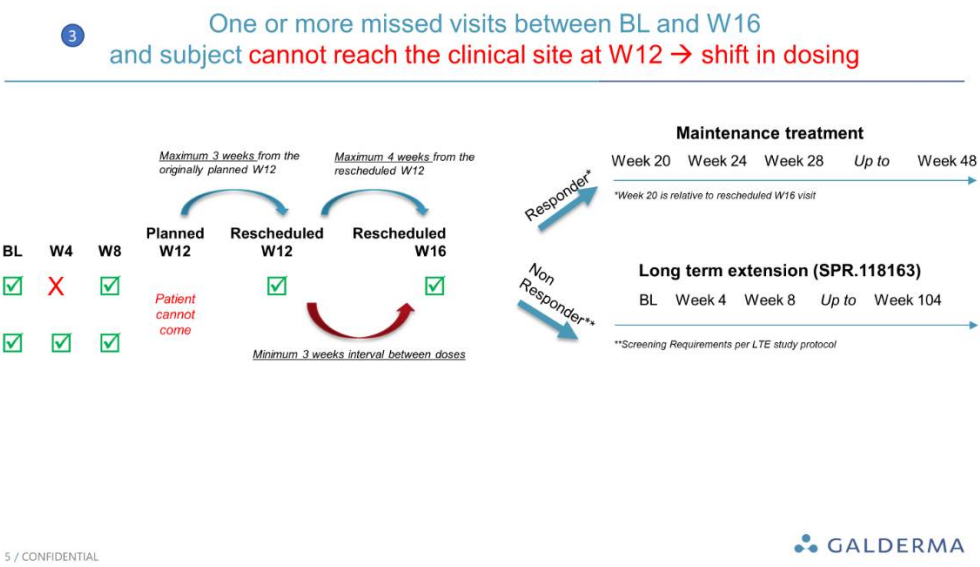
a. Diagram of Management of Subjects due to Scenario 1



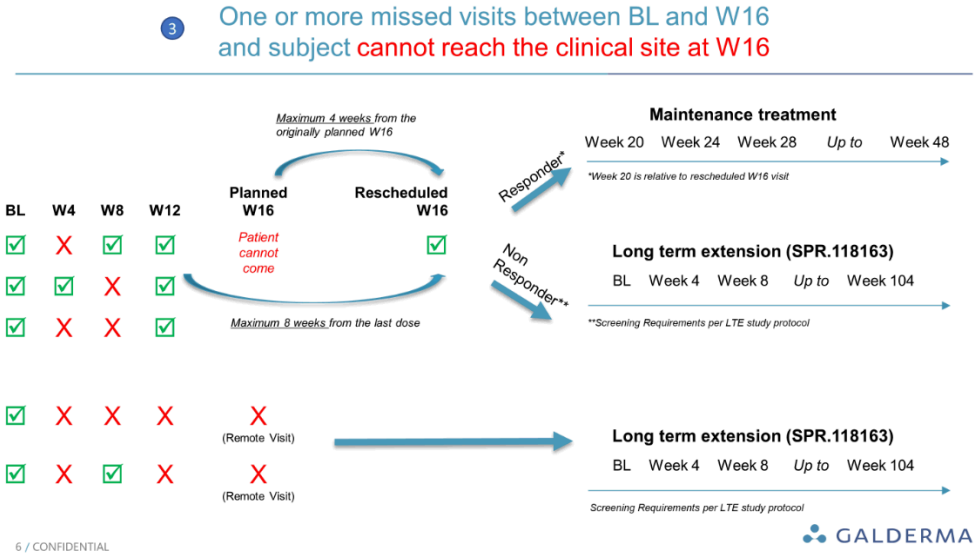
b. Diagram of Management of Subjects due to Scenario 2



c. Diagram of Management of Subjects due to Scenario 3: Cannot reach site at Visit 12



d. Diagram of Management of Subjects due to Scenario 3: Cannot reach site at Visit 16



Appendix 3: CYP Substrates with Narrow Therapeutic Index

CYP enzymes	Substrates with narrow therapeutic index(1)
CYP1A2	Theophylline, Tizanidine
CYP 2B6	-
CYP2C8	Paclitaxel
CYP2C9	Warfarin, Phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, Astemizole, Cisapride, Cyclosporine, Dihydroergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine, Sirolimus, Tacrolimus, Terfenadine
CYP2D6	Thioridazine, Pimozide

(1) CYP substrates with a narrow therapeutic index refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes). This is not an exhaustive list.

Source: Center for Drug Evaluation and Research (CDER), Food and Drug Administration, U.S. Department of Health and Human Services. Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (Draft Guidance). February 2012.

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.

Source: Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016;75(3):494-503.e6.

Appendix 5: 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 four zones, trunk includes the genital area, and lower limbs include the buttocks.

