Official Title

A study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)

NCT Number: NCT03181503

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CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.115828

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TITLE PAGE

Title *A study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)*		
Project Name or CD number: CD14152	**Project Number:** 1295	**Clinical Trial Phase:** II a

EUDRACT NUMBER: 2017-001715-36

IND Number: 117122

Version Number: V00

SPONSOR:

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For any safety questions, please contact the Clinical Safety Officer (CSO) using the contact details provided in Section 7.2.4.2.2.

For any medical questions related to the clinical trial protocol, please contact the Medical Expert (see contact details in study team contact list).

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 Harmonisation (ICH) and the GALDERMA template.

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SYNOPSIS	
Clinical Trial Title: A study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)	
Clinical Trial phase:	II a
Clinical Trial Population:	Adult subjects with clinical diagnosis of PN for at least 6 months with at least 20 nodules on the whole body
Clinical Trial objectives:	**Primary objective:** The primary objective is to assess the efficacy of nemolizumab compared to placebo in the treatment of pruritus in patients suffering from PN. **Secondary objective:** The secondary objectives are: Efficacy and safety: ▪ Evaluation of the safety of nemolizumab compared to its placebo in patients with PN. ▪ Evaluation of the efficacy of nemolizumab compared to its placebo in the treatment of prurigo lesions in patients with PN. ▪ Evaluation of nemolizumab effect compared to its placebo on quality of life in patients with PN **Pharmacokinetics (PK)** ▪ Characterization of nemolizumab PK profile and exposure response relationship in patients with PN **Pharmacodynamics (PD)** ▪ Evaluation of the effect of nemolizumab on biomarkers in patients with PN **Biophysical (exploratory)** ▪ Evaluation of the efficacy of nemolizumab on scratching events and sleep improvement using actigraphy ▪ Evaluation of the efficacy of nemolizumab on lesions improvement using whole body images device only on equipped sites.
Clinical Trial design:	This is a randomized, placebo-controlled, double-blinded, parallel group, multicenter study to evaluate the safety and efficacy of nemolizumab in patients suffering from PN. Approximately 70 adult patients suffering from PN for at least 6 months with severe pruritus defined by the mean of the worst daily intensity of the NRS score ≥ 7 over the previous week at baseline will be randomized in the study. Subjects meeting inclusion/exclusion criteria will be randomized in a 1:1 ratio to nemolizumab or placebo. Each subject will receive three subcutaneous injections of 0.5mg/kg of nemolizumab or matching placebo. Injections will be administered every 4 weeks (baseline, week 4 & week 8). Subjects' participation in the study will be up to 22 weeks, including an up to 4-week screening period, a 12-week treatment period (last study drug injection at week 8) and a 6-week follow-up period (10 weeks after the last study drug injection corresponding to 5 half-lives of nemolizumab).

SYNOPSIS	
Clinical Trial Title: A study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)	
	A total of 10 visits per subject is planned. Schedule of assessments is summarized in Table 2. Safety and efficacy assessments will be conducted throughout the study. Pruritus severity will be self-evaluated by the subjects on a daily basis using the ePRO and following instructions provided by the Investigator. The Investigator will evaluate the evolution of prurigo lesions using appropriate scales. PK profile of nemolizumab in PN patients will be assessed according to Table 2. PD assessments will be performed to evaluate cytokines/chemokine profiles, IL31 and IL31 RA quantification by proteomics, genomic and histology analysis using three 4-mm skin biopsies, D-squames and blood samples collected according to Table 2. Skin biopsies will be optional, patients accepting this procedure will have to sign an additional consent. Exploratory biophysical assessments will be performed by measuring scratching events during the night and sleep duration using actigraphy. The subject will have to wear two watches from Day -7 to baseline and during the first four weeks of the study. In addition, photographs of the entire body will be taken in equipped sites using a whole-body imaging device according to Table 2 An interim analysis may be performed once at least 40 subjects will have completed the week 4 visit or discontinued before (decision will be taken by the Sponsor according to the recruitment rate). This analysis will include efficacy data on all subjects up to that time point. In addition to efficacy, all safety data available (not only data up to week 4) will also be analyzed (Section 9.4).
Total number of subjects (Planned):	As a screen failure rate of approximately 30 percent is expected, approximately 100 subjects may have to be screened in order to get 70 randomized subjects (35 subjects per treatment group).
Number of clinical trial centers (Planned):	Approximately 20 sites
Regions / countries involved (Planned):	Austria, France, Germany, Poland & US
Clinical trial duration:	The planned clinical trial duration (from FSFV to LSLV) is approximately 10 months.
Duration of subject participation:	Clinical trial participation for each subject is approximately 22 weeks.
Key Inclusion criteria	1. Male or female of at least 18 years at screening 2. Clinical diagnosis of PN for at least 6 months with: ▪ Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs ▪ At least 20 nodules on the entire body with a bilateral distribution 3. Severe pruritus defined as follows on a Numerical Rating Scale (NRS) ▪ At the Screening visit 1: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous 3 days ▪ At the Baseline visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous week; ***NOTE:*** *NRS score should be measured on at least 5 days during the week preceding the baseline visit.*

Key Exclusion criteria	1. Chronic pruritus resulting from another condition than PN such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease 2. Unilateral lesions of prurigo (e.g only one arm affected) 3. Cutaneous bacterial or viral infection within 1 week before the baseline visit. 4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit, or during the screening period, unless completely resolved at the screening/ baseline visits respectively, 5. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results and/or put the subject at significant risk according to Investigator's judgment (e.g. solid cancer, AIDS, serious or uncontrolled cardiac disease…) at Screening or Baseline. ***NOTE**: Patients with **controlled diseases such as** diabetes mellitus, thyroid disorders and psychiatric disorders (such as depression and anxiety) are eligible* 6. Any active dermatoses that would need immediate therapy. 7. Subject with active atopic dermatitis or known with recurrent flares of atopic dermatitis ***NOTE**: patients with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e. specific IgE), are eligible for the study* 8. Neuropathic and psychogenic pruritus (notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia) 9. 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** : Subject with a positive HBcAb and a negative HBsAg can be included in this trial if HBsAb is positive (considered immune after a natural infection)* 10. Subject having any of the abnormal lab criteria listed below, at the screening visit: ▪ Elevated ALT / AST ≥ 3 ULN ▪ Elevated CPK > 1.5 ULN, unless not confirmed on a repeat assessment to be performed at least 72h after the first one ▪ Neutrophil count < 1.5 x $10^3/\mu l$ ▪ Creatinine clearance <60ml/min/1.73m² calculated with the CKD-EPI formula (Levey et al 2009) ▪ Any other abnormal lab result that would be considered as clinically significant by the investigator 11. Subjects with a medical history of asthma that fulfill any or more of the conditions 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 at screening or baseline visit 12. Latent or active TB, as determined by a positive Quantiferon-based TB test result at screening visit 1. ***NOTE**: In case of indeterminate result, the test should be repeated in local laboratory at screening visit 2 (only one retest is allowed). If the test is still indeterminate, the subject will not be included.*

<table>
<tr><td>Investigational product and its comparator</td><td>
<table>
<tr><th></th><th>Investigational product</th><th>Comparator</th></tr>
<tr><td>Name</td><td>Nemolizumab</td><td>Nemolizumab placebo</td></tr>
<tr><td>Internal code</td><td>CD14152</td><td>NA</td></tr>
<tr><td>Pharmaceutical form</td><td>Lyophilized powder</td><td>Lyophilized powder</td></tr>
<tr><td>Concentration</td><td>100mg/ml when reconstituted</td><td>NA</td></tr>
<tr><td>Formula number</td><td>NA</td><td>NA</td></tr>
<tr><td>Packaging</td><td>Vial</td><td>Vial</td></tr>
<tr><td>Storage conditions</td><td>Stored between 2 to 8°C (36-46°F) and protected from light</td><td>Stored between 2 to 8°C (36-46°F) and protected from light</td></tr>
<tr><td>Dosage</td><td>0.5 mg/kg</td><td>Not applicable</td></tr>
<tr><td>Route</td><td>Subcutaneous injection</td><td>Subcutaneous injection</td></tr>
<tr><td>Dose regimen</td><td>3 injections (baseline, Week 4, Week 8)</td><td>3 injections (baseline, Week 4, Week 8)</td></tr>
<tr><td>Treatment duration</td><td>12 weeks</td><td>12 weeks</td></tr>
</table>
</td></tr>
<tr><td>Efficacy endpoints:</td><td>Primary: The primary efficacy outcome will be the percent change from baseline in NRS to week 4 (weekly average of the peak).

Secondary:
▪ Absolute and Percent change from baseline in weekly average of the peak and average pruritus NRS to each visit
▪ Change from baseline of VRS at each time point
▪ DPS
▪ PAS: Distribution for item 6 (excoriation/crusts and healed lesions stages) and change from baseline for item 5 (in lesions number)
▪ IGA: Distribution score and success rate (defined as IGA=0[clear] or IGA=1[Almost clear] with two point improvement from baseline).

Other enpoints:
▪ Quality of life (DLQI)
▪ Objective assessments of scratching and sleep by Actigraphy
▪ Sleep disturbance NRS</td></tr>
<tr><td>Safety assessments:</td><td>The safety measures for this study are as follows:
▪ Adverse events
▪ Laboratory tests
▪ Vital signs
▪ Physical exam and body weight
▪ 12-lead ECG
▪ PEF</td></tr>
<tr><td>Pharmacokinetic assessment and anti-drug antibody (ADA) assessment:</td><td>Blood samples will be collected at specific time points according to Table 2 for measurement of PK profile of nemolizumab and anti-nemolizumab antibodies .

The nemolizumab serum exposure will be assessed at the following time-points: baseline, weeks 1, 2, 4, 8, 12, 16 and 18 and at early termination or any unscheduled visit for safety reason.

ADA will be assessed at baseline, weeks 4, 8, 12, 16 and 18 and in case of early termination or unscheduled visit for safety reason.</td></tr>
<tr><td>Pharmacodynamics assessment:</td><td>Blood and skin samples (D-Squames and skin biopsies) will be collected to investigate the effect of nemolizumab on biomarkers according to Table 2

As much as possible, skin sampling will be performed in similar body areas for all samples in all patients, on a selected</td></tr>
</table>

	area at baseline, such as the upper arms. Skin biopsies on prurigo lesions will be performed on lesional and non lesional skin at baseline, and on lesional skin at week 12 (only for patients consenting to have skin biopsies). Non-lesional sample will be taken in areas with no scratch such as the inner part of the upper arm, approximately 5 cm apart from lesional skin The detail of the procedure and storage conditions will be described in an Operational manual. All collected samples will be sent to GALDERMA R&D for analysis. After performance of the planned investigations, the remaining samples 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).
Principal statistical method:	The primary efficacy analysis of the percent change from baseline to week 4 of the weekly average of the NRS (weekly average of the worst score) will be an ANOVA including the Treatment group as factor, presence and absence of background of atopy and country as a cofactors. In addition to the per-protocol analysis, several sensitivity analyses on ITT population will be conducted for the primary endpoint. For ITT, NRS will be set to missing after rescue medication is used. ■ The primary imputation method for any missing data will be the LOCF (Last observation carried forward) approach. □ Multiple Imputation (MI) using the Missing At Random (MAR) assumption will also be used. The MI procedure of the SAS system will be used to generate five sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing NRS score, with the following covariates included in the imputation model: treatment and non-missing data from earlier timepoints. The imputed datasets will be analyzed using the methodology described for percent change from baseline in NRS score. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS system. The seed number to be used will be the protocol number (115828). The PD parameters will be visualized by boxplots (with a logarithm base 10 Y axis where needed). The compound effect will be estimated by Student's t test comparing the change at D85 from D1 for CD14152 vs the change at D85 from D1 for placebo (or other if more appropriate). The multiple testing problem will be taken into account by the Benjamini-Hochberg approach (1995)(or other if more appropriate). Summary statistics will be provided by treatment group for treatment emergent adverse events,
Sample size:	With an effect size of (30/35=) 0.857, a power of 90% and a type I error of 5% two-sided; at least 30 subjects are needed per group. In order to maintain the power of the tests, for per-protocol population, in case of drop outs/major deviations at Week 4, the sample size will be increased to 35 subjects per group, i.e. 70 to be randomized.

