- **Protocol number: RD.03.SPR.114322**
- **Document title: A randomized, double-blind, multi-center, parallel-group, placebo-controlled dose-ranging study to assess the efficacy and safety of nemolizumab (CD14152) in moderate-to-severe atopic dermatitis subjects with severe pruritus receiving topical corticosteroids**
- **Version number: 02**
- **Date of the document: 01 June 2018**
- **NCT number: NCT03100344**

CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.114322

Name	Reason for Signing	Date
CCI	CCI	05-Jun-2018

CONFIDENTIAL

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TITLE PAGE

Title		
A randomized, double-blind, multi-center, parallel-group, placebo-controlled dose-ranging study to assess the efficacy and safety of nemolizumab (CD14152) in moderate-to-severe atopic dermatitis subjects with severe pruritus receiving topical corticosteroids		
CD number: CD14152	**Project Number:** 1260	**Clinical Trial Phase:** 2

EUDRACT NUMBER 2016-005025-37

IND Number 117122

Version Number: 02

SPONSOR

Name: GALDERMA R&D, SNC

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2400 route des Colles
06410 Biot, France

Telephone: CCI

For any safety questions, please contact the Clinical Safety Officer (CSO) using the contact details provided in Section 7.2.5.2.2.

COORDINATING INVESTIGATOR:

Name and Title:	PPD Coordinator Investigator
Address:	PPD United States
Telephone:	PPD
E-mail:	PPD

This clinical trial will be performed in compliance with applicable regulatory requirements and Good Clinical Practice (GCP). This clinical trial protocol follows guidelines outlined by the International Conference on Harmonization (ICH) and the Galderma template.

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<table>
<tr><td colspan="2">SYNOPSIS</td></tr>
<tr><td colspan="2">Clinical Trial Title:
A randomized, double-blind, multi-center, parallel-group, placebo-controlled dose-ranging study to assess the efficacy and safety of nemolizumab (CD14152) in moderate-to-severe atopic dermatitis subjects with severe pruritus receiving topical corticosteroids</td></tr>
<tr><td colspan="2">Short Title:
Dose-ranging study of nemolizumab in atopic dermatitis</td></tr>
<tr><td>Clinical Trial phase:
2</td><td>Clinical Trial Population:
Moderate-to-severe atopic dermatitis (AD) subjects with severe pruritus receiving topical corticosteroids (TCS)</td></tr>
<tr><td>Clinical Trial objectives:</td><td>The primary objective is to assess the efficacy of several subcutaneous doses of nemolizumab in moderate-to-severe AD subjects with severe pruritus receiving TCS, who were not adequately controlled with topical treatments.

The secondary objectives are to evaluate the safety of nemolizumab and to characterize its pharmacokinetic (PK) profile.</td></tr>
<tr><td>Clinical Trial design:</td><td>This is a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study. Eligible subjects will be randomized (1:1:1:1) to receive subcutaneous injection of various doses of nemolizumab or its placebo every 4 weeks, in addition to background TCS therapy. Randomization will be stratified by AD severity (Investigator’s Global Assessment [IGA] 3 or 4).

<table>
<tr><th>Group</th><th>Dose on day 1</th><th>Dose at weeks 4, 8, 12, 16 & 20</th></tr>
<tr><td>1</td><td>20 mg</td><td>10 mg</td></tr>
<tr><td>2</td><td>60 mg</td><td>30 mg</td></tr>
<tr><td>3</td><td>90 mg</td><td>90 mg</td></tr>
<tr><td>4</td><td>placebo</td><td>placebo</td></tr>
</table>
</td></tr>
<tr><td>Total number of subjects (Planned):</td><td>Approximately 250 subjects will be screened to result in 200 randomized subjects (50 subjects per group).</td></tr>
<tr><td>Number of clinical trial centers (Planned):</td><td>Approximately 70 sites</td></tr>
<tr><td>Region(s) involved (Planned):</td><td>Europe/North America/Asia-Pacific</td></tr>
<tr><td>Clinical trial duration:</td><td>The planned duration of this clinical trial (from First Subject In [FSI] to Last Subject Out [LSO] is approximately 15 months, with approximately 6 months of recruitment (from FSI to Last Subject In [LSI]).</td></tr>
<tr><td>Duration of subject participation:</td><td>Each subject will participate in the clinical trial for up to 36 weeks, with a 2 to 4-week run-in period, a 24-week treatment period (with the last drug injection at week 20), and an 8-week follow-up period (12 weeks after the last study drug injection).</td></tr>
</table>

Inclusion criteria (at the screening visit)	1. Male or female subjects ≥18 years (or legal age when higher) 2. Chronic AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 2 years before the visit 3. Eczema Area and Severity Index (EASI) score ≥12 4. IGA score ≥3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) 5. AD involvement ≥10% of Body Surface Area (BSA) 6. Severe pruritus (according to the definition of the Pruritus Categorical Scale [PCS]) on at least 3 of the last 7 days before the visit 7. Documented recent history (within 6 months before the visit) of inadequate response to topical medications Note: - Inadequate response to topical treatments is defined as: 1) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤2) despite treatment with a daily regimen of a medium or high potency TCS, applied for at least 4 weeks or for the maximum duration per prescribing information Or 2) Requirement of a long term treatment (>4 weeks) with a high potency TCS to achieve or maintain remission or low disease activity (equivalent to IGA ≤2) AND 3) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤2) with a topical calcineurin inhibitor (TCI), when applicable - 4) Subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) are also considered as inadequate responders to topical treatments. - Subjects will be considered as having inadequate response to topical treatments if they fulfill any of the three scenarios below or any combination of these three scenarios: ○ 1) and 3) ○ 2) and 3) ○ 4) 8. Have an ongoing TCS treatment (regardless of the potency of the TCS, the dose or the dose regimen), and agree to stop it and to apply the authorized TCS throughout the study starting from the screening visit 9. Agree to apply a moisturizer at least once daily throughout the study starting from the screening visit 10. Female subjects must fulfill one of the criteria below: - Female subjects of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy); - Female subjects of childbearing potential who agree to a true abstinence (when in line with the preferred and usual lifestyle of the subject), or to use an effective or highly effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration 11. Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol 12. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the U.S., Personal Information Protection and Electronic Documents Act (PIPEDA), if in Canada, or local privacy act if in other countries, and willing to share personal information and data, as verified by signing a written authorization. 13. Understand and sign an Informed Consent Form (ICF) prior to any investigational procedures being performed.

<table>
<tr><td>Inclusion criteria (at the baseline/day 1 visit)</td><td>14. EASI score ≥12
15. IGA score ≥3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe)
16. AD involvement ≥10% of BSA
17. Severe pruritus, defined as average of pruritus Numeric Rating Score (NRS) for the maximum intensity ≥7 during the 7 days prior to the visit. NOTE: A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score.
18. No latent or active tuberculosis (TB), as determined by a negative TB test result. The test should be repeated once within 2 weeks in case of an indeterminate result. Subject will be excluded if the repeated result remains indeterminate.</td></tr>
<tr><td>Exclusion criteria</td><td>1. Body weight < 45 kg
2. Subjects with a medical history of asthma that fulfill any one or more of the scenarios below:
- Had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit
- Whose asthma has not been well-controlled (i.e. symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit
- Peak Expiratory Flow (PEF) <80% of the predicted value
3. Cutaneous bacterial or viral infection within 1 week before the screening visit or during the run-in period.
4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit or during the run-in period, unless completely resolved and subject has been off treatment at least 1 week prior to the baseline visit
5. Requiring rescue therapy during the run-in period, or expected to require rescue shortly 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 trial if HBsAb is positive (considered immune after a natural infection).
7. Elevated Alanine Aminotransferase (ALT) and / or Aspartate Aminotransferase (AST) ≥3 x ULN at the screening visit
8. Elevated Creatinine Phosphokinase (CPK) > ULN at the screening visit, unless not confirmed on a repeat assessment within 2 weeks
9. Neutrophil count < 1.5 x $10^3/\mu l$ at the screening visit
10. Prior treatment with nemolizumab
11. Subjects whose pruritus responded to treatment with potential anti-pruritic effect (e.g. antihistamines)
12. Received a live vaccine within 4 weeks before the baseline visit, or planning to receive a live vaccine during the clinical trial
13. Received a non-live vaccine within 1 week before the baseline visit, or planning to receive a non-live vaccine during the clinical trial
14. Having received any of the following treatments within the specified time frame prior to the baseline visit;
<table>
<tr><th>Topical treatments</th><th>Time frame</th></tr>
<tr><td>TCI</td><td>2 weeks</td></tr>
<tr><td>Any topical treatment for AD other than moisturizer and TCS (e.g. prescription moisturizer)</td><td>2 weeks</td></tr>
</table>
</td></tr>
</table>

Exclusion criteria

Systemic treatments	Time frame
Specific or non-specific desensitization therapy	4 weeks
Corticosteroids	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g cyclosporine A, oral tacrolimus, cyclophosphamide, azathiophrine, methotrexate, mycophenolate mofetil)	8 weeks or 5 half-life (whichever is longer)
Phototherapy	4 weeks
Biologic therapies (e.g dupilumab, etanercept, adalimumab, infliximab, omalizumab)	8 weeks or 5 half-life (whichever is longer)
Vitamin D (including supplement) newly initiated or change in dose Stable treatment initiated before screening is allowed	2 weeks
Drugs with a sedative effect such as benzodiazepines, sedative H1 antihistamines, imidazopyridines, barbiturates, or sedative anti-depressants (e.g. amitryptiline) Stable treatment with anti-histamines devoid of sedative effect is allowed.	1 week
Live vaccine	4 weeks
Non-live vaccine	1 week

15. Pregnant women (with a positive serum pregnancy test result at the screening visit), breastfeeding women, or women planning to become pregnant during the clinical trial
16. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, actinic keratoses or squamous cell carcinoma in situ (Bowen's disease) that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) carcinoma in situ of the cervix, or non-invasive malignant colon polyps that have been removed
17. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g. monoclonal antibody)
18. History of intolerance to low or mid potency TCS or for whom TCS is not advisable (e.g. hypersensitivity to TCS or to any other ingredient contained in the TCSs to be used in the study, significant skin atrophy)
19. Known or suspected immunosuppression
20. History of or current confounding skin condition (e.g. Netherton Syndrome, psoriasis, Cutaneous T-Cell Lymphoma [Mycosis Fungoides or Sezary Syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis)
21. Any medical or surgical condition that may interfere with the assessments or the interpretation of study results
22. Any uncontrolled or serious disease that may put the subject at significant risk according to the investigator's judgment if he/she participates in the clinical trial
23. Planned or expect to have a major surgical procedure during the clinical trial
24. Subjects unwilling to refrain from using prohibited medications during the clinical trial
25. Currently participating in any other clinical trial of a drug or device, participated in a clinical trial within the past 3 months prior to screening visit, or is in an exclusion period (if verifiable) from a previous clinical trial
26. Vulnerable subject as defined in ICH/GCP

Background therapies	Starting from the screening visit, subjects will be instructed to apply a moisturizer at least once daily throughout the study. Starting from the screening visit, subjects are required to stop their previous TCS and will receive a standardized background TCS therapy during the study: A medium potency TCS (mometasone furoate 0.1% cream or hydrocortisone butyrate 0.1% cream) for the body, and a low potency TCS (hydrocortisone acetate cream or desonide 0.05% cream) in areas where medium potency TCS is considered unsafe (e.g. face, neck, genital areas). Subjects will apply a thin layer of TCS on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare (e.g. twice weekly, every other day), but does not exceed the maximal frequency recommended in the prescription information (e.g. once daily for mometasone furoate 0.1% cream). The medium potency TCS will not exceed an amount of approximately 100 g/month and the low potency an amount of approximately 30g/month. The TCS regimen will be adjusted during the study, according to the disease activity and tolerability by the subject.
Rescue therapies	If deemed to be medically necessary by the investigator (i.e. significant worsening of signs and/or symptoms of AD), rescue therapies can be prescribed to the subjects at any time during the study. Rescue therapies could include higher potency and/or quantity of TCS, TCI, systemic treatment, phototherapy or combinational usage of different treatment modalities. 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 investigator's judgment (e.g. TCI are applied in large body areas other than the face, neck, or genital areas). If subjects receive a systemic rescue therapy (such as cyclosporine, systemic corticosteroids, methotrexate, mycophenolate mofetil, azathioprine or biologics) or TCI in large body areas, 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.
Investigational product:	
Name (internal code)	Nemolizumab (CD14152)
Pharmaceutical form	Lyophilized powder (for reconstitution in a vial)
Dosage	10mg (with a loading dose of 20mg), 30mg (with a loading dose of 60mg) or 90mg depending on randomization scheme – Reconstituted nemolizumab solution to be diluted with reconstituted placebo solution to yield appropriate dosing solutions.
Route	Subcutaneous injection
Duration of treatment	24 weeks
Dose regimen	Every 4 weeks
Comparator:	
Name (internal code)	Nemolizumab placebo (N/A)
Pharmaceutical form	Lyophilized powder (for reconstitution in a vial)
Dosage	N/A
Route	Subcutaneous injection
Duration of treatment	24 weeks
Dose regimen	Every 4 weeks

Efficacy endpoints:	**Primary efficacy endpoint** - Percent change from baseline in EASI to week 24 **Secondary efficacy endpoints** - Proportion of subjects achieving IGA success (defined as IGA 0 [clear] or 1 [almost clear]) at each visit up to week 24 - Percent change from baseline in EASI at each visit up to week 24 - Absolute and percent change from baseline in weekly average of the peak and average NRS at each visit up to week 24 - Proportion of subjects with an improvement of weekly average pruritus peak NRS $\geq$4 from baseline to week 24 - Absolute and percent change in weekly average sleep disturbance NRS from baseline to week 24 - Proportion of subjects achieving PCS success (defined as a weekly prorated rounded average PCS $\leq$ 1 [none-mild]) at week 24 - Proportion of subjects achieving 50%, 75% or 90% reduction from baseline in EASI score (EASI-50, EASI-75, and EASI-90) at week 24 - Absolute and percent change in SCORing Atopic Dermatitis (SCORAD) score from baseline to week 24
Safety assessment:	- Adverse Events (AEs) including Adverse Event of Special Interest (AESI) and selected AEs at all visits - Physical examination and vital signs at all visits - Clinical laboratory values at screening, baseline, weeks 4, 8, 12, 16, 20, 24 & 32 - Electrocardiogram (ECG) at screening, baseline, weeks 1, 12 & 24 - Respiratory assessment at all visits in all subjects, and Peak Expiratory Flow (PEF) in subjects with a medical history of asthma An Independent Data Monitoring Committee (IDMC) will monitor the safety data at regular intervals throughout the clinical trial.
PK, pharmacodynamics (PD) and anti-drug antibody (ADA) assessment:	- Blood sample collection for PK at baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32 and unscheduled visits for safety reasons - Blood sample collection for anti-drug antibody (ADA) assessment at baseline, weeks 4, 8, 16, 24, 32 and unscheduled visits for safety reasons - Blood sample collection for PD/ biomarker analyses at baseline, weeks 4, 8, 16, 24 & 32 - Blood sample collection for analysis of thymus and activation-regulated chemokine (TARC) at baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28 & 32 - Stratum corneum sample collection for skin biomarker analyses: baseline & week 16
Quality-of-life (QoL) assessment:	- Dermatology Life Quality Index (DLQI) at baseline, weeks 2, 12 & 24 - Hospital Anxiety and Depression Scale (HADS) at baseline, weeks 12 & 24 - Missed work/school days to be recorded at weeks 4, 8, 12, 16, 20 & 24 - EuroQoL 5-Dimension (EQ5D) at baseline and week 24

Principal statistical method:	Primary inference for all the efficacy analyses will be based on the intent-to-treat (ITT) population at the week 24 endpoint. The primary endpoint will be analyzed using a Mixed-effect Model for Repeated Measures (MMRM) approach, including terms of treatment group, and baseline IGA severity. Visit will be fitted as a categorical variable, with the effect of treatment group and baseline varying at each visit. Continuous secondary efficacy endpoints will be analyzed in a similar manner to the analysis of the primary endpoint. All categorical efficacy endpoints will be analyzed using a stratified Cochran Mantel-Haenszel test. Multiple comparison procedures-modeling (MCP-Mod) approach will be applied using a set of candidate dose-response models to test for a dose-response relationship via model-associated statistics. Exposure-response modeling will also be conducted for the primary endpoint of EASI percentage change from baseline at week 24, and for percentage change in pruritus NRS at week 4. Primary inference for all the safety analyses will be based on the safety population. A summary of safety endpoints (treatment-emergent adverse events [TEAE], vital signs, laboratory parameters and ECG etc.) will be presented by treatment group. To impute the missing values for continuous endpoints, mixed-effect MMRM approach will be used for the primary and secondary endpoints. All missing values will be treated as a non-responder for binary endpoints. All efficacy data, except in observed case analysis, will be set to missing after rescue medication is used.
Sample size:	Sample size is estimated using MCP-Mod approach by selecting a set of candidate dose response shapes based on primary endpoint response (percent change in EASI). Assuming placebo response of 35%, standard deviation 45% and a maximum treatment difference of 30%, 50 subjects per arm will provide at least 90% power to detect a statistically significant dose-response for at least one model at 1-sided significance level of 0.025.

