CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.109696

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TITLE PAGE

Safety and efficacy of CD5024 0.3% cream in subjects with atopic dermatitis		
Project Name or CD number	**Project Number**	**Clinical Trial Phase**
CD5024	1145	IIa

Version Number: Version 01 Amendment 01, CA dated Jan 13, 2017

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For any safety questions, please contact the Clinical Safety Officer (CSO) using the contact details provided in Section 7.2.6.2.2.

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 R&D template.

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SYNOPSIS

Clinical Trial Title: Safety and efficacy of CD5024 0.3% cream in subjects with atopic dermatitis	
Short Title: Safety and efficacy of CD5024 0.3% cream in subjects with atopic dermatitis	
Clinical Trial phase: Phase IIa	**Clinical Trial Population:** Adult subjects with atopic dermatitis
Clinical Trial objectives	**The primary objective** of this study is to evaluate the local and systemic safety of CD5024 0.3% cream applied once daily over a 6-week treatment period in adults with chronic lesions of moderate atopic dermatitis (AD), compared to its vehicle. **The secondary objective** is to evaluate the efficacy of CD5024 0.3 % cream versus its vehicle on chronic lesions of moderate AD. CCI [redacted]
Clinical Trial design	This is an exploratory, multi-centric (approximately 5 sites in Canada), randomized, vehicle-controlled, investigator-blind, parallel group study, involving approximately 85 subjects screened to get approximately 60 randomized subjects with chronic lesions of AD meeting specific inclusion/non-inclusion criteria. Subjects will also be blind to treatments. Subjects who consent to be enrolled and fulfil study criteria will be allocated to one of the study treatment according to the randomization list, in a 1:1 ratio (for example Group A: N=30 subjects treated by CD5024 0.3% cream and Group B: N=30 subjects treated by the vehicle). All subjects will undergo a screening period ranging from 30 days to 3 days prior to Day 1, a 6-week treatment period during which all plaques of AD (up to 8% BSA) will receive either CD5024 0.3% cream or its vehicle once daily and a follow-up period of approximately 2 weeks after the last treatment applications. CCI [redacted] Additionally, CCI [redacted] assessments will be conducted on a subset of 20 subjects having received either CD5024 0.3% cream or its vehicle (10 subjects each) for 6 weeks. Tape-strips, D-squames and biopsies will be used to sample the appropriate skin material needed for these assessments. Consequently, each subject having consented to have the procedures will undergo 3 biopsies (4-mm diameter), 20 tape-strips and 10 D-squames.
Total number of subjects (Planned)	As a screen failure rate of approximately 30 percent is anticipated, screening of approximately 85 subjects is planned in order to achieve the target of approximately 60 subjects enrolled (randomized/assigned to treatment) (30

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	per arm).
Number of clinical trial centers (Planned):	Approximately 5
Countries involved (Planned)	Canada
Clinical trial duration	The planned clinical trial duration (from FSFV to LSLV) is approximately 8 months. The planned duration of recruitment (from FSFV to LSFV) is approximately 5 months.
Duration of subject participation	Clinical trial participation for each subject is approximately 3 months .
Key Inclusion criteria	1. The subject is a male or female aged 18 to 60 years old inclusive at Screening; 2. The subject presents with a tBSA ≤ 2,5 m² at Screening; 3. The subject is a female of childbearing potential who agrees to use a highly effective and approved contraceptive method for the duration of the study defined as: 3.1. bilateral tubal ligation OR, 3.2. combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 1 month prior to Day 1 OR, 3.3. hormonal intra-uterine device (IUD) inserted at least 1 month prior to Day 1 OR, 3.4. vasectomized partner for at least 3 months prior to Day 1 and this male is the sole partner for that subject; 4. If the subject is a female of childbearing potential, she has a negative UPT at Screening & Day 1 visits 5. The subject is a female of non-childbearing potential, defined as postmenopausal (absence of menstrual bleeding for 1 year prior to screening, without any other medical reason), or had a hysterectomy or a bilateral oophorectomy; 6. The subject has atopic dermatitis for at least 6 months prior to Day 1. The clinical diagnosis of atopic dermatitis must be confirmed with the criteria of Hanifin and Rajka at the screening visit; 7. Atopic dermatitis must be stable for at least one month before the screening visit (according to subject); 8. The subject has a Body Surface Area (BSA) affected by AD ranging from 1% inclusive to 8% inclusive at Day 1, excluding scalp and genitals 9. The subject has an overall Investigator's Global Assessment (IGA) score of 3 (moderate) at Day 1;
Key Non-inclusion criteria	1. The subject is a pregnant female, is breast-feeding or intends to conceive a child during the study; 2. The subject has any uncontrolled or serious disease, or any medical or

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surgical condition, that may either interfere with the interpretation of the clinical trial results (e.g. extensive scaring or pigmented lesion in a treated area), and/or put the subject at significant risk according to Investigator's judgment if he/she participates in the clinical trial (e.g. active cancer, AIDS, insulin-dependent diabetes…) at Screening or Day 1;

3. The subject presents with an acute flare of AD at Day 1;
4. The subject has active cutaneous bacterial or viral infection in any treated area at baseline (e.g. clinically infected AD) at Screening or Day 1;
5. The subject has a history of confounding skin condition (*e.g.* psoriasis, erythroderma) or a history of Netherton syndrome at Screening;
6. The subject has a past history of serious persistent neurological disorders such as seizures, multiple sclerosis, or neurological signs or symptoms at Screening
7. The subject has a known past or current history of severe psychiatric disorders such as severe depressive or psychotic illness at Screening;
8. The subject presents with abnormal vital signs considered as Clinically Significant as per investigator's judgement at Screening or Day 1;
9. The subject presents with a known cardiopathy or clinically significant ECG abnormalities according to investigator's judgement at Screening or Day 1;
10. The subject has known or suspected allergies or sensitivities to any components of any of the study drugs as detailed in the Investigator's Brochure at Screening;
11. The subject has received, applied, or taken the following treatments within the specified time frame prior to Day 1;

Topical treatments	**Washout periods**
Topical Calcineurin Inhibitors	2 weeks
Topical Corticosteroids	2 weeks
All Other topical therapies on treated areas	2 weeks
Systemic treatments	**Washout periods**
Antihistamines with sedative effects such as hydroxyzine, diphenhydramine or dexchlorpheniramine *Other antihistamine are authorized*	1 week
Immunosuppressive or immunomodulators drugs (e.g. methotrexate, cyclosporine, interferon)	1 month
Anticoagulant and antiplatelet drugs (low dose aspirin are allowed)	1 month
NSAIDs *Short-term use of less than 5 days is authorized*	2 weeks
Biologics	3 months
Corticosteroids *Inhaled and short course therapy (i.e. 5 days) for ear, nose, throat therapy and asthma is authorized*	1 month

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Laser treatments and light therapies	1 month
Oral ivermectin	1 month
Other drugs used for the treatment of AD	1 month
Cytochrome P450 3A4 strong inhibitors and inducers (refer to Table 11)	3 months
Strong P-Glycoprotein inhibitors (refer to Table 11)	3 months
Beverages	**Washout periods**
Grapefruit Juice	1 week

12. The subject presents with presumed drug or alcohol abuse (based on medical history or present clinical symptoms) at Screening or Day 1;
13. The subject presents with any screening abnormal and clinically significant laboratory test results as per investigator's judgment (except for hyper eosinophilia) and regarding renal and hepatic function, defined as:
    - 13.1. Creatinine clearance : estimated glomerular filtration rate < 60 ml/min/1.73m² calculated with the CKD-EPI formula,
    - 13.2. AST > 2xULN,
    - 13.3. ALT > 2xULN,
    - 13.4. Total Bilirubin > 1.5xULN,
14. The subject presents with known hepatic insufficiency with clinical signs such as ascite and encephalopathy at Screening;
15. The subject presents with positive serology results (HbsAg, anti-HCV, anti-HIV 1 or 2) at Screening;
16. The subject was exposed to excessive UV radiation within two weeks prior to Day 1, or is planning exposure during the study (e.g. phototherapy, occupational exposure to the sun, planned holidays in the sun during the study, tanning salon);
17. For subject who consented to skin biopsy: the Subject presents the following criteria not allowing the biopsy sample (Screening visit):
    - 17.1. Inherited or acquired hemostasis disorder;
    - 17.2. Known allergy to local anesthetics and or topical antiseptics planned to be used in the study,
    - 17.3. Past history or physical evidence of abnormal healing (keloids, hypertrophic scars, scars in hollow)
18. The subject is vulnerable as defined in Section 1.61 of International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)" (Screening visit)
    - 18.1. an adult under guardianship, or hospitalized in a public or private institution for a reason other than the Research, or deprived of freedom
    - 18.2. a subject unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function
19. The subject is participating in any other clinical trial of a drug or device OR participated within 1 month prior to Day 1 OR is in an exclusion

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	period from a previous clinical trial of a drug or device (Screening visit)
Investigational product	
INN Name	Ivermectin
Internal code	CD5024
Pharmaceutical form	Cream
Strength	0.3%
Dosage (total daily dose)	Up to 4 g daily (depending on the tBSA and BSA)
Route	Topical
Duration of administration	6 weeks
Dose regimen	Once a day, 7 days a week for 6 weeks (42 applications)
Location of treated area	All body areas (except scalp & genitals)
Comparator	
INN Name	NA
Internal code	CD5024 Placebo
Pharmaceutical form:	Cream
Dosage (total daily dose)	Up to 4 g daily (depending on the tBSA and BSA)
Route	Topical
Duration of administration	6 weeks
Dose regimen	Once a day, 7 days a week for 6 weeks (42 applications)
Location of treated area	All body areas (except scalp & genitals)
Efficacy assessments	Clinical evaluation of IGA, BSA, TSS, Modified Objective SCORAD and EASI by the Investigator. Patient-reported Outcomes : NRS and VRS (Pruritus assessment)
Efficacy endpoints	**Primary efficacy endpoints:** The Primary efficacy endpoint is the EASI percent change from baseline at Week 6. **Secondary efficacy endpoints:** ▪ The EASI percent change from baseline at each other evaluation visit and change from Baseline in EASI at each evaluation visit. ▪ Investigator Global Assessment in terms of distribution and in terms of success rate (Success is defined as a subject with an IGA score of 0 (clear) or 1 (Almost clear) at each evaluation visit. ▪ Percent Change from baseline of the TSS of the target plaque ▪ Percent Change from baseline of the Modified Objective SCORAD ▪ Pruritus (NRS, VRS) and their changes from Baseline at each evaluation visit.
Safety assessment:	▪ Adverse events ▪ Laboratory blood tests ▪ Vital signs and physical examination