Table 1 Clinical trial schematic

	Screening (approximately 100) ↓ Randomization (approximately 70) **Group 1**	**Group 2**
	N= approximately 35	N= approximately 35
Treatment	CD14152 0.5mg/kg	CD14152 placebo
Treatment Frequency	Every 4 weeks (Q4W)	Every 4 weeks (Q4W)
Treatment Duration	12 weeks (last study drug injection at week 8)	12 weeks (last study drug injection at week 8)
Follow up	6 weeks (10 weeks after the last study drug injection)	6 weeks (10 weeks after the last study drug injection)

Table 2 Schedule of Assessments

Study period	Screening period (Day -28 to Day-1)		Treatment period						Observation period/ Follow up		Early termination (E/T) or Unscheduled visit (if applicable)
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
Week	Screening 1	screening 2	Baseline	W1	W2	W4	W8	W12	W16	W18	
Day	D-28 to D-8	Day-7 [a]	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	D113	Day 126	
Visit window				±1 day	±2 days	±2 days	±2 days	±5 days	±5 days	±7 days	
ICF and when applicable country specific consent form	●										
Photo Consent and Biopsies consent form (if applicable)	●										
Demographics	●										
Medical history/ Previous therapies and procedures	●										
Inclusion/Exclusion criteria	●		●								
Concomitant therapies and procedures	●	●	●	●	●	●	●	●	●	●	●
Height			●								
Weight			●			●	●	•			
Blood sample for serology (HIV, Hepatitis B and C test)	●										
Blood samples for specific IgE	●										
Blood samples for TB test [b]	●										
SAFETY ASSESSMENTS											
Vital signs	●		●	●	●	●	●	●	●	●	●
Physical exam	●		●			●	●	●		●	●
Blood samples for hematology and biochemistry [c]		●	●			●		●			●
Blood sample for CPK [d]	●		●			●		●			●
Urinalysis		●	●			●		●			●
12-lead ECG	●		●				●				●
Pregnancy test [e]	Serum		Urine			Urine	Urine	Urine	Urine	Urine	Urine
Respiratory assessment [f]	●	●	●	●	●	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●	●	●	●	●	●
STUDY DRUG											
Randomization			●								
Subcutaneous study drug injection			●			●	●				

(a) Screening visit 2 must be performed at least 7 days prior to Day 1 visit. Eligible subjects according to safety assessments will be provided with the Actigraphy and ePro devices.

(b) In case of indeterminate result for TB test, the test should be repeated at screening 2 in the local laboratory (only one retest is allowed). If the test is still indeterminate, the subject must not be included in the study

(c) Blood samples for hematology and biochemistry must be performed in fasting conditions

(d) In case elevated CPK > 1.5 ULN, the test will be repetead at screening 2. If the result is still abnormal, the subject will not be included.

(e) Only for female of childbearing potential. Serum pregnancy test to be performed at screening visit 1 and urine pregnancy test (UPT) for all other visits. UPT should have a sensitivity threshold of less than 25mIU/mL. There should be at least 14 days between the serum pregnancy test at screening and the UPT at baseline.

(f) Respiratory assessments for all subjects, but PEF will be measured only for subjects with medical history of asthma

Study period	Screening period (Day -28 to Day-1)		Treatment period						Observation period/ Follow up		Early termination (E/T) **or** Unscheduled visit (if applicable)
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
Week	Screening 1	screening 2	Baseline	W1	W2	W4	W8	W12	W16	W18	
Day	D-28 to D-8	Day-7 (a)	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	D113	Day 126	
Visit window				±1 day	±2 days	±2 days	±2 days	±5 days	±5 days	±7 days	
EFFICACY/ PATIENTS REPORTED OUTCOMES											
NRS (g)	●	Once daily by the subject at home in the evening until Day 126									●
VRS (g)		Once daily by the subject at home in the evening until Day 126									●
Sleep disturbance NRS(h)		Once daily by the subject at home in the evening until Day 29									
DPS (i)			●			●					
DLQI			●			●		●			●
Prurigo Assessment Scale (PAS)			●			●	●	●		●	●
IGA			●			●	●	●		●	●
PK AND ADA ASSESSMENTS											
Blood sample for PK			●	●	●	●	●	●	●	●	●
Blood sample for ADA			●			●	●	●	●	●	●
PHARMACODYNAMIC ASSESSMENTS											
Blood sample for biomarkers			●			●		●			
D-Squames samples			●			●		●			
4-mm skin biopsies (j)			●					●			
Control of biopsies healing(k)					●				●		
BIOPHYSICAL ASSESSMENTS											
Photos of whole body (l)			●			●	●	●		●	
Actigraphy		Every day until Day 29									
Exit Form										●	

(a) NRS and VRS must be performed by the subject at home using the device provided by the site once daily in the evening from screening 2 to the last visit.

(b) NRS for sleep disturbance must be performed by the subject at home using the device provided by the site once daily in the morning from screening 2 to Day 29

(c) DPS must be performed by the subject at home following instruction provided by the Nurse on site and then subject should record DPS 24, 48 & 72 hrs after the 1st injection and at week 4 before the injection.

(d) Skin biopsies will be performed on lesional and non lesional skin at baseline and on lesional skin at week 12 only for patients consenting to have skin biopsies.

(e) When applicable, biopsies healing should be checked 2 weeks after skin biopsies

(f) Only for selected equipped sites – at least a Baseline & Week 12; Week 4, week 8 & week 18 if possible.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
°C	Degrees Celsius
°F	Degrees Fahrenheit
ADA	Anti-drug antibodies
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT/ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
Approx.	Approximately
AST/ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area under Curve
CA	Competent Authorities
CI	Coordinating Investigator
Cmax	Maximum Concentration
CPK	creatinine phosphokinase
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Clinical Significant
CSO	Clinical Safety Officer
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
DPS	Dynamic Pruritus Score
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	electronic Case Report Form
e.g	For Example (Latin: exempli gratia)
E/T	Early Termination

etc	Et cetera
EU	European Union
Eur. Ph. or EP	European Pharmacopoeia
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent Form
ICH	International Conference on Harmonisation
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgE	Imunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Injection related Reaction
IRT	Interactive Response Technology
ITT	Intent-to-treat
IU	International Units
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification

LSFV	Last Subject First Visit
LSLV	Last Subject Last Visit
MCMC	Markov Chain Monte Carlo
MCV	Mean Cell Volume
MCVmax	Maximum Mean Cell Volume
MD	Medical Doctor
ME	Medical Expert
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N or n	Number
N/A	Not Applicable
NCS	Non clinically significant
NRS	Numeric rating scale
NSAID	Non steroidal Anti-inflammatory drug
p	Page(s)
PAS	Prurigo Activity Score
PD	Pharmacodynamics
PDE-4	Phosphodiesterase-4
PE	Physical Exmination
PEF	Peak Expiratory Flow
PN	Prurigo nodularis
PK	Pharmacokinetics
Plt	Platelets
PP	Per-Protocol
PR	Pulse Rate
QoL	Quality of Life
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SOC	System Organ Class

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Half-life
TB	Tuberculosis
TCS	Topical corticosteroids
TEAE	Treatment Emergent Adverse Event
Tmax	Time to maximum concentration
TOC	Table of contents
ULN	Upper Limit of Normal
UP	Uremic Pruritus
UPT	Urine Pregnancy Test
US	United States
VAS	Visual Analogue Scale
VRS	Visual rating scale
WBC	White Blood Cell

1 BACKGROUND AND RATIONALE

1.1 Medical background and Short rationale for the clinical trial

Prurigo nodularis (PN) is characterized by the presence of symmetrically distributed multiple (up to hundreds), highly pruritic, hyperkeratotic, erosive or crusted nodules and papules (Hyde JN et al., 1909). This leads to an impaired quality of life and high burden due not only to the severe itch but also the chronic, skin lesions and lack of treatment options (Warlich B., et al 2015).

No reliable data exist about incidence and prevalence of PN in the general population, but it seems to be more frequent and intense in females and elderly (Iking A., et al., 2013).

The physiopathology of PN is still not fully understood; however, the interactions between cutaneous nerve fibres, neuropeptides and immune cells seem to play an important role in the onset of PN (Zeidler C et al. 2016). It was assumed that PN is a subclinical small fibre neuropathy based on the observed reduction of intraepidermal nerve fibre density in patients' biopsies (Bharati et al 2007, Schuhknecht B et al., 2011) and observations with positive response to gabapentin and pregabalin commonly utilized in the treatment of pain and neuropathy [(Fostini et al., 2013). Changes in the morphology of skin nerve fibers with increased dermal neural hyperplasia and inflammation caused by T lymphocytes, eosinophilic, granulocytes and mast cells were described in the development and chronification of PN (Zeidler C et al., 2016).

Recent findings suggest that PN might be a consequence of chronic itch inducing neural sensitization followed by lesion appearance and development of a chronic itch-scratch cycle. A large spectrum of underlying conditions were considered as the origin of chronic pruritus classified in dermatological (e.g. atopic dermatitis), systemic (e.g. chronic kidney failure), neurological (e.g. brachioradial pruritus), psychiatric and mixed origin (Ständer S et al., 2007).

Only few studies have described the incidence and the strength of association of different co-morbidities in representative cohort of patients with PN (Iking et al., 2013). An atopic predisposition seemed to be most commonly associated to PN patients in nearly half of the subjects. The atopic diathesis was also found to predict a significantly earlier age of onset (median age 19 years) compared to non-atopic patients (median age 48 years) (Tanaka et al.1995).

Psychosocial disorders are also significantly associated with PN. These disorders can be a primary association or secondary to the itch in PN, presence of visible scratch-related nodules and inadequate response to currently available therapies. Rowland Payne et al., found that more than 50% of their PN patients had a history of depression or anxiety requiring medical intervention.

The goal of PN treatment is to break the itch-scratch cycle and allow the skin to heal. Treatment of chronic pruritus is still notoriously challenging and frustrating for both dermatologists and

patients as in the majority of cases, the response is either limited or associated with severe adverse events with the current therapy options. There is no standardized or approved therapy for PN up-to-date and evidence from controlled studies is limited (Fostini AC et al., 2013). The difficulty in treating this disease is reflected in the wide range of treatments proposed in the literature.