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

Appendix 6: Pruritus (Peak and Average) Numeric Rating Scale (PP NRS and AP NRS)

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

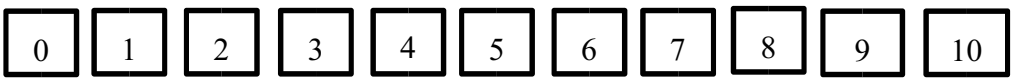
No itch — Worst itch imaginable

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

No itch — Worst itch imaginable

Appendix 7: Sleep Disturbance Numeric Rating Scale (SD NRS)

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



No sleep loss

I did not sleep at all

CCI

[redacted]

CCI

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

Appendix 11: Total Blood Volumes

Periods	Screening	Treatment					Maintenance								Follow-up
Visit	1	2	3	4	5	6/ (ET)	7	8	9	10	11	12	13	14/ (ET)	
Week (relative to baseline)	(2 to 4 weeks before Day 1)	(Day 1)/ Baseline	4	8	12	16	20	24	28	32	36	40	44	48	(12 weeks after last injection)
Window (± days)		0	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
LABORATORY ASSESSMENTS															
Hematology	2.0	2.0		2.0		2.0				2.0				2.0	2.0
Chemistry, CPK, CPK-isoenzymes and pregnancy	8.5	8.5		8.5		8.5				8.5				8.5	8.5
Serology	8.5														
Tuberculosis	4.0														
PK samples		3.5	3.5	3.5	3.5	3.5	3.5	3.5		3.5		3.5		3.5	3.5
ADA samples		3.5	3.5	3.5		3.5		3.5		3.5				3.5	3.5
IgE and TARC/CCL17		3.5		3.5		3.5									
PD samples (blood) for biomarker assessments (Plasma protein)		10.0		10.0		10.0									

Periods	**Screening**	**Treatment**					**Maintenance**								**Follow-up**
Visit	1	2	3	4	5	6/ **(ET)**	7	8	9	10	11	12	13	14/ **(ET)**	
Week (relative to baseline)	(2 to 4 weeks before Day 1)	(Day 1)/ Baseline	4	8	12	16	20	24	28	32	36	40	44	48	(12 weeks after last injection)
Window (± days)		0	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
PD samples (blood) for biomarker assessments (Blood RNA)		5.0		5.0		5.0									
PGx samples (optional)		8.5													
Serum pregnancy (in case of positive urine pregnancy at site)			2.5		2.5		2.5	2.5	2.5		2.5	2.5	2.5		
Maximum amount of blood collected during single visit (mL)	***23.0***	***44.5***	***9.5***	***36.0***	***6.0***	***36.0***	***6.0***	***9.5***	***2.5***	***17.5***	***2.5***	***6.0***	***2.5***	***17.5***	***17.5***
Maximum amount of blood collected during the study (mL)	***236.5***														

Appendix 12: Asthma Control Test (ACT)

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

Appendix 13: Patient Global Assessment of Disease (PGAD)

Overall, how would you describe your atopic dermatitis right now?

- ☐ Clear
- ☐ Almost clear
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Appendix 14: Patient Global Assessment of Treatment (PGAT)

How would you rate the way your atopic dermatitis responded to the study medication?

- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very Good
- ☐ Excellent

Appendix 15: Pruritus Categorical Scale (PCS)

Please rate your overall itch during the previous 24 hours:

Score	Definition
0	Absence of itch
1	Mild itch
2	Moderate itch
3	Severe itch

CCI [redacted]

[redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

CCI

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

CCI

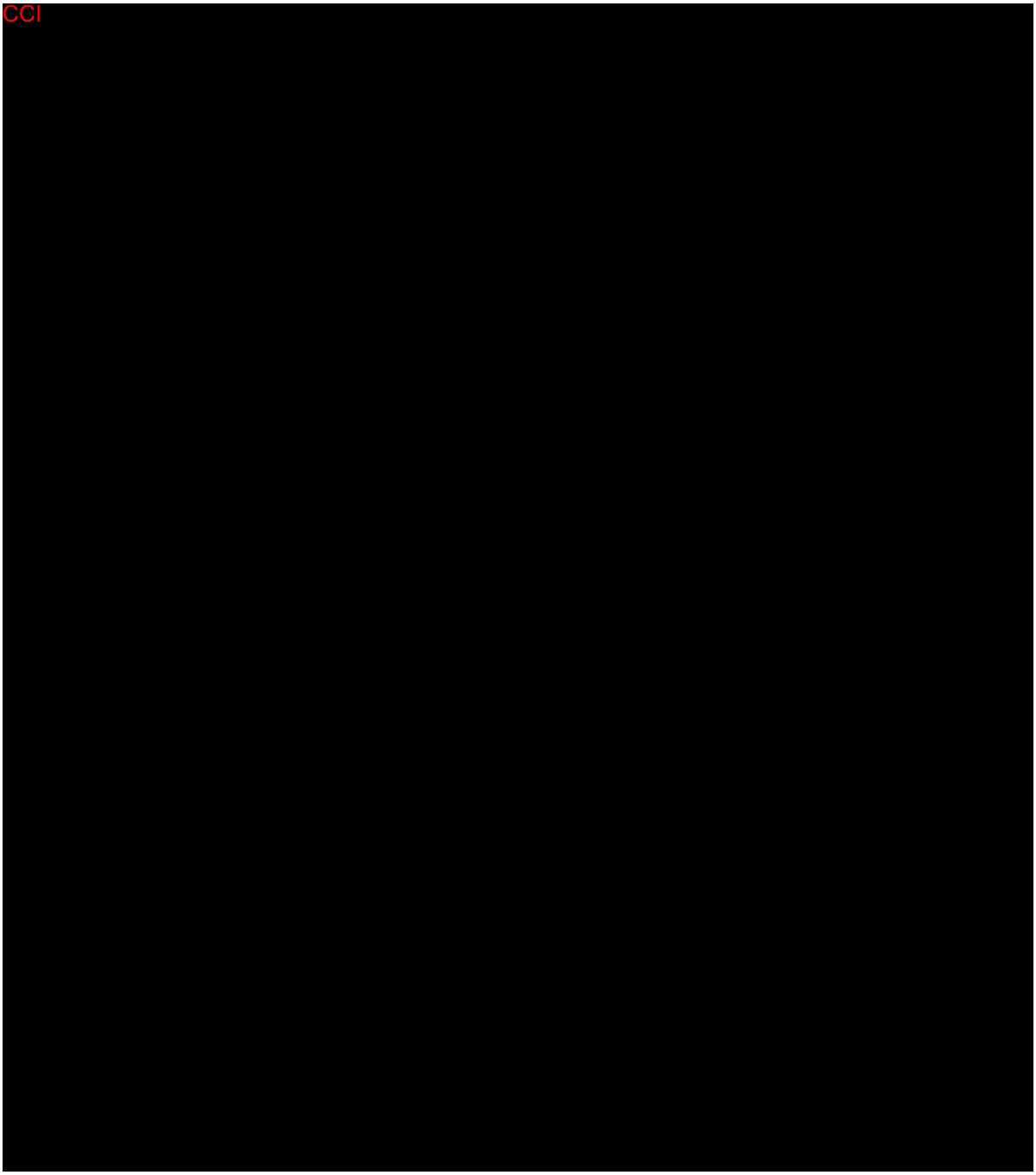
[redacted]