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Safety endpoints:	▪ ECG ▪ Incidence and multiplicity of adverse events ▪ Laboratory blood hematology and blood chemistry ▪ Vital signs and physical examination
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Principal statistical method:	The Primary efficacy endpoint, EASI score least square mean percent change from baseline at week 6, will be analyzed via an analysis of variance with the Treatment group as factor and Center as a cofactor.
Sample size	In a Galderma R&D trial (SPR.18158) where the Vehicle was used in atopic dermatitis in subjects with a BSA between 5% and 20%, the Vehicle percent change from baseline at week 4 of a modified EASI (No Head and Neck) was -40% and the standard deviation (SD) was 45%. In studies evaluating Dupilumab versus placebo, the observed placebo EASI percent changes from baseline at week 4, ranged between -17% and -25% with a standard deviation around 40% (Beck 2014) and was -18% at week 16 with a standard deviation of 40% (Thaci 2016). In this last trial it was observed that these values were reached from week 4 onwards. Based on historical data, the standard deviation was set to 40%. The magnitude of effect of Dupilumab reached 45% over placebo. However, systemic immunosuppressant drug for atopic dermatitis are generally more effective than topical treatments (Thaci 2016). Taking that into account, it is expected that for CD5024 cream 0.3% applied once daily, an effect of 30% over its vehicle would be clinically relevant. Consequently, the effect size (delta/sigma) has been set to 0.75 (30%/40%). Using a randomization ratio of 1:1 for CD5024 cream 0.3%QD and vehicle respectively, a sample size of 30 randomized subjects in each treatment group can ensure a 80% power to detect a difference of 30 % between CD5024 and its vehicle on EASI mean percent change from baseline.

Table 1 Clinical trial schematic

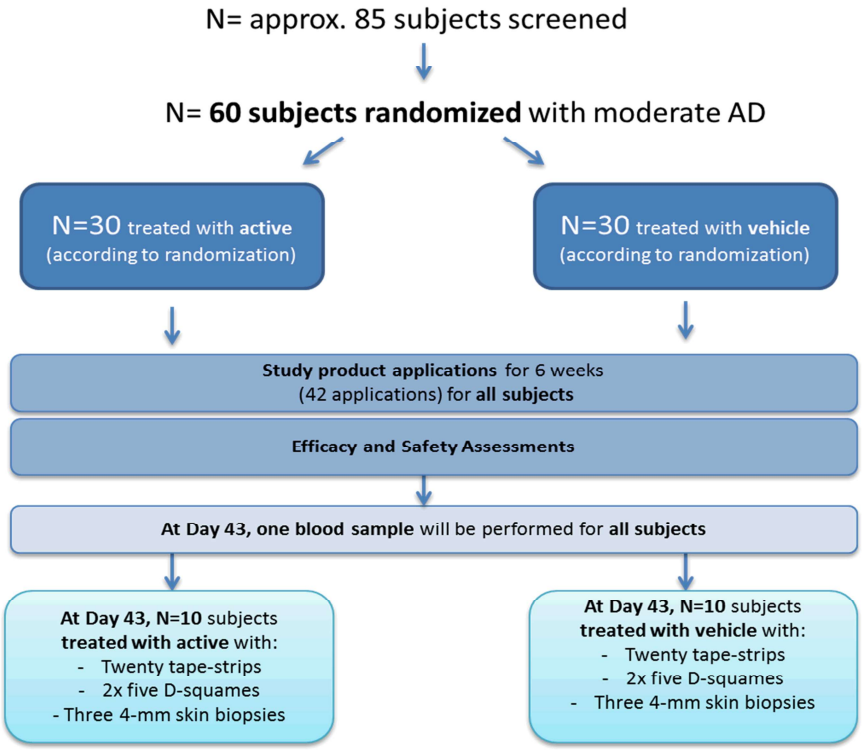

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Table 2 Schedule of Assessments

Study Flow chart / Study 109696	Screening period	Treatment Period													Early Termination	UN-Scheduled	Follow-up
	Week-5 to Week-1	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7			Week 9
	D-30 to D-3	D01	D02 to D07	D08	D09 to D14	D15	D16 to D21	D22	D23 to D28	D29	D30 to D35	D36	D37 to D42	D43			D54±2
Informed Consent Form	X																
Demographics	X																
tBSA (Total Body Surface Area)	X																
Medical History	X																
Previous treatments and procedures	X																
UPT for females of childbearing potential	X (a)	X (a)				X				X				X	X		X
Blood samplings (Virology)	X																
Blood samplings (coagulation, hematology, biochemistry)	X							X						X	X		
Blood samplings (IgE & TARC)	X													X	X		
Physical examination	X	X				X				X				X	X		X
Vital signs	X	X				X				X				X	X		X
ECG	X	X												X	X		
Inclusion and Non-inclusion Criteria	X	X															
Confirmation of AD (Hanifin and Rajka)	X																
BSA (*i.e.* affected by AD)	X	X		X		X		X		X		X		X (b)	X	X	
Photos of the target plaque		X												X (b)	X	X	
Investigator Global Assessment (IGA)	X	X		X		X		X		X		X		X (b)	X		
Hand IGA when applicable		X		X		X		X		X		X		X (b)	X		
TSS		X		X		X		X		X		X		X (b)	X		
Modified-Objective SCORAD		X		X		X		X		X		X		X (b)	X		
EASI Score		X		X		X		X		X		X		X (b)	X	X	
Patient-reported Outcome - Pruritus Numerical Rating Scale & DIARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X (b)	X		
Patient-reported Outcome - Pruritus Verbal Rating Scale & DIARY		X												X (b)	X		

(a) For females of childbearing potential only, at least 14 days between the 2 UPTs;
(b) All assessments are to be done before any procedures are performed.

Study Flow chart / Study 109696	Screening period	Treatment Period													Early Termination	UN-Scheduled	Follow-up
	Week-5 to Week-1	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7			Week 9
	D-30 to D-3	D01	D02 to D07	D08	D09 to D14	D15	D16 to D21	D22	D23 to D28	D29	D30 to D35	D36	D37 to D42	D43			D54±2
Randomization		X															
Subject visit on site	X	X		X		X		X		X		X		X	X	X	X
Dispensation of study products		X		X		X		X		X		X				X	
Collection of study products from subjects				X		X		X		X		X		X	X	X	
Weighing study products (dispensed and returned)		X		X		X		X		X		X		X	X	X	
Products application & DIARY		X (c)	X	X	X	X	X	X	X	X	X	X	X				
CCI																	
Wound Healing																	X (d)
Concomitant treatments and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Form															X		X

(c) The first application is done by on-site under the supervision of a study staff
(d) Only for subjects having undergone cutaneous procedures
(e) Optional. Only for those subjects who consented to have cutaneous procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	*Atopic Dermatitis*
AE	*Adverse Event*
AESI	*Adverse Event of Special Interest*
ALP	*Alkaline Phosphatase*
ALT/ALAT (SGPT)	*Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)*
AST/ASAT (SGOT)	*Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)*
AUC	*Area under Curve*
BSA	*Body Surface Area (i.e. affected by the disease)*
bpm	*Beats per Minute*
CA	*Competent Authorities*
CCI [redacted]	
CNS	*Central Nervous System*
CRA	*Clinical Research Associate*
CRF	*Case Report Forms*
CRO	*Contract Research Organization*
CSO	*Clinical Safety Officer*
CVS	*Cardiovascular System*

DMP	*Data Management Plan*
EASI	*Eczema area and severity index*
ECG	*Electrocardiogram*
e.g.	*For Example (Latin: exempli gratia)*
ET	*Early Termination*
FDA	*Food and Drug Administration*
FOCBP	*Females of childbearing potential*
FSFV	*First Subject First Visit*
LSLV	*Last Subject Last Visit*
GCP	*Good Clinical Practice*
HBsAg	*Hepatitis B Surface Antigen*
HCV	*Hepatitis C Virus*
HIV	*Human Immunodeficiency Virus*
HR	*Heart Rate*
ICH	*International Conference on Harmonisation*
IB	*Investigator's Brochure*
CSO	*Clinical Safety Officer*
ICF	*Informed Consent Form*

IGA	*Investigator's Global Assessment*
IMP	*Investigational Medicinal Product*
IRB	*Institutional Review Board*
ITT	*Intent-to-treat*
IUD	*Intrauterine Device*
IV	*Intravenous*
LOCF	*Last Observation Carried Forward*
MedDRA	*Medical Dictionary for Regulatory Activities*
MS	*Mass Spectrometry*
NCE	*New Chemical Entity*
NOEL	*No Effect Level*
NSAID	*Nonsteroidal anti-inflammatory drug*
PIPEDA	*Personal Information Protection and Electronic Documents Act*
CCI [redacted]	
PI	*Principal Investigator*
CCI [redacted]	
PP	*Per-Protocol*
PR	*Pulse Rate*
QD	*Once Daily (Latin: quaque die)*

RA	*Rheumatoid Arthritis*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SCORAD	*Scoring Atopic Dermatitis*
SIN	*Subject Identification Number*
SmPC	*Summary of Product Characteristics*
SOP	*Standard Operating Procedure*
CCI [redacted]	
CCI [redacted]	
tBSA	*Total Body Surface Area*
TOC	*Table of Contents*
TEAE	*Treatment-Emergent Adverse Event*
TSS	*Total Sum Score*
ULN	*Upper Limit of Normal*
UPT	*Urine Pregnancy Test*
US	*United States*

1 BACKGROUND AND RATIONALE

1.1 Medical background and Short rationale for the clinical trial

Atopic dermatitis (AD) is a common chronic, pruritic, inflammatory skin disease affecting approximately 15-20% of school-age children (Laughter et al, 2000; Shultz Larsen F. et al., 1996) and 10% of adults (Silverberg 2013). Prevalence of AD has significantly increased over the last 10 years (*i.e.* the affected population has doubled). Xerosis (dry skin), eczematous papules, plaques and pruritus are the dominant symptoms of AD and may lead to damaging excoriations, erosions, and lichenification. Other important features include a chronic recurring course, a family or personal history of atopy, and a characteristic distribution of lesions. The burden of AD on health-related quality of life can be profound (Drake et al. 2001).