The current recommendations include identification and treatment of any underlying disease, moisturizers and antipruritics, topical therapies (corticosteroids, calcineurin inhibitors) associated to non-sedating and sedating antihistamines as first-line agents (Weisshaar E et al., 2012). Phototherapy, oral or intra-lesional steroids, topical vitamin D3 (calcipotriol), capsaicin, cryotherapy and antidepressants (amitriptyline, selective serotinine re-uptake inhibitors) are used as second-line therapies with variable efficacy. In third-line, systemic treatments such as cyclosporine (Berth-Jones J et al., 1995), antiepileptic drugs (gabapentin, pregabalin) (Mazza M et al 2013) and thalidomide (Andersen TP et al.2011) showed moderate-to-good response in pruritus reduction after several months of administration, but their use is limited by their unfavorable safety profile. Other off label therapeutic options proposed for pruritus in uncontrolled series referred to opioid receptor agonists and antagonists (naltrexone) (Brune A et al; 2004), NKR1-antagonists (aprepitant) (Ständer S et al., 2010), antibiotics (roxitromycine, erythromicine) (Horiuchi Y et al 2006).

Nemolizumab (CD14152) is a humanized anti-human IL-31 receptor A (RA) monoclonal antibody that inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction.

The T-cell-derived cytokine interleukin-31 (IL-31) has been suggested to be a key player in the development of pruritus, inducing severe pruritus and dermatitis in mouse models (Dillon et al. 2004, Arai et al., 2013). IL-31 binds to a heterodimeric receptor at TRPV1 (+)/TRPA1 (+)-C-fibres, keratinocytes, macrophages and eosinophils, and thus may be involved in transmission of pruritus and promotion of inflammation. Not limited to the skin, the densest area of this receptor seems to be at the dorsal horn of spinal cord where the cell bodies of cutaneous sensory neurons reside (Sonkoly et al., 2006). Therefore, IL-31 may be a link between the immune and the neural system.

In dogs with atopic dermatitis, 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 et al. 2016) and in cynomolgus monkeys, nemolizumab suppressed IL-31 induced scratching (Oyama et al. 2016). Also recent clinical studies of nemolizumab in patients with atopic dermatitis showed a rapid onset of pruritus reduction within one week followed by disease improvement (Ruzicka T et al 2017).

Interestingly, skin biopsies from PN patients with an atopic background, in comparison to healthy skin from healthy individuals, showed a 50-fold upregulation of IL-31 mRNA and 4.5 fold upregulation compared to atopic dermatitis patients (Sonkoly et al., 2006). A significant higher level of IL-31 mRNA was also observed by Park K et al. in PN patients with unknown AD background compared to normal skin.

Taken all together, IL-31 seems to be an important cytokine for the regulation of PN and a potential therapy target.

In conclusion, nemolizumab may present a new treatment option for PN in patients that usually present with severe pruritus, which leads to extensive scratching further aggravating the disease. The main objective of this study is to evaluate the efficacy, safety and pharmacokinetics (PK) of multiple subcutaneous doses of nemolizumab in the treatment of pruritus and lesions associated to PN.

1.2 Drug profile

Nemolizumab is a humanized monoclonal modified immunoglobulin G (IgG) 2 antibody comprising a structure of two H-chains (445 amino acid residues) and two L-chains (214 amino acid residues) connected by 16 disulfide bonds.

Please refer to the Investigator's Brochure (IB) for detailed information on non-clinical and clinical studies. Two clinical studies have been completed and reported for nemolizumab (Phase 1: CIM001JP; and Phase 2a: CIM003JG). In addition, one Phase 2 clinical study in uremic pruritus has been recently completed, but its clinical study report is not yet available (Phase 2: CIM106JP). Final data from studies CIM001JP and CIM003JG and preliminary data from study CIM106JP are summarized below.

The safety, tolerability, and pharmacokinetics 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 (CIM001JP) (Nemoto et al. 2016). There were no deaths or serious adverse events (SAE) reported in the study, and no dose-dependent increase in the incidence of AEs 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 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). The study included a 12-week randomized, double-blind, placebo-controlled period (Part A), a 52-week extension (Part B), and a 12-week follow-up period without treatment. At week 12, all doses of nemolizumab (0.1mg/kg, 0.5mg/kg or 2.0mg/kg) administered subcutaneously every 4 weeks (Q4W) were statistically significantly more effective than placebo in reducing pruritus visual analogue scale (VAS), with 0.5mg/kg and 2.0mg/kg doses being more effective than 0.1mg/kg. No additional benefit was observed with the 2mg/kg Q4W or Q8W compared with 0.5mg/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 0.1mg/kg, 0.5mg/kg or 2.0mg/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 (all groups pooled) than in the placebo group. AEs that occurred in 5% or more of nemolizumab-treated patients (all groups pooled) were (worsening of) atopic dermatitis, nasopharyngitis, upper respiratory tract infection, peripheral edema, and blood CPK increased.
Atopic dermatitis ,peripheral edema , and headache were observed more often in Nemolizumab groups pooled compared to the placebo group, with generally no dose-dependency, except for peripheral edema (which was more frequent in Nemolizumab 2.0mg/kg Q4W group compared to lower dose groups of nemolizumab). However, most of cases of peripheral edema occurred during part A, were transient, of mild or moderate intensity and none led to treatment discontinuation.
Lastly, various AEs that could be grouped as "injection-related reactions (IRRs)" or "skin infection" were also observed with 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, atopic dermatitis , blood CPK increased, upper respiratory tract infection, headache, peripheral edema , and impetigo. The majority of AEs were mild or moderate in intensity.
No clinically relevant findings were observed during the study for laboratory tests, vital signs, physical examination or electrocardiogram (ECG).
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- drug antibodies (ADA) present from baseline developed neutralizing antibodies at 64 weeks.

A randomized, double-blind, placebo-controlled, parallel group Phase 2 study recently completed evaluated the efficacy and safety of a single subcutaneous dose of nemolizumab (0.125mg/kg, 0.5mg/kg or 2mg/kg) compared to placebo in 69 Japanese hemodialysis patients with uremic pruritus during 12 weeks (CIM106JP). The study included an open-label reference product group

(nalfurafine hydrochloride). Preliminary data show that there were no death, no drug-related SAE, no dose-dependent increase in the incidence of AEs and no new safety concern reported in the study. In terms of efficacy, the absolute change in pruritus VAS score from baseline to 4 weeks after administration was selected as the primary outcome measure. Improvement was observed in all nemolizumab groups and placebo. Although there was no statistical significance, a trend was observed in pruritus reduction for 0.5-mg/kg group. also noticed in post-hoc analysis with a higher proportion of patients achieving less than 30 in the VAS, corresponding to a mild severity of pruritus.

1.3 Pharmacokinetic profile

PK profile of Nemolizumab was investigated in two clinical studies (Phase 1: CIM001JP; and Phase 2a in AD patient: CIM003 J Gin 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. The systemic exposure to nemolizumab appeared to be slightly lower in AD subjects compared to healthy volunteers (AUC ratios ranging from 0.63 to 0.92).

1.4 Risk/Benefit assessment

Pruritus is the cardinal symptom in PN, often difficult to be treated with current therapies. Chronic itching is believed to induce and maintain the characteristic PN skin lesions through an itch-scratch cycle. Therefore the goal of PN treatments target pruritus remission in order to allow the skin healing and patients' quality of life improvement.

Results from previous clinical studies with nemolizumab demonstrated a marked effect on pruritus and pruritus-related sleep loss in diseases associating moderate to severe pruritus such as atopic dermatitis and uremic pruritus. The decrease in itching sensation was rapid in both indications, usually within the first week following the first injection and improved with subsequent administrations.

This improvement in the signs and symptoms of AD and UP 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]). Also, continuous treatment led to improvement in overall severity of AD, evaluated with various validated scales (i.e. EASI, SCORAD and IGA).

Based on the safety data from the three completed studies there are no identified risks for nemolizumab.

However, based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the important potential risks for Nemolizumab so far include injection –related reactions(IRR), asthma, skin infection and AD exacerbation. Peripheral edema and headache are considered as non-important potential risks. There is no anticipated additional potential risk in this study conducted in patients with PN.

Exclusion criteria of this clinical trial will prevent high-risk patients from receiving nemolizumab. Subjects will not be eligible if they have a recent history of a current bacterial or viral infection, or a not well-controlled asthma, or active lesions of AD/recurrent flares of AD. As no data are available in pregnant or breastfeeding women, or in patients receiving live vaccines, they are not eligible from this study.

Safety will be evaluated closely throughout the study to minimize the risk, until 10 weeks after the last study drug administration.

The following adverse events have been defined as Adverse Events of Special Interest (AESI) for the study: elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) combined with elevated bilirubin, elevated CPK, newly diagnosed asthma or worsening of asthma (to be reported within 24 hours), IRRs, peripheral edema, skin or systemic infection, headache, and exarcerbation of AD (for patients with medical history of AD).

Additional information regarding these events will be collected, when applicable.

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.

In conclusion, when taking into consideration the potential benefit of nemolizumab in patients with PN, and the risk-minimization approaches implemented in the study, the benefit risk ratio of nemolizumab is considered favorable in this study.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

2.1.1 Primary objective

The primary objective is to assess the efficacy of nemolizumab compared to placebo in the treatment of pruritus in patients suffering from PN.

2.1.2 Secondary objectives

The secondary objectives are:

Efficacy and safety:
- Evaluation of the safety of nemolizumab compared to its placebo in patients with PN.
- Evaluation of the efficacy of nemolizumab compared to its placebo in the treatment of *prurigo* lesions in patients with PN.
- Evaluation of nemolizumab effect compared to its placebo on quality of life in patients with PN

Pharmacokinetics (PK)
- Characterization of nemolizumab PK profile and exposure response relationship in patients with PN

Pharmacodynamics (PD)
- Evaluation of the effect of nemolizumab on biomarkers in patients with PN

Biophysical (exploratory)
- Evaluation of the efficacy of nemolizumab on scratching events and sleep improvement using actigraphy
- Evaluation of the efficacy of nemolizumab on lesions improvement using whole body images device only on equipped sites.

2.2 Clinical hypothesis

The clinical hypothesis is that nemolizumab is more effective than placebo in reducing the pruritus as the major symptom of PN based on the results observed from the previous studies.

3 OVERALL CLINICAL TRIAL DESCRIPTION

3.1 Overview

This is a randomized, placebo-controlled, double-blinded, parallel group, multicenter study to evaluate the safety and efficacy of nemolizumab in patients suffering from PN.

Approximately 70 adult patients suffering from PN for at least 6 months with severe pruritus defined by the mean of the worst daily intensity of the NRS score ≥ 7 over the previous week at baseline will be randomized in the study.

Subjects meeting inclusion/exclusion criteria will be randomized in a 1:1 ratio to nemolizumab or placebo. Each subject will receive three subcutaneous injections of 0.5mg/kg of nemolizumab or matching placebo. Injections will be administered every 4 weeks (at baseline, week 4 & week 8).

Subjects' participation in the study will be up to 22 weeks, including an up to 4-week screening period, a 12-week treatment period (last study drug injection at week 8) and a 6-week follow-up

period (10 weeks after the last study drug injection corresponding to 5 half-lives of nemolizumab).

A total of 10 visits per subject is planned. Schedule of assessments is summarized in Table 2. Safety and efficacy assessments will be conducted throughout the study. Pruritus severity will be self-evaluated by the subjects on a daily basis using the ePRO and following instructions provided by the Investigator. The Investigator will evaluate the evolution of prurigo lesions using appropriate scales.

PK profile of nemolizumab in PN patients will be assessed according to Table 2.

PD assessments will be performed to evaluate cytokines/chemokine profiles, IL31 and IL31 RA quantification by proteomics, genomic and histology analysis using three 4-mm skin biopsies, D-squames and blood samples collected according to Table 2. Skin biopsies will be optional, patients accepting this procedure will have to sign an additional consent.