Table 1 Clinical trial schematic

Screening (Approximately 250 subjects) ↓ Randomization (Approximately 200 subjects)				
	Group 1	Group 2	Group 3	Group 4
	n= 50	n= 50	n= 50	n= 50
Treatment	Nemolizumab 10mg (loading dose: 20mg)	Nemolizumab 30mg (loading dose: 60mg)	Nemolizumab 90mg	Nemolizumab placebo
Treatment Frequency	Every 4 weeks (Q4W)	Q4W	Q4W	Q4W
Treatment Duration	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)
Duration of follow-up period	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)

Table 2 Schedule of assessments

Study Period	Run-in	Treatment									Follow-up		Unscheduled visit [b, c] (if applicable)	Early Termination Visit [b, d] (if applicable)
Visit (V)	**V1[a]**	**V2[b]**	**V3**	**V4**	**V5[b]**	**V6[b]**	**V7[b]**	**V8[b]**	**V9[b]**	**V10[b]**	**V11**	**V12/FINAL[b]**		
Week (W)	**Screening/ D -28 to -15**	**Baseline/ D 1**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**		
Day (D)			**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**		
Visit window (±d)			**± 1d**	**± 1d**	**± 1d**	**± 3d**	**± 5d**	**± 5d**	**± 5d**	**± 5d**	**± 7d**	**± 7d**		
ICF and country specific consent form (if applicable)	X													
Demographics	X													
Medical history/ Previous therapies	X													
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Inclusion/Exclusion criteria	X	X												
EFFICACY/PATIENT-REPORTED OUTCOMES ASSESSMENTS														
DLQI		X		X			X			X				X
HADS		X					X			X				X
EQ5D		X								X				X
5-D itch		X		X										
Missed work/school day					X	X	X	X	X	X				X
Pruritus NRS (daily) [e]	X----------→													
PCS (daily) [e]	X----------→													
Sleep disturbance NRS (daily) [e]	X----------→													
EASI	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
BSA	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
SCORAD		X	X	X	X	X	X	X	X	X	X	X	(X)	X
DPS [f]		X												

Study Period	Run-in	Treatment										Follow-up		Unscheduled visit [b, c] (if applicable)	Early Termination Visit [b, d] (if applicable)
Visit (V)	V1 [a]	V2 [b]	V3	V4	V5 [b]	V6 [b]	V7 [b]	V8 [b]	V9 [b]	V10 [b]	V11	V12/FINAL [b]		
Week (W)	Screening/ D -28 to -15	Baseline/ D 1	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32		
Day (D)			D8	D15	D29	D57	D85	D113	D141	D169	D197	D225		
Visit window (±d)			± 1d	± 1d	± 1d	± 3d	± 5d	± 5d	± 5d	± 5d	± 7d	± 7d		
LABORATORY/SAFETY ASSESSMENTS														
AE recording (including review of laboratory values if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Physical examination (including the evaluation of prurigo nodularis lesions if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Height	X													
Weight	X	X			X	X	X	X	X	X			(X)	
ECG	X	X	X				X			X			(X)	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Respiratory assessment [g]	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X
Urinalysis	X	X			X	X	X	X	X	X		X	(X)	X
Hematology	X	X			X	X	X	X	X	X		X	(X)	X
Blood chemistry	X	X			X	X	X	X	X	X		X	(X)	X
TB test	X												(X)	
Hepatitis B and C test	X													
HIV test	X													
Pregnancy test [h]	Serum	Urine			Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	(Urine)	Urine
TARC		X	X	X	X	X	X	X	X	X	X	X	(X)	
Blood sample for biomarkers (including IgE)		X			X	X		X		X		X		
Stratum corneum sample for biomarkers [i]		X						X						

Study Period	Run-in	Treatment									Follow-up		Unscheduled visit [b, c] (if applicable)	Early Termination Visit [b, d] (if applicable)
Visit (V)	**V1[a]**	**V2[b]**	**V3**	**V4**	**V5[b]**	**V6[b]**	**V7[b]**	**V8[b]**	**V9[b]**	**V10[b]**	**V11**	**V12/FINAL[b]**		
Week (W)	**Screening/ D -28 to -15**	**Baseline/ D 1**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**		
Day (D)			**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225**		
Visit window (±d)			**± 1d**	**± 1d**	**± 1d**	**± 3d**	**± 5d**	**± 5d**	**± 5d**	**± 5d**	**± 7d**	**± 7d**		
PK AND ADA ASSESSMENTS														
PK samples		X	X	X	X	X	X	X	X	X	X	X	(X)	X
ADA samples		X			X	X		X		X		X	(X)	X
STUDY DRUG AND BACKGROUND THERAPIES														
Randomization		X												
Subcutaneous study drug injection		X			X	X	X	X	X					
TCS dispensing (D) / Return (R) and moisturizer dispensing if necessary	D	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	R	(D/R)	D/R

[a] Screening visit must be performed at least 14 days prior to the day 1 visit to ensure that each subject undertakes at least 14 days of TCS treatment prior to randomization.
[b] Subjects are required to fast for at least 8 hours before the visit.
[c] Assessments to be conducted at the unscheduled visit depend on the reason for the visit. PK and ADA analyses are obligatory at unscheduled visits for safety reasons.
[d] Subjects discontinued before the week 24 visit should attend an early termination visit and a final visit 12 weeks after the last study drug injection.
[e] Pruritus NRS and PCS to be recorded by subjects once daily in the evening. Sleep disturbance NRS to be recorded by subjects once daily in the morning.
[f] DPS to be recorded by subjects at 2, 4, 8, 24, 48, and 72 hours after the study drug administration on day 1.
[g] PEF will be measured for subjects with a medical history of asthma only.
[h] Only for females of childbearing potential. Serum pregnancy test to be performed at screening visit, and urine pregnancy test for all other visits.
[I] Stratum corneum sample from lesional and non-lesional skin on day 1 and from lesional skin only at week 16.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
°C	Degrees Celsius
°F	Degrees Fahrenheit
AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BLQ	Below the Limit of Quantification
BSA	Body Surface Area
Cmax	Maximum Concentration
CPK	Creatinine Phosphokinase
eCRF	electronic Case Report Forms
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSO	Clinical Safety Officer
CYP450	Cytochrome P450
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
DPS	Dynamic Pruritus Scale

Abbreviation	*Term*
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
EQ5D	EuroQoL 5-Dimension
FSI	First Subject In
GCP	Good Clinical Practice
GMS	Global Medical Service
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBsAb	Hepatitis B Surface Antibody
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
IRB	Institutional Review Board

Abbreviation	*Term*
IRR	Injection-related Reaction
IRT	Interactive Response Technology
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LSI	Last Subject In
LSO	Last Subject Out
MI	Multiple Imputations
mL	Milliliter
MMRM	Mixed-effect Model for Repeated Measures
mRNA	Messenger RNA
N/A	Not Applicable
NRS	Numeric Rating Scale
OC	Observe Case
PCS	Pruritus Categorical Scale
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PIPEDA	Personal Information Protection and Electronic Documents Act
PK	Pharmacokinetics
PP	Per-Protocol
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of Life
RA	Receptor A

Abbreviation	*Term*
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
SIN	Subject Identification Number
SOP	Standard Operating Procedure
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
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
WBC	White Blood Cell
VAS	Visual Analogue Scale

1 BACKGROUND AND RATIONALE

1.1 Medical background and short rationale for the clinical trial

Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 2% to 10% of the total population (Bieber 2008). 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 (e.g., asthma, allergic rhinitis, food allergy) and AD often constitutes the first step of atopic march (progression from one atopic disease to another). Although not a life-threatening disease, AD has a marked negative impact on

patients' quality-of-life (QoL) and depression and anxiety have been reported as comorbidities among AD patients (Linnet 1999).

The cause of AD, although still not completely understood, is probably multifactorial and involves complex interrelation between susceptible genes, immunological factors, infections and environmental factors to produce a skin barrier disturbance as well as immunologic dysregulation and inflammation (Rutkowski 2014). Abnormal protein (filaggrin and related proteins) and lipid (ceramide) metabolism may also play a key role. Upon stimulation with allergens, dendritic cells in the skin stimulate the type 2 helper T cell (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. The pathophysiology also involves Th1 cells in the chronic phase of AD. Involvement of Th17 and Th22 cells in AD pathogenesis has been more recently reported (Gittler 2012). Of note, non-lesional skin already shows signs of subclinical inflammation with increased numbers of T-helper-2 (Th2) cells, Th22 cells, and to a lesser degree, Th17 cells, and a pro-inflammatory cytokine milieu (Suárez-Fariñas 2011).

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

AD 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 for their anti-inflammatory effect, but their long-term use can lead to side effects, such as skin atrophy and risks associated with systematic absorption (e.g. hypothalamic pituitary axis suppression and Cushing's syndrome). Topical calcineurin inhibitors (TCI) are effective for acute and chronic treatment, 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.

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 (Sidbury 2014). There are various forms, doses and treatment protocols of phototherapy, which lead to heterogeneous treatment outcomes, including common side effects such as actinic damage, local erythema and tenderness, pruritus, burning and stinging, as well as the long-term risk of skin cancer. Systemic corticosteroids, while controlling disease temporarily, should be avoided due to an overall unfavorable risk-benefit profile. 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, mycophenolate mofetil may be considered when systemic treatment is required (Sidbury 2014). Most of these systemic immunosuppressants, except cyclosporine, have not been approved for the treatment of AD and are used off-label. Cyclosporine is approved for treatment of severe AD in the EU and in a few other countries (e.g. Japan), but not in the U.S. 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 developed for the treatment of AD. Dupilumab, a humanized monoclonal antibody blocking the signal pathway of both IL-4 and IL-13, was tested in moderate-to-severe AD patients not adequately controlled with topical medications. (Simpson 2016). Two other anti-IL-13 therapies, lebrikizumab and tralokinumab, are also being developed.

Nemolizumab, a humanized anti-human IL-31 receptor A (RA) monoclonal antibody, inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction. IL-31, a cytokine produced mainly by activated T cells, has been implicated in the induction of pruritus. Transgenic mice overexpressing IL-31 exhibited skin lesions resembling those of AD, and scratching behavior, which could be suppressed by treatment with an anti-mouse IL-31 antibody (Dillon 2004; Grimstad 2009). In dogs, lokivetmab, a caninized, anti-canine IL-31 antibody has been shown to reduce pruritus in a dose-dependent manner with a rapid onset of effect and to decrease the dermatitis score compared to placebo (Michels 2016). In cynomolgus monkeys, nemolizumab suppressed IL-31 induced scratching (Oyama 2016). In humans, IL-31 RA mRNA was identified in several tissues including the dorsal root spinal ganglia, which contain sensory nerve cells (Sonkoly 2006) and keratinocytes (Kato 2014). IL-31 is preferentially produced by Th2 cells, and its expression is consistently increased in the skin lesions of AD patients (Szegedi 2012; Neis 2006). Furthermore, human IL-31 has been shown to be induced by IL-4 and promotes Th2-driven inflammation (Stott B 2013). Together, these findings suggest that IL-31 is involved in the pathogenesis of pruritus and is implicated in the inflammation of AD. In addition, IL-31 was shown to be involved in epidermal cell proliferation and keratinocyte differentiation, which are crucial for the skin barrier function (Singh 2016; Hanel 2016).

In conclusion, nemolizumab may present a new treatment option for AD. Patients with insufficient response to topical therapies and severe pruritus, which leads to extensive scratching further aggravating the disease, could particularly benefit from such a therapy. The main objective of the study is to evaluate the efficacy, safety and pharmacokinetics (PK) of multiple subcutaneous doses of nemolizumab in the treatment of AD, when administered on top of background TCS.

1.2 Drug profile

Nemolizumab is a [redacted] CCI [redacted] The drug product is a vial containing 1 [redacted] CCI [redacted] injection.

Please refer to the Investigator's Brochure (IB) for detailed information on non-clinical and clinical studies. Results of two completed clinical studies of nemolizumab are summarized below.

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 volunteers and 36 Japanese AD subjects (Nemoto 2016). There were no deaths or serious adverse events (SAE) reported in the study, and no dose-dependent increase in the incidence of AE was observed. In healthy volunteers, the incidence of AEs was comparable between the nemolizumab groups and the placebo group, with similar results for Caucasians and Japanese volunteers. Among the healthy Caucasian adult males, increased creatinine phosphokinase (CPK) was more common in the nemolizumab groups, but the CPK increase in most subjects could be explained by excessive exercise.

Efficacy results were also obtained in this phase 1 study with 36 moderate-to-severe Japanese AD subjects receiving a single dose of nemolizumab (0.3mg/kg, 1mg/kg or 3mg/kg) or placebo with concomitant topical hydrocortisone butyrate. Intensity of pruritus decreased as early as week 1 in the nemolizumab groups, by a similar degree with all three doses. Treatment with nemolizumab also increased sleep efficiency as measured by Actigraphy and decreased the use of TCS in the study. Incidence of AE in AD subjects was similar between nemolizumab groups and placebo group, and was not dose-dependent. The most common AEs reported with nemolizumab included aggravated atopic dermatitis, folliculitis and nasopharyngitis. One subject in the group of 3 mg/kg was diagnosed with asthma: the subject experienced some degree of breathlessness from day 9 after nemolizumab administration and symptoms had resolved by day 22. The subject experienced no further respiratory symptoms until the last observation.

In the recently completed phase 2a study, the safety, tolerability and efficacy of nemolizumab monotherapy were evaluated in 264 moderate-to-severe AD subjects who were inadequately controlled by or intolerant to topical therapy (CIM003JG study report 2017). The study included a 12-week randomized, double-blind, placebo-controlled period (Part A), and a 52-week extension (Part B). At week 12, various doses of nemolizumab (0.1 mg/kg, 0.5 mg/kg or 2.0 mg/kg) administered subcutaneously every 4 weeks (Q4W) were statistically significantly more effective than placebo in reducing pruritus visual analogue scale (VAS), with 0.5 mg/kg and 2.0mg/kg doses being more effective than 0.1 mg/kg. No additional benefit was observed with the 2 mg/kg Q4W or Q8W compared with 0.5 mg/kg Q4W. The mean percent changes in Eczema Area and Severity Index (EASI), Body Surface Area (BSA) of AD, SCORing Atopic Dermatitis (SCORAD), Investigator's Global Assessment (IGA) and sleep disturbance VAS were also numerically greater in all treatment groups than in the placebo group. The greatest improvements were generally observed in the nemolizumab 0.5 mg/kg and 2.0 mg/kg Q4W groups. Subjects who received placebo in Part A were randomized to receive 0.1 mg/kg, 0.5 mg/kg or 2.0 mg/kg Q4W in Part B. There was evidence of a progressive improvement in all efficacy parameters with prolonged treatment.