The cause of AD, although still not completely understood, is probably multifactorial and involves complex interrelation between susceptible genes, immunological factors, infections and environmental factors to produce a skin barrier disturbance as well as immunologic dysregulation and inflammation (Rutkowski, 2014, Montes-Torres 2015). Abnormal protein (filaggrin and related proteins) and lipid (ceramide) metabolism might play a key role (Hon et al, 2013). In a vicious circle, the allergic response then contributes to skin barrier deterioration and worsening of the condition.

Cutaneous inflammation is characterised by sequential and progressive patterns of inflammatory cell infiltration, classically biphasic involving T helper type 2 (Th2) and Th1 cells along the acute and chronic phase of AD. Th17 and Th22 cells involvement in AD pathogenesis has been more recently published (Gittler 2012). Of note, non-lesional skin already shows signs of a subclinical inflammation with increased numbers of T-helper-2 (Th2) cells, Th22 cells, and to a lesser degree, Th17 cells, and a pro-inflammatory cytokine milieu (Suarez - Farinas 2011). Th17 and Th22 cells, together with chemokines and cytokines derived from fibroblasts and keratinocytes, such as thymic stromal lymphopoietin, drive tissue remodelling and fibrosis (Weidinger 2016).

Current treatments of mild to moderate AD include regular application of emollients to maintain an effective skin barrier, and topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI *e.g.* tacrolimus) to control signs and symptoms. However TCS and TCI can have safety and tolerability issues, especially for long-term use (Simpson, 2010).

Ivermectin (CD5024) is a member of the avermectin class widely used to treat parasitic infection. CD5024, as a macrocyclic lactone derivative, could also have some immuno-modulatory and anti-inflammatory properties. In immune-pharmacological studies, the drug has been shown to exert anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines, such as tumor necrosis factor alpha and interleukin (IL)-1b, while up-regulating the anti-inflammatory cytokine IL-10 (Ci 2009). It has also been shown to have

immunosuppressive effects, suppressing allergic inflammation by preventing the accumulation of Th2 cytokines such as IL-4, IL-5 and IL-13, in addition to inhibiting airway hyper-responsiveness, in a murine model of allergic asthma (Yan et al, 2011).

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Overall, these results indicate that CD5024 is a potent anti-inflammatory drug, including at lower concentrations, that could have important applications for the treatment of AD. Galderma R&D is therefore proposing to conduct a proof of concept study with CD5024 0.3% Cream to assess its safety and efficacy when applied topically for a 6-week study in subjects with chronic moderate AD.

1.2 Drug profile

The drug profile of CD5024 (ivermectin) is presented in detail in the Investigator's Brochure.

Ivermectin was discovered in the 70s, and was used primarily in veterinary medicine in farm and domestic animals against a wide range of endo- and ectoparasites. Ivermectin given orally is approved for oral use in humans in numerous countries, and licensed under different brand names and as a generic for use as a single or, if required, 2 doses regimen, in a variety of endoparasitic (strongyloidiasis, onchocerciasis and filariasis) and ectoparasitic (scabies and head lice) diseases. A topical lotion containing ivermectin has recently been approved for the treatment of head lice.

CD5024 (ivermectin) 1% (10 mg/g) Cream received marketing authorization for the cutaneous treatment of inflammatory lesions of rosacea in adults in 2014 in the United States (US), and in 2015 in Europe, Australia and Canada (SOOLANTRA/ROSIVER®). In the treatment of inflammatory lesions of rosacea, CD5024 1% cream was shown to significantly decrease the inflammatory lesion counts and to achieve a higher success rate (Clear or almost clear on the Investigator Global Assessment) compared to its vehicle (ROSIVER Product Monograph).

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[redacted]

1.3 Risk/Benefit assessment

The proposed clinical study intends to evaluate the safety and efficacy of CD5024 cream 0.3% in patients with AD and the preclinical and clinical data supporting the positive benefit risk ratio in this particular study are detailed below.

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In the present study a formulation with a lower concentration of CD5024 (0.3%), will be used to take into account a larger BSA of application (up to 8% in the study). An average of 3.4 g of a formulation at 0.3% (containing 10.2 mg of CD5024 which is similar to the dose applied for

rosacea) and a maximum of 4g of formulation (containing 12 mg of CD5024 corresponding to approximately 200 µg/kg body weight) will be applied during the study on subjects with AD. As AD lesions may be characterized by skin barrier impairment, the transdermal absorption might be higher in those subjects in comparison to PPR subjects and therefore a somehow higher systemic exposure is expected than in PPR subjects.

It should be also taken into account that, in addition to these high safety margins after topical exposure, CD5024 has also been used by the oral or subcutaneous routes in humans at doses ranging from 200 to 2000 µg/kg body weight during periods up to 12 weeks and was generally well tolerated (see section 1.3.2). Given the lower relative bioavailability of topical CD5024 compared to the oral or subcutaneous administration, the systemic exposure in the present study is expected to remain lower than the exposure seen in these trials.

With regards to pregnant women, given the animal teratogenicity data and in absence of well controlled data on safety in pregnant women, contraceptive methods will be mandatory for females of childbearing potential.

1.3.2 Clinical safety data

In healthy volunteers and patients, the safety profile of CD5024 has been characterized from safety data obtained from several Phase I, II and III studies performed with the topical form of the drug. During clinical trials, 2047 subjects with inflammatory lesions of rosacea received CD5024 1% cream once daily. A total of 1555 subjects were treated once daily for more than 12 weeks, and 519 for approximately one year. Adverse reactions, reported in < 1% of subjects treated with CD5024 cream for at least 3 months in vehicle-controlled clinical trials, included skin burning sensation, skin irritation, pruritus and dry skin. The safety profile remained stable during long-term use up to one year**.**

In addition CD5024 is widely used since many years by the oral route as an antiparasitic agent at single doses up to 200 µg/kg body weight and is in general well tolerated (STROMECTOL product monograph). The adverse events reported are generally linked to the parasitic load. The main adverse events are asthenia, gastrointestinal (anorexia, diarrhea, nausea…), or related to the nervous/psychiatric system (dizziness, somnolence…). Liver or haematological laboratory abnormalities have been also reported as well as very rare cases of cutaneous drug reactions. In addition CD5024 is now indicated for the treatment of scabies at the same dose and is generally well tolerated.

Moreover, in an ascending dose safety and pharmacokinetic study conducted on healthy volunteers, oral CD5024 was tested up to 120 mg (in a single dose, corresponding to 2000 µg/kg) and up to 60 mg over one week treatment (3 doses per week, corresponding to 1000 µg/kg) (Guzzo 2002). In this study, important systemic exposures were achieved and, taking into account animal toxicities studies, the safety evaluation included the specific assessment of potential neurological effects (mydriasis). No difference was observed compared to vehicle in the

pupil diameter evaluated by pupillometry. The overall rate of adverse events was similar to vehicle, consisted of transient and mild reaction and no consistent trend indicative of a dose response was observed (the most common AE were headache, nausea, dizziness and rash. Slight increases in ALT and/or and/or GGT were also reported).

CD5024 was also evaluated subcutaneously in 10 patients with severe spasticity after spinal-cord injury (Costa 1994). CD5024 was given at weekly or biweekly interval at different doses up to 1.6 mg/kg and for different durations, up to 12 weeks. No clinical adverse effect was observed. The results suggested that CD5024 could reduce spasticity.

Finally, in a mass drug administration study for scabies control in Fiji, 716 patients (including children > 15 kg of body weight) were exposed to one or two doses of 200 µg/kg oral CD5024. Although adverse events were more common than in patients receiving topical permethrin, there was no safety concern. Adverse events were reported in 15.6% of patients, they were generally mild with itching being the most frequent (probably disease specific, due to an inflammatory response to dead mite antigens) followed by headache (Romani, 2015).

1.3.3 Conclusion

Overall, considering the large safety margins observed under maximal use conditions in PPR subjects by topical route, the low relative bioavailability following topical treatment, and the good safety profile of CD5024, including at high doses by oral or subcutaneous route, with higher corresponding systemic exposures than expected in this study, the risk benefit ratio is evaluated to be favourable in this study.

1.3.4 Risks related to the study procedures

Invasive procedures (Blood samplings and skin punch biopsies) will be performed by a study personnel specifically trained according to the objectives defined in the study. Wound healing of biopsies will be controlled during a follow-up visit.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

- Primary objective:

The primary objective of this study is to evaluate the local and systemic safety of CD5024 0.3% cream applied once daily over a 6-week treatment period in adults with chronic lesions of moderate atopic dermatitis (AD), compared to its vehicle.

