CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.112075

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TITLE PAGE

Title *EXPLORATORY STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CD10367 IN SUBJECTS WITH PSORIASIS*		
Project Name or CD number: CD10367	**Project Number:** 315	**Clinical Trial Phase:** Phase 2a

EUDRACT NUMBER 2016-002774-12

Version Number: 01

SPONSOR:

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

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), CCI [redacted]. This clinical trial protocol follows guidelines outlined by the International Conference on Harmonisation (ICH) and the GALDERMA template.

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SYNOPSIS	
Clinical Trial Title: EXPLORATORY STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CD10367 IN SUBJECTS WITH PSORIASIS	
Short Title: EXPLORATORY STUDY TO EVALUATE CD10367 IN PSORIASIS	
Clinical Trial phase: Phase 2a	**Clinical Trial Population:** subjects with psoriasis vulgaris
Clinical Trial objectives:	**Primary objectives:** To evaluate, in a modified Dumas-Scholtz psoriasis mini-zone test, the safety and efficacy of CD10367 solution at 1% and 3% after a three weeks treatment period of once daily application. CCI [redacted]
Clinical Trial design:	Exploratory, single-centre, investigator blinded, randomized, controlled, intra-individual study (Dumas-scholtz design).
Total number of subjects (Planned):	As a screen failure rate of approximately 40% percent is expected, approximately 40 subjects may have to be screened in order to obtain 24 subjects randomized.
Number of clinical trial centers (Planned):	1 site.
Region(s) / country(ies) involved (Planned):	France
Clinical trial duration:	The planned clinical trial duration (from FSFV to LSLV) is approximately 5 months. The planned duration of recruitment (from FSFV to LSFV) is approximately 3.5 months.
Duration of subject participation:	Clinical trial participation for each subject is approximately 9 weeks including screening period.
Key Inclusion criteria	• Adult male or female aged at least 18 and up to 70 years old inclusive at screening visit. • Female of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any

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	other medical reason], hysterectomy or bilateral oophorectomy). • Subject has a skin phototype I to IV on Fitzpatrick's scale. (Screening visit). • The subject has a clinical diagnosis of stable plaque psoriasis, defined as no flare during the month before Screening visit and no change between Screening visit and Baseline visit, of mild to moderate severity. (Screening visit and Baseline Visit). • The subject presents with at least six eligible mini-zones, on at least two psoriasis plaques (Screening visit and verified also at Baseline Visit) with specific severity grades defined in the protocol (Screening and Baseline Visit) • Subject agrees not to wear his/her contact lenses from the Baseline visit till the D19 visit,
Key Exclusion criteria	• The subject presents guttate, erythrodermic, exfoliative, inverse, pustular, palmo plantar, infected or ulcerated psoriasis (Screening visit). • Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results, and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical trial (e.g. history of on-going gastric or duodenal ulcer, clinically significant lung disease, etc.). • Known or suspected allergies or sensitivities to any components of the study drugs or of the keratolytic product (see Investigator's Brochure/Product label) . • Subject with known history of adverse drug reaction or hypersensitivity to a product with the same mode of action • Subject with any abnormal clinically significant findings according to the ophthalmologist, at the ophthalmological exam at Screening, • The subject presents any abnormal laboratory tests defined in the protocol (blood sampling and urinalysis done at Screening visit), • QTc interval >450msec or any abnormal ECG value considered as clinically significant by the cardiologist at Screening, • The subject has received, applied or taken specific treatments within the time frame defined in the protocol prior to the Baseline

SYNOPSIS	
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	visit.
Investigational product:	NA
Name:	NA
Internal code [*if applicable*]:	CD10367
Pharmaceutical form:	Solution
[*Strength/Concentration*]:	1%
Dosage (total daily dose):	50µl
Route:	Topical
Duration of administration:	Five consecutive days a week for two weeks and four consecutive days in the third week (14 applications)
Dose regimen:	Once daily
Location of treated area:	Mini-zones on upper and/or the lower extremities (elbows, knees and shin area excluded) and/or on the trunk
Investigational product:	NA
Name:	NA
Internal code [*if applicable*]:	CD10367
Pharmaceutical form:	Solution
[*Strength/Concentration*]:	3%
Dosage (total daily dose):	100µl (50µl on each mini-zone)
Route:	Topical
Duration of administration:	Five consecutive days a week for two weeks and four consecutive days in the third week (14 applications)
Dose regimen:	Once daily
Location of treated area:	Mini-zones on upper and/or the lower extremities (elbows, knees and shin area excluded) and/or on the trunk
Investigational product:	NA
Name:	NA
Internal code [*if applicable*]:	CD10367 placebo
Pharmaceutical form:	Solution
[*Strength/Concentration*]:	NA
Dosage (total daily dose):	100µl (50µl on each mini-zone)
Route:	Topical
Duration of administration:	Five consecutive days a week for two weeks and four consecutive days in the third week (14 applications)
Dose regimen:	Once daily
Location of treated area:	Mini-zones on upper and/or the lower extremities (elbows, knees and

SYNOPSIS	
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	shin area excluded) and/or on the trunk
Comparator: **Name:** **Internal code:** **Pharmaceutical form:** **[*Strength/Concentration*]:** **Dosage (total daily dose):** **Route:** **Duration of administration:** **Dose regimen:** **Location of treated area:**	Betneval Betamethasone valerate 0.1% NA Ointment 0.1% 50µl Topical Five consecutive days a week for two weeks and four consecutive days in the third week (14 applications) Once daily Mini-zones on upper and/or the lower extremities (elbows, knees and shin area excluded) and/or on the trunk
Efficacy assessment: **Efficacy endpoints:**	The individual scores and clearing scores will be assessed twice weekly by the investigator. **Primary efficacy endpoint(s) or co-primary endpoint(s)** Area Under the Curve (AUC) of Total Sum Score (sum of erythema, scaling and induration scores) from Day 1 to Day 19. **Secondary efficacy endpoint(s)** • AUC of individual clinical scores (erythema, scaling and induration) from Day 1 to Day 19. • TSS and percentage change from baseline at each visit. • Erythema, Scaling and Induration score and their change from baseline at each visit. • Success rate (defined as a clearing score of 0 or 1) at each evaluation visit and the time to first success.
Safety assessment: **Safety endpoints [*only when applicable*]:**	A safety assessment will be conducted for all subjects at screening visit (from the Informed consent signature) and every subsequent visit. • Local tolerance assessed twice weekly by the Investigator using a 4-point scale for each mini-zone • Physical examination at Screening, and Day 19 (or Early Termination visit if any); • Record of vital signs at Screening, Baseline and Day 19 (or Early Termination visit if any); • Ophtalmic examination at Screening, and Day 19 (or Early

SYNOPSIS	
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	Termination visit if any); • ECG at Screening, and Day 19 (or Early Termination visit if any); • Blood samplings for laboratory safety tests at Screening and Day 19 (or Early Termination visit if any); • Urinalysis at Screening and Day 19 (or Early Termination visit if any); • Monitoring and recording of AEs to be recorded as specified in Section 7.2.6.
CCI [redacted]	
Sample size:	CCI [redacted]

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	Therefore 24 subjects are planned to be randomized. This sample size is sufficient to assess also local tolerance in standard tolerance topical studies.

Table 1 Clinical trial schematic

Screening
(Approximately 40 subjects)

↓

1 week pre-treatment with keratolytic product twice Daily at home on one or two psoriasis plaque(s)
(extend one more week if Scaling score ≥2 at the end of one week)

↓

Treatment
(Approximately 24 subjects randomized)

CCI [redacted]

Treated conditions:

Desquamated plaque(s)		Non desquamated plaque(s)			
CD10367 3 % solution	CD10367 Solution Placebo	CD10367 3 % Solution	CD10367 1 % solution	CD10367 Solution Placebo	Positive control: Betneval 0.1% Ointment

↓

Final Visit (D19) / ET

↓

Follow up Visit (D26+/-2)

Table 2 Schedule of Assessments

	Screening period	Pre-treatment period	Treatment Period											Follow-up period
	Up to 3 weeks before pre-treatment period	1 or 2 weeks [a] before treatment period	Week 1				Week 2				Week 3			Week 4 to 5
			D1	D2 &D3	D4	D5	D8	D9 & D10	D11	D12	D15	D16&D17&D18	Final visit D19 /ET	D26 +/- 2
Informed Consent Form	X													
Demographics and Medical history	X													
Previous treatments and procedures	X													
Physical examination	X												X	
Vital signs	X		X										X	
ECG	X [b]												X	
Ophthalmic examination	X [b]												X	
Inclusion Criteria and Exclusion Criteria	X		X											
Selection of target sites	X		X											
Urinalysis	X												X	
Safety tests Blood sampling	X												X	
Randomization			X											
Local Tolerance [c]				D2 only	X		X		X		X		X	
Individual clinical scores	X		X		X		X		X		X		X	
Clearing score					X		X		X		X		X	
Keratolytic product application of selected plaque at home daily		X												
Products application			X	X	X	X	X	X	X	X	X	X		
CCI														
PK blood sampling						X							X	X
CCI														
Concomitant treatments and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit form [e]													X [f]	X

a. if the scaling score did not reach 0 or 1 after 1 week of pre-treatment, the pre-treatment period can be extended to 2 weeks, otherwise the subjects will start D1 visit immediately. b ECG and ophthalmic exams should be done as close as possible to baseline visit. c Local tolerance CCI of the concerned zone must be taken at any visit in case of AE in a treatment zone. d Adverse Events have to be collected from the ICF signature. e Exit form should be signed after subject data collection has been completed. f Exit form should be completed at ET visit only if no follow-up visit is planned (discontinuation)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
ACE	Angiotensin-converting-enzyme
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
AZ	AstraZeneca
BID	Twice Daily (Latin: bis in die)
CA	Competent Authorities
CRA	Clinical Research Associate
CRF/eCRF	Case Report Forms/electronic Case Report Forms
CRO	Contract Research Organization
CSO	Clinical Safety Officer
DMP	Data Management Plan
DS	Drug substance
ECG	Electrocardiogram

Abbreviation	***Term***
e.g.	For Example (Latin: exempli gratia)
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
ET	Early Termination
etc	Et cetera
EU	European Union
FDA	Food and Drug Administration
FSFV	First Subject First Visit (date of first subject included i.e., informed consent signature)
GCP	Good Clinical Practice
GLP	Good laboratory practice
GRD	GALDERMA R&D
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

Abbreviation	***Term***
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identity
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification
LSFV	Last Subject First Visit (date of last subject included i.e., informed consent signature)
LSLV	Last Subject Last Visit (date of last subject's last study visit)
MALDI-FTICR-MS	Matrix Assisted Laser Desorption Ionization
MCV	mean cell volume
MD	Medical Doctor

Abbreviation	***Term***
ME	Medical Expert
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N or n	Number
N/A	Not Applicable
NOAEL	No-observed-adverse-effect level
CCI [redacted]	
OTC	Over-the-counter
p	Page(s)
CCI [redacted]	
PE	Physical Examination
CCI [redacted]	
PK	Pharmacokinetics
Plt	Platelets
PO	Per os (Oral administration)
PP	Per-Protocol
PT	Preferred terms
QD	Once Daily (Latin: quaque die)
RBC	Red blood cell

Abbreviation	***Term***
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TESS	Treatment Emergent Signs and Symptoms
TOC	Table of Contents
TSS	Total Sum Score
UA	Urinalysis
ULN	Upper Limit of Normal
UV	ultraviolet
WBC	White Blood Cell

1 BACKGROUND AND RATIONALE

1.1 Medical background and Short rationale for the clinical trial

1.2 Psoriasis

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin affecting 1.5% to 3% of the general population. The most characteristic lesions consist of chronic, sharply demarcated, dull-red scaly plaques, particularly on extensor parts of limbs. It can affect any body area including the face, palms, soles, folds, scalp and nails leading to erythema, scaling and thickening of the skin.