During Part A, incidence of AEs was slightly higher in the nemolizumab groups than in the placebo group. AEs that occurred in 5% or more of nemolizumab-treated patients (all groups pooled) were (worsening of) dermatitis atopic, nasopharyngitis, upper respiratory tract infection, edema peripheral, and blood CPK increased. Dermatitis atopic, edema peripheral, and headache were observed more often in each of the nemolizumab groups compared to the placebo group, but with generally no evidence that the incidence increased with higher dose. There was an apparent dose relationship for edema peripheral in the nemolizumab Q4W groups; however, most of the cases occurred during part A, were transient, of mild or moderate intensity and none led to treatment discontinuation. Various AEs that could be grouped as "injection-related reactions (IRR)" or "skin infection" were also observed in a higher frequency with nemolizumab than with placebo. Severe AEs were reported more frequently in nemolizumab groups than in placebo group (in Part A), but there was no evidence that the incidence increased with higher dose. During the entire study (Part A and B), AEs that occurred in 5% or more of nemolizumab-treated patients (all groups pooled) were nasopharyngitis, dermatitis atopic, blood CPK increased, upper respiratory tract infection, headache, edema peripheral, 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). Treatment-emergent antibodies to nemolizumab were observed in 7.1% of the patients in the pooled nemolizumab groups. In addition one patient in the 0.1 mg/kg Q4W group with anti-nemolizumab antibodies present from baseline developed neutralizing antibodies at 64 weeks.

Based on the safety data from these two completed studies, no risk of nemolizumab has been identified. Potential important risks to be monitored closely include injection-related reactions (IRR), asthma, exacerbation of AD, and skin infection; while peripheral edema and headache are considered as potential non-important risks.

1.3 Risk/Benefit assessment

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

Results of previous clinical studies demonstrated that treatment with nemolizumab at 0.1-2 mg/kg had a marked effect on pruritus and pruritus-related sleep loss. This improvement in the signs and symptoms of AD was consistent with the observed improvement in sleep quality (evaluated both subjectively and by using the objective measurement of Actigraphy) and QoL (evaluated using dermatology life quality index [DLQI]). Continuous treatment up to 64 weeks led to improvement in overall severity of AD, evaluated with various validated scales commonly used in clinical trials (i.e. EASI, SCORAD and IGA). Nemolizumab also had a good safety profile 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 in this clinical trial include AD exacerbation, IRR, asthma, skin infection, peripheral edema and headache. Specific risk minimization and safety follow-up measures have been planned in this clinical trial.

First, the AD exacerbations observed in the previous phase 2a study could have been related to the withdrawal of TCS prior to the nemolizumab monotherapy, and/or to the protocol predefined criteria for receiving rescue therapy: because only subjects with no improvement on IGA or pruritus could receive rescue therapy, subjects in the nemolizumab groups, who generally had an improvement in pruritus, were less likely to receive rescue therapy. In the current study, a medium or low potency (depending on the body areas to be treated) background TCS regimen will be used on all subjects from the screening visit and throughout the study, with an adapted application frequency to ensure disease stability as much as possible (i.e. prevent AD flare). Rescue therapy including topical and systemic treatments or phototherapy may be provided in the current study according to the judgment of the investigator. This approach ensures that subjects receiving placebo or having an insufficient response to nemolizumab could have their AD adequately treated when medically necessary.

Secondly, the exclusion criteria of this clinical trial will prevent high-risk patients from receiving nemolizumab. Subjects will not be eligible if they have had recent history of, or current bacterial or viral infection, not well-controlled asthma, or known/suspected immunosuppression. As no data are available in pregnant or breastfeeding women, or in patients receiving live or non-live vaccines, they are not eligible from this study.

Finally, safety will be evaluated closely throughout the study, until 12 weeks after the last study drug administration. Elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) associated with elevated bilirubin, elevated CPK related to study drug and newly diagnosed asthma (or worsening of asthma) are considered as adverse events of special interest (AESI) to be reported within 24 hours. Medical interview of signs and symptoms of asthma will be conducted in all subjects at each study visit, and a peak expiratory flow (PEF) measurement will be performed at each study visit on all subjects with a history of asthma. The AEs reported with a higher frequency with nemolizumab than with placebo in previous studies, or which are considered as class effects for other biological products, will be considered as “selected AEs” in this study and additional information regarding those events will be collected when applicable. In addition, an independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study.

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.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

The primary objective is to assess the efficacy of several subcutaneous doses of nemolizumab in moderate-to-severe AD subjects with severe pruritus receiving TCS, who were not adequately controlled with topical treatments.

The secondary objectives are to evaluate the safety of nemolizumab and to characterize its PK profile.

2.2 Clinical hypothesis

The hypothesis is that nemolizumab is more effective in reducing severity of AD than the placebo of nemolizumab.

3 OVERALL CLINICAL TRIAL DESCRIPTION

3.1 Overview

This is 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. The duration of this clinical trial is up to 36 weeks for a given subject, including a 2 to 4-week run-in period, a 24-week treatment period and an 8-week follow-up period (12 weeks after the last study drug administration).

Eligible subjects must have moderate-to-severe AD, severe pruritus and a documented history of inadequate response to topical AD medications. Subjects meeting the inclusion/exclusion criteria at the screening visit will receive background therapy of AD (including a moisturizer, a medium potency TCS for the body, and a low potency TCS for the face, neck etc.) to be used throughout the study. One retest is allowed for the tests of tuberculosis (TB) and CPK. Subjects who still meet the inclusion/exclusion criteria at the baseline visit will be randomized in a 1:1:1:1 ratio to either of the 3 groups of nemolizumab or placebo. Injection of study drug will occur every 4 weeks (at weeks 4, 8, 12, 16 & 20), and a loading dose will be administered on day 1 for the groups of 10mg and 30mg only (20mg and 60mg, respectively). For 90mg group, the same dose will be administered at each injection visit. Randomization will be stratified by AD severity based on the baseline IGA score (3 or 4).

Group	Dose on day 1	Dose at weeks 4, 8, 12, 16 & 20
1	20 mg	10 mg
2	60 mg	30 mg
3	90 mg	90 mg
4	placebo	placebo

The schedule of assessments is summarized in Table 2. Assessments of efficacy, safety and PK will be conducted throughout this clinical trial. Subjects will evaluate the severity of their pruritus daily. The last study drug injection will occur at week 20, and the end of treatment visit will occur at week 24, when the primary endpoint assessment will be conducted. The end of study visit will occur at week 32, 8 weeks after the end-of-treatment visit and 12 weeks after the last study drug administration.

3.2 Independent data monitoring committee (IDMC)

An IDMC will be set-up to monitor safety data generated in this clinical trial on an ongoing basis and make appropriate recommendations to the sponsor. The members of IDMC will not include any sponsor representative or any investigator of the study. The first IDMC meeting will occur before the study start, to present the study and the IDMC processes to all members. During the clinical trial, the IDMC will review the Suspected Unexpected Adverse drug Reactions (SUSARs) and unblinded SAEs on an ongoing basis, other SAEs and AESI on a monthly basis, and accumulating safety data every 4 months. The cut-off date for the first IDMC review meeting will occur once approximately 50 subjects have completed 3 months of treatment, or approximately 4 months after the first subject has been enrolled in the study (whichever is sooner). Unscheduled meetings may occur as needed at the discretion of Sponsor/Contract Research Organization (CRO) or the IDMC members. The IDMC will review data blinded by treatment group, but can request unblinding if judged to be necessary. 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.

3.3 Rationale for study design

Rationale for general study design is detailed below. Rationale for dosage/dose regimen and endpoints are provided in section 3.4 and section 7.6, respectively.

Eligible subjects for this clinical trial will have moderate-to-severe AD with severe pruritus who are not adequately controlled by topical treatments. The study population is selected based on the current unmet need in the management of AD and the mode of action of nemolizumab. The inclusion criteria for IGA, BSA and EASI are consistent with the disease severity targeted in the study: An IGA of 3 or 4 corresponds to moderate or severe AD respectively; BSA of at least 10% and severe pruritus are usually observed in these more severe AD patients; An EASI

threshold of 12 optimally discriminates moderate and severe AD from milder disease population according to a post-hoc analysis using the data from previous phase2a study of nemolizumab (data on file), and is consistent with the published analyses correlating IGA and EASI assessments in patients with AD (Leshem 2015; Barbier 2004). Finally, subjects with severe pruritus are targeted because they are most likely to benefit from treatment with nemolizumab, based on its marked effect on pruritus in previous studies.

The study includes a 24-week treatment period and an 8-week follow-up period (12 weeks after last study drug administration at week 20). Although nemolizumab had a marked effect on pruritus after a single administration, it may require a longer period of treatment in order to break the itch-scratch cycle and subsequently show its maximal effect on disease severity. The duration of follow-up period corresponds to more than 5 half-lives of nemolizumab: the drug plasma level is expected to be lower than the Limit of Quantification (LOQ) at the end of the study, and the follow-up period is therefore considered adequate to ensure the safety of subjects.

Background therapy including moisturizer and TCS will be used throughout this study. This is in line with the current practice to use topical agents in conjunction with systemic treatment in more severe cases (Eichenfield 2014). Background TCS will be started from the screening visit, to ensure disease stability and avoid flares. During the treatment period, TCS may be tapered and subsequently discontinued when the disease has sufficiently improved. The potency of TCS selected for this study is clinically justified: a medium potency TCS will be used on the body, as a more potent TCS would not be appropriate for the long duration of the study (up to 36 weeks for a given subject); a low potency TCS will be used in the areas considered unsafe for medium potency TCS (e.g. face, neck). The amount of TCS to be provided in the study is based on the estimated quantity needed for maintenance regimen (Eichenfield 2015).

This clinical trial is randomized and placebo-controlled. The choice of placebo as comparator is appropriate for the objective of the study, since it will provide the most robust assessment of the efficacy and safety of nemolizumab. For subjects randomized to receive placebo or an ineffective dose of nemolizumab, rescue therapy (including topical and systemic treatment or phototherapy) may be provided if judged to be necessary by the investigator.

3.4 Rationale for dosage and dose regimen

The PK and pharmacodynamics (PD) profile of nemolizumab was evaluated in two clinical trials, in which single doses from 0.1 to 3 mg/kg, or repeated doses of 0.1 mg/kg, 0.5 mg/kg or 2.0 mg/kg Q4W, or 2 mg/kg Q8W were studied. PK assessment after subcutaneous injections of mg/kg doses showed a dose proportional increase of nemolizumab serum concentrations after single and repeated dose administrations. The terminal elimination half-life of nemolizumab was around 2 weeks after single and repeated administrations. Steady state concentrations were achieved from week 16 of treatment and limited systemic accumulation was observed after repeated administrations.

PK data were used to develop a population PK model that allows an accurate simulation of nemolizumab serum concentrations with different doses and dosing regimens.

Based on the results of the previous clinical studies, pruritus VAS endpoint was fitted to an indirect turnover model with placebo effect and maximum inhibition (Imax) equation; the concentration causing 50% inhibition (IC_{50}) of the effect on VAS was estimated at 0.66 µg/mL (Bootstrapped 90% CI from 0.276 µg/mL to 1.93 µg/mL). The concentration causing 90% inhibition (IC_{90}) was estimated at 5.96 µg/mL .

The doses and dose regimen were selected based on the rationale described below:

- Dose:
    - Fixed doses vs mg/kg doses: In this study, the administered dose will not be adjusted to the body weight of the individual subject. Fixed dosing was selected because nemolizumab demonstrated a large therapeutic window between 0.5 and 2.0 mg/kg and a low inter-individual variability in systemic exposure (CV 30%) in the previous phase 2a study, with no sign of dose related toxicity after single administrations of up to 3mg/kg in the previous phase 1 study. The population PK model demonstrated a limited body weight effect compared to the variability in the effect on VAS. The administration of fixed doses was considered as similar to mg/kg doses over a wide range of body weights (from 30 to 150 kg). This fixed dose selection can also avoid errors that could be made in calculating, preparing, and administering a weight-based dose.
    - Dose selection: The population PK model was used to simulate systemic exposure using several fixed doses. The simulations using 10, 30 and 90 mg monthly doses provided a range of well-distributed systemic exposures on the expected exposure-response curve, with a plateau of effect at or below 90 mg. Simulation results show that the proposed fixed doses of 10, 30 and 90 mg are expected to provide similar efficacy outcomes as weight-based dosing with 0.13, 0.4 and 1.2 mg/kg, respectively (assuming a mean body weight of 75kg). These fixed doses are expected to result in systemic exposure levels in a similar range to those observed in the previous Phase 2a study (Table 3). The overall good safety profile of nemolizumab was confirmed with a single dose of up to 3 mg/kg and repeated doses of up to 2 mg/kg Q4W for up to 64 weeks. The highest dose selected for this clinical trial is 90 mg, which corresponds to at most 2 mg/kg (as subjects with a body weight <45 kg will be excluded from the study).

- Loading dose: Subcutaneous administration of nemolizumab resulted in slow absorption with peak serum concentrations achieved after 4 to 9 days. Plateau systemic exposure levels should be achieved after at least 8 weeks of repeated monthly administrations. Therefore, loading doses are necessary to rapidly achieve targeted systemic levels, and to ensure a fast onset of action. Rapid inhibition of pruritus in AD is an important treatment goal in itself, and is also expected to contribute to breaking the itch-scratch cycle and thus to improve the skin condition in AD patients. Loading doses were simulated using the above-described PK model. To achieve targeted steady state systemic concentration levels from the first injection, loading doses of 20 mg and 60 mg are needed for the 10 and 30 mg groups, respectively. The 90 mg dose will be administered without a loading dose, as it is expected to provide systemic exposure that is high enough to achieve the maximum inhibitory effect from the first drug administration.
- Dose regimen: The dose regimen was selected based on results of the previous phase 2a study and the population PK/PD model. The previous phase 2a study demonstrated similar efficacy results (in term of pruritus VAS) for subjects in the 2.0mg/kg Q8W group compared to subjects receiving 0.5 mg/kg or 2.0 mg/kg Q4W at week 8. The PK/PD model showed that the Q4W regimen results in plasma concentrations that fluctuate only 3-fold between peak and trough, and should be sufficient to obtain the required level of therapeutic effect. In addition, PK model simulations demonstrated that the average systemic exposure is similar for the same monthly dose administered once (Q4W) or twice (Q2W) a month; and simulated serum concentration fluctuations were small (1.5 and 3 for Q2W and Q4W, respectively). Thus, similar clinical outcomes on pruritus are expected, and both dosage regimens are expected to result in safe exposure levels. Therefore, a Q4W dosage regimen was selected as it is more convenient for the subjects and should, in theory, facilitate their compliance.

Table 3 Nemolizumab simulated average serum concentrations (µg/mL)

	5mg_Q2W	10mg_Q4W	15mg_Q2W	30mg_Q4W	45mg_Q2W	90mg_Q4W
Mean ± SD	1.20 ± 0.64	1.20 ± 0.64	3.61 ± 1.91	3.53 ± 1.81	10.92 ± 5.71	10.84 ± 5.68
90% CI	[0.46; 2.39]	[0.46; 2.39]	[1.37; 7.14]	[1.38; 6.91]	[4.26; 21.66]	[4.32; 21.91]

Overall, based on the results of the prior Phase 1 and Phase 2a studies, and the PK/PD model, three fixed doses (10, 30 and 90 mg) were chosen to be administered Q4W in this clinical trial to allow future selection of the dose(s) with the best benefit/risk ratio for further development.