Exploratory biophysical assessments will be performed by measuring scratching events during the night and sleep duration using actigraphy. The subject will have to wear two watches from Day -7 to baseline and during the first four weeks of the study. In addition, photographs of the entire body will be taken in equipped sites using a whole-body imaging device.

An interim analysis may be performed once at least 40 subjects will have completed the week 4 visit or discontinued before (decision will be taken by the Sponsor according to the recruitment rate). This analysis will include efficacy data on all subjects up to that time point. In addition to efficacy, all safety data available (not only data up to week 4) will also be analyzed (Section 9.4).

3.2 Rational for study design

Rational for study population:
The selected study population in this study should have a moderate to severe disease that would justify a systemic treatment. As no validated scales are available today to define this condition severity, eligible patients for this clinical trial will present with chronic disease for at least 6 months, severe pruritus and more than 20 nodules on the whole body. Prurigo Activity Score (PAS) (Schedel et al 2013) was recently validated for clinical assessments including descriptive items such as lesions type, number and distribution. Thresholds of 20 and 100 lesions are indicated that could correspond to moderate and severe disease respectively, according to this scale. The lesions distribution should be bilateral, in order to help avoid underlying conditions such as neuropathic disorders. Also for consenting subjects, it is required for the patients to have lesions on the upper arms, in order to perform the biopsies on the same area of the body.
Only patients with controlled underlying disease will be enrolled. Randomization will be stratified according to presence or absence of atopy background as it is considered as a prognostic factor.

Rational for dose and regimen:
The results of previous phase 2a study in AD showed similar efficacy with 0.5 mg/kg and 2 mg/kg doses Q4W and Q8W. Also in the recent phase 2a study in UP preliminary results showed, that 0.5 mg/kg dose presented a trend to better pruritus improvement at 4 weeks following one injection compared to 0.125 mg/kg and 2 mg/kg doses. Thus, the dose of 0.5 mg/kg was selected for the current phase 2a study in PN patients. Patients will be treated with 3 injections of 0,5mg/kg Q4W in order to demonstrate the efficacy or Nemolizumab in lesions of this chronic condition.

Rational for primary endpoint:
Nemolizumab has demontrated its efficacy in terms of pruritus improvement in previous non clinical and clinical studies with a rapid onset of action observed in the first week following administration in clinical studies. Based on the observations that itch is the cardinal symptom of PN, believed to precede lesion occurrence and associated with a high impact on QoL of patients, the effect on pruritus was chosen as the primary endpoint in this study with an effect to be demonstrated in the first month after treatment administration, as in uremic pruritus patients.

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSFV to LSLV) is approximately 10 months. The date of end of the clinical trial is defined as the date of the last visit of the last subject.

Clinical trial participation for each subject is approximately 22 weeks from the first screening visit to the last visit.

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

5 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

5.1 Number of subjects

As a screen failure rate of approximately 30 percent is expected, approximately 100 subjects may have to be screened in order to get 70 randomized subjects (35 subjects per treatment group).

5.2 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must present with a clinical diagnosis of PN for at least 6 months before screening visit, with at least 20 nodules with a bilateral distribution,

on upper limbs with or without lesions on the trunk and/or lower limbs and who must meet the following inclusion and exclusion criteria described in section 5.3 and 5.4 below.

Multiple coexisting and underlying diseases ranging from dermatological, systemic, neurological or even psychiatric disorders are known to be associated to PN (Iking et al. 2013). Therefore, eligible PN patients for the clinical trial, who fulfill all the inclusion and exclusion criteria and presenting with controlled underlying disease(s) or conditions such as atopic diathesis, diabetes, thyroid disorders, or psychiatric disorders (such as depression and anxiety) can be included in the study.
In order to be eligible for the clinical trial, subjects must fulfill all of the following criteria (when applicable), both at screening and at baseline unless specified.

5.3 Inclusion criteria

1. Male or female of at least 18 years at screening
2. Clinical diagnosis of PN for at least 6 months with:
   - Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs
   - At least 20 nodules on the entire body with a bilateral distribution
3. Severe pruritus defined as follows on a Numerical Rating Scale (NRS)
   - At the Screening visit 1: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous 3 days
   - At the Baseline visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous week;
     NOTE: *NRS score should be measured on at least 5 days during the week preceding the baseline visit*.
4. 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 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) hormonal contraception, oral, or intra-vaginal, or transdermal
    - Injectable or implants hormonal contraception
    - Intra-uterine devices
    - Bilateral tubal ligation, or tube insert (such as Essure system) provided it has been inserted at least 3 months before the study
    - Vasectomized partner (for at least 3 months)
5. Willing and able to comply with all the time commitments and procedural requirements of the clinical trial protocol
6. Willing and able to use electronic devices for Patient reported outcomes and actigraphy devices during the study or living with someone who can ensure that the electronic devices will be properly used.
7. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US., as verified by signing a written authorization
8. Understand and sign an Informed Consent Form (ICF) prior to any investigational procedures being performed.
9. Subject agrees that his/her samples (blood and skin) collected for PD analysis will be kept at GALDERMA R&D after analysis as part of a long-term research (Program (2) – "Physiopathological study on skin disease to identify new dermatological medications; Initial declaration CP ECOH : DC-2008-315, 31/01/2009)

5.4 Exclusion criteria

1. Chronic pruritus resulting from another condition than PN such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease
2. Unilateral lesions of prurigo (e.g only one arm affected)
3. Cutaneous bacterial or viral infection within 1 week before the baseline visit.
4. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit, or during the screening period, unless completely resolved at the screening/ baseline visits respectively,
5. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results and/or put the subject at

significant risk according to Investigator's judgment (e.g. solid cancer, AIDS, serious or uncontrolled cardiac disease…) at Screening or Baseline.
***NOTE**: Patients with **controlled diseases such as** diabetes mellitus, thyroid disorders and psychiatric disorders (such as depression and anxiety) are eligible*

6. Any active dermatoses that would need immediate therapy.
7. Subject with active atopic dermatitis or known with recurrent flares of atopic dermatitis
   ***NOTE**: patients with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e. specific IgE), are eligible for the study*
8. Neuropathic and psychogenic pruritus (notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia)
9. 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** : Subject with a positive HBcAb and a negative HBsAg can be included in this trial if HBsAb is positive (considered immune after a natural infection)*
10. Subject having any of the abnormal lab criteria listed below, at the screening visit:
    - Elevated ALT / AST ≥ 3 ULN
    - Elevated CPK > 1.5 ULN, unless not confirmed on a repeat assessment to be performed at least 72h after the first one
    - Neutrophil count < 1.5 x 10^3/µl
    - Creatinine clearance <60ml/min/1.73m² calculated with the CKD-EPI formula (Levey et al 2009)
    - Any other abnormal lab result that would be considered as clinically significant by the investigator
11. Subjects with a medical history of asthma that fulfill any or more of the conditions 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 at screening or baseline visit
12. Latent or active TB, as determined by a positive Quantiferon-based TB test result at screening visit.
    ***NOTE**: In case of indeterminate result, the test should be repeated in local laboratory at screening 2(only one retest is allowed). If the test is still indeterminate, the subject will not be included.*
13. Having received any of the following treatments within the specified time frame prior to the baseline visit:

Table 3 Forbidden therapies

Topical treatments	**Wash-out periods**
Calcineurin inhibitors (tacrolimus, pimecrolimus), TCS, vitamin D analogs , PDE-4 inhibitors	2 weeks
Any topical treatment other than moisturizer (e.g capsaicin, cryotherapy)	2 weeks
Emollients or moisturizer with menthol, capsaicine, polidocanol or other having "anti-itch" claim	1 week
Systemic treatments	**Wash-out periods**
Corticosteroids oral, injectable	4 weeks
immunosuppressive or immunomodulatory drugs (e.g, azathioprine, methotrexate, thalidomide, cyclosporine	8 weeks or 5 half-lives (whichever is longer)
Antihistamines	1 week
Phototherapy	4 weeks
Roxitromycin, erythromycin	1 week
Opiods (naltrexone, naloxone, nalbuphine etc), NK1 receptor antagonists (aprepitant), antiepileptics (gabapentin, pregabalin)	4 weeks or 5 half-lives (whichever is longer)
Biologics, Retinoids	8 weeks or 5 half-lives (whichever is longer)
Live vaccine	4 weeks
Drugs with sedative effect such as benzodiazepines, imidazopyridines, hydroxizine barbiturates, or sedative anti-depressants such as amitryptiline, paroxetine, except if these treatments were taken at a stable dose for at least 3 months before screening	3 months

14. Subject planning to change emollients or moisturizer including over the counter (OTC) preparations, or have bath oil treatment for relief of pruritus during the course of the trial.
15. Pregnant women (positive serum pregnancy test result at the screening visit, or positive UPT at baseline visit), or women planning to become pregnant during the clinical trial
16. Lactating women
17. Prior treatment with nemolizumab
18. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years before screening visit, except for
    - basal cell carcinoma, actinic keratoses or squamous cell carcinoma *in situ* (including Bowen's disease) that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit
    - carcinoma *in situ* of the cervix, or non-invasive malignant colon polyps that have been removed
19. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g. monoclonal antibody)
20. Known or suspected immunosuppression
21. Any social or medical condition such as drug or alcohol abuse, drug dependency, mental disorder that, in the Investigator's judgment might interfere with the subject's ability to comply with the requirement of the protocol
22. Planned or expect to have a major surgical procedure during the clinical trial

23. Subjects unwilling to refrain from using prohibited medications during the clinical trial (see Section 5.4 item 13)
24. 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
25. Vulnerable subject as defined in ICH/GCP

5.5 Specific exclusion criteria for skin biopsies

The following criteria not allowing the biopsy samples (at baseline and week 12) will be checked at screening, only for subjects who accept skin biopsies (by signing an additional consent) :

1. The subject has history of coagulation disorders
2. The subject has known sensitivity to local anesthetics.
3. The subject is using platelet aggregation inhibitors, or anticoagulants (of note, sporadic intake or continuous low-dose intake of aspirin or other NSAIDS is allowed).
4. The subject has history or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of the possible scars of the subject.

5.6 Previous and concomitant therapies

5.6.1 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 PN and underlying disease(s) if any, 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 or formulation) during the course of the clinical trial, or
- any new therapies received by the subject since the screening visit

5.6.2 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

5.6.3 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 7.2.4), in which case the medication will be linked to an item in the medical history.

5.6.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 5.4) or in prohibited concomitant therapies (see Section 5.6.5), all therapies are authorized.

Sedatives and antidepressants as described in Table 3 are allowed if they have been administrated for at least 3 months at a stable dose before screening baseline and dose changes are not planned during the study.

Starting from the screening visit, subjects will be instructed to use their daily moisturizer, if it is not containing any compound with known anti-itch effect (such as menthol, polidocanol; etc.). It is not authorized changing emollients or moisturizers or applying products for itching relief during the course of the study.

5.6.5 Prohibited concomitant therapies

The therapies listed in Section 5.4 item 13 are prohibited because they may interfere with the efficacy and/or safety assessment of the study drug. If prohibited therapies become a necessary treatment for the safety or best interest of the subject, GALDERMA or its designee (i.e. Contract Research Organization (CRO)) should be notified to discuss possible alternatives prior to administration of a prohibited therapy and the pertinence and the modalities for the subject to continue in the clinical trial.