Instructions for POEM scoring:

CCI

[redacted]

CCI



CCI

CCI

[redacted]

CCI

[redacted]

Appendix 27: Subject Information and Interview Guide

Why the Voice of the Patient is Important

Galderma is developing a new treatment for adults and adolescents with atopic dermatitis. As a patient, the FDA considers your input to be important to inform the decisions about new treatments.

- Patients have a unique knowledge of their condition and experience of treatment(s).
- Your feedback is helpful to understand patient experiences, symptoms and treatments associated with AD, in developing new treatment options.

Galderma is partnering with Evidera to conduct an interview-only study to explore patients' perspectives about the disease and meaningful treatment benefit among a small group of patients with moderate-to-severe atopic dermatitis and associated itching, participating in the Phase 3 clinical trial of Nemolizumab (CD14152).

The Patient Voice is Important

Your feedback will help develop new treatments for Atopic Dermatitis to meet your needs.

Your Voice is Needed!

One-Time Patient Interview: Adult and Adolescents with Atopic Dermatitis (AD)

- All information shared will be kept confidential
- Interview lasts between 60 and 90 minutes
- Compensation for your time is provided
- Must be participating in Galderma's Phase 3 clinical trial of Nemolizumab (CD14152)

IF YOU ARE INTERESTED IN PARTICIPATING, PLEASE INFORM YOUR NURSE OR DOCTOR FOR CONTACT INFORMATION.

GALDERMA
Evidera | PPD

SUBJECT CONTACT FORM

This form should be completed and sent to Evidera after the study subject consents to the interview sub-study

Section to be completed by the Site Investigator **Study Number: EVM-25004**

Site Number: _____ Subject Identification Number: _____

Investigator's name: _____

Investigator's phone number: + (0) _____

Inclusion visit date: ____ / ____ / _____

Section to be completed by the Subject (please read the next page carefully before signing)

☐ Mr ☐ Ms

First name: _____ Surname: _____

Address: _____

Zip Code: _____ City/Town:_____

Preferred phone number to contact me: + (0) _____

Best time to reach me from Monday to Friday: _____

By signing this form, I authorize the transfer of my personal contact details to Evidera, so that I may be contacted by telephone to organize an interview as part of the Galderma clinical trial.

Date ____ / ____ / _____ Patient signature

MMM DD YYYY

After completion, this form should be sent to the Evidera as soon as possible via the following secure link:
https://ppdcentral.sharepoint.com/sites/GaldermaAtopicDermatitisClinicalProtocol20191493/Shared%20Documents/Forms/AllItems.aspx

This form should be kept in the patient medical records by the study investigator.

THIS DOCUMENT SHOULD NOT BE PROVIDED TO THE STUDY SPONSOR AND SHOULD NOT BE SENT OVER UNSECURE EMAIL OR FAX LIN

SUBJECT CONTACT FORM

This form should be completed and sent to Evidera after the study subject consents to the interview sub-study

Subject Information:

Evidera is a dedicated company in charge of scheduling and conducting qualitative interviews. Evidera specializes in studying patient experiences with symptoms and treatments associated with specific diseases. We Evidera would like to obtain your contact details to ask you to take part in a telephone interview as part of the Galderma clinical trial. Your contact details will be managed in a way that that fully respects your data privacy.

We would like to inform you that:

- Evidera personnel are bound to professional confidentiality.
- You have the right to contact your doctor to update your contact details if necessary.
- You contact details will not be communicated to any other person than Evidera personnel.
- Your contact details will be used by the Evidera study staff only to contact you to schedule the telephone interview as part of the Galderma clinical trial; your personal contact details will not be used for another study and the Evidera personnel are not authorized to contact you after the interview has been completed.
- All personal contact details received by Evidera will be destroyed once the interview has been completed and a transcript of the interview has been quality checked. Your personal contact details will not be used for another study and the Evidera personnel are not authorized to contact you after the interview has been completed. You have the right to request for your personal contact details to be destroyed at any time, or to ask Evidera personnel not to contact you, without giving any explanation. In this case, you can notify Evidera to withdraw / stop the study by writing an email to the Evidera Principal Investigator (Carla Dias-Barbosa) at Carla.dias-barbosa@evidera.com or **Evidera, The Ark, 201 Talgarth Rd, Hammersmith, London, W6 8BJ, United Kingdom.**
- To ensure privacy, your name and other directly identifying information will not be attached to records released to the study sponsor or its service providers for research purposes. Instead, you will only be identified by a code. It will not be possible to connect this code to your name once the interview has been transcribed, as all your personal details will be deleted.
- The information collected during the interview will be audio recorded to facilitate the interview process and subsequent analysis. The transcription of the audio recording will be de-identified (your name and personal information will be removed) by the agency in charge of the transcription, before being sent to the Evidera study staff in charge of the analysis. The information from your interview will be combined with information from other participants and managed in a way that that fully respects your data privacy.
- You can request for modification or deletion of the data collected during the interview via a request to the Study Principal Investigator.