- Secondary objective

The secondary objective is to evaluate the efficacy of CD5024 0.3 % cream versus its vehicle on chronic lesions of moderate AD.

CCI [redacted]

2.2 Clinical hypothesis

The hypothesis of the study is that CD5024 0.3% cream applied once daily over a 6-week treatment period, is well tolerated by subjects with chronic lesions of AD and superior in efficacy to its vehicle.

3 OVERALL CLINICAL TRIAL DESCRIPTION

This is an exploratory, multi-centric (approximately 5 sites in Canada), randomized, vehicle-controlled, investigator-blind, parallel group study, involving approximately 85 subjects screened to get approximately 60 randomized subjects with chronic lesions of AD meeting specific inclusion/non-inclusion criteria. The investigator and/or other evaluator(s) will not come into contact with the study materials. The subject and members of the study staff do not have access to the correspondence between the kit number and the assigned treatment group.

Subjects who consent to be enrolled and fulfil study criteria will be allocated to one of the study treatment according to the randomization list, in a 1:1 ratio (for example Group A: N=30 subjects treated by CD5024 0.3% cream and Group B: N=30 subjects treated by the vehicle). All subjects will undergo:

- a screening period ranging from 30 days to 3 days prior to Day 1
- a 6-week treatment period during which all plaques of AD (up to 8% BSA) will receive, depending on the randomization, either CD5024 0.3% cream or its vehicle once daily, for a total of 42 applications.
- a follow-up period of approximately 2 weeks after the last treatment applications.

CCI [redacted]

Additionally, CCI [redacted] and CCI [redacted] assessments will be conducted on a subset of 20 subjects having received either CD5024 0.3% cream or its vehicle (10 subjects each) for 6 weeks. Tape-strips, D-squames and biopsies will be used to sample the appropriate skin material

needed for these assessments. Consequently, each subject having consented to have the procedures will undergo 3 biopsies (4-mm diameter) and have 20 tape-strips and 10 D-squames.

Except for the first day of application, all the applications will be made at home by the subjects at approximately the same time in the evening. All subjects will have to use their own emollient throughout the study duration once a day in the morning on AD lesions, including during the screening period. For those subjects who do not have an emollient, they will be prescribed one. Visits to the study center are planned every week to assess both safety and efficacy and to provide subjects with study treatments for the coming week. A total of 9 visits on site are planned.

The safety of the subject will be closely monitored regarding any identified potential risk by means of laboratory safety assessments (hematology, renal and hepatic function parameters), physical examination, control of the vital signs and ECG. Determination and control of the BSA will be done weekly to adjust the quantity of treatment to be applied, as delineated in section 6.4 and to assess the effect of the treatment.

Adverse events will be recorded throughout the study duration. Additionally, regular internal safety review meetings will be held by the Sponsor in order to detect and analyze potential safety signals and ensure that all data are medically valid, complete and consistent.

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSFV to LSLV) is approximately 8 months. The date of end of the clinical trial is defined as the date of the last visit of the last subject (LSLV).

The planned duration of recruitment (from FSFV to LSFV) is approximately 5 months.

Clinical trial participation for each subject is approximately 3 months.

GALDERMA R&D 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(s) 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% is anticipated, approximately 85 subjects will be screened in order to get approximately 60 subjects randomized (30 per arm).

5.2 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must fulfill all of the following criteria applicable at screening and/or baseline as specified.

5.2.1 Inclusion criteria

1. The subject is a male or female aged 18 to 60 years old inclusive at Screening;
2. The subject presents with a tBSA ≤ 2.5 m^2 at Screening;
3. The subject is a female of childbearing potential who agrees to use a highly effective and approved contraceptive method for the duration of the study defined as:
   - 3.1. bilateral tubal ligation OR,
   - 3.2. combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 1 month prior to Day 1 OR,
   - 3.3. hormonal intra-uterine device (IUD) inserted at least 1 month prior to Day 1 OR,
   - 3.4. vasectomized partner for at least 3 months prior to Day 1 and this male is the sole partner for that subject;
4. If the subject is a female of childbearing potential, she has a negative UPT at Screening & Day 1 visits
5. The subject is a female of non-childbearing potential, defined as postmenopausal (absence of menstrual bleeding for 1 year prior to screening, without any other medical reason), or had a hysterectomy or a bilateral oophorectomy;
6. The subject has atopic dermatitis for at least 6 months prior to Day 1. The clinical diagnosis of atopic dermatitis must be confirmed with the criteria of Hanifin and Rajka at the screening visit;
7. Atopic dermatitis must be stable for at least one month before the screening visit (according to subject);
8. The subject has a Body Surface Area (BSA) affected by AD ranging from 1% inclusive to 8% inclusive at Day 1, excluding scalp and genitals;
9. The subject has an AD with an overall Investigator's Global Assessment (IGA) score of 3 (moderate) at Day 1;
10. The subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol;
11. The subject has understood and signed an Informed Consent Form (ICF) at screening, prior to any investigational procedures being performed;

12. The subject is apprised of the Personal Information Protection and Electronic Documents Act (PIPEDA) and is willing to share personal information and data, as verified by signing a written authorization.

Rationale:

#1; 3 to 5: Given the animal teratogenicity data and in absence of well controlled data on safety in pregnant women, contraceptive methods will be mandatory for females of childbearing potential.

#2; 6 to 9: The subject has to present with moderate AD. Subjects with severe AD should not be included because the illness may be uncontrolled and may make a proper assessment of the target plaques more difficult. With respect to the safety considerations and taking into account the quantities to be applied, tBSA and BSA are to be defined for the subject to be enrolled.

#10 to 12: Only those subjects who are willing to participate and provided a written consent/authorisation are allowed to participate in this clinical study, to be compliant with ICH, local regulations and GCP.

5.2.2 Non-inclusion criteria

1. The subject is a pregnant female, is breast-feeding or intends to conceive a child during the study;
2. The subject has any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results (e.g. extensive scaring or pigmented lesion in a treated area), and/or put the subject at significant risk according to Investigator's judgment if he/she participates in the clinical trial (e.g. cancer, AIDS, insulin-dependent diabetes…) at Screening or Day 1;
3. The subject presents with an acute flare of AD at Day 1;
4. The subject has active cutaneous bacterial or viral infection in any treated area at baseline (e.g. clinically infected AD) at Screening or Day 1;
5. The subject has a history of confounding skin condition (*e.g.* psoriasis, erythroderma) or a history of Netherton syndrome at Screening;
6. The subject has a past history of serious persistent neurological disorders such as seizures, multiple sclerosis, or neurological signs or symptoms at screening;
7. The subject has a known past or current history of severe psychiatric disorders such as severe depressive or psychotic illness at Screening;
8. The subject presents with abnormal vital signs considered as Clinically Significant as per investigator's judgement at Screening or Day 1;

9. The subject presents with a known cardiopathy or clinically significant ECG abnormalities according to investigator's judgement at Screening or Day 1;
10. The subject has known or suspected allergies or sensitivities to any components of any of the study drugs as detailed in the Investigator's Brochure at Screening;
11. The subject has received, applied, or taken the following treatments within the specified time frame prior to Day 1;

Topical treatments	**Washout periods**
Calcineurin Inhibitors	2 weeks
Corticosteroids	2 weeks
All Other topical therapies on treated areas	2 weeks
Systemic treatments	**Washout periods**
Antihistamines with sedative effects such as hydroxyzine, diphenhydramine or dexchlorpheniramine Other antihistamine are authorized	1 week
Immunosuppressive or immunomodulators drugs (e.g. methotrexate, cyclosporine, interferon)	1 month
Anticoagulant and antiplatelet drugs (low dose aspirin are allowed)	1 month
NSAIDs *Short-term use of less than 5 days is authorized*	2 weeks
Biologics	3 months
Corticosteroids *Inhaled and short course therapy (i.e. 5 days) for ear, nose, throat therapy and asthma is authorized*	1 month
Laser treatments and light therapies	1 month
Oral ivermectin	1 month
Other drugs used for the treatment of the AD	1 month
Cytochrome P450 3A4 strong inhibitors and inducers (refer to Table 11)	3 months
Strong P-Glycoprotein inhibitors (refer to Table 11)	3 months
Beverages	**Washout periods**
Grapefruit Juice	1 week

12. The subject presents with presumed drug or alcohol abuse (based on medical history or present clinical symptoms) at Screening or Day 1;
13. The subject presents with any screening abnormal and clinically significant laboratory test results as per investigator's judgment (except for hyper eosinophilia) and regarding renal and hepatic function, defined as:
    - 13.1. Creatinine clearance : estimated glomerular filtration rate < 60 ml/min/1.73m² calculated with the CKD-EPI formula,
    - 13.2. AST > 2xULN,
    - 13.3. ALT > 2xULN,

13.4. Total Bilirubin > 1.5xULN,

14. The subject presents with known hepatic insufficiency with clinical signs such as ascite, and encephalopathy at Screening;

15. The subject presents with positive serology results (HbsAg, anti-HCV, anti-HIV 1 or 2) at Screening;

16. The subject was exposed to excessive UV radiation within two weeks prior to Day 1, or is planning exposure during the study (e.g. phototherapy, occupational exposure to the sun, planned holidays in the sun during the study, tanning salon);

17. For subjects who consented to skin biopsy: the Subject presents the following criteria not allowing the biopsy sample (Screening visit):

17.1. Inherited or acquired hemostasis disorder;

17.2. Known allergy to local anesthetics and or topical antiseptics planned to be used in the study,

17.3. Past history or physical evidence of abnormal healing (keloids, hypertrophic scars, scars in hollow)

18. The subject is vulnerable as defined in Section 1.61 of International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)" (Screening visit):

18.1. an adult under guardianship, or hospitalized in a public or private institution for a reason other than the Research, or deprived of freedom,

18.2. a subject unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function,

19. The subject is participating in any other clinical trial of a drug or device OR participated within 1 month prior to Day 1 OR is in an exclusion period from a previous clinical trial of a drug or device (Screening visit).