5.7 Rescue therapies

If deemed to be medically necessary by the Investigator, rescue treatments for pruritus could be added to the study drug from Day 29. In that case, all efficacy and safety assessments should be completed before starting the rescue treatments.

Rescue therapies should prioritize the use of antihistamines, which are commonly used and are not associated with significant side effects. If the investigator considers it necessary, occasional local treatment with TCS of mid-potency might be also combined with antihistamines.

In case of the above mentioned rescue therapies, the administration of study drug can be continued.

If the subject receives another rescue treatment for PN than the ones listed above (e.g. cyclosporine, thalidomide, gabapentin, phototherapy), the study medication must be stopped.

5.8 Procedures/Reasons for subject discontinuation from the study

Subjects may discontinue from the study or only discontinue the study treatment (as described in Section 6.5)

The reasons and procedures for subject discontinuation from the study are described below..

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 4 visit (visit for the primary endpoint) should attend an early termination visit and a final visit 10 weeks after the last study drug injection for safety follow-up. Subjects discontinued after the week 4 visit should attend a final visit 10 weeks 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 “consent withdrawal by the subject” or “others”, the subject will be questioned to rule out the possibility of an AE. If an AE leads to study discontinuation, AE should be chosen as the reason instead of “withdrawal by the 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.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Exit Form.

For discontinuation due to an AE, the Adverse Event Form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

GALDERMA may also decide to prematurely terminate or suspend a subject's participation in the clinical trial.

6 CLINICAL SUPPLIES

6.1 Clinical supply 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	0.5 mg/kg	Not applicable
Route	Subcutaneous injection	Subcutaneous injection
Dose regimen	3 injections (baseline, Week 4, Week 8)	3 injections (baseline, Week 4, Week 8)
Treatment duration	12 weeks	12 weeks

6.1.2 Subject Identification Number (SIN)

Upon signature of the ICF, each subject will be assigned a subject identification number (SIN). The SIN will be allocated in ascending sequential order to each subject.

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 two treatment groups (0,5mg/kg or placebo) in a 1:1 ratio at baseline. Details of the IRT procedure will be described in the IRT manual.

Randomization will be stratified according to presence or absence of background of atopy.

6.1.4 Randomization number

A randomization number will be allocated to each eligible subject at baseline by IRT system.

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 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 unblinded, which means that he/she will be aware of the exact treatment to be administered to the subjects.

Once the dosing solution is prepared, the pharmacist is to calculate the amount of solution to be injected to the subject, taking into account their weight (a dose of 0.5mg/kg is to be administered to the subject). The needed amount of solution 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.

6.1.6 Other supplies

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

6.2 Study drugs 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.

6.3 Supplies management

6.3.1 Accountability

Study drug sent to the 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.

6.3.2 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 Clinical Research Associate (CRA) as specified in the pharmacy manual.

6.3.3 Dispensing and return

All drug preparation must be appropriately performed and documented by the designated personnel (unblinded pharmacist or other qualified personnel). Any error in the preparation of dosing solution must be reported to the 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.

6.3.4 Treatment compliance management and record

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

6.4 Dose modification

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

6.5 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)
- Other systemic rescue therapies for PN (such as cyclosporine, thalidomide, gabapentin, phototherapy)
- 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 Table 2, except those who withdraw their consent for study participation or in case of pregnancy.

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.

6.6 Blinding

6.6.1 Verification of blinding

This is a double-blind clinical trial, which means that neither the subject nor the investigator/evaluator have access to the treatment received by the subject. With the exception of the unblinded pharmacist (or other qualified personnel) who will handle study drug preparation, and the unblinded CRA who will monitor the drug records only, 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 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 filled syringe(s) with required volume of dosing solution ready for injection;

3. The unblinded pharmacist (or other qualified personnel) will be instructed to not discuss the study drug with the investigator/evaluator and the subjects;

4. An 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 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;

6.6.2 Un-blinding 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 Galderma or its designee before breaking the blind. If not possible to discuss before, investigator must document the date, time and reason for the unblinding and notify Galderma or its designee immediately afterwards.

To allow the analysis to be done on the data, up to 4 weeks after the initial injection, a database lock will be done after at least 40 subjects have completed their Week 4 visit or discontinued before. An unblinding of the database will be performed for the study statistician. The Data manager and CRAs will remain blinded during the course of the study.
After this analysis, all efforts will be done to maintain the whole data blinded for other team members (except statistician).

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy measurements

Efficacy assessments 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 Assessment of pruritus and quality of life by the Subject

7.1.1.1 Pruritus Numeric Rating Scale (NRS)

Pruritus NRS (Appendix 2) is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours all along the study from first screening visit to the follow

up visit. Subjects will receive instructions on how to record their pruritus NRS scores on an electronic device, and will complete the assessment once daily at home in the evening throughout the clinical trial (including 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?"

7.1.1.2 Verbal rating scale (VRS)

The VRS (Appendix 3) consists of a list of adjectives describing different levels of symptom intensity (Phan et al., 2012), to be used by the subjects to report the intensity of their pruritus (itch) over the last 24 hours. Subjects will receive instructions on how to record their pruritus VRS scores on an electronic device, and will complete the assessment once daily in the evening from Screening visit 2 and throughout the clinical trial (including the follow-up period). In the eDiary, patients will mark on a 5-point VRS (Ständer et al. 2013), the response that best describes their pruritus intensity in the last 24 hours.

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

- For average itch intensity: "On a scale of 0 to 4, with 0 being 'no itch' and 4 being 'very severe itch', how would you rate your itch overall during the previous 24 hours?"
- For maximum itch intensity: "On a scale of 0 to 4, with 0 being 'no itch' and 4 being 'very severe itch', how would you rate your worst itch during the previous 24 hours?"

7.1.1.3 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 PN (see Appendix 4). 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 from screening 2 (Day -7) to Week 4 visit (Day 29).

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 PN' and 10 being 'I cannot sleep at all due to the signs/symptoms of PN', how would you rate your sleep last night?"

7.1.1.4 Dynamic Pruritus Score (DPS)

The 9-point DPS (Appendix 5) 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 et al. 2017). Subjects will receive instructions on how to record their DPS score on an electronic device displaying the scale in their local language, and will complete the assessment 24, 48h and 72h after the 1st injection at baseline and at W4 before the second injection. This assessment will be performed by the subject based on his itch perception over the 24h hours preceding the baseline injection.

7.1.1.5 Dermatology Life Quality Index (DLQI)

DLQI (Appendix 6) is a validated 10-item questionnaire, covering domains including symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment. 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 given 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).
This assessment will be performed by the subject on the provided electronic device at baseline, week 4 and week 12 and in case of Early termination visit / Unscheduled visit, if applicable.

7.1.2 Assessment of prurigo by the Physician

7.1.2.1 Investigator Global Assessment (IGA) of Prurigo

IGA (see Appendix 7) is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the investigator or trained designee to evaluate the severity of the disease. IGA corresponds to the overall assessment of the severity of prurigo including presence of crust and nodules or skin bleeding that will be evaluated at Baseline, Week 4, Week 8, Week 12, Week 18 & in case of Early termination visit / Unscheduled visit, if applicable.

7.1.2.2 Assessment of Prurigo Activity Score(PAS)

The evaluation of the disease will be performed by the Investigator using the Prurigo Assessment Scale (PAS) (see Appendix 8) at baseline and Week 12 using the entire scale and at week 4, 8,18 and in case of Early termination visit / Unscheduled visit, if applicable using item 5 (number of lesions only) and 6 (excoriation/crusts and healed lesions) (Schedel et al. 2013).

7.1.3 Appropriateness of efficacy measurements

All the above mentioned patient-reported outcomes and investigator evaluations will be used to assess pruritus, lesions severity and the impact on the subject's QoL.

Efficacy on pruritus will be evaluated using pruritus NRS and VRS. NRS initially validated in pain, (Williamson A et al 2005) showed a good correlation with the commonly used Visual Analog Scale (VAS) when assessed in pruritus (Phan et al 2012), with the advantage of an easier usage. The current recommendation for chronic pruritus assessment in clinical trials is to associate NRS in combination with VRS (Ständer et al 2013).

No validated scale defining PN severity is available today. Prurigo Activity score (PAS) (Schedel et al 2013) recently validated for clinical assessments includes descriptive items such as lesions type, number and distribution. An IGA (not validated) will also be used in the current trial to determine the global severity of the disease and the clinical response to the treatment.

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Several instruments have been proposed over time to evaluate the impact of pruritus on patients' QoL (Ständer et al 2013, Erturk et al 2012). DLQI questionnaire being the most frequently used instrument. Many patients with chronic pruritus also report problems with falling asleep or waking up frequently during night impacting the QoL. Thus, a measurement of sleeping disturbance may be a valuable aid in the valid assessment of pruritus. This will be evaluated by the subject using NRS and by objective measurements such as actigraphy (Section 7.5.1) .

7.2 Safety assessment

Safety assessments will be conducted for all subjects at the screening visit (upon the signature of the ICF) and at subsequent visits as defined in Table 2. Safety assessments include:

- AE, SAE, AESI
- 12-lead Electrocardiogram (ECG),
- Physical examination, vital signs, and body weight
- Respiratory assessments for all subjects, and PEF measurement only for subjects with a medical history of asthma
- Laboratory safety tests

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.

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

Physical examination should be performed according to Table 2. The investigator should assess all abnormal findings for clinical significance.

All clinically significant abnormal findings at the screening visit will be recorded in the Medical History form.

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

7.2.2.2 Vital signs

Vital signs assessment should be performed 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).

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 and weight measurement should be performed according to Table 2. Any clinically significant weight changes from the screening visit will be recorded as an AE.

7.2.2.4 Respiratory assessments and PEF measurement

At each visit, investigator or designee will perform a respiratory medical 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 by 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 decreased by ≥20% from baseline 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.

The procedures to be followed for reporting asthma/worsening of asthma are described in Section 7.2.4.2.3.

7.2.3 Laboratory safety tests

The following laboratory safety tests will be performed according to Table 2; whenever possible, the tests will be performed in fasting conditions:

- 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 (semi-quantitative analysis): 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 1, and UPTs monthly at all subsequent visits (including baseline visit) until the end of the study and in case of Early termination visit / Unscheduled visit, if applicable. If the result of UPT is positive, it must be confirmed with a serum pregnancy test.
- Virology, including HBsAg, HBsAb, HBcAb, hepatitis C, HIV-1 and -2 antibody

- TB test (using QuantiFERON-based TB test)
- IgE

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

The Investigator or a medically qualified Sub-Investigator must review and evaluate laboratory values for each subject in a timely manner. The Investigator or designee will check all laboratory reports by affixing his initials and date and note directly on the report whether or not each out-of-range laboratory value is clinically significant. An out of range laboratory value should be considered as clinically significant if either of the following conditions is met:

- 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 study drug, close observation, more frequent follow-up assessments, or further diagnostic investigation

For each out-of-range laboratory result, the Investigator or designee will enter directly in the eCRF the Investigator judgment on the presence or the absence of a clinical significance.

All clinically significant out-of-range laboratory values for blood and/or urine samples collected at screening will be recorded in the medical history (report a diagnosis rather than an individual laboratory parameter abnormality whenever possible).

All clinically significant out-of-range laboratory values for blood and/or urine samples collected after screening, 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., there is a significant change from screening).

If the Investigator observes a clinically relevant laboratory test value, the laboratory tests will be repeated as soon as possible and monitored until the values have returned to normal and/or an adequate explanation for the abnormality is found. This does not apply to screening laboratory test values, except for TB test and CPK, which will be assessed at Screening 1 visit, and for which one retest is allowed at the Screening 2 visit (see Table 2).