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from First Subject In [FSI] to Last Subject Out [LSO]) is approximately 15 months, and the planned duration of recruitment (from FSI to Last Subject In [LSI]) is approximately 6 months.

Each subject will participate in the clinical trial for up to 36 weeks, with a 2-4 week run-in period, a 24-week treatment period, and an 8-week follow-up period (12 weeks after the last drug administration).

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical trial center (e.g. for lack of subject enrollment or non-compliance with clinical trial protocol, regulations, or GCP) or prematurely suspend the clinical trial (e.g., for reasons of safety, quality of study drug, regulatory, efficacy, or logistics) at any time with appropriate notification.

5 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

5.1 Number of subjects

Approximately 250 subjects will be screened to result in 200 randomized subjects (50 subjects per group).

5.2 Clinical trial population characteristics

5.2.1 Inclusion criteria

Subjects must meet the following inclusion criteria (or not applicable for #10) at the screening visit:

1. Male or female subjects ≥18 years (or legal age when higher)
2. Chronic AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014] APPENDIX 1), that has been present for at least 2 years before the visit
3. EASI score ≥12
4. IGA score ≥3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe)
5. AD involvement ≥10% of BSA
6. Severe pruritus (according to the definition of the pruritus categorical scale [PCS]) on at least 3 of the last 7 days before the visit
7. Documented recent history (within 6 months before the visit) of inadequate response to topical medications

Note:

- Inadequate response to topical treatments is defined as:
  1) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤2) despite treatment with a daily regimen of a medium or high potency TCS, applied for at least 4 weeks or for the maximum duration per prescribing information

     Or
  2) Requirement of a long term treatment (>4 weeks) with a high potency TCS to achieve or maintain remission or low disease activity (equivalent to IGA ≤2)

     AND
  3) Failure to achieve or maintain remission or low disease activity (equivalent to IGA≤2) with a TCI, when applicable
- 4) Subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) are also considered as inadequate responders to topical treatments
- Subjects will be considered as having inadequate response to topical treatments if they fulfill any of the three scenarios below or any combination of these three scenarios:
  - 1) and 3)
  - 2) and 3)
  - 4)

8. Have an ongoing TCS treatment (regardless of the potency of the TCS, the dose or the dose regimen), and agree to stop it and to apply the authorized TCS throughout the study starting from the screening visit
9. Agree to apply a moisturizer at least once daily throughout the study starting from the screening visit
10. Female subjects must fulfill one of the criteria below:
    - Female subjects of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy);
    - Female subjects of childbearing potential who agree to a true abstinence (when in line with the preferred and usual lifestyle of the subject), or to use an effective or highly effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration

NOTE: Effective and highly effective methods of contraception are defined below:

- Effective methods of contraception include:
    - Progestogen-only oral hormonal contraception
    - Male or female condom
    - Cap, diaphragm or sponge with spermicide
    - Combination of male or female condom with cap, diaphragm or sponge with spermicide

- Highly effective methods of contraception include:
  - Combined (estrogen and progestogen containing) oral, intra-vaginal, or transdermal hormonal contraception
  - Injectable or implanted hormonal contraception
  - Intra-uterine devices
  - Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
  - Vasectomized partner (for at least 3 months)

11. Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol
12. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the U.S., Personal Information Protection and Electronic Documents Act (PIPEDA), if in Canada, or local privacy act if in other countries, and willing to share personal information and data, as verified by signing a written authorization.
13. Understand and sign an Informed Consent Form (ICF) prior to any investigational procedures being performed.

<u>Subjects must also meet the following inclusion criteria at the baseline / day 1 visit:</u>

14. EASI score ≥12
15. IGA score ≥3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe)
16. AD involvement ≥10% of BSA
17. Severe pruritus, defined as average of pruritus Numeric Rating Score (NRS) for the maximum intensity ≥7 during the 7 days prior to the visit. NOTE: A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score.
18. No latent or active TB, as determined by a negative TB test result. The test should be repeated once within 2 weeks in case of an indeterminate result. Subject will be excluded if the repeated result remains indeterminate.

Rationale:

1-9 & 14-18: To define study-specific population

10: to prevent the inclusion of pregnant subjects into the clinical trial

11-13: To comply with GCP/ICH and local regulations

5.2.2 Exclusion criteria

Subjects who meet any of the following criteria will be excluded from the study. When the visit is not specified, subjects who meet the criteria at either the screening visit or the baseline visit will be excluded.

1. Body weight <45 kg
2. Subjects with a medical history of asthma that fulfill any one or more of the scenarios below:
   - Had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit
   - Whose asthma has not been well-controlled (i.e. symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit
   - PEF <80% of the predicted value
3. Cutaneous bacterial or viral infection within 1 week before the screening visit or during the run-in period.
4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit or during the run-in period, unless completely resolved and subject has been off treatment at least 1 week prior to the baseline visit
5. Requiring rescue therapy during the run-in period, or expected to require rescue shortly 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 trial if HBsAb is positive (considered immune after a natural infection).
7. Elevated ALT and / or AST ≥3 x ULN at the screening visit
8. Elevated CPK > ULN at the screening visit, unless not confirmed on a repeat assessment within 2 weeks
9. Neutrophil count <1.5 x $10^3/\mu l$ at the screening visit

10. Prior treatment with nemolizumab
11. Subjects whose pruritus responded to treatment with potential anti-pruritic effect (e.g. antihistamines)
12. Received a live vaccine within 4 weeks before the baseline visit, or planning to receive a live vaccine during the clinical trial
13. Received a non-live vaccine within 1 week before the baseline visit, or planning to receive a non-live vaccine during the clinical trial
14. Having received any of the following treatments within the specified time frame prior to the baseline visit;

Topical treatments	**Time frame**
TCI	2 weeks
Any topical treatment for AD other than moisturizer and TCS (e.g. prescription moisturizer)	2 weeks
Systemic treatments	
Specific or non-specific desensitization therapy	4 weeks
Corticosteroids	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g cyclosporine A, oral tacrolimus, cyclophosphamide, azathiophrine, methotrexate, mycophenolate mofetil)	8 weeks or 5 half-life (whichever is longer)
Phototherapy	4 weeks
Biologic therapies (e.g dupilumab, etanercept, adalimumab, infliximab, omalizumab)	8 weeks or 5 half-life (whichever is longer)
Vitamin D (including supplement) newly initiated or change in dose *Stable treatment initiated before screening is allowed*	2 weeks
Drugs with a sedative effect such as benzodiazepines, sedative H1 antihistamines, imidazopyridines, barbiturates, or sedative anti-depressants (e.g. amitryptiline) *Stable treatment with anti-histamines devoid of sedative effect is allowed.*	1 week
Live vaccine	4 weeks
Non-live vaccine	1 week

15. Pregnant women (with a positive serum pregnancy test result at the screening visit), breastfeeding women, or women planning to become pregnant during the clinical trial
16. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, actinic keratoses or squamous cell carcinoma in situ (Bowen's disease) that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) carcinoma in situ of the cervix, or non-invasive malignant colon polyps that have been removed
17. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g. monoclonal antibody)
18. History of intolerance to low or mid potency TCS or for whom TCS is not advisable (e.g. hypersensitivity to TCS or to any other ingredient contained in the TCSs to be used in the study, significant skin atrophy)
19. Known or suspected immunosuppression

20. History of or current confounding skin condition (e.g. Netherton Syndrome, psoriasis, Cutaneous T-Cell Lymphoma [Mycosis Fungoides or Sezary Syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis)
21. Any medical or surgical condition that may interfere with the assessments or the interpretation of study results
22. Any uncontrolled or serious disease that may put the subject at significant risk according to the investigator's judgment if he/she participates in the clinical trial
23. Planned or expect to have a major surgical procedure during the clinical trial
24. Subjects unwilling to refrain from using prohibited medications during the clinical trial (see Section 5.3.5)
25. Currently participating in any other clinical trial of a drug or device, participated in a clinical trial within the past 3 months prior to screening visit, or is in an exclusion period (if verifiable) from a previous clinical trial
26. Vulnerable subject as defined in ICH/GCP

Rationale:

#1-24: To ensure subject's safety and to avoid confounding factors for efficacy and safety assessments

#25-26: To comply with ICH/GCP

5.3 Previous and concomitant therapies

5.3.1 Definition

Previous 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, previous therapies for AD should be documented.

Concomitant therapies are defined as follows:

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

5.3.2 Categories

The following two categories are to be considered for previous 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 include but are not limited to laser/radiation procedures, dermal fillers, phototherapy, etc. Procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

5.3.3 Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the electronic case report form (eCRF).

Concomitant therapies are to be recorded, reviewed, and updated at each visit. Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form should be completed to account for the change in therapy, except in some cases such as dose modification for a chronic condition (see section 5.3.4.1), in which case the medication will be linked to an item in the medical history.

5.3.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (see Section 5.2.2) or in prohibited concomitant therapies (see Section 5.3.5), all therapies are authorized.

Although there is no known evidence suggesting that IL-31 affects the level or activity of cytochrome P450 (CYP450) metabolic enzymes, the impact of nemolizumab on such enzymes has not been studied. Therefore, investigators should be attentive to clinical or laboratory signs that might indicate a potential drug-drug interaction between nemolizumab and other therapies that are CYP450 substrates and have a narrow therapeutic index.

5.3.4.1 Background therapies

Details of background therapies received by the subjects during this clinical trial should be documented in the eCRF.

Starting from the screening visit, subjects will be instructed to apply a moisturizer at least once daily throughout the study. Subjects should use their usual moisturizer; if they do not have any moisturizer or do not wish to use their usual one, the investigator can suggest a moisturizer to be used in the study. To allow accurate assessment of skin dryness, moisturizer should not be

applied for at least 8 hours before each clinical visit. Whenever possible, subjects should use the same moisturizer throughout the study.

Starting from the screening visit, subjects are required to stop their previous TCS and will receive a standardized background TCS therapy during the study: A medium potency TCS equivalent to class III-V according to the U.S classification (mometasone furoate 0.1% cream or hydrocortisone butyrate 0.1% cream) will be used for the body, and a low potency TCS equivalent to class VI-VII according to the U.S classification (hydrocortisone acetate cream or desonide 0.05% cream) will be used in areas where medium potency TCS is considered unsafe (e.g. face, neck, genital areas).

The application frequency of TCS will depend on the clinical state of AD: Subjects will apply a thin layer of TCS on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare (e.g. twice weekly, every other day), but does not exceed the maximal frequency recommended in the prescription information (e.g. once daily for mometasone furoate 0.1% cream). In case of new AD lesions appearing during the study, TCS should be applied in those affected areas with the same application frequency used initially at the beginning of the study.

The medium potency TCS will not exceed an amount of approximately 100 g/month (Eichenfield 2015) and the low potency an amount of approximately 30 g/month. The TCS regimen will be adjusted during the study, according to the disease activity and tolerability by the subject: where lesions are cleared, TCS should be applied at a reduced frequency (e.g. from every other day to twice weekly) and then discontinued; they can also be applied at a reduced frequency or discontinued if judged to be medically necessary by the investigator (e.g. due to intolerance).

5.3.4.2 Rescue therapies

If deemed to be medically necessary by the investigator (i.e. significant worsening of signs and/or symptoms of AD), rescue therapies can be prescribed to the subjects at any time during the study. For the purpose of efficacy analysis, subjects receiving any rescue therapies will be considered as treatment failures. Whenever possible, efficacy and safety assessments (e.g. disease severity scores, laboratory tests) should be conducted immediately before administering any rescue therapies.

Rescue therapies could include higher potency and/or quantity of TCS, TCI, systemic treatment, phototherapy or combinational usage of different treatment modalities. 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 (e.g. TCI are applied in large body areas other than the face, neck, or genital areas). If subjects receive a systemic rescue therapy (such as cyclosporine, systemic corticosteroids, methotrexate, mycophenolate mofetil, azathioprine or biologics) or TCI in large body areas, the study drug administration must be permanently discontinued (see Section 6.1.8.2).

Whenever possible, subjects should complete all study visits and assessments (including daily diaries), regardless of whether or not they have received rescue therapies and whether or not they have discontinued the study drug administration.

5.3.5 Prohibited concomitant therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety assessment of the study drug:

- Listed in Section 5.2.2 (item 14), except when authorized as rescue therapy
- TCS other than those to be used as background therapy, except when authorized as rescue therapy

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the Sponsor/CRO and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical trial, the investigator should also notify the Sponsor/CRO and discuss whether or not it is acceptable for the subject to continue the study treatment.

5.4 Procedures/Reasons for subject discontinuation from the study

Subjects may discontinue from the study or discontinue the study treatment only and continue to participate in the study. The reasons and procedures for subject discontinuation from the study are described here, and the reasons and procedures for study treatment discontinuation are described in Section 6.1.8.2.

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

When a subject discontinues from the clinical trial, he/she will be fully assessed whenever possible. Subjects discontinued before the week 24 visit (visit for the primary endpoint) should attend an early termination visit and a final visit 12 weeks after the last study drug injection for safety follow-up. Subjects discontinued after the week 24 visit should attend a final visit 12 week after the last study drug injection.

Potential reasons for study discontinuation include pregnancy, consent withdrawal by the subject, lost to follow-up, lack of efficacy, AEs, protocol deviations and others. If the reason is “withdrawal by subject” or “other”, the subject will be questioned to rule out the possibility of an AE. If an AE leads to study discontinuation, it should be chosen as the reason instead of

"withdrawal by subject" or "other". If a subject discontinues study treatment and study participation at the same time, the reasons for those two discontinuations should be the same.

A subject who has been randomized and assigned a randomization number cannot be replaced by another subject.

6 CLINICAL SUPPLIES

6.1 Study drug identification and use

6.1.1 Study drug description

Table 4 Description and usage of the study drug

	Investigational product	Comparator
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder	Lyophilized powder
Concentration	100mg/ml when reconstituted	NA
Formula number	NA	NA
Packaging	Vial	Vial
Storage conditions	Stored between 2 to 8°C (36-46°F) and protected from light	Stored between 2 to 8°C (36-46°F) and protected from light
Dosage *	10mg (loading dose 20mg), 30mg (loading dose 60mg) or 90mg depending on the randomization scheme	NA
Route	Subcutaneous injection	Subcutaneous injection
Dose regimen	Every 4 weeks (Q4W)	Q4W
Treatment duration	24 weeks (last injection at week 20)	24 weeks (last injection at week 20)

* Depending on randomization scheme, the reconstituted nemolizumab solution will be diluted with reconstituted placebo solution to yield appropriate dosing solutions for injection.

6.1.2 Subject identification number

Upon signature of the ICF, each subject will be assigned a subject identification number (SIN). For the duration of the entire clinical trial, the subject will be identified using the SIN in all documentations and discussion.

6.1.3 Method of treatment assignment

Treatment will be assigned centrally via Interactive Response Technology (IRT). All eligible subjects will be randomly assigned to one of the 4 treatment groups (10 mg, 30 mg, 90 mg or placebo) in a 1:1:1:1 ratio at baseline. Details of the IRT procedure will be described in the IRT manual.

6.1.4 Randomization number

A randomization number will be allocated to each eligible subject at baseline by the IRT system. Randomization will be stratified by baseline IGA score (3 or 4).

6.1.5 Instructions for use and administration

Nemolizumab and placebo will be supplied in single-use vials in the form of lyophilized powder. When the drug product is reconstituted by adding 1.3mL distilled water for injection, the resulting solution contains 100mg/mL nemolizumab. Although the reconstituted solution has been shown to be stable for up to 24 hours at room temperature (25°C or 77°F), it is recommended to use it immediately after preparation, as it does not contain any preservative.

The pharmacist (or other qualified personnel) will prepare dosing solution, by mixing appropriate amounts of reconstituted nemolizumab and placebo, according to the "instruction for use" in the pharmacy manual and the specific instruction provided by the IRT system, which takes into consideration the randomization scheme and the visit. The pharmacist (or other qualified personnel) is partially unblinded, which means that he/she will be aware of the coded treatment group only but not the exact dose to be administered to the subjects. In order to ensure the blinding, subjects to receive placebo will be randomly assigned to use one of the 3 dilution schemes, each mimicking the dilution scheme for one active treatment group.

Group	Dose on day 1	Dose at weeks 4, 8, 12, 16 & 20
1	20 mg	10 mg
2	60 mg	30 mg
3	90 mg	90 mg
4	Placebo	placebo

Once the dosing solution is prepared, 1.0 mL of it will be drawn into a syringe, which will be carried to the investigator or other qualified person, who will administer the study drug subcutaneously in the abdomen of the subjects.

After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. Subjects should remain on site for at least 30 minutes after the first two injections during the study.

6.1.6 Study drug packaging and labeling

The vials will be packaged and labeled in local language according to Good Manufacturing Practice and national regulations/guidelines, specifying that the drug is for use in a clinical trial.

6.1.7 Study drug management

6.1.7.1 Accountability

Study drug sent to the partially unblinded pharmacist (or other qualified personnel) at the investigational site will be accounted for and no unauthorized use is permitted. The designed personnel will acknowledge receipt of the study drug using IRT to confirm the shipment condition and content. If a damaged shipment is received, he/she will notify the Sponsor/ CRO, quarantine the shipment in a specific storage area, and document the event as specified in the pharmacy manual.

The designed personnel will also maintain accurate records of the study drug throughout the clinical trial, including the inventory delivered to the site, the use by each subject, the reconciliation of all delivered and received vials of study drug, and the return of used and unused study drug as specified in the pharmacy manual.

6.1.7.2 Storage of study drug

All vials of study drug must be stored together in a safe and secure area with restricted access. Upon receipt, the study drug must be removed from the shipping cooler, stored in a refrigerator between 2 and 8°C (36-46°F) and protected from light. The refrigerator must be monitored daily, and if temperature excursion occurs, the designed personnel should promptly inform the partially unblinded Clinical Research Associate (CRA) as specified in the pharmacy manual.

6.1.7.3 Dispensing and return

All drug preparation must be appropriately performed and documented by the designated personnel (partially unblinded pharmacist or other qualified personnel). Any error in the preparation of dosing solution must be reported to the partially unblinded CRA promptly and properly documented. At the end of the study, all unused study drug will be returned to the CRO/drug depot for destruction.

6.1.7.4 Treatment compliance management and record

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

6.1.8 Dose modification and study drug discontinuation

6.1.8.1 Dose modification

Dose modification of the study drug will not be permitted throughout the clinical trial. Any inadvertent dose modifications should be discussed with Sponsor/CRO.

6.1.8.2 Study drug discontinuation

The study drug must be permanently discontinued when any of the following conditions is reported for a subject during the clinical trial:

- Serious immediate-type allergic manifestations including anaphylactic reaction
- Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma or basal cell carcinoma)
- Pregnancy
- Any opportunistic infection (such as active TB and other infections whose nature or course suggest an immune-compromised status)
- Systemic rescue therapy (such as cyclosporine, systemic corticosteroids, methotrexate, mycophenolate mofetil, azathioprine or biologics) or TCI used in body areas other than the face, neck, or genital areas
- Asthma /worsening of asthma reported as a serious adverse event

In the event that the study drug is discontinued, the subjects should remain in the study and will be asked to return for all remaining visits and all assessments (including daily assessments of pruritus and sleep disturbance) according to, except those who withdraw their consent for study participation.

In the event of a missed dose (i.e. temporary discontinuation of the study drug), it will be documented in the eCRF that the drug has not been administered at the study visit, together with the reason (e.g. for safety reason). Subjects will be asked to return to the investigational sites for all remaining visits and complete all study assessments and procedures as described in Table 2.

6.2 Blinding

6.2.1 Verification of blinding

This is a double-blind clinical trial. With the exception of the partially unblinded pharmacist (or other qualified personnel) who will handle study drug preparation, the partially unblinded CRA who will monitor the drug records only, the unblinded statistician from the CRO

responsible for providing information to the IDMC and for the primary analysis, and the provisions in section 6.2.2, this study will remain blinded to all study individuals until the pre-specified unblinding at the end of the study.

All study personnel must follow the procedures described below to avoid compromising the blinding:

1. The randomization list will be managed through the IRT system with restricted access to designated personnel only;
2. Study drug management and preparation (including reconstitution and dilution) will be performed by the partially unblinded pharmacist (or other qualified personnel) only, while the evaluator will have no contact with the study drug. The person who will administer the study drug will receive only a syringe filled with 1.0ml of dosing solution ready for injection;
3. The partially unblinded pharmacist (or other qualified personnel) will be instructed to not discuss the study drug with the investigator/evaluator, the subjects or with the blinded CRA involved in the monitoring of study data;
4. A partially unblinded CRA will be responsible for monitoring the record of study drug only, and will have no access to other data collected during the study or to the eCRF. The partially unblinded CRA will also be instructed to not discuss trial-related matters with the investigator/evaluators, the subjects or with the blinded CRA involved in the monitoring of study data

6.2.2 Unblinding during the clinical trial

Emergency unblinding during the clinical trial may be required for therapeutic or for regulatory reasons (e.g. for expedited safety reporting). If unblinding is necessary, the investigator should unblind the study treatment for the specific subject only. If possible, the investigator should discuss with the CRO before breaking the blind. If not possible to discuss before, investigator must document the date, time and reason for the unblinding and notify the Clinical Safety Officer (CSO) from the CRO (contact details in Section 7.2.5.2.2) immediately afterwards.

The IDMC will review data blinded by treatment group during the study, but may request unblinding if necessary. Similarly, the IDMC will unblind the study treatment for specific subject(s) only.

6.3 Other supplies

Syringes, needles, water for injection, peak flow meters, D-squames, and urine pregnancy tests (UPTs, with a sensitivity < 25IU/L) will be provided to the investigational sites to be used in this clinical trial.

TCS of medium potency (mometasone furoate 0.1% cream or hydrocortisone butyrate 0.1% cream) and low potency (hydrocortisone acetate cream or desonide 0.05% cream) will be provided to the investigational site for dispensation to subjects as background TCS therapy in this clinical trial. Subjects (including screen failure subjects) will be instructed to bring the used and unused TCS tubes back to the investigational sites at each visit. TCS returned by the randomized subjects will be weighted first, and destroyed by the sites after monitoring. All other returned TCS will be destroyed by the sites after monitoring.

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

7.1.1 Efficacy measurements

Efficacy measurements should be conducted by the investigators (or trained designees) and subjects (for patient-reported efficacy measurements) according to Table 2. Whenever possible, the same evaluator should make the assessment throughout the study.

7.1.1.1 Eczema Area and Severity Index (EASI)

EASI is a composite score ranging from 0 to 72 (Hanifin 2001, see APPENDIX 2). 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 eCRF.

7.1.1.2 Investigator's Global Assessment (IGA)

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 (Paller 2016; see APPENDIX 3).

7.1.1.3 Body Surface Area (BSA)

The BSA involvement of AD will be assessed by the investigator or trained designee for each part of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]), and will be reported as a percentage of all major body sections combined.

7.1.1.4 SCORing Atopic Dermatitis (SCORAD)

SCORAD ranges from 0 to 103 and has three components: extent (BSA, as described in Section 7.1.1.3), signs and symptoms of AD (European task force on atopic dermatitis 1993, see APPENDIX 4). Investigator or designee will assess the severity of 6 signs of AD (erythema/darkening, edema/papulation, oozing/crusting, excoriation, lichenification/prurigo and dryness), each on a scale ranging from 0 (none) to 3 (severe). Investigator or designee will also ask the subjects to evaluate their symptoms of pruritus and sleep loss (average for the last 3 days/nights), each evaluated on a VAS from 0 to 10. The SCORAD score will be calculated in the eCRF.

7.1.1.5 Pruritus Numeric Rating Scale (NRS)

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

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

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

7.1.1.6 Pruritus Categorical Scale (PCS)

The 4-point pruritus categorical scale will be provided in their local language for the subjects to report the intensity of their pruritus (Kaufman 2006; Paller 2016; see APPENDIX 6). Subjects will receive instructions on how to record their PCS scores on an electronic device, and will complete the assessment once daily in the evening throughout the clinical trial (including the run-in and the follow-up period).

7.1.1.7 Dynamic Pruritus Score (DPS)

The 9-point DPS is a dynamic scale to be used by subjects to evaluate the change of their pruritus compared with an earlier time point (i.e. before injection on Day 1). The scale ranges from 0 (strongly worsened pruritus) to 8 ([almost] no pruritus anymore), including intermediate marks for slightly improved/worsened, moderately improved/worsened, and rather improved/worsened (Ständer 2016; see APPENDIX 7). Subjects will receive instructions on how to record their DPS score on an electronic device displaying the electronic version of the scale in their local language, and will complete the assessment 2, 4, 8, 24, 48 and 72 hours after study drug injection on day 1.

7.1.1.8 5-D itch scale

The 5-D itch scale is a multidimensional measure of itching that has been validated in patients with chronic pruritus (Elman 2010, see APPENDIX 8). The five dimensions included in the scale are degree, duration, direction, disability and distribution. The score for each of the five domains separately will then be summed up to obtain a total 5-D score, which ranges between 5 (no pruritus) to 25 (most severe pruritus). The 5-D itch scale will be administered at baseline and week 2.

7.1.1.9 Sleep disturbance Numeric Rating Scale (NRS)

The sleep disturbance NRS is a scale to be used by the subjects to report the degree of their sleep loss related to AD (see APPENDIX 9). Subjects will receive instructions on how to record their sleep disturbance NRS scores on an electronic device, and will complete the assessment once daily in the morning throughout the clinical trial (including the run-in and the follow-up period).

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

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

7.1.2 Efficacy endpoints

7.1.2.1 Primary endpoint

Percent change from baseline in EASI to week 24

7.1.2.2 Secondary efficacy endpoints

- Proportion of subjects achieving IGA success (defined as IGA 0 [clear] or 1 [almost clear]) at each visit up to week 24
- Percent change from baseline in EASI at each visit up to week 24
- Absolute and percent change from baseline in weekly average of the peak and average pruritus NRS at each visit up to week 24
- Proportion of subjects with an improvement of weekly average pruritus peak NRS ≥4 from baseline to week 24
- Absolute and percent change in weekly average sleep disturbance NRS from baseline to week 24
- Proportion of subjects achieving PCS success (defined as a weekly prorated rounded average PCS ≤1 [none - mild]) at week 24

- Proportion of subjects with EASI-50, EASI-75 or EASI-90 (defined as achieving 50%, 75% or 90% reduction from baseline in EASI score) at week 24
- Absolute and percent change in SCORAD from baseline at week 24

7.1.2.3 Other efficacy endpoints

- Disease severity scores (EASI, IGA, SCORAD, BSA, pruritus NRS, sleep disturbance NRS and PCS) at each visit including at follow up visit (week 28 and 32)
- Change and percentage change in disease severity scores (EASI, IGA, SCORAD, pruritus NRS, sleep disturbance NRS and PCS) from baseline to each visit
- Change and percentage change in disease severity scores (EASI, IGA, SCORAD, pruritus NRS, sleep disturbance NRS and PCS) from week 24/ET to follow up visits (week 28 and 32)
- Change from baseline in each component of EASI score at each visit
- Proportion of subjects with an improvement of weekly average pruritus NRS ≥ 4 from baseline to each visit
- DPS at hour 2, 4, 8, 24, 48, and 72
- Monthly and total amount of TCS used during the treatment period (baseline to week 24)
- Time to rescue therapy
- Change from baseline to week 2 in 5-D itch scale total score
- If applicable, evaluation of the prurigo nodularis lesions over time

7.2 Safety assessment

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

Safety assessments include electrocardiogram (ECG), physical examination, vital signs, respiratory assessments (PEF measurement for subjects with a medical history of asthma only), laboratory safety tests, and AE recording (including serious AEs, AEs of Special Interest [AESI] and selected AEs).

In addition, safety data will be monitored regularly by IDMC and details are described in the IDMC charter.

7.2.1 Electrocardiograms (ECG)

A 12-lead ECG will be performed according to Table 2. ECGs for each subject should be obtained using the same electrocardiograph machine whenever possible. To minimize variability,

subjects must remain in a resting position for at least 10 minutes prior to each ECG recording. Environmental distraction should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. For safety monitoring, the investigator or qualified designee must review, sign and date all ECG tracings. Paper ECG recordings will be kept as part of the subject file at the site. All abnormal ECG findings considered to be clinically significant by the investigator at the screening visit will be recorded in the Medical History form. Any clinically significant changes from the screening visit will be reported as AEs in the eCRF.

7.2.2 Physical examination and vital signs

7.2.2.1 Physical examination

Complete physical examination should be performed at the screening visit and at each subsequent visit according to Table 2. 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.

At baseline, investigator or qualified personnel should assess on each subject whether lesions of prurigo nodularis are present or absent. If the lesions of prurigo nodularis are present, investigator needs to evaluate the lesions at each subsequent visit using a 5-point scale (2: very much improved; 1: improved; 0: no change; -1: worsened; -2: very much worsened).

7.2.2.2 Vital signs

Vital signs will be evaluated at the screening visit and at each subsequent visit according to Table 2. Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been siting 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.

7.2.2.3 Height and Weight

Height will be measured at the screening visit only, and weight will be measured at screening, baseline, weeks 4, 8, 12, 16, 20 & 24). Subject must be at least 45kg at both screening and baseline visits in order to be enrolled into this clinical trial.

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

7.2.3 Respiratory Assessments

At each visit, investigator or designee will perform a respiratory physical examination and ask all subjects whether they have experienced any signs/symptoms of asthma, such as shortness of breath, attack or recurrence of wheezing (described to subjects as a continuous, coarse, whistling sound while breathing), troublesome cough, and wheeze or cough after exercise.

In addition, for subjects reporting a medical history of asthma, PEF will be performed at each visit during the clinical trial using a peak flow meter under the supervision of qualified study personnel. PEF measurements should consist of 3 good efforts, with the best result documented. It is preferable that PEF measurement be performed before noon or at the same time during each study visit whenever possible.

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

- PEF <80% of the predicted value, and/or
- Unexpected worsening of asthma (in particular if the subject has symptoms >2 days per week, nighttime awakening >1-3 times per week, or interference with normal activities)

Subjects without a medical history of asthma must be referred to an appropriate specialist physician if signs/symptoms of asthma have been newly reported during the study.

Newly diagnosed asthma or worsening of asthma during the study will be reported as AESI (see section 7.2.5.1.3).

7.2.4 Laboratory safety tests

The following laboratory safety tests will be performed:

- Hematology: WBC count with differential count (including eosinophils), red blood cell (RBC) count, hemoglobin (Hb), hematocrit (hct), mean cell volume (MCV), and platelet count (Plt)
- Blood chemistry: sodium, potassium, calcium, chloride, glucose, urea, creatinine, AST/ALT, alkaline phosphatase (ALP), total and direct bilirubin, CPK, high sensitivity C-reactive protein (hsCRP), fibrinogen, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total protein, albumin, uric acid, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides

  CPK isoenzyme test will be performed only if CPK is elevated to >2.5X ULN.
- Urinalysis: blood, proteins, leukocytes, glucose, ketones, nitrites, bilirubin, urobilinogen, pH, and specific gravity
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test at the screening visit and UPTs at subsequent visits according to Table 2. If result of 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.
- Virology, including HBsAg, HBsAb, HBcAb, hepatitis C, HIV-1 and -2 antibody
- TB test (e.g. QuantiFERON TB test)

The instruction manuals and supply kits will be provided for all assessments. Subjects will be required to fast for at least 8 hours before the visits when blood chemistry test is planned except screening visit. UPT will be performed at the investigational sites, and all other samples will be sent to central laboratory for analysis. Total blood volumes to be drawn at each visit are provided in Table 5. Additional samples may be required if medically indicated (e.g. at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

The screening visit laboratory values must be available prior to the baseline visit.

Table 5 Volume of blood sample (ml) during the study

Study Period	Screening	Treatment									Follow-up		Unscheduled visit (if applicable)	Early Termination Visit (if applicable)
Visit (V)	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12/ FINAL		
Week (W)	D-28 to -15	Baseline	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32		
LABORATORY/SAFETY ASSESSMENTS														
TB test	6												2	
Virology	12													
Hematology	2	2			2	2	2	2	2	2		2	2	2
Blood chemistry [a]	3	3			3	3	3	3	3	3		3	3	3
Fibrinogen	4.5	4.5			4.5	4.5	4.5	4.5	4.5	4.5		4.5	4.5	4.5
TARC		2	2	2	2	2	2	2	2	2	2	2	2	
IgE		2			2	2		2		2		2		
Blood sample for other biomarkers		10			10	10		10		10		10		
PK samples		2	2	2	2	2	2	2	2	2	2	2	2	2
ADA samples		2			2	2		2		2		2	2	2
Total blood sample volume for each visit (ml)	27.5	27.5	4	4	27.5	27.5	13.5	27.5	13.5	27.5	4	27.5	17.5	13.5
Total blood sample volume during the study (excluding unscheduled and early termination visits) = 231.5 ml														

[a] Blood chemistry sample at screening visit (V1) will also be used for serum pregnancy test. Subjects are required to fast for at least 8 hours before the visits when blood chemistry test is planned except screening visit.

Investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. For each out-of-range laboratory result, the investigator or designee will evaluate whether he/she considers it to be clinically significant, defined as meeting at least one of the following conditions:

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

If the investigator observes a clinically significant laboratory result, the test will be repeated as soon as possible and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found. At the screening visit, one re-test is allowed for TB test and CPK (see sections 5.2.1 and 5.2.2). Subject should be advised to avoid strenuous physical exercise 24 hours prior to the re-test of CPK.

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 (i.e. changed significantly from the screening visit). Whenever possible, the investigator should provide a diagnosis of AE when reporting the abnormal laboratory value.

The following out-of-range laboratory values should be reported as an AESI (see Section 7.2.5.1.3):

- Elevated ALT or AST (>3 ULN) in combination with elevated bilirubin (>2 ULN), whether or not considered as related to the study drug by the investigator;
- Elevated CPK (≥2.5 ULN) if considered as related to the study drug by the investigator.

7.2.5 Adverse Events

7.2.5.1 Definitions

7.2.5.1.1 Adverse events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of the causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the product.

Thus any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms or abnormal laboratory values.
- Pregnancy is not to be considered as an AE; however, it must be monitored as described in Section 7.2.5.2.4.
- Each new episode of a chronic disease (e.g., hay fever, allergy, etc.) from the screening visit should be reported as a new AE.

7.2.5.1.2 Serious Adverse events (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed 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.

NOTE:

The term “life-threatening” refers to an event in which the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.

Inpatient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of hospitalization is defined as a hospital stay that is longer than originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator. Hospitalization should not be considered as a SAE if it is solely for the purpose of diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

When a SAE occurs, the investigator is required to follow the procedures described in Section 7.2.5.2.2.

7.2.5.1.3 Adverse Events of Special Interest (AESIs)

An AESI is a noteworthy event for the study drug that should be monitor closely and reported immediately. It could be either serious or non-serious.

The AESIs for this clinical trial have been defined as follows:

- Elevated ALT or AST (> 3 ULN) in combination with elevated bilirubin > 2 ULN, whether or not considered as related to the study drug by the investigator
- Newly diagnosed asthma or worsening of asthma
- Elevated CPK (≥2.5 ULN) if considered to be related to study drug by the investigator

Study treatment should be permanently discontinued if asthma/worsening of asthma is reported as a serious adverse event, and may be temporarily discontinued for non-serious cases based on the judgment of the investigator, until return to the baseline condition.

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

- PEF <80% of the predicted value, and/or
- Unexpected worsening of asthma (in particular if the subject has symptoms >2 days per week, nighttime awakening >1-3 times per week, or interference with normal activities)

Subjects without a medical history of asthma must be referred to an appropriate specialist physician if signs/symptoms of asthma have been newly reported during the study.

When an AESI occurs, the investigator is required to follow the procedures described in Section 7.2.5.2.3 even if the event is considered non-serious.

7.2.5.1.4 Selected adverse events

Based on the potential risks of nemolizumab and the risks associated with biologics in general (i.e. class effects), the following AEs will be considered as selected AEs:

- Exacerbation of AD: defined as a clinically significant worsening of AD signs and/or symptoms that requires therapeutic intervention (rescue therapy) and that is not considered by the investigator to be a part of the natural course of AD (e.g. change in severity or the nature of the disease). When recording worsening of AD on the AE form in the eCRF, the AE reported term should include an appropriate descriptor (e.g. “worsening of AD” or “AD flare”).
- IRR: defined as any local or systemic reactions (including hypersensitivity) related to the injection, regardless of the time of the AE onset.
- Peripheral edema: defined as swelling of any skin or subcutaneous body tissues (for example legs, hands, etc.) but excluding edema linked to urticaria.
- Skin or systemic infection
- Headache

If applicable, additional information regarding the characteristics and potential cause of these AEs may be required to allow a better evaluation and understanding of the events. In case of IRRs at the injection site or systemic IRRs with skin and/or mucosal tissue involvement, photographs should be taken to document the events. When peripheral edema is reported, weight needs to be assessed and additional tests at the local laboratory need to be conducted (including 24h proteinuria in case of positive protein in urinalysis [defined as ++], and B-type natriuretic peptide analysis).

7.2.5.1.5 Unexpected adverse drug reaction

According to the ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information (e.g. IB for an unapproved investigational product or the package insert/summary of product characteristics for an approved product).

There is currently no expected adverse drug reaction with nemolizumab.

7.2.5.1.6 Adverse event reporting period

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

7.2.5.1.7 Severity

Severity is a clinical determination of the intensity of an AE and not of a disease. The severity of AEs will be evaluated according to the following definitions:

Mild	Awareness of signs or symptom, but easily tolerated.
Moderate	Discomfort, enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

7.2.5.1.8 Relationship to the study drugs and/or study procedure

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

Reasonable possibility:

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

- Between the study drug (nemolizumab or its placebo) and the AE, and/or
- Between the clinical trial protocol procedure (e.g. injection, TCS, blood sample collection) and the AE

No Reasonable Possibility:

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

7.2.5.2 Reporting procedures

7.2.5.2.1 Procedures for reporting Adverse Events

At each visit, the investigator or designee will ask the subject an open question to elicit reporting of AEs (e.g. “Have you noticed any change in your health since the last visit?”). Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether or not related to the study drug and/or study procedure, will be recorded immediately in the source document, and described on the AE form of the eCRF along with the date of onset, severity, relationship to the study drugs and/or study procedure, and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances (e.g. for selected AEs).

AEs assessed as related to the study drug and/or procedure will be monitored until they have resolved or reached a stable condition, with or without sequalae. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

Reporting procedures for SAEs (see Section 7.2.5.2.2), AESIs (see Section 7.2.5.2.3), and pregnancies (see Section 7.2.5.2.4) must be followed.

7.2.5.2.2 Procedure for reporting a Serious Adverse Event

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

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

2. Ensure that the event is evaluated as an SAE. **Immediately** complete the AE and SAE form in the eCRF. This will generate an automatic email alert to Galderma Pharmacovigilance and to the Global Medical Services (GMS) within the CRO. The demographics, medical history, drugs/therapies form, and medical and surgical procedures form must also be completed and available for review in the eCRF at that time. *(Of note, in case there is no access to the eCRF, please refer to the instructions in your Investigator Site File for reporting an SAE).*

3. If required, contact the GMS within the CRO to discuss further actions to be taken; see contact details below:

Investigator contact:
Clinical Safety Officer
CRO Safety mailbox: CCI

4. Send any relevant information or anonymized medical records (e.g. laboratory test results) to the GMS within the CRO (see contact details above), within 24 hours of receipt of this relevant information.

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

6. Obtain and maintain in 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.

7. When the outcome of the event is known, complete an updated SAE form, if appropriate.

8. Prompt notification of SAEs by the investigator to GALDERMA is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. GALDERMA has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GALDERMA or its delegate (i.e. the CRO) will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and GALDERMA policy, and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GALDERMA or its delegate (i.e. the CRO) will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

7.2.5.2.3 Procedure for reporting an Adverse Event of Special Interest

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

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Ensure that the event is evaluated as an AESI. **Immediately** complete the AE form in the eCRF. This will generate an automatic email alert to the GMS within the CRO. The demographics, medical history, drugs/therapies form, and medical and surgical procedures form must also be completed and available for review at that time.
3. Send any relevant information or medical records (e.g. laboratory test results) to the GMS within the CRO (see contact details in Section 7.2.5.2.2), **within 24 hours** of receipt of this relevant information.
4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AE form in the eCRF **within 24 hours** of receipt of the updated information.
5. Obtain and maintain in 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 AE form in the eCRF, if appropriate.

7.2.5.2.4 Procedures for reporting pregnancies

Any pregnancy occurring during clinical trials, where the fetus could have been exposed to the study drug, must be monitored until its outcome in order to ensure the complete collection of safety data.

If a subject becomes pregnant, the investigator must:

1. **Withdraw the subject from the clinical trial. The subject must not receive any further injection of the study drug.**
2. Complete as fully as possible the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy, available in the eCRF. Print and send it by e-mail along with the exit form **within 24 hours** of receipt of the information, to the GMS within the CRO (contact see Section **7.2.5.2.2**). *(Of note, in case there is no access to the eCRF, please refer to the instructions in the Investigator Site File for reporting a pregnancy).*
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 there additional follow-up evaluations, print and send the form by e-mail to the GMS within the CRO **within 24 hours** of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two 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 e-mail to the GMS within the CRO **within 24 hours** of receipt of the information.
6. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.5.2.2).

7.3 Pharmacokinetic and anti-drug antibody assessments

Blood sample will be collected according to Table 2 to determine the PK profile of nemolizumab and to assess anti-nemolizumab antibodies (ADA). The serum concentration of nemolizumab will be assessed at baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32 and at any unscheduled visit for safety reasons. ADA will be assessed at baseline, weeks 4, 8, 16, 24, 32 and at any unscheduled visit for safety reasons.

7.3.1 Technical procedures for blood sampling

At each sampling time for PK assessment, 2 mL of blood will be collected. The 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. At the injection visits (baseline, weeks 4, 8, 12, 16 and 20), PK samples will be collected within 30 minutes before drug injection (pre-dose samples); At weeks 1, 2, 24, 28 and 32, blood samples will be collected at the usual time of drug injection with an allowed time window of ±1h. The date and the time of each sample collection will be recorded in the eCRF, together with the time of study drug injection at the same visit (or missed injection if applicable).

For ADA assessment, 2 mL of blood will be collected at the same time of PK sampling according to Table 2. Additional visits (to be considered as unscheduled visits) after the planned last study visit (12 weeks after the last study drug injection) may be conducted to collect additional samples for further analysis of ADA. Processing of blood samples for PK and ADA assessments will be described in the lab manual.

Details related to the processing of serum samples and the assessments of nemolizumab and 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.

7.3.2 Serum and pharmacokinetic analysis

Concentration of nemolizumab in the serum will be determined on an ongoing basis by a Sponsor representative using a validated ELISA method.

PK analyses will be performed by a Sponsor representative. PK parameters will be determined by a model independent approach (non-compartmental method) using individual serum concentration values. Data from subjects with missing concentration values (missing samples) may be used if pharmacokinetic parameters can be estimated using the remaining data points.

When appropriate, the following PK parameters will be determined for each subject:

From baseline to week 4 and from week 20 to week 32:

- C_{max}: The observed peak drug concentration
- T_{max}: The time at which C_{max} occurs
- AUC_{0-t}: area under the concentration time curve calculated by the mixed linear logarithmic trapezoidal method from T0 up to the sampling time corresponding to the last quantifiable concentration (C_{last})
- AUC_{0-28d}: Area under the concentration time curve from pre dose through 28 days post dosing. AUC_{0-28d} will be calculated by mixed linear logarithmic trapezoidal method

From week 20 to week 32:

- $t_{1/2}$: the terminal half-life value ($t_{1/2}$) will be calculated using the equation ln2/k after the last drug injection (week 20).

At weeks 4, 8, 12, 16, 20, 24, 28, 32:

- C_{trough}: The residual drug concentration (pre dose level).

7.3.3 Anti-drug antibody analysis

ADA will be evaluated by a Sponsor representative using a validated ELISA screening assay. If serum circulating ADA is detected, they will be characterized using a validated assay. Incidence of positive ADA results will be summarized by treatment group (absolute occurrence and percent of subjects).

7.4 Pharmacodynamic assessments

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

Blood samples will be collected for assessment of thymus and activation-regulated chemokine (TARC) and IgE by the central laboratory. In addition, 10 mL of blood samples will be collected for plasma biomarker assessment according to Table 2. Aliquots of plasma sample will be shipped to Galderma for assessment using a set of biomarkers relevant for AD, including but not limited to IL6, IL8 and IL18. Depending on results with protein biomarkers, the quantity of samples left over, and the compatibility of the initially collected samples with further investigations, the expression of miRNA and mRNA markers will be analyzed subsequently.

Stratum corneum samples will be collected using tape strips (D-squames). At baseline prior to administration of study drug, 2 lesional and 2 non-lesional areas will be identified and 4 rectangular D-squames (2.3cm x 3.5cm in dimension) will be collected from each area, making 16 D-squames in total (8 from lesional skin and 8 from non-lesional skin). At week 16, 4 rectangular D-squames will be collected from the 2 lesional areas identified at baseline (8 D-squames in total). Aliquots of samples will be shipped to Galderma for analysis of selected protein biomarkers relevant for AD (including TARC, IL6, IL8, IL18 etc.). In addition, the levels of EOS-ceramides will be quantified. Depending on results with protein and ceramide biomarkers, the quantity of samples left over, and the compatibility of the initially collected samples with further investigations, the expression of lipids and of miRNA and mRNA markers may be subsequently analyzed.

With additional consent of the subject, blood and skin samples remaining after performance of the planned investigations will be integrated into the long term research program being performed

in the research department of Galderma R&D (Program (2) – "Physiopathological study on skin disease to identify new dermatological medications; Initial declaration CP ECOH : DC-2008-315, 31/01/2009).

7.5 Quality of life assessments

7.5.1 Dermatology Life Quality Index (DLQI)

DLQI is a validate 10-item questionnaire, covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment (Finlay 1994, see APPENDIX 10). Subject will rate each question ranging from 0 (not at all) to 3 (very much), and the total score ranges from 0 to 30, with a higher score indicating a poorer QoL. DLQI will be administered according to the schedule of assessments only to the subset of subjects who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries).

7.5.2 Hospital Anxiety and Depression Scale (HADS)

HADS is a validated questionnaire containing 14 items, 7 each for anxiety and depression (Herrmann 1997, see APPENDIX 11). Subject will rate each question ranging from 0 to 3, and the total score ranges from 0 to 21 for each sub-scale. HADS will be administered according to the schedule of assessments only to the subset of subjects who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries).

7.5.3 Sick leave/missed school day

Subjects who are employed or enrolled in school/university at baseline will be asked to report the number of missed work/school days due to AD since the last visit (or since the last 4 weeks at Week 4) not including missed work/school days due to participation in this clinical trial.

7.5.4 EuroQoL 5-Dimension (EQ5D)

EQ5D is a validated questionnaire for the assessment of the general health state (see APPENDIX 12). It contains two parts: a descriptive system and a VAS. The descriptive system is made up of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The VAS consists of a vertical line where the subject can assess his or her own health status. EQ5D will be administered according to the schedule of assessments only to the subset of subjects who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries).

7.6 Appropriateness of measurements

Efficacy on the severity of AD will be evaluated using EASI, SCORAD and IGA. Both EASI and SCORAD are validated measures commonly used in clinical trials and clinical practice to assess the severity and the extent of AD. While a representative site is selected for the evaluation of SCORAD, AD signs at 4 different body parts are included in the EASI evaluation. Another marked difference between the two measurements is that SCORAD includes evaluation on two symptoms of AD, pruritus and sleep loss, while EASI focuses only on the signs of AD. IGA is an objective endpoint used in clinical trials to determine the global severity of AD and the clinical response to a treatment, with treatment success defined as achieving an IGA of 0 (clear) or 1 (almost clear).

Efficacy on the pruritus of AD will be evaluated mainly using pruritus NRS and PCS. Pruritus NRS has been validated in other AD clinical trials and the minimum clinically important difference was shown to be 3 to 4. PCS, including a detailed definition for each category, has been used in several clinical trials of AD.

QoL will be evaluated using validated DLQI, HADS and EQ5D questionnaires. DLQI will be used to measure the impact of a dermatological disease (i.e. AD in this clinical trial) and its treatment on the subject's QoL. HADS will be used to evaluate the level of anxiety and depression, comorbidities among AD patients. EQ5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

8 CLINICAL TRIAL VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of clinical trial visits

Schedule of assessments is summarized in Table 2. A written, signed ICF must be obtained prior to performing any clinical trial-related evaluations and/or procedures. The subject must be provided with a fully completed, dated and signed copy.

At each visit, assessments/procedures should be performed in the following order:

1. Patient-reported outcomes
2. Investigator assessments (including efficacy and safety)
3. Blood sample collection for laboratory assessments
4. Administration of study drugs

8.1.1 Run-in period

8.1.1.1 Visit 1/Screening/Day -28 to Day -15

A signed ICF must be obtained prior to performing any clinical trial-related evaluations and/or procedures.

During the screening visit, the following procedures/assessments will be conducted:

1. Review and explain the nature of the study to the subject, particularly the prohibited activities and constraints.
2. Obtain the signed and dated ICF (and country-specific consent form if applicable) and provide a fully completed, dated and signed copy to the subject.
3. Collect information regarding demographics, relevant medical history, previous therapies and procedures, and concomitant therapies and procedures.
4. Ask the subject how many days in the last 7 days he/she had a severe pruritus according to the PCS.
5. Complete the evaluation of EASI, IGA, and BSA.
6. Perform a physical examination (including height and weight), vital signs measurements and ECG.
7. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
8. Confirm that the subject meets inclusion/exclusion criteria for screening visit.
9. Collect urine for urinalysis.
10. Collect blood sample for hematology, blood biochemistry, TB test and virology.
11. Collect and record any AEs starting from the time of Informed Consent signature.
12. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
13. Instruct the subject on how to use the electronic device for the daily evaluation of pruritus NRS, PCS and sleep disturbance NRS.
14. Schedule the Visit 2/Day 1 visit (at least 14 days after the screening visit).

8.1.2 Treatment period

8.1.2.1 Visit 2/Baseline/Day 1

A minimum of 4 daily scores of pruritus NRS out of the 7 days prior to the visit is required to calculate the baseline average score. During the baseline visit, the following procedures/assessments will be conducted:

1. Ask the subject to complete the DLQI, HADS and EQ5D questionnaire, as well as the 5-D itch scale.
2. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
3. Complete UPT if the subject is a female of childbearing potential.
4. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS.
5. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
6. Perform a physical examination (including weight and the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG.
7. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
8. Confirm subject meets inclusion/exclusion criteria for baseline visit, call the IRT to randomize the subject, and inform the partially unblinded pharmacist (or other qualified personnel) about the new randomization.
9. Collect urine sample for urinalysis.
10. Collect blood sample for hematology, blood chemistry, PK, ADA, and biomarker analysis (including TARC and IgE).
11. Collect stratum corneum sample for biomarker analysis.
12. **Partially unblinded pharmacist** (or other qualified personnel) will:
    - 12.1. Prepare the syringe containing 1.0mL of dosing solution of appropriate concentration of nemolizumab or placebo according to the pharmacy manual and the specific instruction provided by the IRT system;
    - 12.2. Provide the prefilled syringe to the blinded investigator or qualified personnel for injection.
13. Blinded investigator or qualified personnel will administer the study drug subcutaneously to the subject, and observe for at least 30 minutes before discharging the subject.
14. Instruct the subject on how to use the electronic device to evaluate DPS 2, 4, 8, 24, 48, and 72 hours after study drug administration, and remind subject about the daily evaluation of pruritus NRS, PCS and sleep disturbance NRS.

15. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
16. Schedule the Visit 3/Week 1 visit.

8.1.2.2 Visit 3/Week 1/Day 8 ± 1

During the week 1 visit, the following procedures/assessments will be conducted:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS, and remind subject to complete them daily.
3. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
4. Perform a physical examination (including the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG.
5. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
6. Collect blood sample for PK and TARC analysis.
7. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
8. Schedule the Visit 4/Week 2 visit.

8.1.2.3 Visit 4/Week 2/Day 15±1

During the week 2 visit, the following procedures/assessments will be conducted:

1. Ask the subject to complete the DLQI questionnaire and the 5-D itch scale.
2. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
3. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS, and remind subject to complete them daily.
4. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
5. Perform a physical examination (including the evaluation of prurigo nodularis lesions if applicable) and vital signs measurements.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.

7. Collect blood sample for PK and TARC analysis.
8. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
9. Schedule the Visit 5/Week 4 visit.

8.1.2.4 Visit 5 – 9 /Week 4-20

During the visits at week 4 – 20, the following procedures/assessments will be conducted at each visit:

1. Ask the subject to complete the DLQI and HADS questionnaires (both questionnaires **at week 12 visit only)**. Ask the subject about the missed work/school days since the last 4 weeks.
2. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
3. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS, and remind subject to complete them daily.
4. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
5. Perform a physical examination (including weight and the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG (**ECG at week 12 only**).
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Complete UPT if the subject is a female of childbearing potential.
8. Collect urine for urinalysis.
9. Collect blood sample for hematology, blood biochemistry, PK, and TARC analysis. Collect blood sample for biomarker analysis (including IgE) and ADA **(at weeks 4, 8 & 16 only)**.
10. Collect stratum corneum samples for biomarker analysis **(at week 16 visit only)**.
11. **Partially unblinded pharmacist** will:
    - 11.1. Prepare the syringe containing 1.0mL of dosing solution of appropriate concentration of nemolizumab or placebo according to the pharmacy manual and the specific instruction provided by the IRT system;
    - 11.2. Provide the prefilled syringe to the blinded investigator or qualified personnel for injection.
12. Blinded investigator or qualified personnel will administer the study drug subcutaneously to the subject, and observe carefully before discharging the subject **(for at least 30 minutes at week 4 only)**.

13. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
14. Schedule the following visit.

8.1.2.5 Visit 10/End of Treatment/Week 24

During the end of treatment visit at week 24, the following procedures/assessments will be conducted:

1. Ask the subject to complete the DLQI, HADS and EQ5D questionnaires. Ask the subject about the missed work/school days since the last visit.
2. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
3. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS, and remind subject to complete them daily.
4. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
5. Perform a physical examination (including weight and the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Complete UPT if the subject is a female of childbearing potential.
8. Collect urine for urinalysis.
9. Collect blood sample for hematology, blood biochemistry, PK, ADA and biomarker analysis (including TARC and IgE).
10. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
11. Schedule the Visit 11/Follow-up/Week 28.

8.1.3 Follow-up period

8.1.3.1 Visit 11/Follow-up/Week 28

During the follow-up visit at week 28, the following procedures/assessments will be conducted:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.

2. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS, and remind subject to complete them daily.
3. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
4. Perform a physical examination (including the evaluation of prurigo nodularis lesions if applicable) and vital signs measurements.
5. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
6. Collect blood sample for PK and TARC analysis.
7. Complete UPT if the subject is a female of childbearing potential.
8. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring TCS back to investigational site at each visit.
9. Schedule the Visit 12/Final/Week 32 visit.

8.1.3.2 Visit 12/Final/Week 32

During the final study visit at week 32 (or 12 weeks after the last study drug administration for subjects discontinued from the study), the following procedures/assessments will be conducted:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS.
3. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
4. Perform a physical examination (including the evaluation of prurigo nodularis lesions if applicable), vital signs measurements.
5. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
6. Complete UPT if the subject is a female of childbearing potential.
7. Collect urine for urinalysis.
8. Collect blood sample for hematology, blood biochemistry, PK, ADA and biomarker analysis (including TARC and IgE).
9. Collect the returned TCS.

8.1.4 Other visits

8.1.4.1 Early Termination visit

Subjects who discontinue the study drug should remain in the study and will be asked to return for all remaining visits and assessments (including daily assessment of pruritus and sleep disturbance). Subjects who discontinue from the study will be fully assessed whenever possible: Subjects discontinued before the week 24 visit should attend an early termination visit (with procedures/assessments to be conducted outlined below) and a final visit (Section 8.1.3.2) 12 weeks after the last study drug administration; subject discontinued after the week 24 visit should attend a final visit (Section 8.1.3.2) 12 weeks after the last study drug administration.

During the early termination visit, the following procedures/assessments will be conducted:

1. Ask the subject to complete the DLQI, HADS and EQ5D questionnaires. Ask the subject about the missed work/school days since the last visit.
2. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
3. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS.
4. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
5. Perform a physical examination (including the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Complete UPT if the subject is a female of childbearing potential.
8. Collect urine for urinalysis.
9. Collect blood sample for hematology, blood biochemistry, PK and ADA.
10. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.
11. Schedule the final visit (12 weeks after the last study drug administration).

8.1.4.2 Unscheduled visit

Subject should be reminded to adhere to the study schedule, and visits occurring outside of the visit window are not considered as unscheduled visit. Unscheduled visits may be necessary to repeat testing abnormal laboratory results or for follow-up of AEs. Assessments to be conducted at the unscheduled visit will depend on the reason for the visit: any of the listed procedures/assessments may be conducted but not all are required. However, blood sample collection for PK and ADA analyses are mandatory during unscheduled visits for safety reasons.

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Check subject's record for pruritus NRS, PCS and sleep disturbance NRS.
3. Complete the evaluation of EASI, IGA, and SCORAD (including BSA).
4. Perform a physical examination (including weight, and the evaluation of prurigo nodularis lesions if applicable), vital signs measurements and ECG.
5. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
6. Complete UPT if the subject is a female of childbearing potential.
7. Collect urine for urinalysis.
8. Collect blood sample for hematology, blood biochemistry, TARC, PK and ADA. Blood sample for re-test of TB and/or CPK after the initial test may also be collected.
9. Collect the returned TCS. Dispense TCS and, if needed, moisturizer, and provide instruction on their usage. Instruct subject to bring used and unused TCS back to investigational site at each visit.

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

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

The primary analysis will be performed after all randomized subjects have completed week 24 (excluding safety follow-up) visit or have withdrawn from the study. No one directly involved with the conduct of the study will see the unblinded data before the completion of the trial, in order to avoid biasing the remaining data of the study. The final analysis will be performed when the last subject has completed the study (i.e. completed the safety follow-up or has withdrawn from the study).

9.1.1 Data transformations

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

9.1.2 Analysis populations

The following populations and evaluability criteria will be used to analyze the efficacy, safety, PK/PD and QoL endpoints. For the safety analyses, subjects will be analyzed as treated and for efficacy analyses subjects will be analyzed as randomized.

9.1.2.1 Intent-to-Treat (ITT) population

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

9.1.2.2 Per-Protocol (PP) 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 selected secondary endpoints will be analyzed using PP population.

9.1.2.3 Safety population

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

9.1.2.4 PK analysis population

The PK analysis population will include all subjects in the safety population who provide at least one post-baseline evaluable drug concentration value.

9.1.3 Imputation of missing data

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

Continuous Endpoints: To impute the missing values for continuous endpoints, Mixed-effect Model for Repeated Measures (MMRM) approach will be used for the primary and secondary endpoints.

In addition, Multiple Imputation (MI), Last-Observation Carried Forward (LOCF), Worst-Observation Carried Forward, Observed Case (OC), and Pattern-Mixture Model under missing not at random assumption will be carried out as sensitivity analysis for primary and selected secondary endpoints.

Binary Endpoints: All missing values will be treated as a Non-Responder for the binary endpoints.

LOCF, OC, MI and Pattern-Mixture Model under missing not at random assumption approaches will be used as sensitivity analysis to impute the missing values for the selected 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 laboratory, and vital sign data. Further details on imputation of missing data will be provided in the SAP.

9.1.4 Subgroup analysis

Descriptive summary and analysis for primary and selected secondary endpoints will be produced for the following subgroups:

- Region
- Age (18-65 or >65)
- Gender
- Race
- Baseline IGA (3 or 4)
- Baseline EASI (≤ median or > median)
- Intrinsic or extrinsic AD (based on IgE and eosinophil counts)

9.1.5 Descriptive and inferential statistical analyses

9.1.5.1 Demography and baseline characteristics

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

9.1.5.2 Efficacy analyses

Primary inference for all the efficacy analyses will be based on the ITT population at the week 24 endpoint. PP analyses will be carried out as supportive analyses for the primary and selected 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.

9.1.5.2.1 Primary efficacy analysis

The primary endpoint is percentage change in EASI score from baseline to week 24.

The primary endpoint will be analyzed using a MMRM approach, including terms of treatment group, and baseline IGA severity. Visit will be fitted as a categorical variable, with the effect of treatment group and baseline IGA varying at each visit. 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 dose levels and placebo. Other covariates may be explored and will be added into the model, if appropriate. Treatment difference for each nemolizumab dosing regimen versus placebo will be estimated along with associated 95% confidence intervals will be presented.

Multiple comparison procedures-modeling (MCP-Mod) approach will be applied using a set of candidate dose-response models to test for a dose-response relationship via model-associated statistics.

9.1.5.2.2 Secondary and other efficacy analysis

Continuous secondary efficacy endpoints will be analyzed similar to the analysis of the primary endpoint.

All categorical efficacy endpoints will be analyzed using Stratified Cochran Mantel-Haenszel test stratified by baseline IGA severity.

Time to use of rescue therapy and other time to event data will be summarized and analyzed using Kaplan-Meier method. Subjects who do not experience the event at any time will be censored at the last evaluation time.

Sponsor plans to perform further validation of the NRS responder analysis using anchor-based approach based on a Receiver Operating Curve analysis.

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

9.1.5.3 Safety analyses

All safety analyses will be based on the safety population. Summary of all safety endpoints will be presented for each treatment group.

9.1.5.3.1 Extent of exposure

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

9.1.5.3.2 Adverse events

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

Pre-treatment AEs will be listed separately.

9.1.5.3.3 Clinical laboratory

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

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

9.1.5.3.4 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 will be summarized by treatment group.

9.1.5.3.5 Peak Expiratory Flow (PEF)

PEF measurements (absolute values and change from baseline) will be summarized by visit and treatment group.Further details on safety analyses will be provided in the SAP.

9.1.5.4 PK parameters and ADA analyses

The PK parameters derived using non-compartmental techniques will be regarded as primary endpoints for the pharmacokinetic analyses (see details in Section 7.3.3). Primary inference for all the PK parameters will be based on the pharmacokinetic analysis population.

Descriptive statistics (n, arithmetic mean, standard deviation [SD], minimum, median, maximum) by treatment group will be calculated for all derived pharmacokinetic endpoints. Geometric means and between-subject coefficients of variation (CVb) will be calculated for $\log_e$-transformed $AUC_{0\text{-}28d}$, C_{trough} and C_{max} where:

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Following $\log_e$-transformation, $AUC_{0\text{-}28d}$, C_{trough} and C_{max} will be analyzed separately using analysis of variance (ANOVA), fitting a model with treatment group as a fixed effect. The residual variance from the model will be used to calculate point estimates and 90% CIs for the least squares means for each treatment formulation on the $\log_e$ scale. These estimates will be back transformed to give point estimates and 90% CIs on the original scale.

The concentration at each time point will be summarized as arithmetic mean, standard deviation, median, minimum, and maximum, number of BLQs (Below the Limit of Quantification). PK parameters using geometric means will be compared to determine when steady state conditions are achieved during the treatment period.

The potential relationship between plasma concentrations of nemolizumab and change in EASI, pruritus NRS, biomarkers or other indicators of disease activity will be explored using PK/PD modeling, as appropriate.

Incidence of positive ADA results will be summarized by treatment group (absolute occurrence and percent of subjects). ADA results presentation will be detailed in the SAP.

9.1.5.5 Biomarker Analyses

Primary inference for all biomarker analyses (including eosinophil, TARC, IgE etc.) will be based on the observed cases. All biomarker variables (e.g. absolute and change from baseline) will be summarized and compared across treatments at each time point. If the variable is not Gaussian distributed then it will be log transformed. Student T-test will be used to compare the nemolizumab to placebo, where appropriate. P-values will be presented. In addition, a box-plot will be produced for each treatment group at each time point.

Missing values will not be imputed. False Discovery Rate approach (Benjamini 1995) or another appropriate approach will be used to control for multiplicity.

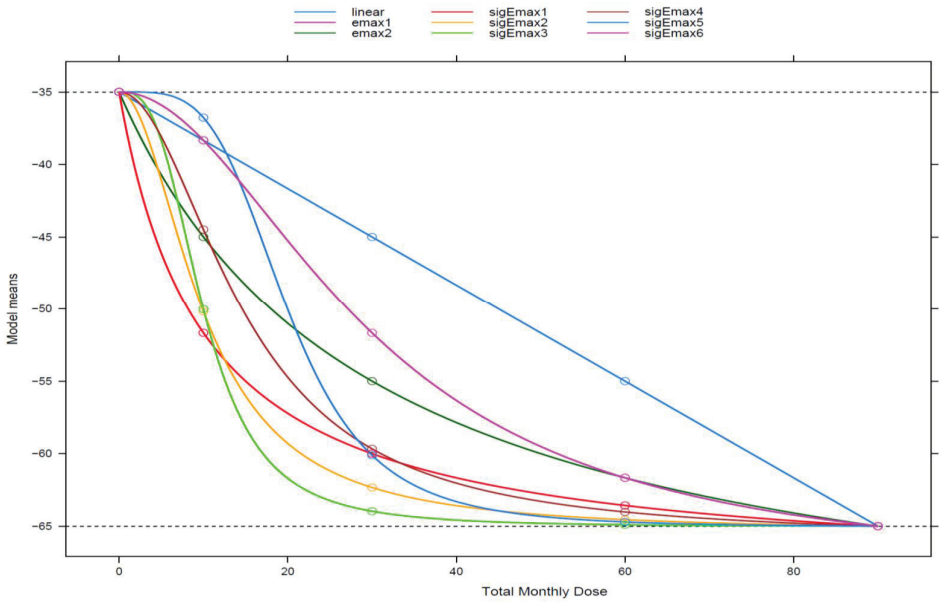
9.1.5.6 Quality of Life and Productivity data Analyses

Primary study population for all quality of life and productivity data analyses will be based on ITT population. The HADS, DLQI, EQ5D and productivity data will be summarized by treatment group and analysis visit. Details of the analyses will be provided in the SAP.

9.2 Sample size assumption

Sample size is estimated using MCP-Mod (Bretz 2005) approach by selecting a set of candidate dose response shapes based on EASI response in previous Phase 2a study (CIM003JG study report 2017). The following models are considered as candidates in the estimation of sample size.

Linear	Emax	Sigmoid Emax
Linear	1. ED50 =10mg	1. ED50=10mg, H (Hill)=1
	2. ED50=30mg	2. ED50=10mg, H (Hill)=2
		3. ED50=10mg, H (Hill)=3
		4. ED50=15mg, H (Hill)=2
		5. ED50=20mg, H (Hill)=4
		6. ED50=30mg, H (Hill)=2
ED50=dose produces 50% of maximum effect		



Assuming a placebo response of 35%, standard deviation 45% and a maximum treatment difference of 30%, in terms of percent change in EASI, 50 subjects per arm will provide at least

90% power to detect a statistically significant dose-response for at least one model at 1-sided significance level of 0.025.

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel training

CRA and all relevant personnel will be trained prior to study initiation on the condition to be treated, the Standard Operating Procedures (SOPs) to be used in this clinical trial, the protocol, and all study-specific procedures. Team organization, communication, and operational issues will also be discussed and agreed upon.

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

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

10.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by Sponsor representatives to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs. All monitoring procedures will be detailed in the monitoring plan.

The investigator will allow the CRO/Sponsor representatives, to have direct access to all clinical trial records, eCRF, corresponding subject medical records, study drug dispensing records, and any other documents considered source documentation. Additionally, the CRO/Sponsor representative is to have access to the study drug storage area and clinical trial facilities. The investigator also agrees to assist the representative if required.

A partially unblinded CRA will be designated for each investigational site, and is responsible only for monitoring the records related to study drug in the pharmacy study file. The partially unblinded CRA will have no access to other data collected during the study (including the source data at the investigational site and the eCRF), and will also be instructed to not discuss trial-related matters with the investigator/evaluator, the subjects or the blinded CRA.

10.3 Data management

All data management procedures will be detailed in a data management plan (DMP).

The DMP will describe the clinical data management system that will be used to collect data, and who is responsible for performing the data management activities. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data clarifications are resolved. The data will be exported to be stored in SAS datasets. After all data clarifications are resolved, coding is approved, SAE/pregnancy reconciliation has been completed and subject's evaluability is determined, the database will be locked.

Pruritus NRS, PCS, sleep disturbance NRS, DPS, DLQI, HADS and EQ5D will be collected using an electronic device.

10.4 Quality assurance / audit / inspection

The clinical trial is conducted under the sponsorship of Galderma in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from sponsor and/or CRO.

Audits of clinical trial centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by regulatory authority inspectorates or IRBs/IECs before, during, or after the clinical trial. The investigator will allow and assist the Sponsor/CRO representatives, IRBs/IECs and any regulatory agency to have direct access to all requested clinical trial-related records. For the audits performed by, or on behalf of, sponsor auditors, audit certificate will be provided by quality assurance.

10.5 Changes in clinical trial conduct / amendments

10.5.1 Clinical trial conduct

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

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

10.5.2 Amendments

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

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

11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This clinical trial protocol and all amendments will be reviewed and approved by the appropriate IECs/IRBs.

11.2 Ethical conduct of the clinical trial

This clinical trial will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

11.3 Subject information and consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCPs guidelines, federal regulations, HIPAA (for the U.S), PIPEDA (for Canada), and guidelines and in accordance with local requirements.

The ICF approved by an IRB/IEC will be fully explained to the subject. Prior to enrolment into the clinical trial, the subject will sign and date the consent form. The investigator is responsible for maintaining each subject's consent form in the site file and providing each subject with a copy of the signed and dated consent form.

11.4 Contractual requirements

A contractual agreement will be signed between the CRO/Sponsor and each investigator/institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical trial schedule, third party responsibility, and publication rights.

11.5 Data collection and archiving

11.5.1 Data collection

The investigator must maintain all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents (including electronic device) and in the eCRF provided by the Sponsor/CRO. All data should be recorded in the eCRF completely and promptly.

11.5.2 Source documentation

The investigator must keep accurate separate records (except those defined below for which eCRF could be considered as source documentation) of all subject visits, and ensure that they include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written ICF. All AEs must be thoroughly documented.

Specifically, source documentation supporting the subjects' inadequate response to topical treatment (inclusion criterion #7, see Section 5.2.1) include medical records (including pharmacy records) and documented conversation between the investigator and other healthcare provided. Information based on subject's medical interview with no other supporting evidence cannot be accepted.

Results of any laboratory tests conducted during the clinical trial should also be included in the source documentation. Scores of EASI and SCORAD will be calculated automatically in the eCRF and will therefore be considered as e-source data; however, the components of EASI and SCORAD must be documented on a separate source document. Data documented on the electronic device directly (e.g. pruritus NRS) will also be considered as e-source data.

11.5.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in sponsor/CRO/investigator/institution archives as specified in section 8 of ICH-GCP, and according to the applicable regulatory requirements, for the legally required duration for archiving. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

If the principal investigator retires, relocates, or withdraws from the responsibility of keeping the clinical trial records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

11.6 Insurance

A certificate attesting third party coverage of CRO/sponsor will be provided upon request.

11.7 Investigator and Administrative Structure

Designation of [redacted] as Coordinating Investigator (CI) was done pursuant to the European Agency for the Evaluation of Medicinal Products (EMA) guidance on "Coordinating Investigator Signature of Clinical Trial Reports".

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13 APPENDICES

APPENDIX 1 AAD 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 (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

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

APPENDIX 2 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

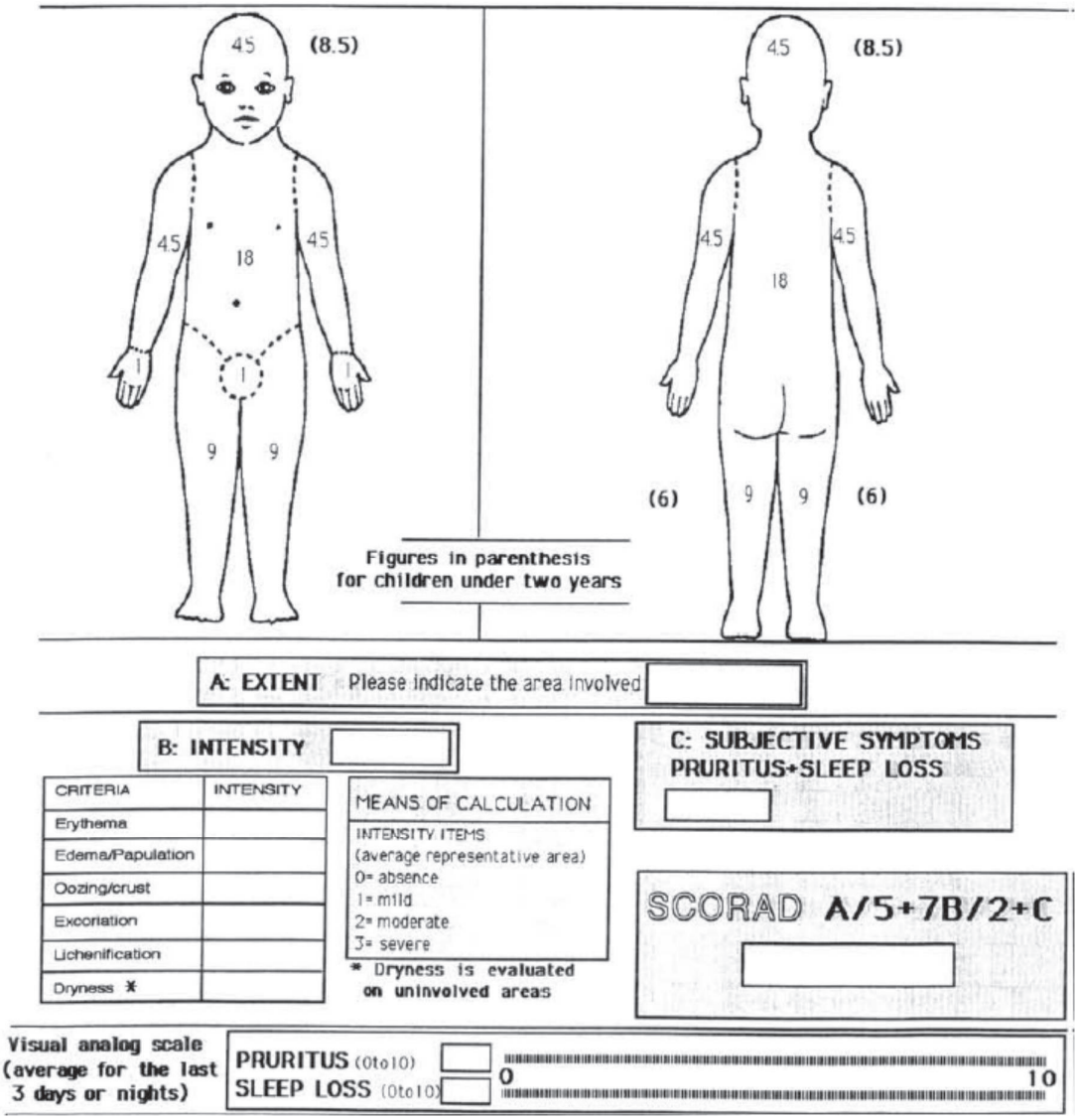
The degree of severity of each sign (E=erythema, I=induration/papulation, Ex=excoriation, L=lichenification) in each of the 4 body regions is evaluated based on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe), with half points allowed.

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 (Hanifin 2001).

APPENDIX 3 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.

APPENDIX 4 SCORing Atopic Dermatitis (SCORAD)



Extent: The extent of body area affected by atopic dermatitis

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

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

APPENDIX 5 Pruritus Numeric Rating Scale (NRS)

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

No itch worst itch imaginable

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

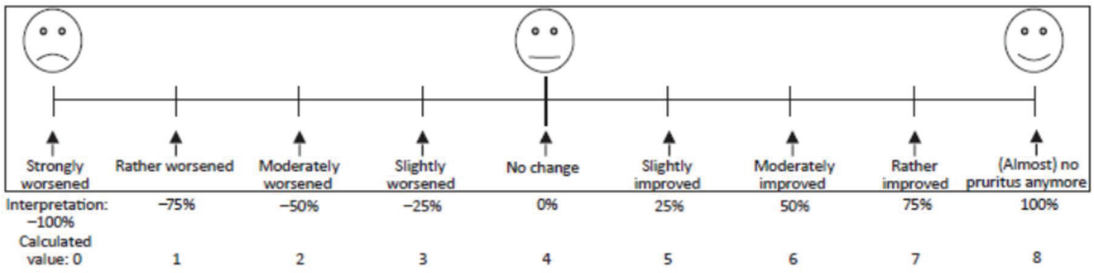
No itch worst itch imaginable

APPENDIX 6 Pruritus Categorical Scale (PCS)

Please rate your overall itch during the previous 24 hours

Score	Definition
0	absence of pruritus
1	mild pruritus (occasional slight itching/scratching)
2	moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep)
3	severe pruritus (bothersome itching/scratching that disturbs sleep).

APPENDIX 7 Dynamic Pruritus Scale (DPS)



APPENDIX 8 5-D ITCH SCALE

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX 9 Sleep disturbance Numeric Rating Scale (NRS)

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

0	1	2	3	4	5	6	7	8	9	10

No sleep loss I cannot sleep at all

APPENDIX 10 Dermatology Life Quality Index (DLQI)

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

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

Please check you have answered EVERY question. Thank you.

APPENDIX 11 Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

APPENDIX 12 EuroQoL 5-Dimension (EQ5D)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today