Rationale:

#1: Given the animal teratogenicity data and in absence of well controlled data on safety in lactating or pregnant women.

#2 to 9; 12 to 16: To avoid any confounding factor in study safety evaluation

#10: For safety reasons

#11: Only subjects without treatments within the specified time-frame could participate, to avoid interferences due to co-administrations, and misinterpretations of the results obtained.

#17: In order to not put the subject at risk in case skin samples will be performed for that subject (optional).

#18 and 19: To comply with ICH-GCP and regulatory requirements.

5.3 Previous and concomitant therapies

5.3.1 Definition

Previous therapies are defined as therapies that have been stopped within the 3 months preceding the screening visit.

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,
- any new therapies received by the subject since the screening visit

5.3.2 Categories

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

- Drugs/therapies 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.

5.3.3 Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the 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 adverse event (AE). A corresponding Adverse Event Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

5.3.4 Authorized concomitant therapies

Unless listed under the non-inclusion criteria (Section 5.2.2 item 11) or in prohibited concomitant therapies (see Section 5.3.5), all therapies are authorized.

5.3.5 Prohibited concomitant therapies

The therapies listed in section 5.2.2 item 11 are prohibited because they may interfere with the efficacy and/or safety (for example interaction with the study drug(s) metabolism) assessment of study drug(s).

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, GALDERMA R&D should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives a prohibited therapy during the clinical trial, GALDERMA R&D should be notified to discuss the pertinence and the modalities for the subject to continue the clinical trial.

5.4 Procedures and Reasons for subject discontinuation from the study

An Investigator may decide to discontinue a subject from the clinical trial for safety reasons.

Although the importance of completing the entire clinical trial should be explained to the subject by the clinical trial personnel, any subject is free to discontinue participation in this clinical trial 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.

For those cases when the study treatment is to be stopped for any reason such as intolerance, aggravation of the conditions, deemed as related to the study drug, the investigator should make every attempt to keep the subject enrolled in the study after study drug discontinuation and compliant with the study time-points for efficacy and safety assessments until D54±2 as planned in the protocol. The use of a concomitant/rescue therapy should be documented in the e-CRF.

When a subject does not complete the clinical trial, he/she will be fully assessed with procedures included in the Early Termination visit, if such assessment is possible. The procedures designated for the Early Termination visit should be completed for all subjects discontinuing the clinical trial and the eCRF should be completed

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.

A subject who has been randomized and assigned a kit number/randomization number cannot be replaced by another subject if (s)he discontinues the clinical trial for any reason. Additional subjects could be enrolled (randomized/assigned to treatment) in order to attain the number of evaluable subjects.

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

Potential reasons for discontinuation, as listed on the Exit Form, are defined below:

- Pregnancy: **Withdraw the Subject from the clinical trial and follow the procedure described in Section 7.2.6.2.4**
- Lack of Efficacy: Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark "withdrawal by subject" and document it in the comment section of the eCRF Exit Form.
- Adverse Event: Complete an Adverse Event Form.
- Withdrawal by Subject: Includes consent withdrawal, subject relocation, schedule conflicts, etc. Does not include AE. Explain the reason for withdrawal in the comment section of the eCRF Exit Form.
- Protocol Deviation: Explain the deviation in the comment section of the eCRF Exit Form.
- Lost to Follow-up: Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF Exit Form.
- Other: This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF Exit Form.

If reason for discontinuation is "withdrawal by subject" or "other", the subject will be questioned to rule out the possibility of an AE and this should be documented. If the AE led to discontinuation, then "adverse event" should be chosen as the reason for discontinuation, rather than "withdrawal by subject" or "other".

6 CLINICAL SUPPLIES

6.1 Clinical supply identification and use

6.1.1 Study drug(s) description

Table 4 Description and usage of the study drug(s)

	Investigational product	Comparator
Trade Name or Equivalent	Not Applicable	Not Applicable
Name of Drug Substance	Ivermectin	Not Applicable
Internal Code	CD5024	CD5024 (Placebo)
Pharmaceutical Form	Cream	Cream
Concentration	0.3%	Not Applicable (placebo)
Formula number	575.767	575.754P
Packaging (type and size)	CCI	CCI
Storage Conditions	CCI	CCI
Dosage (total daily dose)	Up to 4 g daily (depending on tBSA and BSA)	
Route	Topical	
Dose Regimen	Once a day, 7 days a week for 6 weeks (42 applications)	
Location of Treated Area	All body except scalp & genitals	

CCI

6.1.4 Kit number / Randomization number

The kit number, a unique randomization number will be assigned to each eligible subject at baseline according to the Inclusion/Non-inclusion criteria. Kit and randomization numbers will be allocated to each subject by the IRT system which will need to be accessed by the designated study site personnel in order to provide the intended kits.

6.1.5 Instructions for use and administration

All subjects randomized

The percentage of the body surface affected by the disease (BSA) will be estimated using the rule of nine's by the investigator and will be documented on the CRF and communicated to the subject.

Except for the first application, study drug will be applied at home by the subject on all the AD lesions (except scalp and genitals) as a thin layer corresponding to approximately 2 mg/cm² (Shah 1992) using the Finger Tip Unit (FTU). A finger-tip unit is the amount of ointment expressed from a tube with a 5 mm diameter nozzle applied from the distal skin-crease to the tip of the index finger (Long 1991). A member of the staff will instruct the subject on how to measure the prescribed dose using fingertip units (FTU): two FTUs are about the same as 1g of topical product.

Subjects will be instructed by the person in charge of dispensing study products, on the importance of being compliant with the daily applications, and the weekly visits on site. Please also refer to section 6.4 for the rules regarding dose modifications.

All explanations and training materials will be provided to the study centers before initiation of the study.

Applications should be made every evening approximately at the same time, preferably after showering. The subjects will be asked to complete a diary on a daily basis to record the products applications. Do not wash off within 2 hours after applications (hands included).

Additionally, in order to monitor the quantity of study product that has been applied by the subject during the previous week, the subject will have to return all used & unused tubes (i.e. the kit of the previous week) to the study centre during the planned study visits. Tubes will be weighed and the application procedures will be reminded to the subject so that the required quantity of products is applied, in compliance with the BSA.

All subjects will have to use their own emollient throughout the study duration once a day in the morning, including during the screening period.

Subjects dedicated to cutaneous procedures

The estimated time (HH:mm) when application of Day 42 is performed should be recorded by the subject and reported by a study staff member in the eCRF. The time of performance of the cutaneous procedures will be recorded by the study team at Day 43. A time-window of 12h±2h should apply between the last product application and the cutaneous procedures.

6.1.6 Other supplies

Not Applicable.

CCI

CCI

[redacted]

6.4 Dose modification

In case the study treatment needs to be discontinued for any reason, as far as possible and if the subject agrees (see below) he/she should be followed as planned until the end of the clinical trial (also refer to section 5.4)

6.4.1 Tolerance issues

In case of significant sign and/or symptom of intolerance reported by the subject or assessed by the investigator, applications may temporarily be discontinued to allow the irritation to subside (treatment application could be performed every other day according to the Investigator judgement). The investigator should attempt to resume the daily applications as soon as possible, with respect to the local tolerance. This should be documented in the CRF and reported as an AE.

6.4.2 Decrease BSA

In case of improvement of the disease (*i.e.* a BSA decrease), the dose should remain unchanged throughout the study period, and subject will be asked to apply on all affected areas, even if they cleared.

Of note, the BSA should reflect the actual percentage of the zones affected by the disease; the previously affected areas that have cleared should no longer be taken into consideration for the calculation of this new BSA, even if they are still receiving the IMP.

6.4.3 Increase in BSA

In case of an increase in the BSA such as emergence of new plaques or extent of the surface of the identified ones, and within the limit of 8% (equivalent to 4g/day), the quantity of product to be applied will be recalculated during the study visit.

In case the BSA decreases afterwards, the rules of section 6.4.2 apply: the updated quantity that was calculated further to BSA increase will continue to be applied.

Should the BSA change because new plaques arise and former ones clear, the adjustment of the quantity of IMP should take into account the fact the applications should be maintained on the cleared zones. The BSA will be re-calculated, and the applications may be stopped on the oldest previously affected areas, to focus on the latest zones that have cleared, up to a maximum of 8%. The subject should be instructed not to use more than 4 gr/day (*i.e.* 8 FTUs). In case of flare (s)he should come back for an unscheduled visit.

Should the BSA increase above 8%, the investigator is to define whether treatment discontinuation and a rescue therapy is needed or not and whether the aggravation of the disease should be recorded as an AE. The investigator may also decide to maintain the products application, within a maximum amount corresponding to 8 FTUs/day (4g/day). **Should the treatment be discontinued, all efforts should be made for the subject to remain in the study until completion of study visits (see treatment discontinuation).”**

6.5 Blinding

6.5.1 Verification of blinding

This is an investigator-blind study. Test products are applied by the subject himself and the dispensation is done by a person who will not be involved in the assessment/evaluations. The investigator and/or other evaluator(s) will not come into contact with the study materials. The subject and members of the study staff do not have access to the correspondence between the kit number and the assigned treatment group.

6.5.2 Un-blinding during the clinical trial

Emergency un-blinding during the clinical trial may be required for therapeutic or for regulatory reasons (for expedited safety reporting).

A blind-break system will be available for Investigators. At the clinical trial center, use of an IRT system containing the identification of the assigned study drug(s) will be revealed in emergency situations only. In such an emergency, the Investigator will only break the blind for the subject involved.