In instances when a laboratory abnormality is reported as an AE or AESI, whenever possible, the Investigator is to provide a diagnosis rather than reporting individual laboratory abnormalities.

The following out-of-range laboratory values should be reported as an AESI (see Section 7.2.4.2.1):

- 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.

A summary of sample volumes and the number of blood samples is detailed in Appendix 1.

7.2.4 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the eCRF with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial center personnel for reporting AEs and medical emergencies.

7.2.4.1 Definitions

7.2.4.1.1 Adverse events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) 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 also be reported as an AE.
- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Pregnancy is not to be considered as an AE; however, is an important medical event that must be monitored as described in Section 7.2.4.2.4.
- Each new episode of a chronic disease (e.g. hay fever, allergy, etc.) from the screening visit should be reported as a new AE.

7.2.4.1.2 Serious Adverse events (SAE)

A SAE is any untoward medical occurrence that meets any of the following criteria :

- 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 a 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 was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical 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).

7.2.4.1.3 Adverse Events of Special Interest (AESIs)

An AESI is a noteworthy event for the particular study drug that can be appropriate to monitor closely. It could be 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
- Elevated CPK (≥ 2.5 ULN), if considered as related to the study drug by the investigator
- Asthma or worsening of asthma ; this AESI will have to be reported within 24 hours, see Section 7.2.4.2.3
- IRR (local and systemic reactions, including hypersensitivity)
- Peripheral edema
- Skin or systemic infection
- Headache
- Exacerbation of AD, in subjects with medical history of AD

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. Refer to Section 7.2.4.2.3 for the procedures to be followed in case of new occurrence or worsening of asthma.

If applicable, additional information may be required (e.g. photo documentation of the AE) to allow a better evaluation and understanding of the above listed AEs.

7.2.4.1.4 Unexpected adverse drug reaction

According to 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. Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approved product).

7.2.4.1.5 Adverse event reporting period

The clinical trial period during which AEs must be reported is starting from the subject's signature of the Informed Consent Form to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical trial, even after the subject has completed the clinical trial. The Investigator should be diligent in looking for possible latent safety effects that do not appear until a medication has been discontinued.

7.2.4.1.6 Severity

Severity is a clinical determination of the intensity of an AE and not of a disease.

The Investigator is to classify the intensity of AEs using 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

7.2.4.1.7 Relationship to the study drug(s) and/or clinical trial 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(s) (i.e. nemolizumab or placebo) and/or study procedure (e.g. injection, blood sample collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction,

temporal relationships, positive dechallenge or rechallenge, 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:

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 a clinical trial protocol procedure (e.g. injection, 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 a clinical trial protocol procedure and the AE.

7.2.4.2 Reporting procedures

7.2.4.2.1 Procedures for reporting Adverse Events

The collection of AEs is from the time that a subject signs the ICF to their final visit.

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

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

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

Reporting procedures for SAEs (see Section7.2.4.2.2), AESI to be reported within 24 hours (see Section7.2.4.2.3) , and pregnancies (see Section7.2.4.2.4) must be followed.

7.2.4.2.2 Procedure for reporting a Serious Adverse Event

For a SAE occurring during the clinical trial, regardless of whether it is related to the study drug and/or study procedure or not, 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 classified 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: NEM0-SRP115828-SAE@PAREXEL.com

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.

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

7.2.4.2.3 Procedure for reporting asthma/worsening of asthma

In this study, AESIs have been defined as described in Section 7.2.4.1.3. Among these AESIs, new occurrence of asthma/worsening of asthma will have to be reported within 24 hours according to the procedure described below.

Whether new occurrence of asthma or worsening of asthma is assessed as related to the treatment or not, the Investigator is to do the following:

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. *(Of note, in case there is no access to the eCRF, please refer to the instructions in the Investigator Site File for reporting an AESI).*
3. Send any relevant information or medical records (e.g. laboratory test results) to the GMS within the CRO (see contact details in Section 7.2.4.2.2), **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.

7.2.4.2.4 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 is to do the following:

7. **Withdraw the subject from the clinical trial. The subject must not receive any further injection of the study drug.**
8. 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 7.2.4.2.2**)**. *(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).*
9. 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.
10. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, 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.
11. 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.
12. 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 7.2.4.2.2).

7.3 Pharmacokinetic assessments

Blood samples will be collected at specific time points according to Table 2 for measurement of PK profile of nemolizumab and Antibodies anti-nemolizumab (ADA).

The nemolizumab serum exposure will be assessed at the following time-points: baseline, weeks 1, 2, 4, 8, 12, 16 and 18 and in case of early termination or any unscheduled visit for safety reason.

ADA will be assessed at baseline, weeks 4, 8, 12, 16 and 18 and or in case of early termination or unscheduled visit for safety reason.

7.3.1 Technical procedures for pharmacokinetic blood sampling

At each sampling time for PK assessment, 2 mL of blood will be collected for the assessment of nemolizumab concentrations in serum samples.

For ADA assessment, 2 mL of blood will be collected at the same time as PK sampling.

PK samples are to be collected before drug injection (pre-dose samples) at Baseline, weeks 4, 8; the maximum allowed time windows for PK blood sampling is 30 minutes before drug injection. At weeks 1, 2, 12, 16 and 18 blood samples will be collected at the corresponding usual time of drug injection with an allowed time window of ±1h.

The date and time of collection for each sample along with the time of the last study drug injection and missed injections have to be recorded on the eCRF.

Processing of blood samples for PK and ADA assessments will be described in a specific manual.

Volumes of blood to be obtained for PK, ADA tests are summarized in Appendix 1.

7.3.2 Serum and PK analyses

Nemolizumab serum concentrations will be determined using validated ELISA method by a sponsor representative. A bioanalytical plan describing the details of the bioanalytical work related to serum samples of nemolizumab assessment will be written before the beginning of the sample analysis.
The results will be described in a bioanalytical report, which will be included as an appendix in the final clinical study report.
The PK analyses will be performed by a Sponsor representative. The results will be described in a PK report, which will be included in the final study report.

The PK parameters will be determined by a model independent approach (non-compartmental method) using individual serum concentration. 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:

- 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 12 to week 18 (or Early termination or Unscheduled visit if applicable):

- $t_{1/2}$: the terminal half-life value ($t_{1/2}$) will be calculated using the equation ln2/k after the last drug injection (week 8).
- $AUC_{0\text{-}t}$: 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}).
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve calculated by the mixed linear- logarithmic trapezoidal method from T0 and extrapolated to time infinity as: $AUC_{0\text{-}inf}=AUC_{0\text{-}t}+ C_{last} / k_{el}$. When the extrapolation represents more than 20%, $AUC_{0\text{-}inf}$ and $t_{1/2}$ will not be reported.

At weeks 4, 8, 12, 16, 18 (or Early termination or Unscheduled visit if applicable):

- C_{trough}: The residual drug concentration

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 skin samples (D-Squames and skin biopsies) will be collected to investigate the effect of nemolizumab on biomarkers.

As much as possible, skin sampling will be performed in similar body areas for all samples in all patients, on a selected area at baseline, such as the upper arms. Biopsies on prurigo lesions will be performed at baseline and post-treatment only for consenting subjects. Non-lesional sample will be taken at baseline in areas with no scratch such as the inner part of the upper arm approximately 5cm, apart from lesional skin.

The detail of the procedures for PD samples and storage conditions will be described in an Operational manual.

All collected samples will be sent to GALDERMA R&D for analysis. After performance of the planned investigations, the remaining samples 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).

Volumes of blood to be obtained for PD tests are summarized in Appendix 1.

7.4.1 Blood samples for PD

Blood samples for speficic IgE will be collected at baseline only for all subjects. These samples will be analysed by the central laboratory.
Plasma samples will be collected at baseline, week 4 and week 12 for analysis of IL-31 protein expression levels for all randomized subjects.

7.4.2 D-Squames samples

Stratum Corneum (SC) samples will be collected for all randomized subjects using D-Squames to evaluate the microbiome, and cytokine and chemokine expression levels. SC samples will be collected for all randomized subjects at baseline visit, at Day 29 (week 4) and at Day 85 (week 12) as described below:

- Baseline visit (proteomic and microbiome analyses)
  - Non lesional skin
  - Lesional skin at baseline
- Week 4, day 29 (proteomic analysis only):
  - Lesional skin
- Week 12, day 85 (proteomic and microbiome analyses) :
  - Lesional skin

For proteomic analysis, 10 large rectangle D-squames (D100 Monaderm) will be used for consecutive tape stripping. Cytokine/chemokine profile including IL-31 will be performed using ELISA-like technologies. The 3 lesional samplings of D-squames at baseline, week 4 and week 12 will be taken on exactly the same anatomical location, no matter if the lesion regressed or not.

For microbiome analysis, one D-squame will be used (DS100 Monaderm, 2.2 mm diameter) being successively applied in the targeted area at least 20 times.

D-squames sampling should be performed as far as possible in a similar body location for every patient (e.g.upper arms) on selected areas and recorded in the CRF.

7.4.3 Skin biopsies

Three 4-mm skin biopsies will be performed (only for subjects who accept skin biopsies by signing the additional consent form) for IL-31 and IL-31RA quantification by immunohistochemistry techniques and IL-31 and IL-31RA mRNA by genomics analysis, if sufficient biological material is available.

Body location for biopsy sampling should be performed as far as possible in a similar body location for every patient (e.g. upper arms) and recorded in the eCRF.

The samples will be collected as much as possible on the same anatomical area than D-squames, in an adjacent lesion with as much as possible a similar clinical presentation.

Skin biopsies will be performed as it follows:

- Baseline visit:
  - One biopsy on lesional skin (nodule)
  - One biopsy on non lesional skin (e.g. inner arm): approx. 5 cm apart from lesion skin

- Week 12 (day 85) visit:
  - One biopsy on lesional skin after treatment (on a nodule selected at baseline)

7.5 Biophysical assessments

7.5.1 Actigraphy

High resolution actigraphy will be used in this study to evaluate scratching events and duration of sleep during the night. This is a non-invasive, ambulatory, wrist-mounted device designed to capture, record, and store all wrist movements, which is an indicator of whole body movement. The High resolution actigraphy provides an objective method for measuring scratching events during the night and other parameters such as sleep quality (Almazan et al 2016).
Philips will, in accordance with procedures, centrally analyze assessment data for scratching events and sleep parameters obtained from the actigraphy device and submit data to the CRO.
Patients will wear two devices, one on each wrist, from D-7 and every day during the first 4 weeks of the study, by following the instructions provided by the CRO.

7.5.2 Whole body imaging

This device will be used in equipped sites only and the photographs of the entire body will be taken according to the operational manual provided by the Sponsor at least at baseline and Week 12 (Day 85) and if it is possible at Week 4 (Day 29), Week 8 (Day 57) , and Week 18 (Day 126. It is for illustration and as exploratory evaluation of the lesions improvement.

8 CLINICAL TRIAL VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of clinical trial visits

Please refer to the Schedule of Assessments table in the Synopsis (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, PK and PD assessments
4. Administration of study drug

8.1.1 Screening period (Day -28 to Day -1)

*8.1.1.1 **Visit 1** / Screening visit 1 (Day – 28 to Day -8)*

Screening visit 1 must be performed between Day -28 and -8 prior to Day 1 visit.

At this Screening visit, the Investigator or designee will:

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, photo and biopsy 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. Assign the subject a SIN.
5. Perform a physical examination, vital signs measurements and ECG.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Confirm that the subject meets inclusion/exclusion criteria for screening visit.
8. Complete serum pregnancy test if the subject is a female of childbearing potential.
9. Collect and record any AEs starting from the time of Informed Consent signature.

10. Collect blood sample for CPK, TB test, IgE analysis and viral serology
11. Ask the subject about the mean worst itch daily intensity over the previous 3 days according to NRS and record the information and record the information on the electronic device.
12. Schedule the Visit 2/Screening visit 2 and instruct the subject about the precautions to be taken for visit 2 (Avoid intensive sport, fasting condition for biochemistry analysis)

*8.1.1.2 **Visit 2** / Screening visit 2 (Day –7)*

At this Screening visit, the Investigator or designee will:

1. Collect information regarding concomitant therapies and procedures and AEs.
2. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
3. Check TB result previously performed. In case of inderterminate results, collect blood sample to retest this parameter.
4. Check IgE & virology results
5. Collect blood sample for hematology, blood biochemistry.
6. Collect urine for urinalysis.
7. Instruct the subject on how to use the electronic device for the daily evaluation of pruritus NRS, VRS, sleep disturbance NRS. Remind the subject to report the assessments on a daily basis on the ePRO according to the protocol.
8. Provide the subject with electronic devices for pruritus assessments.
9. Instruct the subject on the use of the watches for Actigraphy
10. Provide the subject with the watches for Actigraphy assessments
11. Schedule the Visit 3/Day 1.

8.1.2 Treatment period

8.1.2.1 Visit 3 / Baseline visit (**Day 1**)

At the Baseline visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Check laboratory results (hematology, biochemistry, virology, urinalysis, IgE, TB tests) from the Screening visits.

3. Complete urine pregnancy test if the subject is a female of childbearing potential.
4. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
5. Perform a physical examination (including height and weight), vital signs measurements and ECG.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma
7. Check subject's record for pruritus NRS and VRS and sleep disturbance NRS.
8. Confirm the eligibility of the subject according to inclusion and exclusion criteria. Enroll the subject in the clinical trial and record the corresponding SIN in the eCRF
9. Complete the evaluation of PAS and IGA.
10. Take whole body photographs (selected centers only).
11. Ask subject to complete the DLQI.
12. Check subject's use of watches for Actigraphy
13. Collect urine for urinalysis.
14. Collect blood sample for hematology, and entire blood biochemistry
15. Perform D-Squames.
16. Perform 4-mm biopsies for subjects who consented by signing the additional ICF
17. Collect blood samples for PK, ADA & biomarkers before drug injection.
18. The pharmacist (or other qualified personnel) will:
    a. Prepare the syringe of dosing solution of appropriate volume of nemolizumab or placebo according to the pharmacy manual and the specific instruction provided by the IRT system;
    b. Provide the prefilled syringe to the blinded investigator or qualified personnel for injection.
19. Blinded investigator or qualified personnel will administer the study drug subcutaneously to the subject, who will remain under medical observation for at least 30 minutes before been discharged.
20. Instruct the subject on how to use the electronic device to evaluate DPS 24, 48, and 72 hours after study drug administration, and remind subject about the daily evaluation of pruritus NRS, VRS and sleep disturbance NRS.
21. Complete the Subject Enrollment Log.
22. Schedule the next visit V4 Day 8.

8.1.2.2 Visit 4 / Day 8 Week 1 (+/-1 day) & Visit 5 / Day 15 Week 2 (+/-2 days)

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Perform vital signs measurements.
3. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma
4. When applicable check biopsy healing (for subjects who have consented).
5. Collect PK blood samples.
6. Check subject's record for pruritus NRS and VRS and sleep disturbance NRS

   Remind the subject to evaluate NRS and VRS and sleep disturbance NRS daily by completing their device
7. Check subject's use of watches for Actigraphy
8. Schedule the next visit.

8.1.2.3 Visit 6 / Day 29 Week 4 (+/-2 days) & Visit 7 / Day 57 Week 8 (+/-2 days)

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Perform physical examination & vital signs measurements (**including weight**).
3. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
4. Perform ECG at visit 7/Day 57 only
5. Complete urine pregnancy test for female of childbearing potential only.
6. Complete the evaluation of PAS and IGA.
7. Check subject's record for pruritus NRS and VRS & sleep disturbance NRS
8. Ask subject to complete the DPS & DLQI before injection at Visit 6/Day 29 only
9. Collect the watches for Actigraphy analysis at Visit 6/Day29 only
10. Collect urine for urinalysis at Visit 6/Day29 only.
11. Collect blood sample for hematology and entire blood biochemistry, at Visit 6/Day29 only
12. Collect blood samples for biomarkers at Visit 6/Day29 only.

13. Collect PK blood samples for PK and ADA before drug injection.
14. Perform D-Squames sampling at Visit 6/Day29 only.
15. Take whole body photographs (selected centers only) if possible
16. Perform subcutaneous study drug injection and observe for at least 30 minutes before discharging the subject.
9. Remind the subject to complete the device daily
10. Schedule the next visit

8.1.2.4 Visit 8 / Day 85, Week 12 (+/- 5 days)

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Perform physical examination (including weight) & vital signs measurements.
3. Collect blood samples for hematology & entire biochemistry.
4. Collect urine to perform urinalysis test.
5. Complete urine pregnancy test for female of childbearing potential only.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Check subject's record for pruritus NRS and VRS and remind subject to complete them daily
8. Ask subject to complete the DLQI.
9. Complete the evaluation of PAS and IGA.
10. Collect blood samples for PK, ADA & biomarkers.
11. Perform D Squames.
12. Perform 4-mm biopsies for subjects who consented.
13. Take whole body photographs when applicable.
14. Schedule the next visit for Visit 9.

8.1.3 Follow up period

8.1.3.1 Visit 9 / Day 113, Week 16 (+/- 5 days)

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Perform vital signs measurements.
3. Complete urine pregnancy test for female of childbearing potential only.
4. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
5. Collect blood samples for PK, ADA
6. Control the good healing of biopsies when applicable.
7. Check subject's record for pruritus NRS and VRS and remind subject to complete them daily
8. Schedule the next visit for Visit 10.

8.1.3.2 Visit 10 / Day 126, Week 18 (+/- 7 days)

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Check subject's record for pruritus NRS and VRS.
3. Perform physical examination & vital signs measurements.
4. Complete urine pregnancy test for female of childbearing potential only.
5. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
6. Complete the evaluation of PAS and IGA.
7. Collect blood samples for PK, ADA
8. Take whole body photographs (selected centers only).
9. Collect the device used for Pruritus assessments
10. Complete the exit form.

8.1.4 Early Termination visit or unscheduled visit:

The Investigator or designee will:

1. Collect information regarding AE (including review of laboratory values) and concomitant therapies/procedures.
2. Check subject's record for pruritus NRS and VRS.
3. Ask subject to complete the DLQI.

4. Complete the evaluation of PAS and IGA.
5. Perform physical examination & vital signs measurements and ECG.
6. Conduct respiratory medical assessments, including PEF for subjects with a history of asthma.
7. Complete urinalysis.
8. Complete urine pregnancy test for female of childbearing potential only.
9. Collect blood samples for hematology & biochemistry
10. Collect blood samples for PK and ADA.
11. Complete the exit form in case of early termination and collect e-devices.

8.2 Subject instructions (other than study drug administration)

Throughout the study duration, subjects should be instructed to use their own moisturizer emollient including OTC preparations or bath oil. They will be instructed to avoid any topical product for pruritus relief containing capsaicin, menthol or other during the course of the study

Subjects will be instructed to avoid intensive physical exercise before blood sampling for biochemistry (CPK) to limit false positive and to come on site for Screening visit 2 in fasting conditions.

9 STATISTICAL METHODS PLANNED

9.1 Variables to be analyzed

9.1.1 Efficacy endpoints

The primary efficacy endpoint will be the percent change from baseline in NRS to week 4 (weekly average of the peak).

The secondary efficacy endpoints will be:

- Absolute and Percent change from baseline in weekly average of the peak and average pruritus NRS to each visit
- Change from baseline of VRS at each time point
- DPS
- PAS: Distribution for item 6 (excoriation/crusts and healed lesions stages) and change from baseline for item 5 (in lesions number)
- IGA: Distribution score and success rate (defined as IGA=0[clear] or IGA=1[Almost clear] with two point improvement from baseline).

9.1.2 Safety endpoints

The safety endpoint measures for this study are as follows:
- Adverse events
- Laboratory tests
- Vital signs
- Physical exam and body weight
- 12-lead ECG
- PEF

9.1.3 PK endpoints

The PK endpoints measures for this study are as follows:
- Serum IL-31 concentration
- Anti-CD14152 antibodies

9.1.4 PD endpoints

The pharmacodynamic endpoints measures for this study are as follows:
- Serum: IL-31 concentration
- Dsquames : IL-31, IL-31RA expression level and Cytokine/chemokine profiling in Dsquames
- Skin biopsies : IL-31 and IL-31 RA quantification by immunohistochemistry techniques and IL-31 and IL-31RA mRNA quantification by genomics analyses.

9.1.5 Other endpoints

- Quality of life (DLQI)
- Objective assessment of scratching and sleep with Actigraphy
- The sleep disturbance NRS

9.2 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.

9.2.1 Data transformations

9.2.2 Populations analyzed, evaluability and limitation / evaluation of bias

The statistical analyses will be performed based on the following subject populations.

9.2.2.1 ***Intent-to-treat (ITT) Efficacy Population***

The ITT Population is defined as comprising all subjects who are randomized. All primary efficacy variables and secondary efficacy variables will be analyzed based on the ITT Population.

9.2.2.2 ***Per-protocol (PP) Efficacy Population***

The PP Population is defined as comprising the ITT subjects who have no major protocol deviations. This will be the primary population for this study.

Major deviations are categorized into 4 categories:

1) Entrance criteria deviations,
2) Non compliance,
3) Concomitant therapies taken during the study, interfering with efficacy,
4) Administrative errors such as unblinding or study drug dispensing errors.

PP analysis will be conducted only up to Week 4.

9.2.2.3 ***Safety Population***

The Safety Population is defined as comprising the ITT Population subjects who receive the study drug at least once. 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.

9.2.2.4 ***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.

9.2.2.5 ***PD analysis population***

The PD statistical analyses will be performed based on the PP population, and after exclusion of samples unable to produce reliable quantifications of cytokines, and/or immunohistological markers and/ or transcriptomic biomarkers, due to the material quantity and/or quality.

9.2.3 Data presentation and graphics

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

All efficacy variables will be summarized by treatment at each visit. The categorical variables [VRS, IGA, PAS (Item 6)] will be summarized by frequency and percentage for each response category (N, %). The continuous variables [weekly average NRS peak and mean, PAS (Item 5)] will be summarized using means, medians, minimum, maximum, and standard deviations for the data collected at each visit.

Quality of life questionnaire (DLQI) at each visit and the change from baseline will be summarized by treatment using descriptive statistics. Categorization of the score will also be summarized. (Hongbo Y, et al.,2005)

Treatment-emergent Adverse Events (TEAEs) will be tabulated in frequency tables by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (MedDRA). Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study drug(s), by severity, AESIs, and AEs leading to discontinuation. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

In addition, AEs with an onset prior to baseline will be listed separately.

Therapies and procedures ongoing at the baseline visit or starting after the baseline visit will be summarized separately from those ending at baseline or before.

PEF measurements (absolute values and change from baseline) will be summarized by visit and treatment group.

Vital sign measurements and the changes from baseline (Day 1/pre-dose) to the each post baseline timepoint will be summarized using descriptive statistics (n, means, standard deviation, median, minimum and maximum value).

For each vital sign a shift table with the number and percentage of subjects who are normal, abnormal (CS) and abnormal (NCS) will be displayed with the last pre-treatment value versus the post baseline scheduled on-treatment. Subjects with missing pair of data will not be counted in the percentages.

For physical exams, the number and percentage of subjects who are normal, abnormal (CS) and abnormal (NCS) will be displayed with the last pre-treatment value versus the post baseline scheduled on-treatment.

9.2.4 Inferential statistical analyses

The primary efficacy analysis of the percent change from baseline to week 4 of the weekly average of the peaks pruritus NRS, will be an ANOVA including the Treatment group as factor, presence and absence of background of atopy and country as a cofactors.

In addition to the per-protocol analysis, several sensitivity analyses on ITT population will be conducted for the primary endpoint. For ITT, NRS will be set to missing after rescue medication is used.

- The primary imputation method for any missing data will be the LOCF (Last observation carried forward) approach.
- Multiple Imputation (MI) using the Missing At Random (MAR) assumption will also be used. The MI procedure of the SAS system will be used to generate five sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing NRS score, with the following covariates included in the imputation model: treatment and non-missing data from earlier timepoints. The imputed datasets will be analyzed using the methodology described for percent change from baseline in NRS score. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS system. The seed number to be used will be the protocol number (115828).

For secondary endpoints:

The percent change from baseline to any visits of the weekly average of the peak and of the average pruritus NRS, will be analyzed separately via an ANOVA including the Treatment group as factor, presence and absence of background of atopy and country as a cofactors. The absolute change will be analyzed via an ANCOVA, same factors as the percent change but with including baseline NRS as a covariate.

IGA, DPS and PAS will be analyzed at any visits by the CMH test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS).

Proportion of subjects achieving success (IGA=0[clear] or IGA=1[Almost clear] with two point improvement from baseline) will be analyzed at each evaluation visit using the Cochran-Mantel-Haenszel (CMH) test stratified by background of atopy and by country with the ridit transformation and the general association statistic (FREQ procedure from SAS).

PP and ITT (Criteria will be set to missing after rescue medication is used and imputed to LOCF, for continuous outcomes and to failure for binary outcomes) will be conducted on secondary endpoints.

DLQI data will be analyzed on observed cases by CMH test test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS)on the data in categories and also in terms change from baseline via an

ANCOVA including treatment, baseline DLQI as a covariate, background of atopy and country as cofactors

The absolute and the percent change in weekly average sleep disturbance NRS from baseline up to week 4 will be analyzed by CMH test stratified by background of atopy and by country with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS)

The PD parameters will be visualized by boxplots (with a logarithm base 10 Y axis where needed). The compound effect will be estimated by Student's t test comparing the change at D85 from D1 for CD14152 vs the change at D85 from D1 for placebo (or other if more appropriate). The multiple testing problem will be taken into account by the Benjamini-Hochberg approach (1995)(or other if more appropriate).

9.2.5 Pharmacokinetic parameters and ADA analyses

The PK parameters derived using non-compartmental techniques will be regarded as primary endpoints for the pharmacokinetic analyses. Primary inference for all the PK parameters will be based on the pharmacokinetic analysis population.

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). Pharmacokinetic parameters using geometric means will be compared to determine when steady state conditions are achieved during the treatment period. 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:

Geometric mean = exp(mean on log scale)

CV_b (%) = sqrt[exp(SD^2) - 1] x 100

– where SD is the standard deviation of the $\log_e$-transformed data.

Following $\log_e$-transformation, C_{trough} will be analyzed using analysis of variance (ANOVA), the model will include time and subject 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 potential relationship between plasma concentrations of nemolizumab and change in 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). Individual PK profiles of subjects with our without ADA will be plotted to explore ADA impact on systemic exposure levels.

9.3 Sample size determination

9.3.1 Historical data

Two recent studies comparing several doses (among them, 0.5 mg/kg) of Nemolizumab to the placebo conducted in two different indications were evaluating the weekly average of the worst itching score over the past 24 hours at week 4 on a VAS (CIM003JG and CIM106JP). The following results were observed:

Indication	N(0.5 mg/kg ; Placebo)	Mean Effect versus Placebo (in terms of percent change from baseline)	SD
Uremic pruritus	14;14	18%	35
Atopic Dermatitis	51;45	40%	30

9.3.2 Assumptions

VAS and NRS are considered highly correlated (Reich et al 2012), thus all estimators for VAS are assumed to be the same for NRS.

For the current study, it is assumed that the common standard deviation is 35 and that the true difference between Nemolizumab and the placebo is 30% in terms of percent change from baseline in worst ichting score on a NRS at Week 4.

9.3.3 Sample size calculation

With an effect size of (30/35=) 0.857, a power of 90% and a type I error of 5% two-sided; at least 30 subjects are needed per group. In order to maintain the power of the tests, for per-protocol population, in case of drop outs/major deviations at Week 4, the sample size will be increased to 35 subjects per group, i.e. 70 to be randomized.

9.4 Interim analysis at Week 4

An interim analysis may be performed once at least 40 subjects will have completed the week 4 visit or discontinued before (decision will be taken by the Sponsor according to the recruitment rate). This analysis will include efficacy data on all subjects up to that time point. In addition to efficacy, all safety data available (not only data up to week 4) will also be analyzed. This interim analysis may be performed to inform the Sponsor for the subsequent clinical program. Blind will be broken for a limited Galderma R&D Staff involved in this trial according to the communication plan. The study will remain blinded to Investigators, CRO clinical team and sites staffs, as no results will be sent out. Furthermore, only summary statistics (by treatment) and

individual listings (without treatment identity) will be provided for this analysis. This will avoid individual unblinding. No discontinuation rules have been defined for this study based on the outcome of this interim analysis.

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/initiation 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.

A study initiation visit will be conducted for each study center prior to the enrolment of any subjects. All personnel involved in the study conduct will receive on-site 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 representatives of GALDERMA to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical trial records, CRFs, corresponding subject medical records, study drug(s) dispensing records, and any other documents considered source documentation. Additionally, the CRO/Sponsor representative is to have access to the study drug(s) storage area and clinical trial facilities.

The Investigator also agrees to assist the representative if required.

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, VRS, DPS, sleep disturbance NRS, DLQI, Actigraphy will be collected using separate electronic devices provided to the subject. Data collected from Pruritus NRS, VRS, DPS, sleep disturbance NRS, DLQI will be exported to be stored in datasets.

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 GALDERMA and/or the Contract Research Organization (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 CRO/Sponsor's 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 GALDERMA auditors, audit certificate(s) will be provided by Quality Assurance.

10.5 Changes in clinical trial conduct / amendments

10.5.1 Clinical trial conduct

With the exception of eliminating an immediate hazard 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 the Ethics Committees. However, non-substantial amendments should 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), 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 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 NRS, VRS will be calculated automatically in the eCRF and will therefore be considered as e-source data; however, the components of PAS must be documented on a separate source document. Data documented on electronic devices directly (pruritus NRS, VRS, PCS, sleep disturbace NRS, DLQI and Actigraphy) 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 for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical trial documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

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 a Coordinating Investigator (CI) will be done pursuant to the European Agency for the Evaluation of Medicinal Products (EMA) guidance on "Coordinating Investigator Signature of Clinical Study Reports".

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13 APPENDICES

Appendix 1 Volume of blood sample (ml) during the study

Study period	Screening period		Treatment period						Observation period/Follow up		Unscheduled visit or Early termination
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	
Week	**Screening 1**	**screening 2**	**Baseline**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W18**	
Day	**D-28 to D-8**	**Day-7**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**D113**	**Day 85**	**Day 126**	
TB test	4										
Virology (HIV, hepatitis B and C)	8,5										
Hematology		2	2			2	2	2			2
Chemistry		2	2			2	2	2			2
IgE	1										
Pregnancy	1										
CPK	3,5		3,5			3,5	3,5	3,5			2
Fibrinogen		2,7	2,7			2,7	2,7	2,7			2
Pregnancy											
PD			10			10		10			
PK with or without ADA			5*	3,5	3,5	5*	5*	5*	5*	5*	5
Total blood samples per visit	18	6,7	25,2	3,5	3,5	25,2	15,2	25,2	5	5	13
Total volume 132,5 ml											

**PK and ADA samples are included in the same tube*

Appendix 2 Numerical Rating Scale (NRS)

Appendix 3 Verbal Rating Scale (VRS)

☐ 0 = no itch ☐ 1 = mild itch ☐ 2 = moderate itch ☐ 3 = severe itch ☐ 4 = very severe itch

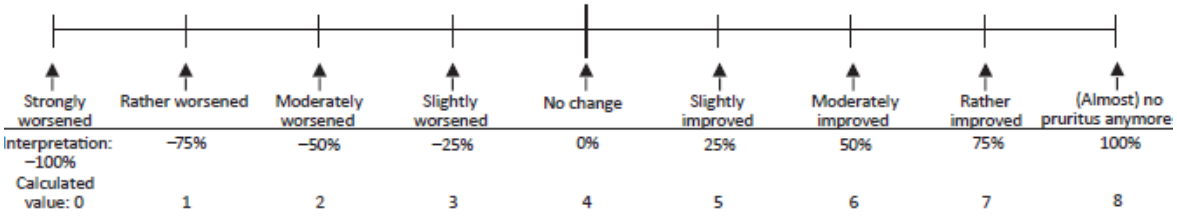
Appendix 4 Sleep disturbance Numeric Rating Scale (NRS)

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

0	1	2	3	4	5	6	7	8	9	10

No sleep loss

Appendix 5 Dynamic Pruritus Score (DPS)



Appendix 6 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 7 Investigator Global Assessment (IGA) on PN

Status	**Score**
Clear	0
Almost clear	1
Mild	2
Moderate	3
Severe	4

Appendix 8 Prurigo Activity Score (PAS)

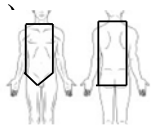
1. Type
a) Which efflorescences do you see?
□ papules
□ nodules
□ plaques
□ umbilicated ulcers
□ ulcers
□ hypo-/hyperpigmented maculae

b) Which type of prurigo is predominant?
□ Prurigo papular type
□ Prurigo nodular type
□ Prurigo plaques type
□ Prurigo ulcerated type
□ Prurigo umbilicated "Kyrle" type
□ completely healed

2. Number
a) How many Prurigo lesions do you see on the whole body? (estimate; do not count; do not consider scars)
□ 0
□ 1 - 19
□ 20 – 100
□ > 100

3. Distribution:
□ disseminated
□ localized (only 1 or 2 areas affected)
□ neither of them

4. Please mark the affected area(s)
(for definition of trunk see imag
whole body except head □
whole body head included □
or



forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal
head	□ capillitium	□ face

5. Please choose a representative area:

forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal

Number of prurigo lesions in the selected representative area (do not count scars):_____

6. Activity. Please mark the stage.

	stage 0	stage 1	stage 2	stage 3	stage 4
Prurigo lesions with excoriations/crusts compared to all prurigo lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
Healed prurigolesions compared to all prurigo lesions	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

7. Take photos of the patient (optional using your own device): Overview front and back, area(s) of marked monitor lesions to recognize on next visit