Genetic-environmental interaction is usually considered for the causation of psoriasis. Smoking, alcohol consumption, diet, psychological stress, infections and physical trauma have been suggested as factors which may influence the onset of the disease and/or may affect severity or the response to treatment.

The clinical course is unpredictable but in the majority of cases psoriasis is a chronically remitting and relapsing disease. Chronic stable plaque psoriasis (*psoriasis vulgaris*) is the most common form of the disease, accounting for 85% to 90% of cases. The circumscribed infiltrated skin lesions are scaly and erythematous and often symmetrically distributed over the body. Most of the patients suffer from mild to moderate plaque psoriasis with a body surface involvement of less than 10%. The majority of these patients can be treated with topical treatments, which generally provide both efficacy and safety (Menter et al., 2007).

Psoriasis principal histological features are: thickening of the epidermis, parakeratosis, elongated rete ridges, and a mixed cellular infiltrate in the dermis (Griffiths and Barker, 2007). The inflammatory infiltrate consists mainly in the dermis of dendritic cells, mast cells, macrophages, natural killer cells and different T-cell types such as CD4+ helper cells, CD8+ cytotoxic cells (Jullien, 2006).

Keratinocytic hyperproliferation is mediated by pro-inflammatory cytokines produced by T-cells and dendritic cells that accumulate in diseased skin. Several inflammatory cytokines (e.g. interleukin 1 (IL-1), IL-6, IL-8, interferon-γ, and tumor necrosis factor-α (TNF-α)) are known to trigger epidermal hyperplasia through direct or indirect pathways (Jullien, 2006).

Although there is no cure for psoriasis, a variety of treatments is available to reduce the severity of symptoms and lessen their impact on the patient's quality of life.

For patients with less than 20% body surface involvement, topical therapy is the most appropriate choice for the initial treatment. Commonly used topical therapies include corticosteroids, calcipotriol (a vitamin D analogue), tazarotene (the first topical retinoid approved for the treatment of psoriasis) and anthralin. Each of these treatments is effective in mild to moderate psoriasis, but each is also associated with varying degrees of safety and tolerability concerns.

For patients with more severe, recalcitrant, or extensive psoriasis, phototherapy and systemic therapies are available. These therapies are more effective than topical therapy, but are also associated with significant cutaneous and systemic adverse effects.

Epidermal growth factor receptor (EGFR) is normally expressed in the skin, primarily in the proliferating undifferentiated keratinocytes of the basal cell layers of the epidermis and plays a key role in cellular proliferation, survival and differentiation. EGFR over-expression or over-activity was associated with a number of cancers (e.g. lung, anal, head and neck, etc), but recent data also showed an overexpression of EGFR ligands in lesional psoriasis skin (Johnston et al, 2011). Varani et al showed in an in vitro study that psoriatic plaque skin incubated for eight days in the presence of a potent EGFR tyrosine kinase antagonist reverted to a normal histological appearance (Varani et al, 2005).

There are also several case reports of patients with cancer treated by EGFR inhibitors showing an improvement of their psoriasis (Overbeck and Griesinger, 2012).

CCI [redacted] CCI [redacted]. This outcome was already described in a mouse model by El-Abaseri (El- Abaseri 2013).

Therefore the purpose of this study is to evaluate the safety, efficacy, CCI [redacted] of CD10367 topical solution in psoriasis.

1.3 Drug profile

CD10367 is a potent and selective inhibitor of the tyrosine-kinase domain of the epidermal growth factor receptor (EGFR-TKI). This compound was initially developed as an oral formulation by AstraZeneca (AZ) for the treatment of solid tumors (including non-small cell lung cancer). CCI [redacted] The compound is currently evaluated by GALDERMA R&D for the topical treatment of several indications such as psoriasis.

1.4 Risk/Benefit assessment

This is an exploratory study to evaluate on psoriasis mini-zones the safety, efficacy, CCI [redacted] of CD10367 topical solution at 1% and 3%. As only mini-zones will be treated in this study no individual benefit is expected for the subjects who will participate to the study.

All investigational medicinal product (IMP) will be applied on mini-zones, located on psoriatic plaques, and the quantity applied will be under the control of the qualified staff who will perform all the applications at the site and no IMP will be given to the subjects for applications at home.

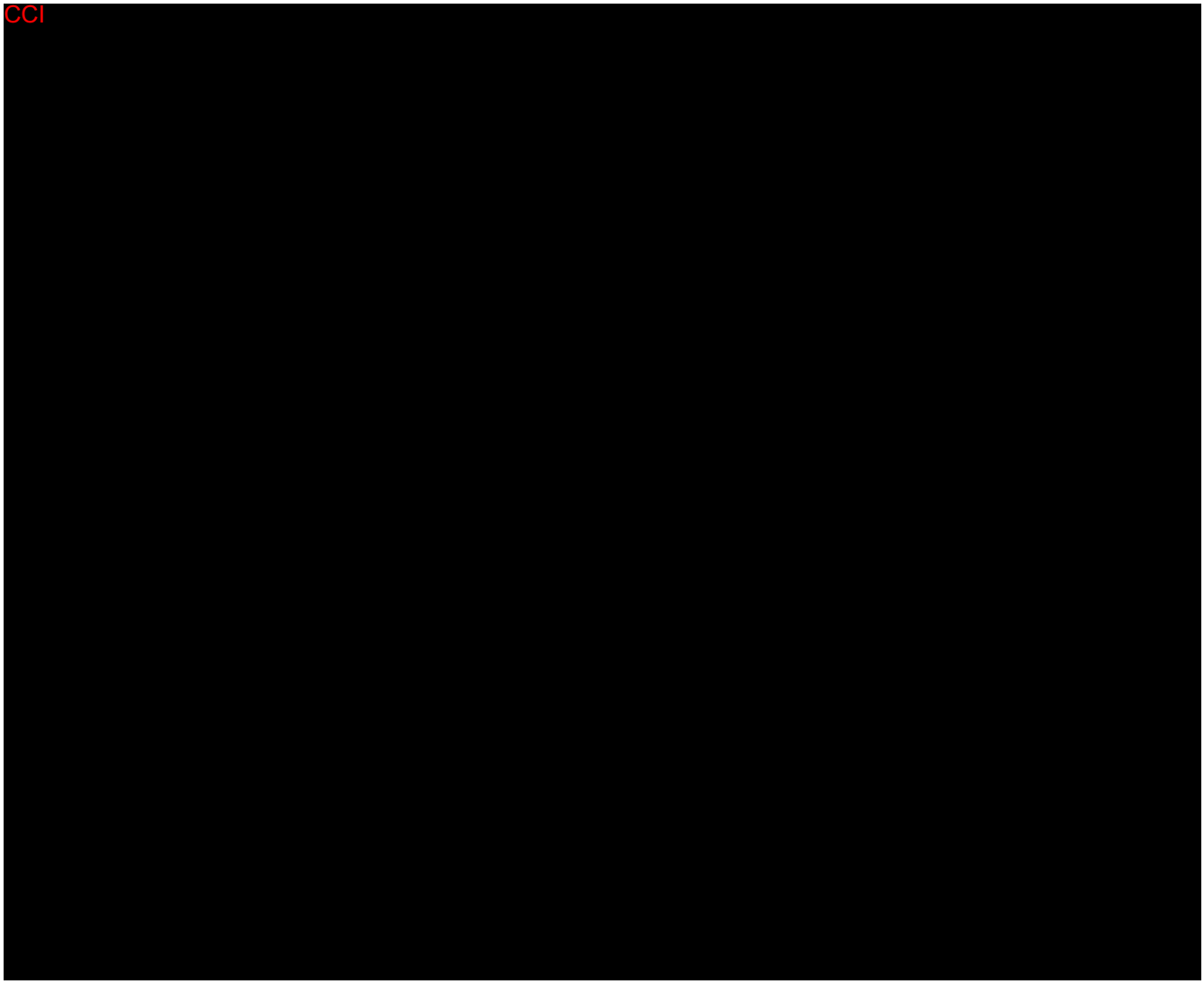
In order to improve the drug penetration, in this study, one or two psoriasis plaque(s) will be desquamated using a marketed cosmetic keratolytic agent CCI containing urea and low concentration of salicylic acid prior to application of CD10367 and its placebo on mini-zones. In clinical practice, urea and salicylic acid-based products are usually associated with local psoriasis treatments in order to increase and fasten their efficacy. Only mild irritation has been reported as the most common side effect, making urea a safe and well-tolerated topical drug (Pan, 2013; Jacobi, 2015). This keratolytic product will be applied twice daily by the subjects at home.

CCI

The safety ratios calculation for the current study were estimated using two approaches: 1) in accordance with regulatory guidance (FDA Guidance for Industry July 2005), CCI .

CCI

CCI



Considering the estimated safety ratios for the proposed study and the short treatment duration, these safety risks are not expected to occur. However, appropriate inclusion/ exclusion criteria and safety follow-up measures have been planned.
Regarding the ocular toxicity risk, even if clinical studies done by AZ and GRD did not confirm this risk in human being, specific inclusion/exclusion criteria have been defined to minimize this risk for the subjects, e.g. exclusion of subjects with abnormal ophthalmic examination according to the ophthalmologist at Screening, etc.
As to the cardiac risk, an ECG is planned at screening with exclusion of subjects with any clinically significant ECG findings; an ECG monitoring is planned during the study.

Other toxicities have been reported for marketed oral or injectable EGFR inhibitors such as acneiform skin rash, gastrointestinal side effects (diarrhea), interstitial lung disease, hepatotoxicity or renal toxicity (MacDonald JB et al. 2015, Gillespie et al. 2009).
As mentioned above for the ocular toxicity risk and the cardiac risk, these potential reactions are not expected to occur in the proposed study, considering the limited quantity of product applied and the short treatment duration.
During the study, subjects safety will be closely monitored on a daily basis during product application period and at the follow-up visit taking into account data generated during the development of the oral route by AZ and the GRD studies for the topical route.