EVM-25004 Patient Interview Guide Instructions and Questions

Note: *Below is a semi-structured script. It is to be used as a guide only. The actual areas of conversation are fluid and may be discussed at moments different from the order appearing below. The interview will be approximately 60-90 minutes with breaks as needed. The interviewer may adapt the guide in order to cover the topics in the amount of time allotted for the session or in order to best elicit concepts from the participants.*

Interviewer is responsible for pre-populating dates throughout interview guide and the scores in the PRO Data section.

Prior to the start of the discussion, please check that:

Patient has been deemed eligible.	☐ Yes	☐ No
Patient has consented prior to the discussion.	☐ Yes	☐ No

Introduction

Thank you for agreeing to take part in this interview. Before we get started:

When did you first enroll in the trial? _____ *(enter date)*

[Interviewer: have date available for confirmation if patient cannot come up with exact date]

Are you still in the study, or did you withdraw early?

If the patient stopped the study prematurely, please STOP the interview.

Number of visits completed: _____ *(enter number of visits)*

If the patient has not completed the week 16 visit, please STOP the interview.

As you read in the consent form at the beginning of the clinical trial, this session will be audio-recorded. However, your name will not be linked with the recording, transcription, or your responses during the interview. Is it okay for me to record the conversation today?

If yes, continue to "Background for All Interviews."

If no (interview to restate information that is present on the consent form):

Unfortunately, since you do not agree to the recording of this interview, you won't be able to participate in the study. Thank you for your willingness to participate in the study.

Notes for the Reviewer

Objective of the Interview: The purpose of this interview is to assess the experience of AD and treatment benefit among adults and adolescents with AD in the US, the UK, Canada and Australia who have participated in the Galderma clinical Study RD.06.SPR.118161: a Phase III, multi-center, randomized, double-blind, placebo-controlled trial that assesses the efficacy and safety of nemolizumab (CD141152) in adults and adolescents with moderate-to-severe AD.

Interviews will be conducted within a two-week time window after completion of Week 16.

Written informed consent will be obtained by the clinical site personnel prior to the interviews. Results from these interviews will be documented in a study report and will not be part of the clinical study report (CSR).

Exit Interviews*:* The specific aims of the exit interviews are to:

- The perceived treatment effects and changes in a patient's daily life since receiving the study treatment (placebo or Nemolizumab)
- The meaning and importance of changes in different atopic dermatitis (AD) elements, including associated symptoms
- The relevance and importance of pruritus and sleep disturbance (SD) concepts
- To document treatment satisfaction and subjects' experience with clinical trial participation

The interviews will last approximately 60 minutes and will be conducted in English by moderators trained by Evidera.

Overview of Interview Guide:

The guide is divided into three parts: Part 1. Past and Current Experience of Atopic Dermatitis (AD) and Expectations of the Trial; Part 2. Changes During the Clinical Trial related to AD Symptoms and Sleep Disturbance; Part 3: Overall Perception of Treatment/Clinical Trial

This is a ***semi-structured*** interview guide:

- The discussions during the interview will be largely driven by how much the study participant is willing to share about their experience. Probes are included to encourage the participant when necessary.
- *The script in the interview guide is meant to help focus the content of the discussion.*
- *The actual areas of conversation are fluid and may be discussed at moments different from what appears below.*

Depending on the information emerging from the interview and timing, some questions may be modified or not asked by the interviewer. Detailed interviewer training will be provided prior to the first interview to ensure interviewers clearly understand the content of the guide and priority questions. Additional instruction may be added for interviewer training as the interviews progress.

In addition to this interview guide, interviewers will be provided with tables on AD symptoms and impact to complete during the interview.

Interview Guide

Note: The following section includes key points or concepts that will be covered during the interview. This is not a script and the language and wording of the questions can be adjusted to the patient's level of understanding and adapted where appropriate to keep the conversation fluid. If the participant does not understand a question, an example can be provided to facilate understanding. The definition of a meaningful change/ meaningful improvement is also provided.

In each section of the interview there are probes (or follow-up questions) to elicit additional information from patients. Some of these probes may not be asked depending on the flow or the timing of the interview.

The interview guide includes instructions for interviews in red. Questions in green are optional and will be asked if time permits.

Background for All Interviews [5 min]

Great, thanks again for taking the time to speak with me today. As explained in the form that you signed, we are talking to people who have atopic dermatitis (AD) with itching and are experiencing sleep disturbance (SD) who are involved in Galderma's Phase III clinical trial. We are particularly interested in your experiences with your condition, your experiences in the trial, and your impressions of any changes you experienced throughout the study to date.