The Investigator must notify the Sponsor's CSO immediately in the event of such an emergency (see contact details in Section 7.2.6.2.2). If possible, the Investigator should notify the Sponsor before breaking the blind in order to discuss this decision with the Sponsor. The Investigator is required to document each case of emergency un-blinding on the appropriate form (provided by the Sponsor) and fax the completed form to the CSO immediately.

Bioanalytical and PD local un-blinding:

Sample assay for PK analysis (blood and skin) will only be performed on samples from subjects treated with CD5024. Prior to sample assay, local un-blinding will be performed (based on the randomization list transferred directly by the assigned representative of the clinical packaging organization), restricted to the Bioanalytical study director and his/her direct collaborators, in order to select the appropriate samples for the assay. Unblinded (SIN Number) bioanalytical results will only be disclosed after database lock, following a formal authorization provided by the Clinical Project Manager.

The same way, a list will be also transmitted to the Molecular Dermatology Unit study director, in charge of the PD analysis. Molecular dermatology results will only be disclosed, after database lock, following a formal authorization provided by the Clinical Project Manager.

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

7.1.1 Investigator Global Assessment (IGA)

IGA should be a global static evaluation of the severity of the disease. A 5-point IGA (ranging from 0 to 4) will be performed by the investigator at screening and on Day 1, Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43 or earlier in case of early termination. IGA (whole body assessment) should be equal to 3 at Day 1.

Table 5 IGA

Status	Score	Definition
Clear	0	Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting.
Almost clear	1	Trace, faint pink erythema with almost no induration/papulation and no oozing/crusting.
Mild	2	Faint pink erythema with mild induration/papulation and no oozing/crusting.
Moderate	3	Pink-red erythema with moderate induration/papulation and there may be some oozing/crusting.
Severe	4	Deep/ bright red erythema with severe induration/papulation with oozing/crusting.

7.1.2 Hand IGA

If the subject presents with atopic dermatitis on one or both hands at baseline, the investigator will also assess the severity of the hand eczema from 0 to 4 (0:clear, 1:almost, 2:mild, 3:moderate, 4: severe) at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43 or earlier in case of early termination.

7.1.3 BSA

The BSA is the percentage of the total body surface area (tBSA) affected by atopic dermatitis, presenting with some, or all, of the individual features of the disease. It can evolve throughout the study duration. It should reflect the actual percentage of the body surface (except scalp and genitals) area affected by the disease; the previously affected areas that have cleared should no longer be taken into consideration for the calculation of the new BSA, even if they are still applied the IMP, as discussed in section 6.4.

The BSA, determined using the Rule of Nine's, is a good indicator of the disease's state and will also be used for the calculation of the modified objective SCORAD. The BSA will be assessed

at screening, at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43 or earlier in case of early termination and at the unscheduled visit if applicable.

Of note, at Day 1, BSA should comprise between 1% inclusive and 10% inclusive (excluding scalp and genitals).

tBSA is the subject's surface of the body, expressed in square meter. Several publications deal with the way to calculate tBSA. The mosteller formula is however recommended for use in this protocol: BSA (m^2) = SQRT([Height(cm) x Weight(kg)]/3600) or in inches and pounds: BSA (m^2) = SQRT([Height(in) x Weight(lbs)]/ 3131) (Mosteller 1987).

7.1.4 Total Sum Score (TSS)

The TSS (ranging from 0 to 15) will be calculated directly in the e-CRF, as the sum of the individual clinical scores, assessed on a target plaque selected by the investigator. The target plaque should be representative of the subject's disease severity. It should be located on a covered area and should not be located neither on hands, feet, scalp nor genitals. Individual clinical scores will be assessed at Day 1, Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43 or earlier in case of early termination, using the following 4-point scales.

Table 6 Individual Clinical Scores

ERYTHEMA		
0	None	No detectable erythema.
1	Mild	Faintly detectable erythema: very light pinkness
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep, dark red
INDURATION / PAPULATION		
0	None	Normal skin thickness. No elevation of skin
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
OOZING / CRUSTING		
0	None	No oozing/crusting
1	Mild	Faint sign of oozing and/or weeping
2	Moderate	Definite oozing
3	Severe	Marked and extensive oozing/weeping; heavy crusting
EXCORIATION		
0	None	No shedding
1	Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions

LICHENIFICATION		
0	None	No lichenification
1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated.
2	Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern.
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern.

7.1.5 Modified Objective SCORAD

The modified objective SCORAD (ranging from 0 to 65) will be calculated on Day 1, Day 8, Day 15, Day 22, Day 29, Day 36 and Day 43 or earlier in case of early termination. BSA and data of the individual clinical scores of the targeted plaque, used to calculate the TSS (section 7.1.4, Table 6) will be used for calculation.

Additionally, the investigator or designee will have to assess skin dryness scored from 0 (None) to 3 (Severe), on a non-treated area. The intensity (***B***, ranging from 0 to 18) is the sum of each individual clinical score including dryness.

The modified objective SCORAD calculation will be done directly in the eCRF using the following formula : (***BSA***/5) + (7***B***/2).

7.1.6 Eczema Area and Severity Index (EASI)

The EASI score is a tool used to measure the extent (area) and severity of atopic eczema (**E**czema **A**rea and **S**everity **I**ndex). The EASI score will be calculated directly in the e-CRF on Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, and Day 43 or earlier in case of early termination and at the unscheduled visit if applicable. . The investigator or designee will have to fill in, for each of the four body regions listed below, the area score and the severity score needed for EASI score calculation.

7.1.6.1 The four body regions

Head and Neck, Trunk, Upper limbs, Lower limbs (including buttocks).

7.1.6.2 The area score (A)

The area score will be recorded for each body region, as the percentage of skin affected by atopic dermatitis for this region. The area score is defined in the Table 7 below.

Table 7 Area Score for EASI calculation

Area Score	Percentage of skin affected in this region
0	No eczema
1	1% to <10% affected
2	10% to <30% affected
3	30% to <50% affected
4	50% to <70% affected
5	70% to <90% affected
6	90% to 100% affected

7.1.6.3 The severity score (S)

For each body region, the individual scores of each of the four individual clinical signs of AD will be assessed by the investigator on a 4-point scale (0-3) as presented in Table 8. The severity score is the sum of theses individual scores.

Table 8 Severity Score for EASI calculation

REDNESS (Erythema, Inflammation)		
0	**None**	No detectable erythema.
1	**Mild**	Faintly detectable erythema: very light pinkness
2	**Moderate**	Dull red, clearly distinguishable
3	**Severe**	Deep, dark red
THICKNESS (Induration, Papulation, Swelling)		
0	**None**	Normal skin thickness. No elevation of skin
1	**Mild**	Barely perceptible elevation
2	**Moderate**	Clearly perceptible elevation but not extensive
3	**Severe**	Marked and extensive elevation

SCRATCHING (Excoriation)		
0	**None**	No shedding
1	**Mild**	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2	**Moderate**	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	**Severe**	Many erosive or crusty lesions
LICHENIFICATION (Lined skin, prurigo nodules)		
0	**None**	No lichenification
1	**Mild**	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated.
2	**Moderate**	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern.
3	**Severe**	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern.

7.1.6.4 The EASI Score

The EASI score (ranging from 0 to 72) calculation will be done directly in the eCRF using the following formula.

Table 9 Calculation of the EASI Score

Body region	Redness	Thickness	Scratching	Lichenification	Severity score	Area score	Multiplier	Region score
Head/neck	_____	+_____	+_____	+_____	=_____	X_____	X 0.1 (If ≤7 yrs, X 0.2)	=_____
Trunk	_____	+_____	+_____	+_____	=_____	X_____	X 0.3	=_____
Upper limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.2	=_____
Lower limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.4 (If ≤7 yrs, X 0.3)	=_____
					The final EASI score: add up the 4 region scores			=_____ (0-72)

7.1.7 Subject-reported Outcomes

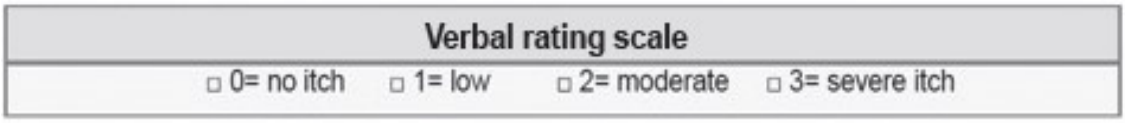
7.1.7.1 Pruritus - Numerical Rating Scale (NRS)

The severity of the pruritus will be assessed twice daily (early morning and evening before study product application) by the subject at home throughout the study (from Screening to Day 43 or earlier in case of early termination) using the pruritus Numerical Rating Scale (NRS) completed on a diary that will be collected at each visit at the study center (once weekly). Data will be reported in the e-CRF by a staff member. Subjects will be asked to assign a numerical score representing the intensity of their symptoms on a scale from 0 to 10. (Phan 2012).

The following question will have to be answered by the subject "*Within the last 12 hours, how would you rate your itch on the numerical rating scale, from 0 (No itch) to 10 (worst imaginable itch) ? Half-scores are not allowed*"

7.1.7.2 Pruritus - Verbal Rating Scale

The intensity of the pruritus over the last 24 h will be assessed at Day 1 and Day 43 by the subject at home using the verbal rating scale (VRS) completed on a diary that will be collected at study site at Day 43 or earlier in case of early termination. Data will be reported in the e-CRF by a staff member. The VRS consists of a list of adjectives describing different levels of symptom intensity (Phan 2012).



7.1.8 Efficacy endpoints

Primary efficacy endpoint:

The Primary efficacy endpoint is the EASI percent change from baseline at Week 6.

Secondary efficacy endpoints:

- The EASI percent change from baseline at each other evaluation visit and change from Baseline in EASI at each evaluation visit.
- Investigator Global Assessment in terms of distribution and in terms of success rate (Success is defined as a subject with an IGA score of 0 (clear) or 1 (Almost clear) at each evaluation visit.
- Percent Change from baseline of the TSS of the target plaque
- Percent Change from baseline of the Modified Objective SCORAD
- Pruritus (NRS, VRS) and their changes from Baseline at each evaluation visit.