Local tolerance during the drug application period will be assessed systematically in order to evaluate any potential irritancy, sensitization reaction or papulo-pustular eruption.

In conclusion, based on the current non-clinical and clinical data presented above and detailed in the Investigator's Brochure, CCI [redacted], the Sponsor considers that CD10367 topical solution at 1% and 3% does not raise any safety concerns when applied under the defined clinical study conditions.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

The purpose of this study is to evaluate, in a modified Dumas-Scholtz psoriasis mini-zone test, the safety and efficacy of CD10367 solution at 1% and 3% after a three weeks treatment period of once daily application.

CCI [redacted]

2.2 Clinical hypothesis

The hypothesis of the study is that the CD10367 solutions at 3% and/or at 1% applied once daily during 3 weeks in patients with psoriasis are well tolerated and significantly superior in efficacy to their vehicle when applied in the same conditions (once daily on desquamated plaques or not).

3 OVERALL CLINICAL TRIAL DESCRIPTION

3.1 Overall description

This is an exploratory, single-centre, investigator blinded, randomized, controlled, intra-individual study, involving approximately 24 subjects with psoriasis vulgaris meeting specific inclusion/exclusion criteria.

The study will be conducted in France and consists of:

- a screening period (within 3 weeks before pretreatment period);

- A pretreatment period 1 week before Baseline visit in order to decrease the scaling on selected target psoriasis plaque(s), before treatment with IMPs. This period can be extended to 2 weeks if sufficient desquamation does not occur and the scaling score does not reach 0 or 1 (none or mild scaling). During this period, the subjects will apply a keratolytic product at home twice a day on the selected plaque(s).
- a 3-week treatment period during which the treatments will be applied on mini-zones according to the randomization list, CCI [redacted]
- a final visit at Day 19 (or early termination visit if any), to evaluate safety and efficacy of the treatments, CCI [redacted];
- CCI [redacted]

In total, for each subject six-treatment mini-zone will be tested:

- on one or more psoriatic plaque, four mini-zones will be tested:
  - CD10367 3% solution
  - CD10367 1% solution
  - CD10367 solution placebo
  - Betneval 0.1% ointment
- on one or two desquamated psoriatic plaque (pre-treated), two mini-zones will be tested:
  - CD10367 3% solution
  - CD10367 solution placebo

CCI [redacted]

Figure 1: Schematics of the treated mini-zones CCI [redacted]

Local tolerance assessments will be performed twice a week from Day 2 to Day 19/ET visit and at any visit if a cutaneous AE occur on a treated zone.

Psoriasis severity scores will be performed at screening visit before desquamation, then two times a week from Day 1 to Day 19/ET.

CCI [redacted]

All samples will be shipped to GALDERMA R&D or its contractors at the end of the study. CCI [redacted]

3.2 Discussion of study design

3.2.1 The modified Dumas-Scholtz psoriasis mini-zone model

The method of the psoriasis plaque test first described by Dumas and Scholtz (Scholtz J.R. and Dumas K.J 1968, Dumas K.J. and Scholtz J.R 1972) and modified by Baadsgaard (Baadsgaard,. 1995) allows multiple intra-individual comparisons in the targeted pathology. This method has been used to test the efficacy of corticosteroids (Scholtz J.R. and Dumas K.J 1968), immunomodulating molecules (Remitz, 1999) and vitamin D derivatives (Baadsgaar, 1995).

The pertinence of this test in the assessment of the anti-psoriatic activity has been already validated several times with Betneval® CCI [redacted] chosen in this study as positive control or with other products from the therapeutic arsenal of psoriasis, CCI [redacted].

3.2.2 Pretreatment: Keratolytic agent

In this study, one or two psoriasis plaque(s) will be desquamated prior to application of CD10367 3% and its vehicle with a marketed cosmetic keratolytic agent. The purpose is to remove a part of superficial layers in order to eliminate any potential penetration issues linked to the barrier effect created by the squames.
In order to avoid any potential interaction with the other mini-zones tested under normal conditions, the desquamation will be done on one or two entire psoriasis plaque(s) separated from the other ones to be used for the standard application zones. These plaques should be big enough to include two mini-zones (one zone for CD10367 solution 3% and one zone for its vehicle).

CCI [redacted]

The cosmetic product used as keratolytic agent will be CCI [redacted] extreme cream from PPD [redacted] (tube 50ml) with 50% of urea and 2% of salicylic acid (other components: serine, histidine, glycenin, protease, fragrance free and paraben free).

Urea is a moisturizer and keratolytic agent usually used in the treatment of psoriasis as adjuvant. Different cosmetics are available on the market with variable concentrations in urea. A high content of urea is responsible for its keratolytic properties.

Salicylic acid acts as a keratolytic agent as well and enhances the keratolytic effect produced by urea.

3.2.3 Control groups

In this study, CD10367 solution will be tested on once daily application under normal psoriatic skin condition and on desquamated psoriatic skin condition. The vehicle, tested in both corresponding skin conditions, will be used as negative control for efficacy objective.

Betneval® 0.1% ointment (Betamethasone Valerate 0.1%) was chosen as positive control to validate the study. As mentioned in section 3.2.1, this active was successfully used in a previous Dumas-Scholtz design study.

CCI [redacted]

3.2.5 Choice of concentrations

Two concentration of CD10367 solution will be applied in this study for a better understanding of the local tolerability and efficacy. The choice of concentration of CD10367 is based on the maximal concentration of the molecule to be formulated (3%) and a lower intermediary concentration (1%). CCI [redacted] In the clinical phototoxicity study performed last year with three concentrations (0.1%, 1% and 3%) the reduction of UV induced erythema was in a dose proportional manner and statistically different from vehicle for the 1% and 3% solutions.

3.2.6 Treatment application

According to the modified Dumas-Scholtz psoriasis mini-zone test, the application of CD10367 will be limited to mini-zones of about 3 cm². Sixteen (16) mg/cm² *i.e.* 50 µL of each product will be applied once daily on each mini-zone, according to the application instructions. As all products applications will be carried out in the site by a qualified person, the applied amounts will be secured.

3.2.7 Evaluation of CD10367 efficacy

In order to evaluate the efficacy of CD10367 the primary criteria will be based on clinical evaluations. CCI

CCI

CCI

3.2.9 Safety monitoring

The Subjects safety will be closely monitored 5 days a week during the treatment period with the daily seeking of Adverse Events. The inclusion to the study will be conditional to a normal medical exam including a physical exam, the check of the vital signs, a blood test and a urinalysis, a normal ECG exam, and a normal Ophthalmic exam. At the end of the treatment period the same medical exams will be performed.

Local tolerance will be assessed twice weekly by the Investigator using a 4-point scale for each mini-zone (see section 7.2.5).

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSFV to LSLV) is approximately 5 months. The date of end of the clinical trial is defined as the date of the last visit of the last subject.

The planned duration of recruitment (from FSFV to LSFV) is approximately 3.5 months.

Clinical trial participation for each subject is approximately 9 weeks including screening period.

GALDERMA may decide to prematurely terminate or suspend the participation of a particular clinical trial center (for example, for lack of subject enrollment or non-compliance with clinical trial protocol, regulation, or GCP) or prematurely suspend the clinical trial (for example, for safety, study drug(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 40% percent is expected, approximately 40 subjects may have to be screened in order to obtain 24 subjects randomized.

5.2 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must fulfill all of the following criteria (when applicable). These criteria are applicable at both screening and baseline unless specified.

5.3 Inclusion criteria

1. Adult male or female aged at least 18 and up to 70 years old inclusive at screening visit.
2. Female of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy).
3. Subject has a skin phototype I to IV on Fitzpatrick's scale. (Screening visit).
4. The subject has a clinical diagnosis of stable plaque psoriasis, defined as no flare during the month before Screening visit and no change between Screening visit and Baseline visit, of mild to moderate severity. (Screening visit and Baseline Visit).
5. The subject presents with at least six eligible mini-zones, on at least two psoriasis plaques (Screening visit and verified also at Baseline Visit) which:

5.1. are located on the upper and/or lower extremities (anterior crest of tibia, apex of knees and apex of elbows excluded) and/or on the trunk. Plaques on the face, scalp, hands, feet and folds will not be eligible as test areas.

5.2. have a Total Sum Score (TSS = erythema + induration + scaling) ≥ 6 before desquamation; each item separately being ≥2,

5.3. have identical severity (i.e. identical TSS or variation of ±1 grade) before desquamation,

5.4. are approximately 2 cm in diameter and at least 2 cm apart from each other.

5.5. for the two desquamated zones at Baseline visit:

5.5.a. have a scaling score of 0 or 1,

5.5.b. have identical severity between the zones or variation of ±1 grade for the sum of induration and erythema scores, each item separately being ≥2

6. Subject agrees not to wear his/her contact lenses from the Baseline visit till the D19 visit, (Screening visit)
7. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol. (Screening visit)
8. Subject understands and signs an Informed Consent Form (ICF) at screening, prior to any investigational procedures being performed. (Screening visit)
9. The subject is covered by a National Social Security System (Screening visit)

Rationale:

Criterion	Rationale
1	To ensure appropriate age requirements for adults
2	No reproduction toxicity studies conducted with this IMP to date.
3	To allow proper assessment of clinical and biophysical skin imaging evaluation
4, 5	To ensure that the subjects have a stable psoriatic skin condition, which is comparable for each tested condition
6	To ensure no issue related to ocular toxicity risk
7 & 8	To ensure that all Subjects are fully informed and comply with the study requirements. Only the Subjects providing written consent are allowed to participate into the clinical trial, to be compliant with ICH, local regulations and GCP.
9	To be compliant with country regulation

5.4 Exclusion criteria

Any subject who is meeting one or more of the following criteria at Screening and/or Baseline visits will not be included in this study:

1. The subject presents guttate, erythrodermic, exfoliative, inverse, pustular, palmo plantar, infected or ulcerated psoriasis (Screening visit).
2. The subjects has any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results, and/or put the

subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical trial (e.g. history of on-going gastric or duodenal ulcer, clinically significant lung disease, etc.) (Screening visit).