All of your responses will be anonymous, meaning your name will not be linked with any of your responses. I want to hear about your experience so please share as much information as you feel comfortable with telling me. There are no right or wrong answers.

Your participation is voluntary which means that you do not have to do this. You can skip any question you do not want to answer, and you can choose to stop the interview at any time.

[U.S. PATIENTS ONLY] Although your participation is voluntary, please remember that you will be compensated for your time when you complete the interview.

As a reminder, this interview may take up to 90 min to complete.

I want to remind you that the interview is being recorded. I will try not to use your name from the point I turn the recorder on, and I will ask you to try and not to use your name, the names of your friends, family members or medical doctors, name of the places you live, location of the hospital/ clinic etc. This will help to keep the interview anonymous.

Before we begin, let me suggest some things that will make our discussion more productive.

- Your name and any other personally identifiable information will be kept as confidential and you won't be able to be individually identified in any of the reports that result from the interviews. The information collected during the interview study will be used to help make important decisions about research on this medication in the future.
- My role here is to ask questions and to listen. I'll also be summarizing information at times. I'll ask questions about issues related to your experience and I'll move the discussion from one question to the next, to try to keep us on track so that we can finish within the scheduled time.
- I am not a medical doctor, so I am not qualified to give medical advice. I encourage you to follow-up with your regular doctor if you have any questions about your medication or condition after this interview.

- [U.S. PATIENTS ONLY] When we are done with the interview, I will have the honorarium of $100.
- Please feel free to let me know if you need a break. You can ask me questions at any time.

What to Expect from the Interview:

This interview will occur in two parts. In Part 1, we will explore your experience of the disease (symptoms and impacts) prior to the clinical trial, along with treatments you've tried. In Part 2, we will explore your experiences with the study treatment that you received between baseline **[date]** and Week 16 **[date],** and any perceived effects or changes you've experienced as a result of treatment. We will explore what aspects are most meaningful to you and ask you to rate the significance of any change.

Any questions before we begin?

I will now start audio-recording.

Begin Recorder: This is participant ID *[insert ID number from Clinical Trial here]* for Study EVM-25004 on *[Date].* Do I have your permission to record this interview? ***Affirmative verbal response required.*** And can you please confirm that you completed the informed consent form? ***Affirmative verbal response required.***

Part 1. Past and Current Experience of Atopic Dermatitis (AD) and Expectations of the Trial

First, I would like to ask you questions about your past and current experiences with AD and related symptoms and impacts. We'll then discuss the perceived changes as a result of the clinical trial in Part 2 of this interview.

1.1 Past symptoms of AD [15 min]

Before you started the current study, what are the symptoms you experienced that you think may be related to your AD?

> [Interviewer]: Please make sure patient is describing symptoms BEFORE study entry, within the 2 weeks prior to starting the study. Please provide the patient with the date of the baseline visit and ask them to recall experience BEFORE baseline. Please ask them to recall any significant personal, work or other event happened at this period to help them to recall back and anchoring their answer.
>
> We are only interested in the 2 weeks prior to the start of the study and do not need to assess a lifetime of symptoms.
>
> Let the patient spontaneously report symptoms first, and then probe. Obtain the list of symptoms first, then go into more detail (i.e. frequency, duration, etc.) for each symptom individually. Please enter symptoms the patient indicated that they had PRIOR to the current study in Table 1.

For each symptom reported by the patient, please ask if the symptom severity changed since the patient started the clinical trial? [Optional]

For each symptom endorsed by the patient:

- **Frequency**: How often did you experience this [symptom] before the trial?
- **Location:** Where on your body did you experience this [symptom]?
- **Duration**: Did the [symptom] come and go or was it present all the time?
    - If the [symptom] comes and goes: How long did the [symptom] last for?
- Symptom severity:

- On a scale of 0 to 10, where 0=not severe at all and 10= extremely severe, how bad or severe was this [symptom] **when you began the study?**
- Using the same scale, how severe was this symptom for you **at Week 16**?

[Interviewer]: Please be ready to remind the patient of their Week 16 visit date. During this interview we are only interested in the patients experience before the trial and between Baseline and Week 16.

Of these symptoms you have mentioned (*such as…list 3-4 symptoms mentioned – see Table 1*), which of the symptoms that you experienced would you call the worst one?

[Interviewer]: Let the patient spontaneously report what they feel is the worst symptom, and then probe if needed.

Table 1. AD Symptoms Prior to Study Entry

Spontaneous or Probed? (S/P)	Symptom description	Had prior to study? Within 2 weeks (Y/N)	Symptom severity changed since baseline? (Y/N)	Frequency	Location	Duration	Severity at study entry (0-10)	Severity at Week 16 (0-10)
	Itch							
	Dry skin							
	Inflammation/ swelling of the skin							
	Skin Bleeding							
	Open wounds							
	Peeling skin							
	Skin discoloration							
	Burning sensation of the skin							
	Skin Redness							
	Painful skin							
	Sensitive skin							
	Other: specify							
	Other: specify							
	Other: specify							

1.2 Past impact of AD Symptoms on Daily Lives [10 min]

1. Before you started the current study, how did the ADs symptoms affect your daily life?
   Probes: sleep disturbance, daily activities, leisure activities, rrelationships affected, emotions, other?

   [Interviewer]: Please make sure patient is describing impacts BEFORE study entry, within 2-weeks of starting the study. Please provide the patient with the date of the baseline visit and ask them to recall experience BEFORE baseline. Please ask them to recall any significant personal, work or other event happened at this period to help them to recall back and anchoring their answer.

   We are only interested in the 2 weeks prior to the start of the study and do not need to assess a lifetime of impacts.

   Let the patient spontaneously report impacts first, and then probe based on table. Obtain the list of impacts first, then go into more detail (i.e. changed, resolved, etc.) for each impact individually. Please enter impacts the patient indicated that they had PRIOR to the current study in Table 2.

   If subject states multiple categories under the main impact concept, no need to ask follow-up for each sub-category if more than 5 different impacts are reported. Only focus on the main category. If not many impacts are reported, you may have time to go through each sub-category.

2. For each impact reported by the patient, please ask if the impact changed/solved since the patient started the clinical trial? Yes/ no

   [Interviewer]: Please make sure patient is describing change between Baseline and Week 16 only.

3. For each impact reported by the patient, please ask if that impact was related to itch or other symptom? if other, which one?

4. Of all the impact you have been talking about (*such as…list 3-4 impacts mentioned – see Table 2*), which one would you say is the worst one? Why?

   [Interviewer]: Let the patient spontaneously report what they feel is the worst impact, and then probe if needed.

Table 2. AD Impacts Prior to Study Entry

Spontaneous or Probed? (S/P)	Impact description	Had prior to study? Within 2-weeks. (Y/N)	Impact Changed since baseline to Week 16? (Y/N)	Resolved? Between Baseline and Week 16 only (Y/N)	Did this impact relate to itch or other AD symptoms? (Y/N/Unknown) (If Y/N, which one?)
	Sleep disturbance ☐ Falling asleep ☐ Staying asleep ☐ Night-time awakening ☐ Feeling like as you did not get enough sleep ☐ Early morning awakening ☐ Feeling unrested/ unrefreshed ☐ Daytime fatigue / tired during the day ☐ Trouble staying awake during the day ☐ Feeling drowsy or sleepy during the day ☐ Need for a nap during the day ☐ Other: specify				
	Daily activities ☐ Daily routine ☐ Chores/ housework/ gardening ☐ Working ☐ Studying ☐ Other: specify				
	Leisure activities ☐ Social activities limited e.g. going to the cinema, pub or out to dinner ☐ Hobbies ☐ Sport (swimming, other) ☐ Other, specify				
	Relationships affected				

Spontaneous or Probed? (S/P)	Impact description	Had prior to study? Within 2-weeks. (Y/N)	Impact Changed since baseline to Week 16? (Y/N)	Resolved? Between Baseline and Week 16 only (Y/N)	Did this impact relate to itch or other AD symptoms? (Y/N/Unknown) (If Y/N, which one?)
	¨ Relationship with spouse ☐ Relationship with family ☐ Relationship with friends & acquaintances ☐ Work relationship / school relationship ☐ other, specify				
	Emotions ☐ Anxiety ☐ Embarrassment ☐ Depression ☐ Worry ☐ Stress ☐ Frustration ☐ Other, specify				
	Other: specify				
	Other: specify				
	Other: specify				
	Other: specify				
	Other: specify				
	Other: specify				
	Other: specify				

1.3 Experience of AD Treatment [5 min] [Optional]

Now I would like to ask you some questions about previous treatments you have had for AD PRIOR to enrollment in the trial.

[Interviewer]: Only probe on most recent treatments. We do not need a comprehensive list of all treatments ever used.

1. Prior to your involvement in the clinical trial did you use any treatments specifically for your AD?
    - If so, what were they? How much did they help to manage your itch? How much did they help to manage your sleep disturbance?
    - What would you look for in an ideal treatment?
    - What factors do you consider when selecting a course of treatment? What type of things do you take into considerations when you are deciding how successful a treatment is or could be?

1.4 Decision and Expectations of the Trial [5 min]

I would now like to ask you some questions about your decision to enroll in this trial.

1. What made you decide to enroll in Galderma's clinical trial?
2. Did you have any expectations when entering the clinical trial? If so, what were they?
3. Did you have any concerns when entering the clinical trial? If so, what were they?
4. What were you hoping for in terms of a change in your **itch** from the study treatment?
5. What were you hoping for in terms of change in your **sleep disturbance** from the study treatment?

Part 2. Changes During the Clinical Trial related to AD Symptoms and Sleep Disturbance

2.1 Exploration of NEW Symptoms [5 min]

So far, we have been talking about symptoms you had before the study. Now, I would like to know about any NEW SYMPTOMS you had since the being in this study that were new for you (i.e. had not experienced before the study). Can you describe the new symptoms?

[Interviewer]: Please make sure you clarify with the patient that we are only interested in new symptoms from Baseline to Week 16. Please remind the baseline and week 16 dates if necessary.

Let the patient spontaneously report new symptoms and then probe. Obtain the list of new symptoms first, then go into more detail (i.e. frequency, duration, etc.) for each symptom individually. Enter NEW symptoms the patient indicated that they had during the study up to Week 16 in Table 3.

For each new symptom (Table 3)

1. For each symptom endorsed:
    a. When this [new symptom] was first noticed in the trial?
    b. Frequency: How often did you experience *[symptom]* during the trial?
    c. *Location: Where on your body did you experience [symptom]?*
    d. *Duration: Did the [symptom] come and go or was it present all the time?*
    e. *If [symptom] comes and goes:* How long did the *[symptom]* last for?
    f. Severity:
        i. On a scale of 0 to 10, where 0=not severe at all and 10= extremely severe, how bad, severe was this symptom when it was at its worst during the study (Baseline to Week 16).
        ii. Using the same scale, how severe is this symptom for you at Week 16?

Table 3. New Symptoms Since Being in the Study

Symptom description	Point in CT that this new symptom was noticed (x weeks)	Frequency	Location	Duration	Severity at its worst during the trial (0 – 10)	Severity at Week 16 (0-10)
Sensitive skin						
Other: specify						
Other: specify						
Other: specify						

2.2. Exploration of Meaningful Changes: Symptoms (New and previous Symptoms) [15 min]

Now I would like to discuss your experience in Galderma's clinical trial as it relates to any changes you may have experienced with regard to your AD symptoms. We are only interested in your experience between Baseline to Week 16.

[Interviewer]: Please recall any personal, work or other event reported by the patient soon after they started the trial to help them to recall back and anchoring their answer.

1. At the beginning of the interview, you mentioned [X symptoms] experienced prior to study entry and during the trial you mentioned [X new symptoms].

[Interviewer]: please report the symptoms that the patient indicated had changed since they started the clinical trial in the Table 4.

[Interviewer]: for each symptom change endorsed, please probe for improvement and worsening when appropriate

For each symptom change endorsed (prior to study entry and during the trial)

a. What specifically did you notice? Probe for the nature of the change

b. When during the trial did you first notice the change? Probe weeks into the trial (up to Week 16)

   i. Please give us some examples of how you noticed the change? What made you realize there was a change?

c. Has the change stayed consistent during the trial?

   i. If no: Did it come and go? If so, how long did it stay? Did it disappear or increase/decrease?)

d. Rating of the change (between Baseline to Week 16) using a Global Assessment of Change (GAC) scale: “much worse,” “a little worse,” “the same,” “a little better,” , or “much better”

   i. Those who reported worsening on GAC, ask: Is this increase in [symptom] a meaningful or important change for you?’ (Yes/No)

[Interviewer]: If the patient has difficulties understanding what a meaningful change means, please tell them that this is a change, positive or negative, that results in a change in their life, in the way they feel, function and their capacity to do things.

- In what ways? Can you provide some examples? *Probe for examples/participant rationale*

[Interviewer]: Please probe for the following examples. If yes, was the change good or bad? How big was that change? Was the amount of change important for you? How did it affect your life?

   ii. Those who reported improvement on GAC, ask: Is this decrease in [symptom] a meaningful change for you? (Yes/No)

- In what ways? Can you provide some examples?

Table 4. Change in Symptoms After Starting the Clinical Trial Between Baseline and Week 16 [From Tables 1 and 3]

Symptoms (prior to the trial and new symptoms during the trial)	Improved or Worsened?	Point in CT that change was noticed (x weeks)	Constant change Y/N	How much worse or better?*	Is this increase in [symptom] a meaningful change for you?' (Yes/No) – In what ways?	In what ways (add descriptions)
itching						

*"much worse" "a little worse", "the same", "a little better", or "much better"

2.3 Exploration of NEW Impacts [5 min]

So far, we have been talking about impacts you had before the study. Now, I would like to know about any new impacts you had since the beginning of this study (up to Week 16) that were new for you (had not experienced before the study). Can you describe these new impacts?

> [Interviewer]: Please make sure you clarify with the patient that we are only interested in experience from Baseline to Week 16. Please remind the baseline and week 16 dates if necessary.
>
> Let the patient spontaneously report new impacts first, and then probe. Obtain the list of new impacts first, then go into more detail for each impact individually. Enter NEW impacts the patient indicated that they had during the study in Table 5.

1. For each impact reported by the patient, please ask if the impact worsen, improved or was resolved during the trial?
2. When this new impact was first noticed?

Table 5. New Impacts Since Being in the Study

New Impact description	Point in CT that this new symptom was noticed (x weeks)	Improved or Worsened?	Resolved? Between Baseline and Week 16. (Y/N)

2.4 Exploration of meaningful change in impacts (NEW and PREVIOUS impacts) [15 min]

Now I would like to discuss your experience in Galderma's clinical trial as it relates to any changes you may have experienced with regards to impacts.

3. Did you notice any changes in how CTCL symptoms **impact** your day-today life since you started the clinical trial or during the trial? (*Probe: for example, prior to your entry into the clinical trial you mention x impact; has that changed?) **(Table 6)***
4. At the beginning of the interview, you mentioned [X impacts] experienced prior to study entry during the trial you mentioned [X new impacts].

[Interviewer]: Please report the impacts the patient indicated that they had changed since they started the clinical trial or during the trial (up to Week 16) in the Table 6.

[Interviewer]: for each impact change endorsed, please probe for improvement and worsening when appropriate

<u>For each impact endorsed:</u>

a. What specifically did you notice? *Probe for the nature of the change*

b. When during the trial did you first notice the change? *Probe weeks into the trial*

   i. What are some examples of how you noticed the change? What made you realize there was a change?

c. Has the change stayed consistent during the trial?

   i. If no: Did it come and go? If so, how long did it stay? Did it disappear or increase/decrease?)

d. Rating of the change using a GAC scale: “much worse”, “a little worse”, “the same”, “a little better”, or “much better”

   i. Those who reported worsening on GAC then ask: Is this increase in [impact] a meaningful change you?’ (Yes/No)

      [Interviewer]: If the patient has difficulties understanding what a meaningful change means, please tell them that this is a change, positive or negative, that results in a change in their life, in the way they feel, function and their capacity to do things.

      - In what ways? Can you provide some examples? *Probe for examples/participant rationale*

[Interviewer]: Please probe for the following examples. If yes, was the change good or bad? How big was that change? Was the amount of change important for you? How did it affect your life?

ii. Those who reported improvement on GAC were then asked: Is this decrease in [impact] a meaningful change for you? (Yes/No)

- In what ways? Can you provide some examples? *Probe for examples/participant rationale*

Table 6. Change in Impacts After Starting the Clinical Trial (Between Baseline and Week 16) [From Tables 2 and 5]

Impact	Improved or Worsened?	Point in CT that change was noticed (x weeks)	Constant change Y/N	How much worse or better?*	Is this increase in [impact] a meaningful change for you?' (Yes/No) – In what ways?	In what ways (add descriptions)

*"much worse", "a little worse", "the same", "a little better", or "much better"

2.5 PRO Data [10 min]

At the beginning of the trial and throughout the trial you completed a few sleep questionnaires, including the Sleep Diary. For the next phase of the interview, I would like to explore with you which changes on the sleep diary questions would matter to you.

Thank you. For the next phase of the interview, I would like to explore with you which changes in the sleep diary questions would matter to you.

Sleep Diary

Item 3:

The item 3 of the sleep diary asks about the time it takes you to fall asleep.

Before entering in the clinical trial, how long did it take you to fall asleep during a typical nighttime sleep?

a. Were these difficulties usually related to AD symptoms or other things?

iii. What would be the smallest improvement (in time gained of sleep) that would be meaningful or important to you? Why?

> [Interviewer]: If the patient has difficulties understanding what a meaningful improvement means, please tell them that this is an improvement that results in a positive change in their life (emotions or capacity to do things).

b. What would that change or improvement of ***[XXX improvement reported by the patient]*** in your sleep mean for you in terms of quality of sleep?

Item 4:

The item 4 of the sleep diary asks about the number of times you wake up during the night, due to the symptoms of atopic dermatitis (for example itching, burning).

Before entering in the clinical trial, how many times did you usually woke up due to AD symptoms during a typical nighttime sleep?

iv. What would be the smallest improvement (in number of awakenings due to AD) that would be meaningful or important to you? Why?

[Interviewer]: If the patient has difficulties understanding what a meaningful improvement means, please tell them that this is an improvement that results in a positive change in their life (emotions or capacity to do things).

c. What would that change or improvement of ***[XXX improvement reported by the patient]*** in your sleep mean for you in terms of quality of sleep?

Item 5

The item 5 of the diary asks about the total time your nighttime awakenings due to AD symptoms last.

d. Before entering in the clinical trial, how long did your awakenings related to AD symptoms usually last during a typical nighttime sleep?

e. What would be the smallest improvement (in time gained of sleep) that would be meaningful or important to you? Why?

[Interviewer]: If the patient has difficulties understanding what a meaningful improvement means, please tell them that this is an improvement that results in a positive change in their life (emotions or capacity to do things).

f. What would that change or improvement of ***[XXX improvement reported by the patient]*** in your sleep mean for you in terms of quality of sleep?

Items 6/7:

The sleep diary also asks about the awakenings related to other things (for example to drink water, to go to the bathroom).

g. Based on your experience, can you please describe the differences between awakenings related to AD symptoms and awakenings related other things?

h. Does the experience of a nighttime awakening related to AD and the experience a nighttime awakening related to other things mean the same for you? Why or why not?

[Interviewer]: If the patient has difficulties understanding this question, ask them when they wake up during the night because of their AD, if the duration and discomfort of this awakening is the same as when they wake up during the night to drink, go to the bathroom or for other things not related to their AD.

Part 3: Overall Perception of Treatment/Clinical Trial

3.1 Treatment Perception [5 min]

Now, switching gears to your general impressions of the treatment between Baseline and Week 16.

1. Overall, what did you like and what did you not like about the treatment?
2. Overall, would you say the treatment you received helped you in the management of your condition?
    a. If yes, why?
    b. If no, why?
3. Overall, was the treatment able to meet your expectations?
4. Overall, how satisfied were you with your treatment?
    a. On a scale of 0 to 10, please rate how satisfied you currently are with the study treatment. A zero would mean you are not satisfied at all and a 10 mean you are extremely satisfied.
5. What would need to change to consider the treatment successful?
6. How does the treatment you received in the clinical trial compare to the treatment(s) you took previously? *Probe on differences in efficacy and preferences for mode of administration*
7. Did you experience any effects/changes from the treatment that you did not expect?
8. Based on your experience, would you recommend this treatment to others with **itch** and **sleep disturbance**?
    a. If yes, why?

b. If no, why?

3.2 Trial Perception [Optional] [5 min]

And finally, I would like to ask about your general thoughts on the clinical trial overall.

1. Overall, what did you think about the clinical trial? *Probe on experience with study visits, study procedures, study assessments (frequency and length of patient questionnaires)*
2. Did being a part of the trial impact your day-to-day life? *Probe for examples; Probe about the nature, extent, frequency, and duration of impacts*
3. Anything else you would like to share that I did not ask about related to your experience with AD, itch, sleep disturbance, or the clinical trial?

Thank you for your time and for all the insightful information and experiences you have shared with us today. *Answer any questions or provide information, as needed about the payment card.*

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number: RD.06.SPR.118161

Confidentiality and Current GCP Compliance Statement

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

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

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

Information developed in this clinical study may be disclosed by Galderma S.A./Galderma R&D, 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