7.2 Safety assessment

7.2.1 Physical examination

A standard physical exam will be conducted at screening, on Day 1, Day 15, Day 29, Day 43 and Day 54±2 by the Investigator or earlier in case of early termination.

This physical exam should include a standard neurological exam performed by the investigator. The standard neurological exam should collect potential neurological signs or symptoms affecting the gait, speech, sensory and motor system including the optic and oculomotor nerves (pupillary reaction (such as mydriasis)).

All abnormal findings identified as clinically significant by the Investigator at screening visit, and present before the visit, will be recorded in the Medical History form. All new abnormal findings identified as clinically significant by the Investigator from the signature of the ICF will be recorded in the Adverse Event form.

7.2.2 Vital signs

The evaluation of vital signs (pulse rate and blood pressure) will be performed, after five minutes of rest in sitting position, at screening, on Day 1, Day 15, Day 29, Day 43 and Day 54±2 or earlier in case of early termination. Vital signs will be evaluated as “normal” or “abnormal” by the Investigator.

All abnormal findings identified as clinically significant by the Investigator at screening visit, and present before the visit, will be recorded in the Medical History form. All new abnormal findings identified as clinically significant by the Investigator from the signature of the ICF will be recorded in the Adverse Event form.

7.2.3 Electrocardiogram

A 12-lead ECG will be performed at screening, on Day 1 and Day 43 or earlier in case of early termination. Any subject presenting with a clinically significant abnormal ECG at screening or on Day 1 will not be included in the study.

All abnormal findings identified as clinically significant by the Investigator at screening visit, and present before the visit, will be recorded in the Medical History form. All new abnormal findings identified as clinically significant by the Investigator from the signature of the ICF will be recorded in the Adverse Event form.

7.2.4 Laboratory Tests

Table 10 Blood tests

Test	Criterion for clinically significant value	Screening	Day22	Day42/ET
Coagulation				
Prothrombin Ratio	Out of range and clinically significant	X	X	X
Virology				
HBsAg	Positive	X		
HCVab	Positive	X		
HIV 1 and 2 antibodies	Positive	X		
Hematology				
WBC count with differential	Out of range and clinically significant	X	X	X
RBC count	Out of range and clinically significant	X	X	X
Haemoglobin (Hb)	Out of range and clinically significant	X	X	X
Hematocrit (Hc)	Out of range and clinically significant	X	X	X
Mean Cell Volume	Out of range and clinically significant	X	X	X
Platelets Count (Plt)	Out of range and clinically significant	X	X	X
Blood Chemistry				
Creatinine	Out of range and clinically significant	X	X	X
ALP (alkaline phosphatase)	Out of range and clinically significant	X	X	X
AST (aspartate aminotransferase)	> 2 x Upper Laboratory Norm	X	X	X
ALT (alanine aminotransferase)	> 2 x Upper Laboratory Norm	X	X	X
TB (total bilirubin)	> 1,5 x Upper Laboratory Norm	X	X	X
Creatinine clearance	Estimated glomerular filtration rate < 60 ml/min/1.73m² (using CKD-EPI formula)	X	X	X
Other				
Total IgE	Value to be reported	X		X
TARC	Value to be reported	X		X

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 initial and date all laboratory reports 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., change of dose, discontinuation of the 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 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 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.

An out-of-range laboratory value that is identified as clinically significant and related to the study drug(s) is considered by the Sponsor to be an Adverse Event of Special Interest (AESI) (see Section 7.2.6.1.3).

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.

7.2.5 Urine Pregnancy Tests

For female of childbearing potential, UPT will be done at Screening, Day 1, Day 15, Day 29, Day 43 and Day54±2 or earlier in case of early termination.

At least 14 days should be respected between Screening & Baseline visits.

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7.3.3 Photographs

Standardized photographs of the target plaque will be performed at Day1 before products application and Day 43 and at the unscheduled visit if applicable to document the effect of the study treatments. Details of the procedures will be described in a biophysical manual provided by the Sponsor.

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.

8.1.1 Screening visit (Day -30 to Day-3)

A maximum of 30 days is allowed between Screening and the first study drug administration at Baseline. The minimum time period between Screening and Baseline is 3 days, and not less than the amount of time necessary for the Investigator to receive laboratory test results done during the Screening visit.

At the 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 (e.g., restrictions in the use of topical and systemic medications, avoiding sun exposure…).
2. Obtain the signed and dated ICF, and PIPEDA; provide a fully completed dated and signed copy to the subject and/or the subject's legal guardian.
3. Assign the subject a SIN.
4. Collect information regarding demographics, relevant medical history, previous therapies and procedures, and concomitant therapies and procedures.
5. Determine and record the Body Surface Area of the subject : tBSA
6. Confirm the clinical diagnosis of Atopic dermatitis using the criteria of Hanifin and Rajka
7. Assess the BSA.
8. Assess IGA score.
9. Complete pregnancy test if the subject is a female of childbearing potential.
10. Collect a blood sample for coagulation, hematology, biochemistry, virology & IgE / TARC.
11. Perform a physical examination of the subject, including neurological examination and vital signs (blood pressure, pulse rate);
12. Perform an ECG.
13. Confirm that the subject meets inclusion/non-inclusion criteria.
14. Complete the Subject Screening Log.
15. Ask the subject to evaluate its pruritus severity using the NRS twice daily, every day until the next visit and to collect the data on the dedicated diary, to be taken with him to the center at each study visit.
16. All AEs reported by the subjects during the screening period should be recorded as appropriate on the corresponding eCRF pages;

17. Any changes in the concomitant therapies/procedures (added, removed, or changed) occurring during the screening visit should be documented on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
18. Schedule the Baseline visit (for women of childbearing potential, there must be at least 14 days between Screening and Baseline Visit (for UPT reason)).

8.1.2 Baseline visit (Day 1, Week 1)

At the Baseline visit, the Investigator or designee will:

1. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding eCRF pages;
2. Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
3. Check laboratory results from the Screening visit.
4. Complete pregnancy test if the subject is a female of childbearing potential.
5. Perform a physical examination of the subject, including neurological examination and vital signs (blood pressure, pulse rate);
6. Perform an ECG.
7. Confirm subject meets inclusion/non-inclusion criteria.
8. Assess the BSA.
9. Assess IGA score (and hand IGA if applicable).
10. Select and identify a target plaque that is representative of the overall disease of the subject and take standardized photo of this target plaque
11. Assess the TSS and the modified-objective SCORAD :
    a. Assess the individual clinical scores of the target plaque
    b. Assess skin dryness scored on a non-treated area
12. EASI Score : Assess the area score and the severity score of each body region
13. Assign a randomization number.
14. Weigh the study products to be provided to the subject and record the weights
15. Dispense study product and provide written/oral instructions for study drug application/administration.

16. A member of the staff other than the Investigator will explain the subject how to apply the study product and will supervise the subject while applying the appropriate quantity of study products on targeted areas.
17. Instruct subject to complete the application diary for the coming applications at home on a daily basis.
18. Ask the subject to evaluate its pruritus severity using the NRS twice daily, every day until the next visit and to collect the data on the dedicated diary, to be taken with him to the center at each study visit.
19. Ask the subject to evaluate its pruritus severity over the past 24h, using the VRS and to collect the data on the dedicated diary, to be taken with him to the center at each study visit.
20. Complete the Subject Enrollment Log.
21. Remind the subject for the next visit date.

8.1.3 Weekly visits (Day 08, Day 15, Day 22, Day 29, Day 36)

The Investigator or designee will:

1. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding eCRF pages;
2. Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
3. Assess the BSA.
4. Assess IGA score (and hand IGA if applicable).
5. Assess the TSS and Modified-objective SCORAD :
    a. Assess the individual clinical scores of the target plaque
    b. Assess skin dryness scored on a non-treated area
6. EASI Score : Assess the area score and the severity score of each body region
7. Collect the used & unused containers provided to the subject at the previous visit. Perform accountability for returned study drug.
8. Weigh the product and record the data in the source document.
9. Dispense new study products and provide written/oral instructions for study drug application/administration.

10. Instruct subject to complete the application diary for the coming applications at home on a daily basis.
11. Ask the subject to evaluate its pruritus severity using the NRS twice daily, every day until the next visit and to collect the data on the dedicated diary, to be taken with him to the center at each study visit.
12. Remind the subject for the next visit date.

Additionally at Day 15 & Day 29 only, the investigator or designee will also:

13. Complete pregnancy test if the subject is a female of childbearing potential.
14. Perform a physical examination of the subject, including neurological examination and vital signs (blood pressure, pulse rate);

Additionally at Day 22 only, the investigator or designee will also:

15. Collect a blood sample for coagulation, hematology and biochemistry.

Additionally at Day 36 only, a member of the study should remind the subject to complete the diary regarding VRS at Day 43 before the Day 43 visit (at the same time as the NRS is recorded).

8.1.4 Home Applications (Day 02 to Day 07, Day 09 to Day 14, Day 16 to Day 21, Day 23 to Day 28, Day 30 to Day 35, Day 37 to Day 42)

Applications will be made at home by the subject, in the evening, using the FTU methodology. Emollients should be applied in the morning. Subjects should be instructed to complete the diary on a daily basis, regarding both the applications (once daily) and the assessment of their pruritus (twice daily).

8.1.5 End-of-Treatment Visit (Day 43, Week 7) / Early Termination visit

The Investigator or designee will:

1. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding eCRF pages;
2. Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
3. Complete pregnancy test if the subject is a female of childbearing potential.
4. Collect a blood sample for coagulation, hematology, biochemistry, IgE & TARC .