3. The subjects has known or suspected allergies or sensitivities to any components of the study drugs or of the keratolytic product (see Investigator's Brochure/Product label). (Screening visit).
4. The subjects has known history of adverse drug reaction or hypersensitivity to a product with the same mode of action
5. The subject presents with presumed drug or alcohol abuse (based on medical history or present clinical symptoms) (Screening visit).
6. The subjects has any abnormal clinically significant findings according to the ophthalmologist, at the ophthalmological exam at Screening visit,
7. The subjects has any of the following laboratory test results (blood samplings and urinalysis done at Screening visit):
   - 7.1. Positive serology (HbsAg, HCV, HIV 1 or 2)
   - 7.2. ALT, AST, ALP or total bilirubin > 1.5ULN - Gilbert's disease is accepted,
   - 7.3. Creatinine clearance <60mL/min/1.73m2 calculated with the CKD-EPI formula (Levey et al., 2009)
   - 7.4. Any other lab test parameter or urinalysis outside the normal ranges defined by the laboratory and these results are judged clinically significant by the investigator
8. The subjects has QTc interval >450msec or any abnormal ECG value considered as clinically significant by the cardiologist (Screening visit).
9. The subject has received, applied or taken the following treatments within the specified time frame prior to the Baseline visit:

Table 3 Prohibited therapies

Treatment name/type	**Wash-out period**
Topical treatments on all psoriatic areas:	
Corticosteroids (use of corticoids on the face for short course therapy ,up to 5 days is authorized)	4 weeks
Retinoids	2 weeks
Vitamin D analogs	2 weeks
Immunomodulators	2 weeks
Antracen derivatives, tar and salicylic acid preparations	2 weeks
Topical treatment on treated areas:	
Other topical products, including emollients	2 days
Systemic treatments:	**Wash-out period**

Anti-histaminic drug	1 week
Corticosteroids (inhaled products are authorized)	2 weeks or 5 half-lives (whichever is longer)
Immunosuppressive drugs	3 month or 5 half-lives (whichever is longer)
Biotherapies	3 months or 5 half-lives (whichever is longer)
Drugs with known ocular toxicity according to ophthalmologist	5 half-lives
Drugs that can prolong the QT interval as defined in the Crediblemeds.org list: http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All	5 half-lives
Strong CYP inhibitors as defined in the below reference, Table 5 strong inhibitors of CYP enzymes: (see list in appendix) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm	5 half-lives
Retinoids, isotretinoin	6 months
Any systemic treatment that may impair hemostasis (anti-coagulant, antiplatelet, etc.)	4 weeks
Other treatments	**Wash-out period**
Phototherapy	3 months

10. The subject is under the following systemic treatments (unless they have been on a stable dose of medication for at least 3 months prior to Screening (Screening visit)):

    10.1. Antimalarials

    10.2. Lithium

    10.3. ACE (angiotensin-converting-enzyme) inhibitors

    10.4. Beta blockers

    10.5. Indomethacin and other non-steroidal anti-inflammatory drugs (except sporadic intake of no more than 3 consecutive days).

11. The subject is planning to sunbathe or to overexpose to UV-light (Screening visit).

CCI

13. Current participation in any other clinical trial of a drug or device OR participated within 1 month prior to baseline OR is in an exclusion period from a previous clinical trial (when possible). (Screening visit).

14. The subject is vulnerable as defined in French law "Code de la Santé Publique" (Screening Visit) such as:

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

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

Rationale:

Criterion	Rationale
1, 2,	To ensure that no medical or skin condition will interfere with study protocol results interpretation
2, 3, 4, 5, 6, 7, 8	To ensure safe medical conditions at inclusion concerning potential identified IMP risks
9, 10, 11, 13	To ensure no interference with the study product and misinterpretations of the results
CCI	[redacted]
14	To be compliant with ICH-GCP and country regulation

5.5 Previous and concomitant therapies

5.5.1 Definition

Previous therapies are defined as therapies that have been stopped within 6 months preceding the screening visit. Only relevant therapies (i.e. therapies that may have an impact on study assessments) will be recorded.

Concomitant therapies are defined as follows:

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

5.5.2 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.

5.5.3 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 CRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

The subjects may use a moisturizer on the psoriasis plaques, except the plaques that will be treated with the study products. They may use their own moisturizer or CCI [redacted] which is provided by the sponsor.

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.

5.5.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 5.4) or in prohibited concomitant therapies (see Section 5.5.5), all therapies are authorized.

5.5.5 Prohibited concomitant therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety (for example interaction with the study drug(s) metabolism) assessment of the study drug(s):

- Listed in Section 5.4

For topical products: No other topical medication, or product (including emollient) other than the study drugs, will be permitted on the treated areas from the start of the pretreatment procedure on the selected pre-treated plaques and from 2 days before Baseline visit until the end of the study on all plaques selected for application of the study drugs.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, GALDERMA 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 should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

5.6 Procedures/Reasons for subject discontinuation

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.

When a subject does not complete the clinical trial, he/she will be fully assessed, 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 appropriate Case Report Form (CRF) should be completed. The Follow up visit should then occur approximately one week after the Early Termination visit.

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 randomization number cannot be replaced by another subject if he/she 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 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:

- 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 CRF Exit Form.
- Protocol Deviation: Explain the deviation in the comment section of the CRF 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 CRF 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 CRF 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	***Investigational product***	***Vehicle***	**Reference**
Trade Name or Equivalent	*NA*	*NA*	NA	Betneval
Name of drug substance	*NA*	*NA*	NA	Betamethasone valerate 0.1%
Internal Code	*CD10367*	*CD10367*	CD10367 placebo[a]	NA
Pharmaceutical Form	*Solution*	*Solution*	Solution	Ointment
Concentration	*1%*	*3%*	NA	0.1%
CCI [redacted]				
Dosage (total maximal daily dose)	50µl	100µl (50µl on each mini-zone)	100µl (50µl on each mini-zone)	50µl
Route	Topical			
Dose Regimen	Once daily			
Duration of administration	Five consecutive days a week for two weeks and four consecutive days in the third week (14 applications)			
Location of Treated Area	Mini-zones on upper and/or the lower extremities (elbows, knees and shin area excluded) and/or on the trunk			

a CD10367 solution placebo is the same vehicle solution as the CD10367 solution but without the active ingredient
b The most restrictive storage conditions will be applied.

CCI [redacted]

6.1.2 Subject Identification Number (SIN)

Upon signature of the ICF, each subject will be assigned a Subject Identification Number (SIN).

The SIN will be allocated in ascending sequential order to each subject.

For the duration of the entire clinical trial, the subject will be identified using the SIN for all documentation and discussion.

6.1.3 Method of treatment assignment

Prior to the start of the study, a randomization list will be generated by a statistician from GALDERMA R&D and will be transmitted to the assigned clinical packaging organization. CCI

[redacted]

Coding of the study products will be defined independently by the Pharmaceutical Unit at GALDERMA.

CCI [redacted]

6.1.4 Randomization number

At Baseline visit (Day 1), each Subject who fulfills all inclusion/non-inclusion criteria will be assigned a Randomization Number. The randomization number will be allocated in ascending sequential order and no number should be omitted or skipped. The date and time of randomization define this number, independently of the Subject Identification Number that was initially assigned at Screening visit.

6.1.5 Instructions for use and administration

The keratolytic product will be supplied by GRD, and distributed to the subjects by the investigational centre. They will be applied by the subjects at home during the pre-treatment period.

From Baseline visit, all study drugs applications will be performed by a person from the investigational team other than the Investigator at the study centre to make sure the investigator remains blinded.

All study drugs will be accounted for and in no case used in any unauthorized situation. All used and unused study drugs will be appropriately inventoried by the study centre.

6.1.5.1 Selection of target plaque(s) and mini-zones

During Baseline visit, validation of the stability of the psoriatic plaques selected at Screening will be checked by the Investigator.

At Baseline visit, the selected target mini-zones for standard psoriatic skin conditions (n=4) should:

- be located on the upper and/or lower extremities (anterior crest of tibia, apex of knees and apex of elbows excluded) and/or on the trunk. Plaques on the face, scalp, hands, feet and folds will not be eligible as test areas.
- have a Total Sum Score (TSS = erythema + induration + scaling) ≥ 6; each item separately being ≥ 2 (see Table 5),
- have identical severity (*i.e.* identical baseline TSS or variation of ± 1 grade),
- be approximately 2 cm in diameter and be at least 2 cm apart from each other in order to avoid any interference between products.

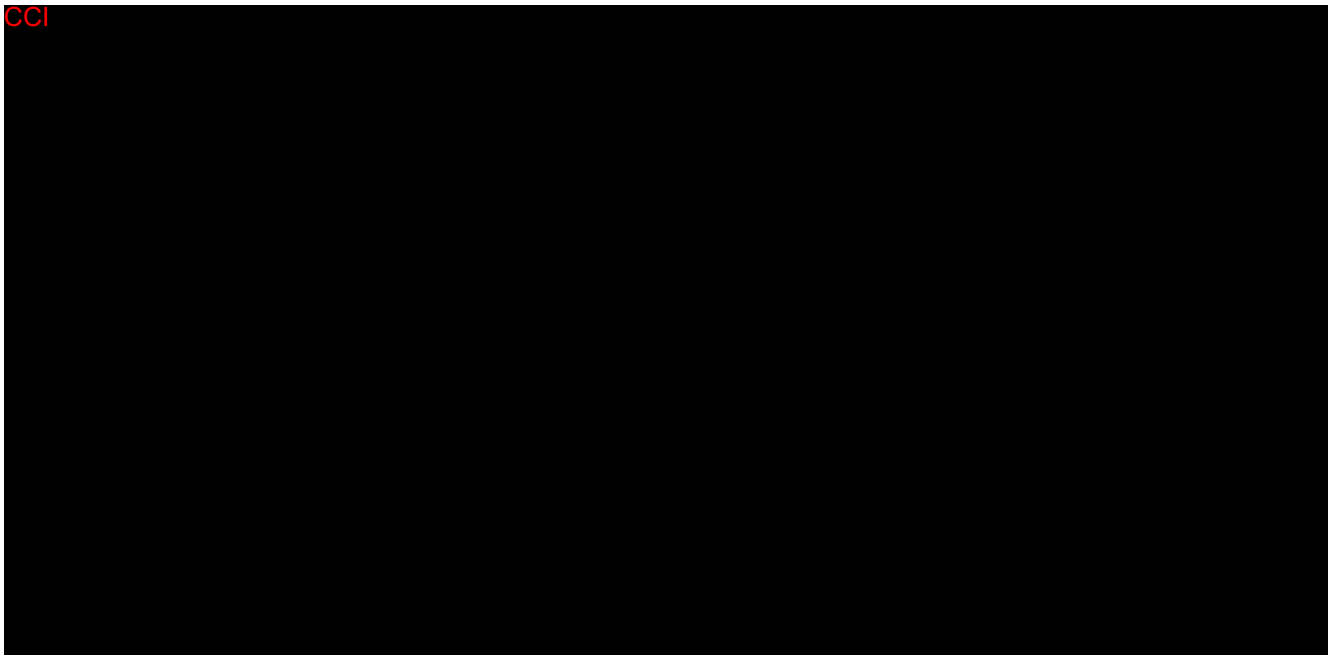
Target mini-zones previously selected at Screening visit for desquamated psoriatic skin conditions (n=2) should at Baseline visit:

- be located on the upper and/or lower extremities (anterior crest of tibia, apex of knees and apex of elbows excluded) and/or on the trunk. Plaques on the face, scalp, hands, feet and folds will not be eligible as test areas.
- have a scaling score of 0 or 1,
- have identical severity between the two zones or variation of ±1 grade for the sum of induration and erythema scores, each item separately being ≥2
- are approximately 2 cm in diameter and at least 2 cm apart from each other.

If the scaling score is not at 0 or 1 after 2 weeks of pre-treatment period, they will not be randomized in the study.

CCI

[redacted]



6.1.6 Other supplies

Galderma R&D will provide keratolytic product (CCI PPD), and emollient CCI .

These supplies will be monitored during the study to be sure the site has always enough supplies to conduct the study in compliance with the protocol requirements.

6.2 Study drug(s) packaging and labeling

The investigational products will be supplied by GALDERMA R&D (see Table 4).
The labels will be printed in the local language. The text of the label will detail the information requested by Good Manufacturing Practice and local regulations.

6.3 Supplies management

6.3.1 Accountability

Upon receipt of the study drug(s), the Investigator or designee will maintain accurate records of the study drug(s) delivery to the clinical trial center, the inventory at the clinical trial center, the use by each subject, the reconciliation of all study drug(s) received from the Sponsor, and the return to the Sponsor or alternative disposal of used and unused study drug(s).

The Investigator or designee is required to sign the appropriate form upon receipt and inspection of the supplies, fax the signed copy to GALDERMA or the Depot and retain the receipt within the clinical trial file.

All used and unused study drug(s) will be appropriately inventoried by the monitor and returned to the Sponsor for for destruction as instructed by GALDERMA/CRO.

All study drug(s) sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted.

6.3.2 Storage of study drug(s)

Study drug(s) must be stored in a safe and secure area with restricted access, under the storage conditions specified by GALDERMA (see Table 4).

6.3.3 Dispensing and return

Each subject will receive the keratolytic and the emollient products at Screening visit.

Subjects will be instructed by the investigator on the importance of being compliant with the use of the keratolytic product throughout the week(s) proceeding Baseline visit.

From Baseline, no drug will be dispensed directly to the subject. [redacted]

As this study is an Investigator/evaluator blinded study, the Investigator should not have access to the study drugs. The person in charge of product applications will not be the Investigator/evaluator.

In the event of Screen failure (e.g. due to abnormal laboratory results), the Investigator or designee must immediately instruct the subjects to stop the keratolytic product regimen.

In the event of early termination/suspension of the clinical trial, a rapid recall of study drug(s) to Galderma will be initiated.

6.3.4 Treatment compliance management and record

Since product applications will be performed by a qualified person, treatment compliance will be ensured and documented appropriately by study staff.

In case of missed visit corresponding to clinical evaluation visit; clinical evaluations will be performed on the following visit.

6.4 Dose modification

In case of significant irritation on one mini-zone according to investigator's judgment, the dosage regimen may be temporarily discontinued on this mini-zone to allow the irritation to subside.

When a study drug dosage modification has been required, the investigator should attempt to return the subject to the pre specified dosage regimen as soon as possible. The other mini-zones on that same subject should continue to be treated with the planned treatment.

All temporary and permanent treatment discontinuations must be documented and justified. In the case of permanent treatment interruptions for safety reasons, an AE form should be filled in and considered as an AESI if there is a relationship between this AE and the study treatment.

6.5 Blinding

6.5.1 Verification of blinding

This study design is not considered double-blind since study products and the comparator (Betneval®) are different in appearance (formulation and packaging).

However, the design is considered Investigator-blind since the following procedures will be followed in order to prevent the Investigator and/or other Evaluator(s) from coming into contact with the study materials thereby compromising the blinding of the study:

- The study materials will be applied according to the randomisation list by a designated person other than the Investigator or other Evaluator(s). Additionally, both the person in charge of drug applications and the Subject will be instructed not to discuss the study materials with the Investigator or other Evaluator(s).

CCI [redacted]

- Sealed envelopes will contain the description of test medications. Access to the identification of treatment codes will be limited to the designated personnel directly responsible for packaging and labelling of study materials.

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, the blinded label (sealed envelopes) 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 treated zone 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.

CCI [redacted]

CCI [redacted]

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

7.1.1 Efficacy measurements

Throughout the study, the individual clinical scores and the clearing score for each individual mini-zone will be performed, to the extent possible, by the same Investigator. In the event there is a change in the assigned Investigator for a given Subject, the reason for change must be documented. If it is not possible to use the same Investigator for a given Subject, the Sponsor recommends that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the Subject together and discuss findings) for at least one visit.

7.1.1.1 Individual clinical scores

The status of the psoriasis for each mini zone will be evaluated by recording Individual clinical scores (erythema, scaling and induration) at screening and twice weekly during the treatment period from Day 1 visit (before treatment application) to Day 19/ET visit using the following 5-point scale.

However, data collected during the Screening visit will be used for the pre-selection of the mini-zones only and not for data analysis.

Table 5 Individual clinical scores

ERYTHEMA		
0	**None**	No detectable erythema.
1	**Mild**	Slight pinkness present
2	**Moderate**	Definite redness, easily recognized.
3	**Severe**	Intense redness
4	**Very Severe**	Very intense redness
SCALING		
0	**None**	No shedding
1	**Mild**	Barely perceptible shedding, noticeable only on light scratching or rubbing.
2	**Moderate**	Obvious but not profuse shedding
3	**Severe**	Heavy scale production
4	**Very Severe**	Very thick scales
INDURATION		

0	**None**	Normal skin thickness. No elevation of skin
1	**Mild**	Barely perceptible elevation (by touching) of the psoriasis plaques.
2	**Moderate**	Obvious elevation above the normal skin level; moderate thickening
3	**Severe**	Definite thick elevation above normal skin level
4	**Very Severe**	Very thick elevation

Evaluations will be done for the entire treatment period of the study even if a mini zone clears.

In case of treatment discontinuation (on one or several zones) for poor local tolerance, the individual clinical scores will continue to be assessed.

7.1.1.2 Clearing score

The clearing score evaluation will be done for each individual mini-zone from Day 4 visit and then twice weekly during the treatment period (before treatment application) up to Day 19/ET visit, using the following 3-point scale.

Table 6 Clearing Score

CLEARING SCORE		
0	Complete clearing	No scaling and no infiltration even on palpation. Post inflammatory hypopigmentation or hyperpigmentation may be present.
1	Almost clear	Residual erythema with some induration / infiltration (not clinically visible but palpable) without scaling, or residual erythema and residual scaling with no infiltration.
2	Unchanged	No change or less than almost clear.

7.1.2 Efficacy endpoints

7.1.2.1 Primary Criterion

Area Under the Curve (AUC) of Total Sum Score (sum of erythema, scaling and induration scores) from Day 1 to Day 19.

7.1.2.2 Secondary Criteria

- AUC of individual clinical scores (erythema, scaling and induration) from Day 1 to Day 19.
- TSS and percentage change from baseline at each visit.
- Erythema, Scaling and Induration score and their change from baseline at each.

- Success rate (defined as a clearing score of 0 or 1) at each evaluation visit and the time to first success.

7.2 Safety assessment

A safety assessment will be conducted for all subjects at the screening visit (from the Informed consent signature) and every subsequent visit. The safety parameters are:

- Physical examination at Screening, and Day 19 (or Early Termination visit if any);
- Record of vital signs at Screening, Baseline and Day 19 (or Early Termination visit if any);
- Blood samplings for laboratory safety tests at Screening and Day 19 (or Early Termination visit if any);
- Urinalysis at Screening and Day 19 (or Early Termination visit if any);
- ECG at Screening, and Day 19 (or Early Termination visit if any);
- Ophtalmic examination at Screening, and Day 19 (or Early Termination visit if any);
- Local tolerance assessed twice weekly by the Investigator using a 4-point scale for each mini-zone
- Monitoring and recording of AEs to be recorded as specified in Section 7.2.6.

7.2.1 Physical examination and vital signs

7.2.1.1 Physical examination and vital signs

A standard physical examination will be performed at Screening and Day 19 / ET visits and it will be noted as “normal” or “abnormal” by the Investigator. Abnormalities will be recorded on the CRF.

Vital signs will be evaluated at the screening visit, at baseline visit and at Day 19 / ET. Vital signs will include systolic and diastolic blood pressure and pulse rate and will be measured after the subject has been sitting for at least 5 minutes.

The Investigator may choose to investigate any sign that he/she observes during the examination and should assess all abnormal findings for clinical significance.

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

For any clinically significant changes from the screening visit, an AE is to be recorded.

7.2.2 Laboratory safety tests

The following laboratory safety tests will be performed at the screening visit, and the D19/ET visit:

The following laboratory safety tests will be performed:

- Haematology:

White blood cell (WBC) count with differential, red blood cell (RBC) count, haemoglobin (Hb), haematocrit (hct), mean cell volume (MCV), and platelet count (Plt)

- Blood chemistry:

Creatinine, uric acid, urea nitrogen, alkaline phosphatase (ALP), aspartate aminotransferase (ASAT=SGOT), alanine aminotransferase (ALAT=SGPT), and bilirubin (total and conjugated), Sodium (Na^+), Potassium (K^+) and Chlorides (CL^-).

Creatinine clearance will be calculated with the CKD-EPI formula.

- Virology only at Screening

HBsAg, HCV, and HIV antibodies

- Urinalysis:

A semi-quantitative urinalysis using dipsticks will be performed at Screening and Day 19 (or ET visit). The following parameters will be evaluated: blood, proteins, leukocytes, glucose, ketones, nitrites, bilirubin, urobilinogen, pH, and specific gravity.

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

The Investigator or another 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

In case of clinically significant out-of-range laboratory values for blood and/or urine samples collected at Screening, the subject will not be included in the study.

All clinically significant out-of-range laboratory values for blood and/or urine samples collected after screening, are to be reported as an AE if this abnormality was not present at

the screening visit or is assessed as having worsened since the screening visit (i.e., there is a significant change from screening).

If the Investigator observes a clinically relevant laboratory test value, the laboratory tests will be repeated as soon as possible and monitored until the values have returned to normal and/or an adequate explanation for the abnormality is found. This does not apply to screening laboratory test values. No retest at screening is allowed.

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.

A summary of sample volumes and the number of blood samples is detailed in Appendix (section 13.2).

7.2.3 12-lead electrocardiogram

A single standard 12-lead ECG will be conducted during Screening period (as close as possible to Baseline visit), and at Day 19 or early termination visit.

To participate in the study, the subject should not present:

- QTc interval >450msec
- And/or any abnormal ECG value considered as clinically significant by the investigator

The subject should be kept in the supine and resting position for at least 10 minutes prior to obtaining the ECG in order to achieve a steady heart rate.

The ECG reading will be performed in a real time by the investigator or a cardiologist.

Any abnormal ECG result will be assessed by the investigator or a cardiologist for clinical significance.

If an ECG abnormality at Day 19 was not present at Screening or is assessed as having worsened compared to Screening ECG, the Investigator is to report it as an Adverse Event.

Any increase of QTc interval from Baseline superior to 60msec or a value >500msec at the Day 19 / ET visit and assessed as related to the study drug is considered as an Adverse Event of Special Interest (see section 7.2.6.1.3).

7.2.4 Ophthalmic examination

The ophthalmic examination will be performed by an ophthalmologist during Screening period (as close as possible to Baseline visit), and at Day 19 or earlier in case of study discontinuation (ET).

The examination will consist of visual acuity measurement, slit lamp exam with fluorescein and Tear Film break-up time.

The global ophthalmic examination will be scored with a 'normal' / 'abnormal' answer system.

In addition, subjective ophthalmologic symptoms will be also asked and recorded as comments if any.

In case of abnormal clinically significant findings at Screening, the subject will be not included in the study and the information will be recorded in the Medical History form.

For any abnormal clinically significant changes from Screening, an AE is to be recorded.

A treatment-emergent abnormal ophthalmic examination result that is identified as clinically significant and related to the study drug is considered as an Adverse Event of Special Interest (see section 7.2.6.1.3).

7.2.5 Local tolerability assessment

Local tolerability assessment will be performed using the following twice a week from Day2 to Day 19/ET visits scales two times per week during the treatment period. If at any visit, a treatment leads to discontinue applications either temporarily or permanently, an AE must be declared, and local tolerability assessments and photos of the concerned zone must be performed even if it was not planned in study flowchart for this visit. Grading for local tolerability assessments will take into consideration the time period from the last local tolerability assessment up to the current visit. The worst severity since the previous visit will be recorded. Local tolerability (Irritation, stinging/burning, pruritus) will be assessed separately on each mini-zone using the following scales:

Table 7 Local tolerance 4-point scales

Irritation	**Skin irritation Assessment**	
0	None:	No signs of irritation
1	Mild:	Slight signs of irritation
2	Moderate:	Moderate signs of irritation: Obvious increase in redness as compared to the non-treated surrounding area
3	Severe:	Severe signs of irritation
Stinging/ Burning	**Prickling pain sensation**	
0	None:	No stinging/burning
1	Mild:	Slight warm, tingling/stinging sensation; not really bothersome
2	Moderate:	Definite warm, tingling/stinging sensation that is somewhat bothersome
3	Severe:	Hot, tingling/stinging sensation that causes severe discomfort
Pruritus	**Itch sensation**	
0	None:	No itching
1	Mild:	Itching is noticeable but not really bothersome
2	Moderate:	Definite itching that is somewhat bothersome
3	Severe:	Marked itching, urge to scratch and causes definite discomfort

Irritation, will be clinically evaluated by the Investigator. The Investigator will record stinging/burning and pruritus after discussion with the subject. The severity of stinging/burning sensation occurring after the last drug application before the visit will be asked. The Investigator will ask an open-ended question, taking care not to influence the subject's answer, such as "Have you experienced any sensations such as stinging/burning?"
An Adverse Event page must be completed if the severity of the signs and symptoms is such that:

- The subject temporary or permanently discontinues the treatment at his/her request or at the Investigator's request.
- The subject requires concomitant treatment, including OTC products (other than moisturizer).

In case of permanent treatment discontinuation, skin sensitization or papulo-pustular reaction an AESI must be declared (see section 7.2.6.1.3).

7.2.6 Adverse Events

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

7.2.6.1 Definitions

7.2.6.1.1 Adverse events (AE)

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

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

Each new episode of a chronic disease (e.g., hay fever, allergy, etc.) from the screening visit should be reported as a new AE.

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.
- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- The "date of onset" should be the date that the first symptom occurred.

7.2.6.1.2 Serious Adverse events (SAE)

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note:

The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

7.2.6.1.3 Adverse Events of Special Interest (AESIs)

An AESI is a noteworthy event for the particular study drug that can be appropriate to monitor closely. It could be serious or non-serious and AESIs could include events that might be potential precursors or prodromal symptoms for more serious medical conditions in susceptible individuals.

The AESIs for this protocol have been pre-defined as follows:

- Suspected sensitization or photosensitization
- Any non-dermatological treatment-emergent related adverse events (AE), including:
    - Increase in QTc interval from Baseline >60msec or a value>500msec at D19/ET ECG assessed as related to the study drug
    - Out-of-range laboratory results that are identified as both clinically significant and related to the study drug(s)
    - Any treatment-emergent signs/symptoms suggestive of keratitis or corneal ulceration (e.g. pain of the eye, injected/red eye, blurred vision, etc.), or treatment-emergent keratitis or corneal ulceration diagnosed at the ophthalmological examination, or any other treatment-emergent acute ophthalmological findings assessed as related to the study drug
- Any dermatological treatment-emergent related adverse events (AE) leading to permanent treatment discontinuation on any zone
- Treatment-emergent skin rash assessed as related to the study drug, defined as a papulopustular eruption commonly described as acneiform eruption

For AESIs, the Investigator is required to complete the Adverse Event Form on the CRF and follow the AESI reporting procedures in Section 7.2.6.2.3 even if the event is considered non-serious according to the usual regulatory criteria.

7.2.6.1.4 Unexpected adverse drug reaction

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

7.2.6.1.5 Adverse event reporting period

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

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

7.2.6.1.6 Severity

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

The Investigator is to classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

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

7.2.6.1.7 Relationship to the study drug(s) and/or clinical trial procedure

The Investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study drug(s) and/or clinical trial procedure (for example, moisturizer, or keratolytic use). AE reporting for moisturizer use should be detailed, taking into account whether moisturizer use is recommended or mandatory. Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive dechallenge or rechallenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

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

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA:

Reasonable possibility:

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

- The study drug (investigational product, active comparator, or vehicle, etc.) and the AE,
- The clinical trial protocol procedure (such as CCI , CCI , blood test or intraocular pressure measurement, ancillary products provided by the sponsor, such as moisturizers, keratolytic, etc.) and the AE.

The Investigator has to complete these 2 causality assessments on the AE form.

No Reasonable Possibility:

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

7.2.6.2 Reporting procedures

7.2.6.2.1 Procedures for reporting Adverse Events

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

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

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

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

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

For SAEs (see Section 7.2.6.2.2), AESIs (see Section 7.2.6.2.3), the CSO is to be informed immediately by e-mail/fax. The event must be reported by fax or sent by e-mail to the CSO within 24 hours of receipt of the information (contact details in Section 7.2.6.2.2).

7.2.6.2.2 Procedure for reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.
2. Ensure that the event is classified as an SAE. Immediately inform the CSO of the event by e-mail/fax and discuss further actions to be taken.

Investigator contact:
Local Clinical Safety Officer
E-mail: pharmacovigilance@galderma.com

Phone: +33 (4) 92 95 29 69 – Fax: +33 (4) 93 95 70 92

Additional contact details are provided in the Investigator's site file.

3. Complete the Adverse Event Form provided in the CRF as fully as possible.
4. Complete the Serious Adverse Event Form provided by the Clinical Research Associate (CRA) at the start of the clinical trial. Fax or send by e-mail the completed form accompanied by demographics, medical history, Drugs/Therapies form, Medical and Surgical Procedures form, and adverse event pages of the CRF, and any other relevant information or medical records (e.g., laboratory test results) within 24 hours of receipt of the information to the GALDERMA CSO.
5. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, fax or send by e-mail all additional follow-up information on the SAE to the GALDERMA CSO within 24 hours of receipt of the updated information. Serious Adverse Events (SAEs) will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
6. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
7. Inform the CSO of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.

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

9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the Independent Ethics Committee (IEC).

7.2.6.2.3 Procedure for reporting an Adverse Event of Special Interest

For any AESI (see Section 7.2.6.1.3) occurring during the period of the clinical trial, whether related to the treatment or not, and whether expected or not, the Investigator is to do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Ensure that the event is classified as an AESI. Immediately inform the CSO by e-mail/fax of the event and discuss further actions to be taken.
3. **Investigator contact: Refer to Section 7.2.6.2.2**
4. Complete the Adverse Event Form provided in the CRF as fully as possible.
5. Fax or send by e-mail the completed form accompanied by demographics, medical history, Drugs/Therapies form, Medical and Surgical Procedures form, and adverse event pages of the CRF, and any other relevant information or medical records (e.g., laboratory test results) within 24 hours of receipt of the information to the GALDERMA CSO.
6. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all the additional follow-up evaluations, fax or send the additional follow-up information by e-mail to the GALDERMA CSO within 24 hours of receipt of the updated information. AESIs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
7. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further information such as anonymized medical records.
8. Inform the CSO of the final outcome of the event. Send a revised or updated Adverse Event Form, if appropriate.

7.2.6.2.3.1 Procedure for suspected allergic contact reaction

This is a general procedure and any other details might be discussed with the sponsor.

- Stop the study product.
- Take a picture of the affected area and the non-affected surrounding skin
- Document the event as an Adverse Event of Special Interest, e-mail/fax the CSO immediately, and report the event within 24 hours of receipt of the information to the CSO as described in section 7.2.6.2.3

a. <u>In case of suspicion of allergic contact dermatitis</u>

1. After all signs and symptoms of AESI have resolved and after a minimum of two weeks from last dose application, perform a re-challenge test with the assigned study product.
2. Ensure the subject has not been under any treatment with corticosteroids or antihistamines, regardless of the route of administration, the week before testing.
3. Ensure that the skin on the back has not been exposed to the sun or artificial ultraviolet sources the week before testing.
4. Apply an appropriate quantity of the assigned study product to fill in the cupule of the test chamber on the skin of the upper back on either the right or left side of the centre line (or the inner forearm if the back cannot be tested). If no test chamber is available on-site, patch test units will be provided. It may be preferable to perform the test under semi-occlusive conditions depending on the irritant potential of the study product and the intensity of the reaction that was observed. The method to be used should be discussed with the sponsor.

   Choose a skin site that was not previously involved in the inflammatory skin reaction. Cover it for 48 hours with a hypoallergenic tape.
5. Patient should be informed about avoiding exercise, showers, application of toiletries products, etc. to keep the test system dry
6. After 48 hours, remove the tests and evaluate the site:
   - at approximately 30 minutes after patch test removal (1st reading) and,
   - 24 to 48 hours later (i.e. 72 or 96 hours after application) (2nd reading).
   - A facultative 3rd reading must be performed 96 to 120 hours later (i.e. 6 to 7 days after application of the patch) if the overall assessment so far is equivocal or if asked by the sponsor.
   - Pictures of the tested areas will be taken systematically at each reading and properly documented.

Duration of study product application	1st Reading	2nd Reading	3rd reading (optional)

48 hours	48 hours after study product application (30 minutes after patch test removal)	72 to 96 hours after study product application (24 to 48 hours after patch test removal)	6 or 7 days after study product application (96 to 120 hours after patch removal)

7. Refer to the scoring system (Spiewak – 2008) used by the International Contact Dermatitis Research Group (ICDRG) to assign a score at each reading:

Score	Morphology	Interpretation
-	No skin changes in the tested area	Negative
?	Faint, non-palpable erythema	Doubtful reaction
+	Palpable erythema (moderate oedema or infiltrate), papules not present or scarce, vesicles not present	Weak positive reaction
++	Strong infiltrate, numerous papules, vesicles present	Strong positive reaction
+++	Erythema, infiltration, confluent vesicles, bullae or ulceration	Extreme positive reaction
ir	Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles	Irritant reaction
Nt		Not tested

8. At last reading, the investigator will provide an assessment regarding a possible sensitization reaction using the following scale:

Sensitization Reaction	
0	Negative (absence of reaction or might be irritant reaction)
1	Equivocal
2	Positive

9. Report the results from the re-challenge test as directed by the sponsor and document with photographs.
10. In case of absence of reaction, the subject may resume treatment if appropriate
11. If the re-challenge is positive or equivocal, notify the CSO immediately. Except specific situations, a new series of patch test will be initiated as directed by the sponsor (with individual ingredients at different concentrations if applicable, and possibly negative and positive controls) after a minimum of additional two weeks (but not later than 6 months) and after all signs and symptoms have resolved. The patch tests will be placed on the subject's back (or the inner forearm if the back cannot be tested) distant from the site of the re-challenge test (e.g., the left upper back skin if the re-challenge test was done on the right side). Follow the same procedure for the patch test as for the re-challenge.

b. In case of suspicion of immediate contact skin reaction (such as urticaria)

A case by case approach will be applied and the procedure to follow will be discussed with the sponsor

7.2.6.2.4 Procedures for reporting pregnancies

Not Applicable

CCI

[redacted]

CCI [redacted]

7.4 Pharmacokinetic assessments

CCI [redacted]

7.4.1 Plasma concentration

All subjects will have blood samples performed to quantify the concentration of CD10367 in plasma at visits D5, D19/ET and D26.

The detail of the procedures for PK samples and storage conditions will be described in an operational manual provided by the Sponsor.

CCI [redacted] CD10367 plasma concentrations will be determined by GALDERMA R&D Sophia Antipolis France, using an LC MS/MS method developed for the purpose of the method. CCI [redacted]

CCI [redacted]

CCI

[redacted]

7.5.4 Quality of Life Assessment

Not applicable.

7.6 Appropriateness of measurements

Efficacy is evaluated by dermatologists using appropriate scorings CCI [redacted].

Safety is documented by the recording of adverse events, the local tolerance scales, the physical examination, the vital signs assessments, the ophthalmic examination, the ECG, and the laboratory tests.

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.

The Investigator representative will review and explain the nature of the study to the Subject and particularly the prohibited activities and the constraints of the study. A copy of the signed and dated ICF will be provided to the Subject, another copy will be filed in the Investigator site file.

8.1.1 **Screening visit** (up to 5 weeks before Baseline visit)

A maximum of 5 weeks is allowed between Screening and the first study drug administration at Baseline, including 3 weeks of screening period and up to 2 weeks of pre-treatment period. The minimum time period between Screening and Baseline is the amount of time necessary for the Investigator to receive laboratory test results from the Screening visit and allow at least one week of pre-treatment. The Screening period may be performed using several visits during this screening period, especially ECG and ophthalmic exam should be performed as close as possible to Baseline visit, which may be performed during the pretreatment period.

At the Screening visit, the Investigator or designee will:

1. Review and explain the nature of the study in detail to the Subject, particularly the prohibited activities and constraints (e.g., restrictions in the use of topical and systemic medications).
2. Ensure that the Subject reads, date and signs the Informed Consent Form(s); provide a fully completed dated and signed copy to the subject.
3. Assign to the Subject a Subject identification Number and give the Subject card.
4. Collect information regarding demographics, relevant medical history, previous medications/procedures and concomitant therapies/procedures.
5. Confirm clinical diagnosis of psoriasis vulgaris
6. Collect urine for a semi-quantitative (“dipstick”) urinalysis.
7. Perform a physical examination (PE) and check vital signs.
8. Preselect six (6) target mini-zones, on two or more psoriasis plaques which:
   - are located on the upper and/or lower extremities (anterior crest of tibia, apex of knees and apex of elbows excluded) and/or on the trunk. Plaques on the face, scalp, hands, feet and folds will not be eligible as test areas.

- have a Total Sum Score (TSS = erythema + induration + scaling) ≥ 6; each item separately being ≥ 2,
- have identical severity (*i.e.* identical baseline TSS or variation of ± 1 grade),
- are approximately 2 cm in diameter and at least 2 cm apart from each other.
- include two mini-zones for the desquamation pre-treatment located on one or two plaque(s) isolated from the other plaques intended to be used for normal applications.

9. Perform a 12-lead electrocardiogram (should be done as close possible to Baseline visit)
10. Perform an ophthalmic examination (should be done as close possible to Baseline visit)
11. Check that the subject meets inclusion/exclusion criteria.
12. Perform clinical evaluations by measuring the individual clinical scores of psoriasis (erythema, scaling and induration) on each individual target mini-zones.
13. Collect a blood sample for hematology, biochemistry, and virology.
14. Complete the Subject Screening & Enrolment log.
15. Record any AEs on the CRF.
16. Explain to the subject how, where, when to apply the keratolytic product. Distribute one tube of the keratolytic product to the subject and explain instructions for application at home only on the plaque(s) selected for desquamation according to the protocol. Also, distribute one tube of emollient if necessary. Explain to the subject that no application must be done at home the of Day 1 visit before visiting the site.
17. Give the Subject an appointment for the Day 1 visit. (and additional screening visits if applicable)

8.1.2 **Baseline visit** [Day 1]

At the Baseline visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding CRF form(s).
2. Check laboratory results hematology, biochemistry, virology, urinalysis from the Screening visit.
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the CRF.
4. Check vital signs
5. Confirm the six target mini-zones according to the inclusion criteria,

6. CCI [redacted]

7. Perform clinical evaluations by measuring the intensity of the erythema, scaling and induration on each mini-zone using the individual clinical score, and record scores in the source document and CRF..

   For non-desquamated zones TSS (erythema + induration + scaling) should be superior or equal to 6 on a 13 point scale (0 to 12), with individual score of erythema, induration and scaling separately being ≥ 2. The zones must present a similar severity, i.e.: identical Baseline TSS or variation of ± 1 grade.

   For desquamated zones scaling score should be equal to 0 or 1 on a 5 point scale (0 to 4), and individual score of erythema, and induration separately being ≥ 2. The zones must present a similar severity, i.e.: identical Baseline sum of erythema and induration or variation of ± 1 grade.

8. Confirm subject meets inclusion/exclusion criteria.
9. Assign a randomization number to the Subject (this number will be assigned to randomized Subjects in increasing order and no numbers will be omitted).
10. CCI [redacted]

A member of staff other than the Investigator will:

11. Apply 50µl of the tested products on the Subject's selected mini-zones according to the randomization list generated by the sponsor and in compliance with the operational manual.
12. Instruct the Subject to avoid wetting areas (swimming, bath, sauna, hammam are not allowed). However, showers are permitted at least eight hours following applications.
13. Complete the Subject Enrollment Log and subject identification code list.
14. Schedule the next visits (D2 to D19).

8.1.3 **Interim visits** (from Day 2 to Day 18)

At each of the following visits, Subjects will be asked to return to the clinical centre every day (except Saturdays and Sundays) for study drug applications and site evaluations.

At each visit, the Investigator or the designated study person 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 CRF 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 Concomitant Therapy form of the CRF.

A member of staff other than the Investigator will:

3. Apply 50 µl of the tested products on the Subject's selected mini-zones according to the randomization list and in compliance with the operational manual
4. Instruct the Subject to avoid wetting areas (swimming, bath, sauna, hammam are not allowed). However, showers are permitted at least eight hours following applications.
5. Schedule an appointment for the next Visit

Moreover at Day 2, the Investigator, **before any applications** will:

6. Assess local cutaneous tolerance of each mini-zone.

Also at Day 4, Day 8, Day 11, Day 15 the Investigator, **before any applications** will:

7. Assess local cutaneous tolerance of each mini-zone.
8. Perform clinical evaluations of efficacy by measuring the intensity of the erythema, scaling and induration on each individual mini-zone.
9. Perform clinical evaluations of the clearing score for each mini-zone

Moreover at Day 5 visit:

10. Collect a blood sample for plasma PK analysis.

8.1.4 **Final/ Early Termination visit** (Day 19 visit)

At the Day 19/ET visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate, on the corresponding CRF form(s).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the CRF.
3. Perform a PE and vital signs measurements.
4. Collect urine for a semi-quantitative ("dipstick") urinalysis.
5. Collect a blood sample for hematology and biochemistry and for plasma PK analysis.
6. Assess local cutaneous tolerance of each mini-zone.
7. Perform clinical evaluations of efficacy by measuring the intensity of the erythema, scaling and induration on each individual mini-zone.
8. Perform clinical evaluations of the clearing score for each mini-zone
9. CCI [redacted]
10. Perform a 12-lead electrocardiogram (before keratolytic product application)
11. Perform an ophthalmic examination
12. CCI [redacted]

CCI [redacted]

16. Give the Subject an appointment for the Day 26±2 visit.

8.1.5 **Follow-up visit** (D26 ±2 visit)

The Investigator 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 CRF page(s)
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 Concomitant Therapy form of the CRF
3. Check the results of the laboratory tests performed at Day 19
4. CCI
5. [redacted]
6. Remove the suture (if applicable)
7. Complete the Exit Form.

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

Each subject will receive specific requirements or instructions to follow until the end of the study.

During the study, the Subject will be allowed to use, if needed, all types of therapies excluding those listed in the 5.5.5 Prohibited concomitant therapies.

Subjects will be instructed not to apply any treatment oremollient to the target psoriasis plaques receiving the pre-treatment or the treatments during the study. Subjects may treat the other psoriasis plaques (other than the one(s) with selected mini-zones) only with their regular emollient, or using the emollient provided by the Sponsor.

Scalp psoriasis may be treated with non-steroid shampoo.

The Subject will be instructed to apply the keratolytic product at home every day two times per day, preferably after washing, from 7 days before the planned Baseline visit appointment on the plaque(s) selected by the investigator only and not on the other plaques. No application should be performed the day of Baseline visit. This period may be extended to one more week based on investigator judgment.

If a Subject needs to take a concomitant treatment (topical or systemic), he/she should inform the Investigator of it as quickly as possible (at the latest, at the next visit).

The Subject will be instructed to keep the treated areas as dry as possible. Showers will be allowed at least eight hours after the applications. Some additional gauze may be used to protect the treated areas from getting wet (*i.e* use of "Cellofrais"). Bathing (swimming, bath, sauna, hammam) will be prohibited during the duration of the study. In addition, the Subject will be instructed to avoid excessive sun exposure and vigorous exercise that may result in excessive sweating during the study.

The subjects should never remove the bandages on treated zones.

The contact lens wearing is prohibited during the treatment period.

The Subject should come to the site each day for study procedures and study drugs applications except on Saturdays and Sundays.

The Subject will be instructed not to discuss the study materials with the Investigator or other Evaluator(s).

For safety precautions, participation in any other clinical trial is prohibited during the course of the study and for the following month.

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

9.1.1 Data transformations

Baseline assessments are accounted for deriving specific criteria (Change and percent changes). Concentrations data will logarithmically transformed before analysis.

9.1.2 Populations analyzed and evaluability

The intent-to-treat efficacy population (ITT) consists of the entire randomized population.
The ITT population will be analyzed for TSS, clinical scores and their percent change and change from baseline. A last visit for treatment period will be created, Endpoint, containing the last observation carried forward LOCF. Only Baseline and Endpoint/LOCF will be descriptively summarized.

The per-protocol efficacy population (PP) consists of all randomized subjects, except some subjects considered as not evaluable due to major deviations from the protocol.
Major deviations will be defined after data entry and before breaking the treatment blind, and may include: inclusion criteria not respected, interfering therapy, protocol deviation, poor compliance to study treatment administration or protocol requirements, unblinding. The decision on determining whether a subject is excluded from the PP population will be made during a blind review meeting.
The per-protocol population as defined above will be analyzed for efficacy at each evaluation visit during treatment period.

All Subjects having received a treatment at least once will be included in the safety population.

If applicable, an additional safety population will be defined for the pretreatment period with keratolitic.

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9.1.3 Data presentation and graphics

The subject disposition, demographics, baseline characteristics, previous therapies, concomitant therapies will be summarized by descriptive statistics.

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

The area under the curve of the TSS (sum of individual clinical scores erythema, induration/plaque elevation and scaling), as well as those of each individual clinical score will be calculated from Day 1 (before application) up to Day 19 by subject and by treatment, using the trapezoidal rule.

The time to success (defined as a clearing score of 0 or 1) will be summarized by treatment. Only the earliest day of success will be considered in defining the time to partial clearing, independently of the subsequent days.

The local tolerance scores will be summarized using frequency and percentage by visit and study product. The worst scores will also be summarized.

Adverse Events will be tabulated by study treatment. Adverse Events will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary. Additional summary tables will be provided for Adverse Events that will be considered as severe, serious (SAEs) and Adverse Events leading to discontinuation. Any AE and related AE will be summarized for each category. Analyses of adverse events will be based on Treatment Emergent Signs and Symptoms (TESS) *i.e.* adverse events occurring on the day of, or after, treatment application (Baseline).

Events having occurred before the day of treatment application (*i.e.* before Baseline) will be listed only.

Due to the intra-individual study design and whenever possible (known from e-CRF), AE will be imputed to the treated area, when not possible then the AE will be imputed to all treated area.

Physical examination, vital signs, ECG and ophthalmic examination will be summarized by descriptive statistics.

Shift tables for the laboratory data (and urinalysis) will be tabulated for each laboratory parameter.

Pharmacokinetics parameters will be descriptively summarized.

9.1.4 Inferential statistical analyses

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For all zones, TSS and percent change from baseline, Clinical scores and their change from baseline will be descriptively summarized by visit and by treatment received.

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9.2 Sample size determination

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Therefore 24 subjects are planned to be randomized.

This sample size is sufficient to assess also local tolerance in standard tolerance topical studies.

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel training

A study initiation visit will be conducted by the Sponsor with the Investigators and the study teams. During this visit, an extensive review and discussion of the protocol, procedures, CRF, and any other study material will be conducted. Sponsor's monitoring visits will be performed.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOP), the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

10.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by representatives of GALDERMA to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs.

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

The Investigator also agrees to assist the representative if required.

10.3 Data management

All data management procedures will be detailed in a Data Management Plan (DMP).

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect data (CRF), and whether the data management activities are performed internally or outsourced. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data clarifications are resolved. The data will be exported to be stored in SAS datasets. After all data clarifications are resolved, coding is approved, SAE/pregnancy reconciliation has been completed (if applicable) and subject's evaluability is determined, the database will be locked.

10.4 Quality assurance / audit / inspection

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

Audits of clinical trial centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IECs before, during, or after the clinical trial.

The Investigator will allow and assist the CRO/Sponsor's representatives, IECs and any regulatory agency to have direct access to all requested clinical trial-related records.

For the audits performed by, or on behalf of, GALDERMA auditors, audit certificate(s) will be provided by Quality Assurance.

10.5 Changes in clinical trial conduct / amendments

10.5.1 Clinical trial conduct

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

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

10.5.2 Amendments

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

The Sponsor does not have to notify non-substantial amendments to the competent authorities or the Ethics Committees. However, non-substantial amendments should be recorded and detailed in subsequent submissions e.g., in the subsequent notification of a substantial amendment.

11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Independent Ethics Committee (IEC)

This clinical trial protocol and all amendments will be reviewed and approved by the appropriate IEC.

11.2 Ethical conduct of the clinical trial

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

11.3 Subject information and consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCPs guidelines, federal regulations, and guidelines and in accordance with local requirements.

The ICF approved by an IEC, will be fully explained to the subject. An additional ICF will also be approved relating to the long term research program (see section 7.3.3).

Prior to enrolment into the clinical trial, the subject will sign and date the consent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject with a copy of the signed and dated consent form(s).

11.4 Contractual requirements

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

11.5 Data collection and archiving

11.5.1 Data collection

The Investigator must maintain all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents and on the CRFs provided by the Sponsor. All data should be recorded on the CRFs completely and promptly.

11.5.2 Source documentation

The Investigator must keep accurate separate records (other than the CRFs) of all subject visits, being sure to include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written Informed Consent Form. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical trial should also be included in the source documentation.

11.5.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in Sponsor/CRO/Investigator/Institution archives for the legally required duration for archiving.

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

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

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

11.6 Insurance

A certificate attesting Third Party coverage of CRO/Sponsor will be provided upon request.

11.7 Investigator and Administrative Structure

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

12 LITERATURE REFERENCE LIST

12.1 Literature references

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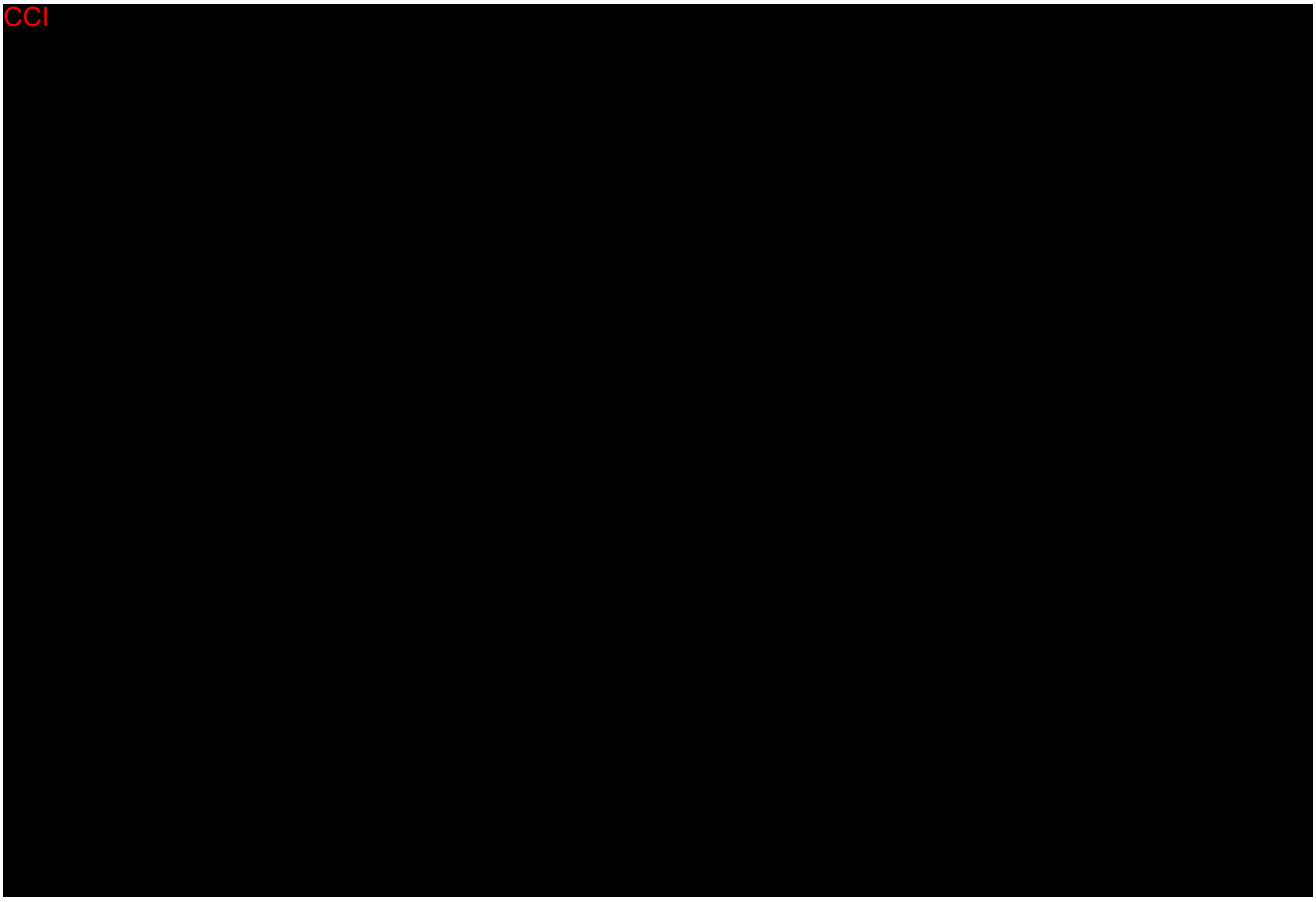

13 APPENDICES

13.1 Classification of CYP Inhibitors

From FDA site:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Classification of In Vivo Inhibitors of CYP Enzymes(1) (7/28/2011) Drug Development and Drug Interactions. (Table 5 on the website)

CYP Enzymes	Strong Inhibitors(2) **≥ 5**-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors(3) **≥ 2 but < 5**-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors(4) **≥ 1.25 but < 2**-fold increase in AUC or 20-50% decrease in CL
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein,(5), disulfiram, Echinacea,(5) famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil(6)		Fluvoxamine, ketoconazole, trimethoprim
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole,(7) Fluvoxamine,(8) ticlopidine(9)	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives(10)
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,(11) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,(11) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,(5) goldenseal,(5) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea,(5) escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link
2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
4. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
5. Herbal product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

13.2 Summary of blood sample volumes

	Standard Analysis (Volumes in mL)	Blood Sample Total Volume (mL)
Screening - Virology - Haematology - Biochemistry	 5 3 3	 11
Day 5 visit - PK	 5	 5
Day 19 or Early Termination - Biochemistry - Haematology - PK	 3 3 5	 11
Day 25 visit - PK	 5	 5
TOTAL AMOUNT		32