5. Perform a physical examination of the subject, including neurological examination and vital signs (blood pressure, pulse rate);
6. Perform an ECG
7. Assess the BSA.
8. Take standardized photo of the target plaque
9. Assess IGA score (and hand IGA if applicable).
10. Assess the TSS and Modified-objective SCORAD :
    a. Assess the individual clinical scores of the target plaque
    b. Assess skin dryness scored on a non-treated area
11. EASI Score : Assess the area score and the severity score of each body region
12. Collect data from the subject regarding pruritus severity using NRS and VRS.
13. Collect the used & unused containers provided to the subject at the previous visit. Perform accountability for returned study drug.
14. Weigh the product and record the data in the source document.
15. Remind the subject for the next visit date.

Only for the End-of-Treatment Visit (Day 43, Week 7):

16. Perform one blood sampling on an AD-free zone or on a non-treated area, to avoid sample contamination. Those subjects who, at Day 43, do not present with an area that allows the blood sample to be done will not be sampled.

Only for those subjects who consented to, and for the End-of-Treatment Visit (Day 43, Week 7): approximately 12 hours after the last product application:

17. REFER TO THE OPERATIONAL MANUAL: Perform the 5 D-Squames procedures per area, sample the 20 tape-strips and perform the three 4-mm skin punch biopsies.

8.1.6 Follow-up visit (Day 54±2, Week 9)

During this visit, this investigator or designee will:

1. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding eCRF pages;

2. Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
3. Complete pregnancy test if the subject is a female of childbearing potential.
4. Perform a physical examination of the subject, including neurological examination and vital signs (blood pressure, pulse rate);
5. Check the good healing of the biopsies (if applicable).
6. Remove the suture (if applicable).
7. Complete the exit form

8.1.7 Unscheduled Visit

In the event the subject has to come back to the center for an unscheduled visit, due to an increase in the BSA (see section 6.4.3), the procedures described hereunder will have to be performed.

During this visit, this investigator or designee will:

1. Ask the subject about AEs by asking an open-ended question taking care not to influence the subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding eCRF pages;
2. Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies and/or Medical/Surgical Procedures form of the eCRF;
3. Assess the BSA.
4. Select and identify a target plaque that is representative of the increasing of the disease of the subject and take standardized photo of this target plaque
5. Define wether the treatment is maintained, up to 8 FTUs, or discontinued
6. EASI Score : Assess the area score and the severity score of each body region
7. Remind the subject for the next visit date.

8.2 Subject instructions (other than study drug(s) administration)

Throughout the study duration, subjects should be instructed to avoid concomitant use of other potentially irritating topical products such as medicated or abrasive soaps & cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentration of alcohol, astringents, spices or limes.

Exposure to sunlight, including sunlamps, should be avoided during the study duration. The use of a protective apparel is recommended when exposure cannot be avoided. Sunscreens may be used when sun exposure is unavoidable.

The subjects should also be instructed to not participate to another clinical trial of a drug or device within one month after the last visit.

All subjects will have to use their own emollient throughout the study duration once a day in the morning on AD lesions, including during the screening period. For those subjects who do not have an emollient, they will be prescribed one.

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

A statistical analysis plan (SAP) will be developed and issued as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analysis strategies that are specified in the sections of the clinical trial outline below. Changes to CCI or other non-confirmatory analyses made after the SAP has been finalized, along with an explanation as to when and why they occurred, will be documented in the clinical study report. Post hoc exploratory analyses will also be clearly identified in the Clinical Study Report (CSR).

Any change made to the finalized SAP will be documented in the clinical trial report.

9.1.1 Data transformations

C_t, cumulated concentration in the SC, concentration in the skin biopsy (epidermis and dermis), and cumulated concentration in the total skin will be log transformed before any analysis.

9.1.2 Populations analyzed and evaluability

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

9.1.2.1 Intent-to-treat (ITT) Efficacy analysis set

The ITT set is defined as any subjects who are randomized. Data from subjects included in the ITT population will be analyzed according to the treatment as randomized.

9.1.2.2 Per-protocol (PP) Efficacy analysis set

Per Protocol (PP) set is defined as the ITT population, after exclusion of subjects deemed non-evaluable for efficacy due to major deviations from the protocol. Major deviations are categorized into 4 categories:

- Entrance criteria deviations,
- Non compliance,
- Concomitant therapies taken during the study and/or Concomitant illnesses, interfering with efficacy,
- Administrative errors such as unblinding or study drug dispensing errors.

Major deviations will be identified and categorized before database lock and unblinding, during a blind data review meeting.

9.1.2.3 Safety Analysis set

The Safety set is defined as comprising the ITT Population subjects who applied/were administered the study drug(s) at least once. In practice, only the subjects who return their study drug(s) unopened will be excluded from the Safety Population. All safety data will be summarized based on the Safety Population.

9.1.3 Data presentation and graphics

For statistical analyses purpose, baseline is defined as the last measurement prior to the first application of the study drug.

A type I error of 0.05 (two-sided test) will be used to declare statistical significance.

The subject disposition, demographics, Baseline characteristics, previous therapies/procedures, concomitant therapies/procedures will be summarized by descriptive statistics based on the ITT population. Treatment duration and compliance data will be summarized based on the Safety Population.

For statistical analysis purposes, previous therapies/procedures are defined as those ending at Baseline or before; and concomitant therapies/procedures are defined as those ongoing at the Baseline visit or starting after the Baseline visit.

All efficacy variables will be summarized by treatment at each visit. The categorical variables (e.g. IGA), and their changes from Baseline will be summarized by frequency and percentage for each response category (N, %). The continuous variables (EASI, objective SCORAD, TSS, and their percent changes, Pruritus (weekly average NRS), VRS and their changes from baseline)

will be summarized using means, medians, Q1, Q3, minimum, maximum, and standard deviations.

Treatment-emergent Adverse Events (TEAEs) are defined as AEs with onset on or after first dose of study drug; or those AEs with onset prior to first dose of study drug but worsened during treatment.

TEAEs will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA). Additional summary tables will be provided for SAEs, AEs considered related to the study drug, severe AEs, 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, non TEAEs will be summarized or listed separately.

Descriptive statistics for each laboratory parameter at Screening and any time points and shift table for laboratory parameters at Screening versus end of study will be provided.

Vital signs and physical examinations will be descriptively summarized.

Plasma concentration, Skin parameter concentration, as well the Skin/plasma ratio will be descriptively summarized

Subgroup analyses will be explored by IgE on the primary endpoint.

9.1.3.1 Analysis of the primary efficacy endpoint

The Primary efficacy endpoint, EASI score least square mean percent change from baseline at week 6, will be analyzed via an analysis of variance with the Treatment group as factor and Center as a cofactor.

9.1.3.2 Analysis of the Secondary Efficacy Endpoint

EASI score least square mean percent change from baseline at any other evaluation visit, will be analyzed via an analysis of variance with the Treatment group as factor and Center as a cofactor.

Objective SCORAD and TSS least square mean percent change from baseline at each evaluation visit, will be analyzed individually via an analysis of variance with including the Treatment group as factor and Center as a cofactor.

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

Change in Pruritus (Weekly average NRS) will be analyzed at each evaluation visit by the CMH test stratified by analysis center with the ridit transformation and the row mean difference statistic (FREQ procedure from SAS).

9.1.3.3 Imputation of missing data

For the primary endpoint several sensitivity analyses will be conducted:

- The primary imputation method will use the LOCF (Last observation carried forward) approach.
- For sensitivity purpose method of imputation for missing data will be MI (Multiple Imputation) using the Missing At Random (MAR) assumption. 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 EASI 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 EASI 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 (109696).

For secondary endpoints:

- The primary imputation method will use the LOCF (Last observation carried forward) approach.

In addition, all analyses for primary and secondary endpoints will be conducted on the Per Protocol set.

9.1.3.4 Handling of Multiplicity

The primary purpose is to compare CD5024 cream 0.3% QD daily to its vehicle in terms of EASI score. P-values for secondary criteria will be given for indicative purposes so no adjustment will be made. All tests will be two-sided and significance will be declared at a 5% two-sided level.

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9.2 Sample size determination

9.2.1 Historical data

In a Galderma R&D trial (SPR.18158) where the Vehicle was used in atopic dermatitis in subjects with BSA between 5% and 20%, the Vehicle percent change from baseline at week 4 of a modified EASI (No Head and Neck) was -40% and the standard deviation (SD) was 45%.

In studies evaluating Dupilumab versus placebo, the observed placebo EASI percent changes from baseline at week 4, ranged between -17% and -25% with a standard deviation around 40% (Beck 2014) and was -18% at week 16 with a standard deviation of 40% (Thaci 2016). In this last trial it was observed that these values were reached from week 4 onwards.

9.2.2 Assumptions

Based on historical data, the standard deviation was set to 40%.

The magnitude of effect of Dupilumab reached 45% over placebo. However, systemic immunosuppressant drug for atopic dermatitis are generally more effective than topical treatments (Thaci 2016). Taking that into account, it is expected that for CD5024 cream 0.3% applied once daily, an effect of 30% over its vehicle would be clinically relevant. Consequently, the effect size (delta/sigma) has been set to 0.75 (30%/40%).

9.2.3 Sample size calculation

Using a randomization ratio of 1:1 for CD5024 cream 0.3%QD and vehicle respectively, a sample size of 30 randomized subjects in each treatment group can ensure a 80% power to detect

a difference of 30 % between CD5024 and its vehicle on EASI mean percent change from baseline.

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12 LITERATURE REFERENCE LIST

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13 APPENDICES

Table 11 Prohibited concomitant treatment

CYP	INHIBITORS	INDUCERS
3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort Bosentan, efavirenz, etravirine, modafinil, nafcillin Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide.
P-gp	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	
This list might be not exhaustive, strong CYP3A inhibitors, all CYP3A inducers and all P-gp inhibitors should not be used during the trial. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit		