CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: N° RD.03.SPR.114384

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CONFIDENTIAL

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TITLE PAGE

Title:		
Subject reported outcomes on satisfaction, safety and efficacy with Luxerm® in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis of the face or the scalp		
Project Name:	**Project Number:**	**Clinical Trial Phase:**
834	RD.03.SPR.114384	Phase IV

EUDRACT NUMBER 2017-000066-29

Version Number: 01

Sponsor Contact details:

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For any urgent medical questions, including safety reasons, please use the contact details provided in Section 8.2.2

This clinical trial will be performed in compliance with applicable regulations, Good Clinical Practice (GCP) and the ethical principles that have their origin in the Declaration of Helsinki. This clinical trial Protocol follows guidelines outlined by the International Conference on Harmonization (ICH) and the *GALDERMA R&D* Phase IV department template

CLINICAL TRIAL ADMINISTRATIVE STRUCTURE

The following table contains the details of GALDERMA R&D employees involved in the conduct of the trial.

SPONSOR PERSONNEL		
Name/Title	**Affiliation/Address/Tel./Fax**	**Responsibilities**
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SIGNATURE PAGE

Investigator's Agreement

I agree to:

- Implement and conduct this clinical trial diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations.
- Accurately record all required data on each patient's electronic Case Report Forms (eCRFs) in a timely manner on an ongoing basis.
- Use the investigational product(s) for this clinical trial only. Maintain a complete and accurate inventory during and at the completion of the clinical trial. Maintain records of all investigational product units received, dispensed, returned by the subjects, and the number of product units returned to *GALDERMA R&D*.
- Allow authorized representatives of *GALDERMA R&D* or regulatory authorities to conduct on-site visits to review, audit, and copy clinical trial documents. I will personally meet these representatives at mutually convenient times to answer any clinical trial-related questions.
- Comply strictly with the agreement signed for the carrying out of my services within the scope of this protocol, especially with the provisions regarding confidentiality and intellectual property (results and publications).

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

PRINCIPAL INVESTIGATOR **SIGNATURE** **DATE**

PRINTED NAME:

GALDERMA R&D **SIGNATURE** **DATE**

PHASE IV MEDICAL EXPERT

PRINTED NAME:

RAJEEV CHAVDA

SPONSOR REPRESENTATIVE

PRINTED NAME:

PHILIPPE MARTEL

RETURN THE ORIGINAL SIGNED COPY TO G*ALDERMA R&D* AND KEEP A COPY AT YOUR SITE

DISTRIBUTION

Copy of the Protocol: All signatories and,

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Géraldine LANCELOT	Industrial Property, GALDERMA R&D

Copy of the Synopsis:

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Birgit JANNING	Medical Marketing Manager, Prescription
Harold DUMONT	Global Brand Manager, GALDERMA Global Marketing
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Original Protocol: Archives (GALDERMA R&D Sophia Antipolis)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
AK	Actinic Keratosis
APT	All Subjects Treated (Safety Population)
CDMS	Clinical Data Management System
c-PDT	Conventional Photodynamic Therapy
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DL	Daylight
DMP	Data Management Plan
EC	Ethics Committee
FSI	First Subject In *(first subject who signs the Informed Consent Form)*
FU	Follow-Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
i.e.	That is (Latin: id est)
IB	Investigator Brochure
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intra Uterine Device
ITT	Intent-To-Treat
LSI	Last Subject In (Last subject randomised/assigned to treatment)
LSO	Last Subject Out (Last subject who completed its last clinical trial visit)
MAL	Methyl Aminolevulinate
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non Melanoma Skin Cancer
NRS	Numeric rating scale

Abbreviation	**Term**
OTC	Over-The-Counter
PDT	Photodynamic Therapy
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (SAS Institute Inc., Cary, NC)
SIN	Subject Identification Number
SCC	Squamous cell carcinoma
SOC	System Organ Class
SOP	Standard Operating Procedure
SmPC	Summary Product Characteristics
UPT	Urine Pregnancy Test
UV	Ultraviolet

1 SYNOPSIS

Clinical trial title:		
Subject reported outcomes on satisfaction, efficacy and safety with Luxerm® in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis of the face or the scalp		
Short title (± acronym): SESAME 2		
Project number: 834	**Clinical trial phase:** Phase IV	**Clinical trial period** Planned First Subject In: May 2017 Planned Last Subject Out: Nov. 2017
Objective(s):	Luxerm® with daylight photodynamic therapy has been approved in Germany, for the treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis (AK) on face and scalp. The main objective of this trial is to evaluate the subject reported outcome of Luxerm® Daylight field-directed treatment of thin or non-hyperkeratotic and non-pigmented AK lesions on the face or scalp after one session. Also the efficacy and safety of Luxerm® in terms of subject complete response rate will be assessed.	
Methodology:	It is an interventional open label prospective and multicentre study conducted in Germany in subjects with thin or non-hyperkeratotic and non-pigmented multiple AKs in one anatomical area on the face (e.g., forehead or cheek or chin), excluding nose eyelids, lips and mucosa or balding scalp, using Luxerm® DL-PDT treatment. The study will collect the subject's characteristics and medical history, how Luxerm® treatment has been performed, concomitant treatments, safety information, investigator and subject's satisfaction with the efficacy and safety of Luxerm® DL-PDT in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented AK.	
Total number of planned subjects:	50 subjects will be enrolled	
Total number of planned sites:	Approximately 8 sites	
Approximate number of subjects/site:	5 to 10 subjects per site	
Country(ies) involved:	Germany	
Population and main inclusion criteria:	Subjects over 18 years old with thin or non-hyperkeratotic and non-pigmented AKs in one anatomical area on the face (e.g., forehead or cheek or chin) excluding nose, eyelids, lips and mucosa, or balding scalp requiring field treatment with Luxerm® DL-PDT.	
Clinical trial duration per subject	maximum 15 weeks	
Number of visits:	3 study visits (baseline, day 1 post-treatment, week 12 post-treatment).	

Clinical trial title:		
Subject reported outcomes on satisfaction, efficacy and safety with Luxerm® in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis of the face or the scalp		
Short title (± acronym): SESAME 2		
Project number: 834	**Clinical trial phase:** Phase IV	**Clinical trial period** Planned First Subject In: May 2017 Planned Last Subject Out: Nov. 2017
Investigational product:		
Name:	Luxerm®	
Pharmaceutical form:	Cream	
Dose/concentration:	160mg/g of methyl aminolevulinate	
Total daily dose:	One application	
Mode and frequency of administration:	One session of Luxerm® daylight photodynamic therapy: a sunscreen with chemical filters will be applied to all sun exposed areas including the treatment area to prevent subsequent UVA and UVB exposure (as provided for the study). After the sunscreen has dried, the selected anatomical area should be prepared to facilitate access of the cream and light to all lesions. An abrasive pad should be used to roughen the affected area. Following skin preparation, a thin layer of Luxerm® cream should be applied on the anatomical area (field application), without occlusion. After Luxerm® application, subject will go outdoor under direct daylight no later than 30 minutes. On sunny days, should the subject feel uncomfortable in direct sunlight, shelter in the shade may be taken. After 2-hour of daylight exposure, subjects will return indoors and Luxerm® will be removed. Subjects will be instructed to avoid sun exposure and use sunscreen for the next 48 hours. The subject will be assessed at baseline and day 1 post-treatment as well as at week 12 post-treatment.	
Location of treated area:	Face or scalp	
Duration of treatment:	One day	
Comparator product:	Not applicable	
Non-investigational product to be provided for the clinical trial:	• Urine Pregnancy Test • Actinica sunscreen SPF 50+ on all exposed areas. • Cetaphil moisturizer cream at night for 8 days on the treated area after Luxerm DL-PDT • Skin abrasive pad for skin preparation on the anatomical area	

<table>
<tr><td colspan="3">Clinical trial title:</td></tr>
<tr><td colspan="3">Subject reported outcomes on satisfaction, efficacy and safety with Luxerm® in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis of the face or the scalp</td></tr>
<tr><td colspan="3">Short title (± acronym): SESAME 2</td></tr>
<tr><td>Project number:
834</td><td>Clinical trial phase:
Phase IV</td><td>Clinical trial period
Planned First Subject In: May 2017
Planned Last Subject Out: Nov. 2017</td></tr>
<tr><td>Measurement criteria</td><td colspan="2">Subject-reported outcomes
• Subject questionnaire the day of treatment after the daylight photodynamic session and at last visit (Week 12/Early termination) (appendices 1-2)

Efficacy:
• Count of AK lesions at baseline in the anatomical area
• Lesion response at week 12 of treated AK lesions in the anatomical area
• Subject’s skin aspect assessed at week 12 for lesion complete response using a 4-point scale
• Count of new AK Lesions at week 12 in the anatomical area

Safety
• Subject’s self-assessment of pain post daylight PDT procedure using a 11-point Numeric Rating Scale (NRS) (appendix 1);
• Incidence and severity of adverse events throughout the study

Other variables
• Photodamage score (Dover scale) assessment at baseline and week 12
• Physician questionnaire once all subjects from a site have completed the study (appendix 3)
• Photographs at baseline and week 12 at selected sites</td></tr>
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<tr><td colspan="3">Clinical trial title:</td></tr>
<tr><td colspan="3">Subject reported outcomes on satisfaction, efficacy and safety with Luxerm® in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented Actinic Keratosis of the face or the scalp</td></tr>
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834</td><td>Clinical trial phase:
Phase IV</td><td>Clinical trial period
Planned First Subject In: May 2017
Planned Last Subject Out: Nov. 2017</td></tr>
<tr><td>Analysed variables</td><td colspan="2">Subject-reported outcomes
• Subject questionnaire the day of treatment after daylight session and at last visit (week 12 or early termination)

Efficacy endpoints:
• Lesion complete response rate, defined as the percentage of preexisting and treated lesions in the anatomical area at baseline assessed as clear at week 12
• Subject complete response rate defined as the percentage of subjects with all treated lesions clear in the anatomical area at Week 12.
• Subject partially clear defined as the percentage of subjects with at least 75% lesion complete response in the anatomical area at week 12
• Number of new AK lesions in the anatomical area at week 12
• Clinical assessment of subject's skin aspect at week12: mean score on anatomical area at week12

Safety variable
• Subject's self-assessment of maximal pain using a 11-point Numeric Rating Scale (NRS) from 0 (no pain) to 10 (extreme pain) after the treatment session
• Incidence and severity of adverse events

Other variables
• Photodamage score with Dover's scale at baseline visit and week 12
• Physician questionnaire once all subjects from a site have completed the study.</td></tr>
<tr><td>Principal statistical methods and sample size calculation:</td><td colspan="2">The objective of this trial is to evaluate the subject reported outcome with Luxerm® Daylight field treatment after one session. Also the efficacy and safety of Luxerm® in terms of subject complete response rate will be assessed.

The Intent-to-Treat (ITT) population consists of all enrolled subjects. The safety population (APT) consists of the ITT population, after exclusion of subjects who never took the treatment.

The efficacy endpoint will be analysed on the intent to treat (ITT) population, using a worst case approach, in which the lesions with missing lesion response assessment will be considered as having not responded.

No inferential statistics will be performed. All variables will be descriptively summarized on ITT population and on APT population for the safety variables.</td></tr>
</table>

2 BACKGROUND AND RATIONALE

2.1 Medical background and short rationale for the clinical trial

AK is a common epithelial non-infiltrative lesion caused by chronic exposure to ultraviolet (UV) radiation damaging cell cycle regulators and leading to proliferation of cytologically abnormal epidermal keratinocytes. They are characteristically found on sun-exposed areas such as the face, bald scalp, neck, chest, back of the hands and forearms. The etiology of AK is multifactorial, common in elderly, fair-skinned men with a history of extensive outdoor activities (Goldberg et al 2010). A review of epidemiological studies showed that the prevalence and incidence of AK are highly variable depending on the population studied, location, age, and gender (Frost et al 1994). For example, estimated rates of nearly 1.7 million AK cases have been reported in Germany, with standardized prevalence of 1.8%. Age-specific rates were below 1.5% for up to 60 years and rose to 8.2% in the group of 80-89 years old with as high as 13.2% in men in this sub-population of elderly patients (Schaefer et al 2014). In particular, no robust data on the German prevalence are available. Investigations from Australia reveal a rate about 60% (Frost et al 1994; Frost et al 2000). In Europe, prevalence rates of 1.4%–6% (women) and 15% (men) have been reported in selected regions (Schaefer et al 2014). AKs themselves are deemed not serious but they are very common, highly widespread and recurrent. Many authors suggest that AKs should be classified as early in situ SCCs. It is, however, not possible to predict which lesions will progress into SCC (Ferrandiz et al 2017; Fernandez et al 2015).

Various treatment options are available for the treatment of AK lesions, including destructive lesion directed therapies (e.g. cryosurgery, laser or excisional surgery) and topical field directed therapies (e.g. 5-fluorouracil [5-FU], imiquimod, diclofenac, ingenol mebutate) (Gold et al 2006; Fenske et al 2010). However, patient satisfaction with many of these treatments, especially cryotherapy, can be affected by considerable discomfort and residual scarring while with topical treatments the longer duration of treatment (imiquimod, diclofenac, 5FU) and/or frequent and unpredictable local skin reaction (ingenol mebutate, imiquimod, 5FU) and/or low efficacy (diclofenac cream) may be a contributing factor. Photodynamic therapy (PDT) is a highly effective treatment for AK, offering the advantage of excellent cosmesis (Sidoroff et al 2010). However, issue with conventional PDT (cPDT) was pain. More recently daylight (DL) PDT has been approved based on its non-inferiority *vs* cPDT for efficacy and superiority in terms of pain intensity (Rubel et al 2014; Lacour et al 2015). As with DL-PDT large and/or multiple AKs can be treated at the same time, it is recommended as a first-line treatment for individual with multiple and/or confluent AKs (Wiegell et al 2012; Morton et al 2013).

Metvix®, a cream formulation containing Methyl Aminolevulinate (MAL), has been approved with a red LED light via a suitable lamp (conventional PDT) for the treatment of AK, Bowen's Disease and Basal Cell Carcinoma in several countries worldwide (for further details on Metvix® use, known benefits and risks, please refer to the Product label). Topical application of MAL results in the formation of photoactive protoporphyrin IX (PpIX) which leads to a photochemical

reaction and thereby phototoxicity to the exposed target cells. The effectiveness and safety of MAL conventional and Daylight PDT have been demonstrated in several clinical trials for the treatment of AK (Wiegell et al 2008; Fargnoli et al 2015; Lacour JP et al 2015). Several clinical studies have shown that Metvix® can be activated by natural daylight (Genovese et al 2016; Fargnoli et al 2015; Lacour et al 2015; Rubel et al 2014, Wiegell SR et al 2008). Most recently, clinical studies performed in Australia and Europe have confirmed that Metvix® with Daylight Photodynamic Therapy (DL-PDT) treatment regimen was non-inferior to cPDT in terms of efficacy, with the advantage of being almost painless and leading to less treatment-related adverse events (Rubel et al 2014; Lacour et al 2015). Metvix® DL-PDT treatment regimen is currently approved for the treatment of AK in Europe, Australia and Latin American countries. Metvix® DL-PDT is an effective, safe and alternative treatment for thin or non-hyperkeratotic and non-pigmented AK lesions and is associated with high subject satisfaction (See et al 2015). .

Patients with AKs usually suffer from multiple and coalescent lesions. Clinical markers relate it to an increased risk of developing malignant epithelial cancers. This can occur even on seemingly unimpaired skin areas surrounding AK. Such pathological condition is described as "field cancerization" reflecting the field actinic damage, raising the basis of 'field cancerization' concept (Samrao et al 2013). This concept suggests that subclinical pre-neoplastic changes exist in the apparently normal skin surrounding AKs. Studies confirm the presence of neoplastic changes involving the entire field and not only areas of clinically evident NMSCs. The management of AK and field cancerization with field-directed treatments as photodynamic therapy (PDT) is recommended by international guidelines (Rossi et al 2009; Stockfleth et al 2008; Dreno et al 2014). AKs have been described to be a field disease and not limited to single clinically apparent lesions. In the definition of field cancerization, clinically normal appearing skin surrounding AKs contains subclinical features of genetically damaged cells which may develop into new AKs and NMSCs (Sotiriou et al 2015). Treatment should therefore target an area of field change especially when patients present with multiple AK which may reduce the risk of development of further AKs, secondary tumors and local recurrence (Wiegell et al 2012; Szeimies et al 2012; Bagazgoita et al 2011).

Metvix® DL-PDT is an attractive treatment for treating AKs and different ways of simplification of the procedure have been investigated. More recently researchers/physicians' attention has been focused not only on how to activate the photosensitizer but also on how to prepare the skin prior to its application. Daylight -PDT is a novel and simplified modality, less expensive and less time-consuming and has been shown to be more tolerated. Besides, recent trials have demonstrated that DL-PDT has a similar effectiveness compared with cPDT for the treatment of AK using field treatment (Rubel et al 2014; Wiegell et al 2008). These studies showed similar AK clearance with tolerability profile superior for DL-PDT in terms of local skin responses and pain. DL-PDT was more cosmetically acceptable but skin preparation technique was not precised (Wiegell et al 2012). Pre-treatment of the skin is essential for adequate penetration of topical photosensitizing agents and subsequent PpIX accumulation. For skin preparation procedure, microneedling, curettage, fractional lasers or ablative fractionated laser systems (AFXL) or abrasive skin preparation pads or microdermabrasion are the most popular ways to prepare the skin as an effective, acceptable and relatively inexpensive but also for cosmetic purposes. A recent study

showed microdermabrasion with skin pad led to attain same levels of PPIX and erythema as with curettage (Bay et al 2017). Other keratolytic therapy in patients with AK prior to MAL-PDT with 10% salicylic acid or 40% urea cream are also effective in respect of higher lesion response rates but are associated with a higher rate of localised side effects such as pain and local skin reactions (Gholam et al 2016).

2.2 Investigational product profile

In Germany MAL Daylight PDT has been approved with the brand name Luxerm® and is indicated for thin or non-hyperkeratotic and non-pigmented AKs.

In the proposed study, we aim to evaluate the patient reported outcomes on satisfaction and efficacy and safety of MAL with Daylight Photodynamic Therapy (DL-PDT) in the treatment of AK lesions in one anatomical area on the face (e.g., forehead or cheek or chin), excluding nose, eyelids, lips and mucosa or balding scalp.

Table 1 - Investigational study Product profile

	Investigational product
Trade Name or Equivalent	Luxerm®
Name of Drug Substance	methyl aminolevulinate hydrochloride
Pharmaceutical Form	Cream
Strength	160 mg/g
Packaging (type and size)	2g collapsible aluminium white tubes
Storage Conditions	Between 2 to 8 °Celsius
Dosage (total daily dose)	Thin layer on selected anatomical area of either face or scalp
Route	Topical
Dose Regimen	Single dose
Duration of administration	2 hours and 30 minutes
Location of Treated Area	Face or scalp

2.3 Risk/Benefit assessment

Based on the previous studies (Rubel et al 2014; Wiegell et al 2008), the use of natural daylight PDT is expected to improve the tolerability of the treatment (less pain during illumination) and simplify the use of Metvix® while maintaining a similar efficacy compared to the previous studies with conventional PDT.

The use of red LED light can result in discomfort for patients due to large amounts of PpIX which is photobleached in a short period of time. The continuous activation of PpIX associated with the use of natural daylight would result in a corresponding reduction in pain.

Overall, the cumulative post-marketing experience as well as the information from clinical studies and literature confirm that the benefit-risk ratio remains positive for the use of methyl aminolevulinate in the approved indications.

MAL Daylight PDT (marketed under the name Luxerm® in Germany) is a commercial product that will be used according to the approved indications and usage. Warnings and precautions with MAL Daylight PDT are well known and documented in the product monograph. For more details regarding the clinical adverse reactions and/or the post-marketing experience, please refer to the product monograph.

3 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

3.1 Clinical trials objectives

The objective of this multi-centre study is to evaluate the subject reported outcomes on satisfaction with Luxerm® DL-PDT in the field-directed treatment of thin or non-hyperkeratotic and non-pigmented multiple AKs in one anatomical area on the face (e.g., forehead or cheek or chin) excluding nose, eyelids, lips and mucosa, or balding scalp at 12 weeks.

The other objectives are to assess the efficacy of Luxerm® DL-PDT in subjects with actinic keratosis, safety assessments including adverse events and assessment of skin appearance.

3.2 Clinical hypothesis

Based on previous results available, the efficacy of MAL DL-PDT is non-inferior to cPDT and Ingenol mebutate in treatment of AKs (Wiegell et al 2008; Fargnoli et al 2015; Genovese et al 2016). The assumption is also to have similar efficacy in terms of field treatment with better tolerability in terms of pain.

4 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

4.1 Number of subjects

A total of 50 subjects presenting with thin or non-hyperkeratotic and non-pigmented actinic keratosis on the face or scalp will be enrolled in approximately 8 sites located in Germany.

4.2 Clinical trial population

Subjects who meet all of the following criteria will be eligible for the clinical trial.

4.2.1 Inclusion criteria

In order to be eligible for the clinical trial, the subject must meet all of the following inclusion criteria:

1. Male or female age ≥ 18 years old.

2. Subject with at least 5 clinically confirmed thin or non-hyperkeratotic and non-pigmented actinic keratoses in an anatomical area on the face (e.g., forehead or cheek or chin) excluding nose, eyelids, lips and mucosa, or balding scalp, at baseline visit.

3. Subject or caregiver capable of performing the skin preparation and Luxerm® treatment application as per the investigator instructions.

4. Female subject of childbearing potential must have a negative UPT at baseline (UPT should have a sensitivity of 25 IU/L or less) and agree to be strictly abstinent or use a highly effective method of birth control during the study (i.e. progestogen-only oral hormonal contraception; male or female condom; cap, diaphragm or sponge with spermicide; bilateral tubal ligation; combined (estrogen and progestogen-containing) oral hormonal contraception, or injectable or implants hormonal contraception (at a stable dose for at least 1 month prior to baseline); intra-uterine devices inserted at least 1 month prior to baseline; vasectomized partner for at least 3 months prior to baseline).

5. Female subject of non-childbearing potential, e.g.: post-menopausal (absence of menstrual bleeding for 1 year without any other medical reason), hysterectomy or bilateral ovariectomy.

6. Subject has read and signed the approved informed consent form (ICF) prior to any participation in the study.

7. Subject has read and signed a Photograph Release Consent Form if he/she is willing to be photographed.

8. Subject (or caregiver) willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.

4.2.2 Exclusion criteria

Any subject who meets one or more of the following exclusion criteria will not be included in this clinical trial.

1. Subject with a clinical diagnosis of a skin disease other than AK (including non-melanoma skin cancer) on the target anatomical area.

2. Subject with severe AK (thick, hyperkeratotic AK) per anatomical area (face or scalp).

3. Subject with clinical diagnosis of other skin disease on the target anatomical area.

4. Subject with pigmented AK on the target anatomical area.

5. Subject with melanoma at any location.

6. Immunocompromised subject or requiring immunosuppressive therapies.

7. Subject with porphyria; photosensitivity- related disorders, active infectious disease.

8. Subject with known or suspected hypersensitivity to the active substance or to any excipients of Luxerm® (see Summary of Product Characteristics).

9. Female subject who is pregnant, nursing or planning a pregnancy during the study.

10. Subject who has used any of the following topical preparations on the area to be treated: keratolytics including urea (greater than 5%), alpha hydroxyacids [e.g. glycolic acid, lactic acid, etc. greater than 5%], salicylic acid (greater than 2%) within 2 days of initiation of treatment.

11. Subject with a wash-out period from baseline for topical or systemic treatment or medical/surgical procedure in the anatomical area (for AKs) less than the following:

• Retinoids, including tazarotene, adapalene, tretinoin, retinol	4 weeks
• Cryotherapy, diclofenac, corticosteroids or other treatments for AK	8 weeks
• Microdermabrasion, laser ablative treatments or chemical peels	8 weeks
• 5-FU, imiquimod	24 weeks
• Surgical: excision and reconstructive surgery, chemosurgery,	12 weeks
• Any Photodynamic Therapy, ingenol mebutate (Pep-005), Radiotherapy and UV radiation therapy	12 weeks
• Investigational therapies for Actinic Keratoses	12 weeks
• Immunosuppressive drugs (such as glucocorticoids, cytostatic, antibodies, drugs acting on interferon, opioids, TNF binding proteins, Mycophenolate, small biologics agents)	12 weeks

12. Subject who is currently participating to/ or who has participated in another investigational treatment or device research study within 4 weeks of baseline visit.

13. Subject may be unreliable for the study including subjects who engage in excessive alcohol intake or drug abuse, or subjects who are unable to return for scheduled follow-up visits.

14. Subject who is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

15. Subject who is unwilling to refrain from use of prohibited medication during the clinical trial (see section 4.3.5).

16. Subject who is vulnerable (such as deprived of freedom) as defined in Section 1.61 of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP).

17. Subject with clinically significant abnormal laboratory finding (if any available report) at the baseline visit or medical/surgical condition (other than for actinic keratoses), which might, in the Investigator's opinion, interfere with study evaluations or pose a risk to subject safety during the study.

18. The subject is a study site staff member (investigator, study nurse, etc.) or a relative of one.

19. Subjects with any condition that may be associated with a risk of poor protocol compliance

4.3 Prior and concomitant therapies

4.3.1 Definition

Previous therapies (drugs and/or procedures) are defined as therapies that have been stopped within 12 weeks prior to the investigational product application.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the baseline visit , or
- 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 baseline visit

4.3.2 Categories

The following two categories will 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.

4.3.3 Recording

Previous and concomitant therapies will 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 case report form (CRF).

Concomitant therapies will be recorded, reviewed, and updated at each trial visit.

Every attempt should be made to keep concomitant therapy dosing and regimen constant during the study. Any change to the concomitant therapy should be noted on the CRF. 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.

4.3.4 Authorised therapies during the clinical trial.

Unless listed in the exclusion criteria above or in the prohibited therapies (see sections 4.2.2 and 4.3.5), all therapies are authorised.

Subject may use the sunscreen and moisturizer provided for the trial as required for the symptomatic relief of skin dryness or irritation (use of moisturizer other than the provided one will be captured in the CRF as concomitant therapy).

Note: *It is preferred that a moisturizer (provided one or a one not containing alpha hydroxy acid) be added to the treatment regimen as opposed to implementing an altered dosage regimen.*

4.3.5 Prohibited therapies during the clinical trial

The following therapies are prohibited because they may interfere with the efficacy and/or safety assessment of the investigational product, or because they may interact with the metabolism of the investigational product:

- On the anatomical area, all topical treatment, medical/surgical procedures listed as exclusion criteria (section 4.2.2).
- All systemic therapies listed in exclusion criteria (section 4.2.2).
- Any other drugs/procedures which in the investigator's judgment are liable to interfere or interact with the efficacy or safety of Luxerm®.
- Any UV-therapy should be discontinued before treatment.

- As a general precaution, sun exposure of the treated anatomical area should be avoided for about 2 days following treatment

- If any outdoor sun exposure the subject will be recommended to apply the provided sunscreen.

- Any treatment including cryotherapy is prohibited except at the end of the study to treat AK lesions at last visit after study clinical assessments.

- If subject presents mild/moderate/severe AKs outside anatomical area and investigator wishes not to wait the end of study before treating them, he/she can do so but in this case only cryotherapy can be used. In order to avoid interference with subject pain assessment, it should be done once all study assessments, including subject questionnaire completion, have been performed at the baseline visit.

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, *GALDERMA R&D* will be notified to discuss possible alternatives prior to administration of a prohibited therapy and to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

4.4 Procedures / reasons for 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 his/her participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without prejudice.

Subjects who discontinue the clinical trial prematurely should be fully evaluated, whenever possible. The procedures designated for the week 12 post-treatment visit will be performed for all premature discontinuation subjects. The appropriate CRF pages should be completed.

For all subjects who prematurely discontinue the clinical trial, the reason must be carefully documented by the investigator on the Exit Form, and, if applicable, on the Adverse Event Form if discontinuation is due to an AE.

At 1 week post-baseline the investigator will call the subject if he has not heard from the subject since baseline visit, to check if the study treatment has been performed:

- **If the subject was not able to perform the study treatment during the week post-baseline due to bad weather conditions, another additional period of maximum 7 days is offered to perform the study treatment.**

- **For an additional period greater than 7 days the decision to maintain the subject in the study will be based on discussion between investigator and sponsor.**

- **If the subject decides to stop his participation for whatever reason, he/she will be asked to return the study product to the site. The study product must not be reallocated to another subject and should be discarded from the study product stock. Investigator has the possibility to replace the subject.**

In the case of early termination, the investigator should ensure that the subject receives appropriate therapy for his/her condition.

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

All data gathered on the subject prior to termination will be made available to *GALDERMA R&D*.

Reasons for clinical trial completion/discontinuation, as listed on the Exit Form of the CRF are described below:

Normal study Completion	Subject completes the clinical trial as planned in protocol.
Pregnancy	Withdraw the subject from the clinical trial following the procedure described in the protocol section 8.3
Adverse Event	Complete CRF 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 comments section of the CRF Exit Form.
Protocol Violation	Explain the violation in the comments section of the CRF Exit Form
Lost to Follow-up	Confirm with 2 documented phone calls and a certified letter (delivery receipt requested) without response. Explain in the comments section of the CRF Exit Form.
Other	This category is to be used for a subject who discontinues for a reason other than those specified in the predefined categories above. Explain the reason for discontinuation in the comments section of CRF Exit Form.

If reason for discontinuation is “withdrawal by subject” or “other”, the subject must be questioned to rule out the possibility of an AE; this should be documented in the CRF.

5 INVESTIGATIONAL PLAN

5.1 Overall clinical trial design

This clinical trial will be conducted as a multicentre, open label clinical trial involving male or female subjects of any race, aged ≥ 18 years with clinically confirmed thin or non-hyperkeratotic and non-pigmented multiple AKs in an anatomical area on the face or scalp , and meeting other specific eligibility criteria.

A total of 50 subjects will be enrolled in approximately 8 sites in Germany. Approximately 5 to 10 subjects are planned for each site.

At baseline subject eligibility will be validated and the anatomical area to be treated on the face (e.g., forehead or cheek or chin) excluding nose, eyelids, lips and mucosa, or balding scalp, will be selected by the investigator.

Subjects will receive from the investigator adequate training and detailed instructions about Luxerm® treatment. Eligible subjects will apply the Luxerm® treatment with daylight PDT within 1 week (± 7 days) to the baseline visit depending on appropriate weather conditions to allow daylight exposure.

Subjects will be evaluated up to three times during the study; at baseline, Day 1 post-treatment (±2 days) and week 12 post treatment (±7 days).

5.2 Discussion of clinical trial design

Luxerm® is registered in Germany; this study is therefore considered as Phase IV. Luxerm® cream is a topical therapy currently approved for treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AKs) on the face and scalp. In several clinical trials it has been shown to be highly effective, safe, well-tolerated and to give excellent cosmetic outcomes with minimal risk of scaring.

An interventional design is applied in this study because it allows assessment of patient reported outcomes to Luxerm® treatment satisfaction in addition to safety and efficacy evaluations of Luxerm® daylight photodynamic therapy as per local SmPC. Information on the treatment application will be recorded by the subject in a questionnaire and reported in an electronic Case Report Form (eCRF).

Although several studies have already been conducted with MAL DL-PDT to treat different skin conditions, it is felt that a clinical trial is required to confirm the subject reported outcomes with DL-PDT to assess the level of satisfaction.

5.3 Clinical trial duration and termination

The average planned period for the clinical trial from First Subject In (FSI) to Last Subject Out (LSO) is 6 months. The end date of the clinical trial will be the date of the last visit of the last subject who participates in the clinical trial.

The planned duration of recruitment (i.e. From FSI to Last Subject In (LSI)) is approximately 3 months.

The clinical trial may be terminated by the investigator at his/her clinical trial site at any time with appropriate notification to *GALDERMA R&D*. Likewise, *GALDERMA R&D* may terminate the clinical trial and/or the participation of the clinical trial site(s) with appropriate notification.

The expected duration of subject participation is approximately 15 weeks.

5.4 Clinical trial flow chart

STUDY PROCEDURES	**Baseline Visit 1** D0	**Treatment Day[g] (at patient's home)**	**Day 1 post-treatment Visit 2** (± 2 days)	**Week 12 post-treatment Visit 3** (± 7 day)
Informed consent	X			
Inclusion/Exclusion criteria	X			
Demography/Medical history	X			
Previous therapies [a]	X			
Urine pregnancy test [d]	X			X [e]
Concomitant therapies	X		X	X [e]
Lesion mapping and counting [c]	X			X [e]
Sunscreen application		X		
Skin preparation	X[k]	X[i]		
Luxerm® application and DL treatment session		X		
Lesion response using the transparent plastic sheet (for initial treated AK lesions)				X [e]
Clinical assessment of skin aspect for AK lesions in complete response				X [e]
Count of new AK lesions using the transparent plastic sheet				X
Photodamage Dovers assessment	X			X [e]
Adverse events [b] (including local skin reaction)	X		X	X [e]
Subject questionnaire		X[f]		X [e]
Physician questionnaire [j]				X [e]
Photographs [h]	X			X [e]
Treatment Dispensed	X			
Subject Compliance			X	
Study treatment return			X	
Exit form				X [e]

a. Treatment that continues after visit 1 should be recorded on the concomitant therapies form of the CRF.
b. Adverse Events have to be collected from the moment the Informed Consent signature is obtained and recorded on the AE form of the CRF.
c. Actinic keratosis lesions in the treated area will be counted. For accurate counting, lesion localization and follow-up, a clear plastic sheet will be placed over the anatomical area of the face or scalp being treated and other anatomical landmarks will also be marked on this sheet
d. For subject of childbearing potential: The determination of UPT is mandatory at baseline and at week 12 or before if there is early termination. UPT must have a sensitivity of less than at least 25IU/L. In case of positive UPT during the study the investigator will withdraw the subject from the clinical trial according to the procedure for reporting pregnancy details in the protocol.
e. To be performed at week 12 or before in case of early termination.

f. After the 2 hours daylight exposure.
g. Subject advised to ensure the treatment as close as possible to the baseline visit (within 1 week (± 7 days)) and with appropriate weather conditions, to ensure the treatment instructions are followed. At 1 week post-baseline, if the investigator has not heard from subject, he will call the subject to check if the study treatment has been performed (see section 4.4). Subject instructs to call the investigator to confirm the treatment has been well completed and to schedule the day 1 post-treatment visit.
h. At selected sites and for subjects who have signed a photograph release informed consent form.
i. Using the skin pad as per investigator instructions.
j. To be completed once all subjects from the site have completed the study
k. Removal of any scales and crusts in the anatomical area by the investigator if deemed necessary

5.5 Clinical trial visit description and procedures

5.5.1 Visit 1 - Baseline visit

1. Explain the nature and the constraints of the clinical trial to the subject particularly the study treatment instructions.
2. Have the subject read, understand, date and sign an approved informed consent form (ICF). Give a dated and signed copy to the subject.
3. Perform a urine pregnancy test (UPT) for female subjects of childbearing potential.
4. If subject female of childbearing potential agrees to participate to the clinical trial, make sure she is using the requiring method(s) of contraception (see inclusion criteria 4.2.1). Make sure that the urine pregnancy test is done and the result is negative before subject inclusion in the trial
5. Check inclusion/exclusion criteria (see sections 4.2.1 and 4.2.2).
6. Log into the electronic case report form (eCRF) to get a Subject Identification Number.
7. Question the subject about demography, relevant medical history, prior and concomitant therapies.
8. Inform the subject about authorized and prohibited concomitant therapies. If the subject requires a medication washout period, the subject's baseline evaluation must be conducted after the washout period has been completed.
9. Select the subject's anatomical area on the face (e.g., forehead or cheek or chin) excluding nose, eyelids, lips and mucosa, or balding scalp to be treated according to inclusion criteria 2 (see 4.2.1)
10. Map the selected anatomical area on the transparent plastic sheet and mark and count the AK lesions
    a) Delimit clearly the anatomical area on a transparent plastic sheet using a permanent marker to ensure clinical assessments are always done on the exact same area (indicate some reference to "landscape markers" such as: eyebrows, nose, ears, joints, nevus, etc.) and draw the clinical margins of each AK lesion.

b) Circle and mark each AK lesion of the anatomical area on the transparent plastic sheet.

c) Record the total number of AK lesions presents in the anatomical area in the CRF.

d) If necessary, scales and crusts should be carefully removed on the treated areas of the face and/or balding scalp.

11. If the subject is eligible, dispense the study treatment (see specific section 6.1.2):

    a) Fill in a prescription form.

    b) Dispense to the subject the investigational product according to the prescription form

    c) Affix the tear-off portion of the label on the product dispensation log and report the required information on the labels if applicable.

    d) Provide appropriate verbal and written instructions on how to properly use the investigational product(s) and how to perform the treatment procedure (see instruction in section 6.1.4)

    e) Emphasize the importance of complying with the given instructions and treatment; instruct the subject to bring back the dispensed investigational product(s) at the next visit.

12. Dispense to the subject any associated non-investigational product(s).

13. Give and provide instruction to the subject how to use the provided Moisturizer in case some tolerability reactions occur (see 0).

14. Remind the Subject to avoid sun exposure of the treated anatomical area and the use of sunscreen for about 2 days following treatment procedures.

15. Assess the skin photodamage of the selected anatomical area using the Dover's modified global photodamage score (see 7.4.1).

16. Provide guidance on the satisfaction questionnaire (see appendix 1) and ask the subject to fill it out the day of treatment after the daylight exposure. Remind the subject to return it at the next study visit (Day 1 post-treatment).

17. *For selected sites only*, take photographs of the target anatomical area according to the provided procedure only if subject has agreed on the approved photo release consent form.

18. For all female subjects of childbearing potential, emphasize the guidelines about contraception and risks in case of pregnancy.

19. Instruct the subject to call you the day of treatment to confirm the treatment has been well completed and to schedule the next study visit (Day 1 post-treatment). **If you have not heard of subject one week after the baseline, contact him/her to get news and refer to section 4.4.**

At a minimum, tasks numbered 9, 10 and 15 have to be performed by a Dermatologist.

5.5.2 Visit 2 (day 1 after treatment ±2 days)

1. Question 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, including any potential skin reaction in the treated anatomical area?". Record all events (including Local Skin Reaction), as appropriate on the corresponding CRF pages.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the CRF.
3. Collect the first subject questionnaire and ensure it is fully completed including the SIN and the treatment date. Report the subject's questionnaire in the eCRF.
4. Assess subject's compliance with regard to the study treatment. Based on the subject's questionnaire and discussion with the subject. Check the study treatment has been performed according to the provided instructions. Report the results in the eCRF.
5. Ensure that the subject has returned all used/unused investigational product.
   a) Missing investigational product must be documented in the product dispensation log comments section and on other accountability form.
   b) For all female subjects, reiterate the guidelines about contraception and risks in case of pregnancy.
6. Schedule the next follow up visit, week 12 (±7 days).

In case of early termination of the Clinical Trial for whatever reason:

a) The subject will be fully evaluated.
b) The procedures designated for the week 12 visit should be performed.

5.5.3 Week 12 / Last clinical trial visit or Early trial termination visit

1. Question 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, including any potential skin reaction in the treated anatomical area?". Record all events (including Local Skin Reaction), as appropriate on the corresponding CRF pages.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the CRF.
3. Using the transparent sheet which was completed at Baseline, relocate the anatomical area defined at baseline and each treated AK lesion. Assess the lesion response for each treated AK mapped at Baseline (see Sections 7.2.1 and 7.2.1.2). Identify new lesions.

   Note: Any lesion in the anatomical area identified at Week 12 but not at Baseline is defined as a new lesion. Total number of new lesions should be recorded in the eCRF.

4. On each AK lesion that has completely responded, perform Investigator Clinical Assessment of the subject's Skin Aspect (see 7.2.2).
5. Assess the skin photodamage of the selected anatomical area using the Dover's modified global photodamage score (see 7.4.1).
6. Conduct a pregnancy test on any female of childbearing potential. In case of positive result, please refer to Section 8.3.
7. *For selected sites only*, take photographs of anatomical area according to the provided procedure only if subject has agreed on the approved Photo release consent form.
8. Ask the subject to fill out the subject week 12 questionnaire and collect it. Ensure it is fully completed and with SIN number. Report the week 12 questionnaire in the eCRF.
9. Complete CRF Exit form and discharge Subject from the study.
10. Physician questionnaire should be completed once all subjects from the site have completed the study

At a minimum, the tasks numbered 3, 4, 5, and 9 have to be performed by a Dermatologist.

5.6 Subject instructions

At baseline, subject will be requested to comply with the treatment procedure instructions. After having trained the subject, the investigator will provide him/her with the written study treatment instruction sheet including storage conditions.

Throughout the study, Subject will be requested to comply with the following:

1. To avoid the use of antalgics the day of treatment and the day before treatment until the subject self-assessment of pain is complete.
2. To avoid Sun exposure of treated anatomical area and use sunscreen during the 2 days following the treatment.
3. To apply a moisturizer in case signs of local skin irritation such as dryness or erythema are observed after the PDT procedure. The subject will be instructed that the use of a moisturizer should be considered only after the study treatment and when self-assessment of pain is performed.
4. To respect the visit timeframe.
5. In case the subject is using forbidden topical therapy listed in exclusion criterion (Section 4.2.2) or any other treatment on an area other than the anatomical area, the Investigator will remind him/her to pay a strict attention to not apply any of these therapies on the anatomical area.

Please refer to Section 4.2.1 and Section 4.2.2 for other items linked to eligibility criteria.

6 CLINICAL SUPPLIES

Investigational product and supplies will be provided by the sponsor and shipped by the clinical supply unit to each investigator site. The investigational product used during this clinical trial is marketed product.

6.1 Investigational product identification and use

6.1.1 Product identity

	Investigational Product
Trade Name	Luxerm®
Name of Active Ingredient	methyl aminolevulinate hydrochloride
Pharmaceutical Form	Cream
Dose or Concentration	160 mg/g
Formula number	0401
Total Daily dose	Thin layer on field area of either face or scalp
Mode and frequency of administration	Topical, single dose
Duration of administration	2 hours and 30 minutes
Location of treated area	Face or scalp
Manufacturer *(Name and address)*	Laboratoires Galderma Zone Industrielle de Montdésir 74540 ALBY SUR CHERAN
Packaging type and size (primary)	2g collapsible aluminium white tubes
Storage Conditions	Between 2 to 8 °Celsius

6.1.2 Method of treatment assignment

This study is an open study without randomization. Indeed there is no treatment assignment, the investigational product will be provided in bulk.

A tracking of the investigational products used will be done by recording the dispensation in the investigational product dispensation log.

6.1.3 Subject Identification Number (SIN)

Upon signature of the informed consent, a subject meeting all inclusion/exclusion criteria will be allocated a unique Subject Identification Number at baseline automatically generated by the eCRF.

During the whole clinical trial, the subject will only be identified using the SIN for all documentation and discussion.

6.1.4 Instructions for use and administration

At baseline visit the investigator or designee will give each subject verbal and written instructions on how to use the investigational and non-investigational products. It will be confirmed to treat the selected AKs anatomical area on the face excluding nose (e.g., forehead or cheek or chin), or balding scalp (excluding eyelids, lips and mucosa) with field therapy by providing the subject with the study treatment and by explaining in details the procedure.

Table 2: Procedures for Luxerm® DL-PDT treatment

Baseline Visit 1	Anatomical area and lesion mapping by the investigator using a transparent plastic sheet (after confirmation that all inclusion criteria and none of the exclusion criteria are met). Removal of any scales and crusts in the anatomical area by the investigator if deemed necessary.	
	Subject provided with oral and written instructions on the treatment procedure of the anatomical area (lesions and field). The patient should undergo treatment at home in the following week (± 7 days), with appropriate weather conditions, as follow:	
Treatment day*	t -15 min	The subject applies Actinica sunscreen on the selected anatomical area and all other sun exposed skin. The quantity of sunscreen will be sufficient to cover all areas exposed during the DL exposure step.
	t=0 min	After approximately 15 min once the sunscreen (Actinica sunscreen) has dried, the subject prepares the anatomical area to be treated with an abrasive pad to remove scales and crusts and roughen the surface of the lesions
		Then, the subject applies a thin layer of Luxerm® on the entire anatomical area using the provided finger glove and avoiding contact with eyes, lips and mucous membranes.
	t=30 min	The subject goes outdoors no later than 30mins of application of Luxerm® for 2 hours daylight exposure. On sunny days, should the subject feel uncomfortable in direct sunlight, shelter in the shade may be taken.
	t=2h30	The subject returns indoors and Luxerm® is removed by washing

* Subject will be advised to follow the instructions as close to the baseline visit (within 1 week ± 7 days) with appropriate weather condition to ensure the instructions are well followed.

As a general precaution, sun exposure of the treated anatomical area should be avoided for about 2 days following treatment. Subjects are advised to use a sunscreen in all exposed areas, including the treated area, during this period

At 1 week post-baseline the investigator will call the subject to check if the study treatment has been performed:

If the subject was not able to perform the study treatment during the week post-baseline due to bad weather conditions, another additional period of maximum 7 days is offered to perform the study treatment.

For an additional period greater than 7 days the decision to maintain the subject in the study will be based on discussion between PI and sponsor.

If the subject decides to stop his participation for whatever reason, he/she will be asked to return the study product to the site. Appropriate treatment will be decided at investigator discretion. The study product must not be reallocated to another subject and should be discarded from the study product stock. Investigator has the possibility to replace the subject.

6.2 Other supplies

Galderma will provide the sites with:

- The Urinary Pregnancy Tests (UPT) that may detect urinary Human Chorionic Gonadotropin concentrations equal to or greater than 25 international unit)
- Cetaphil moisturizer cream
- Actinica Sunscreen SPF 50+
- Nitril finger gloves for Luxerm® cream application
- An abrasive pad for skin preparation
- Cool bag for Luxerm® cream transportation

No specific labels will be used.

No accountability will be conducted on these products.

The provided sunscreen has been selected so as not to prevent the transmission of light wavelengths required for activation of PpIX and to offer an adequate sun protection for the 2-hour duration of the DL exposure. The provided sunscreen will be used only for the treatment preparation and will be applied if any sun exposure is expected following the treatment.

Cetaphil moisturizer cream will be used on the whole anatomical area at night for 8 days after treatment. It is provided in case of occurrence of phototoxicity reaction on the anatomical area treated (burning sensation, prickling or tingling skin, irritation such as dryness, redness, edema or crusts) after the daylight exposure or soon after, requiring the use of moisturizer. **Moisturizer application should not be done before the treatment procedure or before the Subject Self-assessment of Pain is completed.**

6.3 Investigational product packaging and labeling

Each Luxerm® tube will be supplied with single label. Label on secondary packaging (box) will comprise affixed and tear-off portions.
For treatment documentation, the affixed portion of the label will remain on the appropriate box. The tear-off portion of the label is to be removed at the time of dispensation and affixed to the product dispensation log.
The label (including tear-off part) will be printed in German and will contain information required by Good Manufacturing Practice (GMP) and local regulations and will be printed in local language.

6.4 Investigational product management

6.4.1 Accountability

Upon receipt of the clinical supplies at the site, the investigational product dispenser will conduct a complete inventory of all investigational products and assume responsibility for their storage, accountability and dispensation.

The Investigator or designee will sign the original Acknowledgement of receipt form upon receipt and inspection of the supplies, fax the signed copy to *GALDERMA R&D* and retain the receipt in the Investigator Site File (ISF).

All supplies sent to the investigator site will be accounted for and in no case used in any unauthorized situation.

At the end of the trial, all used and unused investigational product will be appropriately inventoried by the monitor and will be returned to *GALDERMA R&D* for further reconciliation, appropriate inventory and destruction.

6.4.2 Dispensing

All investigational products will be prescribed only to subjects enrolled into the clinical trial, at no cost and in accordance with the conditions specified in the protocol.

Dispensation will be appropriately documented on the product dispensation log by the investigational product dispenser at each visit.

Each subject will receive 1 tube of Luxerm® 2g at Baseline.

6.4.3 Investigational product compliance management and record

Each subject will be instructed by the investigator about the importance of being compliant with clinical trial treatment as well as the importance of returning their investigational product (used and/or not used) at day 1 post-treatment.

The investigational product will be collected and counted at day 1 post-treatment by the investigator or designee.

Subjects will also be questioned by the investigator regarding the skin preparation, application technique of investigational product, the daylight exposure conditions and the use of any other additional topical, systemic drug as well as OTC product.

A subject's questionnaire will be given to each subject in order to record the information on treatment procedure. The investigator will review the subject's questionnaire at visit 2.

The return of used/unused investigational product will be appropriately documented on the product dispensation log by the investigator or designee.

6.4.4 Storage of investigational product

The investigator has to agree to keep all investigational products in a safe, temperature controlled and secure area with restricted access, in accordance with applicable regulatory requirements (e.g., in the site pharmacy, if applicable).

Investigational products should be stored at appropriate storage conditions specified by *GALDERMA R&D* (see section 6.1.1).

The investigator will inform each subject about the storage conditions until treatment application.

6.4.5 Return of investigational product

The investigator will inform each subject about the importance of returning their investigational products (used and/or not used) at the visit 2.

In the event of early termination/suspension of the clinical trial for safety reasons, a rapid recall of the trial product(s) will be initiated. The investigator or designee must immediately instruct all subjects to not perform the clinical trial treatment procedure and return the investigational product to the clinical trial site.

As a general procedure, *GALDERMA R&D* will provide the investigator with a detailed list of units being recalled so that any of the units remaining on site can be put immediately into quarantine.

6.5 Blinding

The present study design is considered as an open study and subjects will receive commercially packaged study products.

7 STUDY ASSESSMENTS

Clinical evaluations should be performed by the same investigator throughout the clinical trial.

If it is not possible to use the same investigator to follow a subject, then evaluations should overlap for at least one visit in order to examine the subject together and discuss findings. This should be documented in medical source documents.

7.1 Subject Reported Outcomes (PRO):

The day of treatment after daylight exposure and at Week 12/Early termination, subjects will complete a questionnaire regarding the treatment procedure (skin preparation, study product application, weather condition daylight exposure, skin discomfort, efficacy, overall satisfaction, etc.) (Appendices 1 & 2).

7.2 Efficacy assessments

7.2.1 AK lesion assessment

7.2.1.1 AK lesions mapping and numbering at baseline

At baseline, the investigator will map the targeted anatomical area and mark each AK lesion within the anatomical area using a transparent plastic sheet. The total number of lesions will be reported in the eCRF.

7.2.1.2 Lesion's response at week 12

At last visit the investigator will use the transparent plastic sheet to locate the anatomical area defined at baseline and the treated AK lesions.

For each pre-existing AK treated lesion present at Baseline, the lesion response will be evaluated at week 12 as follow and reported in the eCRF:

Table 3 - Lesion response

Complete response (CR)	1	Complete disappearance of the lesion, visually and by palpation
Non-complete response (NCR)	0	Non-complete disappearance of the lesion

7.2.1.1 New AK lesions numbering at week 12

Any AK lesion in the anatomical area identified at Week 12 but not at Baseline is defined as a new lesion. The total number of new lesions will be recorded in the eCRF but not taken into account in the lesion response assessment.

At the last visit, lesions in non-complete response or newly appeared lesions will be treated at the discretion of the investigator (off study).

7.2.2 Clinical assessment of the subject's skin aspect

At last visit, for each lesion that has responded completely (see table 3) the investigator will assess the subject's skin aspect on the following signs or symptoms: scarring, atrophy, induration, redness or change in pigmentation. The clinical assessment of skin aspect will be graded for each lesion as follow:

Table 4 – Skin aspect assessment

Excellent	3	No scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared to adjacent skin
Good	2	No scarring, atrophy or induration but moderate redness or change in pigmentation compared to adjacent skin
Fair	1	Slight to moderate occurrence of scarring, atrophy or induration
Poor	0	Extensive occurrence of scarring, atrophy or induration

7.3 Safety assessments

A safety assessment will be conducted for all subjects at the baseline visit (after the ICF has been signed) and every subsequent visit. The safety parameters which are adverse events and subject's self-assessment of pain should be recorded as described in the section 7.3.1 and 7.3.2.

7.3.1 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial.

All AEs including local skin reactions are to be reported on an Adverse Event Form of the eCRF with complete information as required. If AEs occur, the main concern will be the safety of the subject. At the time of the ICF signature, each subject must be provided with the name and telephone number of clinical trial center personnel for reporting AEs and medical emergencies.

7.3.2 Subject's self-assessment of pain

After the treatment procedure when 2 hours daylight exposure is completed, the subject will be requested to assess the maximal pain felt during the duration of the light exposure. The pain sensation will be assessed on an 11-point Numeric Rating Scale (NRS), where 0 = no pain at all and 10 = extreme pain and will be reported by the subject in the first subject questionnaire.

Table 5 - NRS - subject's self-assessment of pain

0	1	2	3	4	5	6	7	8	9	10
❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
No pain at all										Extreme Pain

7.4 Other assessments

7.4.1 Photodamage assessment by Dovers Scale

At baseline visit and last visit, the investigator will assess the skin photodamage of the anatomical area using the following scale:

Table 6 - Dover's modified global photodamage score

0	Skin smooth to the touch without significant fine lines, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, or unevenness in pigmentation in any of the scalp/facial areas (cheeks, forehead, and the perioral area)
1	Scalp/facial skin (on the cheeks, forehead, or the perioral area) shows 1 area of significant roughness, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines
2	Scalp/facial skin (on the cheeks, forehead, or the perioral area) shows 2 areas of significant roughness, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, dyspigmentation, or fine lines; or shows roughness, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, dyspigmentation, and fine lines in 1 area
3	Scalp/facial skin (on the cheeks, forehead, or the perioral area) shows 3 areas with significant roughness, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, dyspigmentation, or fine lines; or shows roughness, coarse lines, erythema, telangiectasia, sebaceous hyperplasia, dyspigmentation, and fine lines in 2 areas
4	Scalp/facial skin shows any degrees of photodamage greater than level 3

7.4.2 Photographs (for selected sites)

At selected sites only, standardized digital photographs of the anatomical area will be taken at baseline and week 12 using a digital camera. Detailed procedures will be provided separately.

Only subjects who have signed a Photography Release Consent Form will be photographed at baseline and last visit.

7.4.3 Investigator questionnaire

The investigator will be asked to fill out a questionnaire (appendix 3) once all subjects from his site have completed the study.

7.5 Appropriateness of measurements

All measurements planned in this study are non-invasive.

PRO will be evaluated using a questionnaire after treatment and at the end of the study. Treatment compliance will be evaluated based on the recording of treatment information on the subject questionnaire. The questionnaire will collect specifically information on the treatment

procedure, the subject's opinion on the treatments and on the associated cosmetics products used in the trial.

Efficacy will be evaluated by assessing the lesion response which is a sensitive endpoint widely used in clinical practice to assess cure of AKs. At the Week 12 visit, the Investigator will identify all AK lesions (new or initial) on the anatomical area and will define, for each lesion pre-existing at Baseline, the lesion response as CR or non-CR (see 7.2.1.2). This will allow determining the number and percentage of cured lesions.

The safety of investigational product will be assessed through the reported AEs. To complete safety assessment, the Subject's pain assessment after treatment and Subject's skin aspect at Week 12 will also be measured.

The same investigator will evaluate the same subject at each visit throughout the clinical trial.

8 ADVERSE EVENT

8.1 Definitions

8.1.1 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 clinically significant increase in the intensity of an existing sign, symptom or disease since the first visit (including the disease being treated), should be considered as an adverse event. Lack of efficacy should not be 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.
- Pregnancy should not be considered as an adverse event but must be followed up as described in section 8.3
- For an AE of irritation, the "date of onset" should be the date that the first symptom occurred.

8.1.2 Serious Adverse Events (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires 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 as 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 which hypothetically might have caused death if it was more severe.
- Inpatient hospitalization is considered to have occurred if the subject has had to stay in hospital overnight. The criterion for the prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an hospitalization if it is solely for the purpose of diagnostic tests, (even if related to an AE), elective hospitalization for an intervention which 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).

8.1.3 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 (in this clinical trial: the summary of product characteristics for an approved product at the time of AE occurence).

8.1.4 Adverse event reporting period

The clinical trial period during which AEs must be reported is the period from when the subject signs 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.

8.1.5 Severity

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

The investigator will 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 sign or symptom, but easily tolerated
Moderate	Discomfort, enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

8.1.6 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 and/or clinical trial procedure. Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, positive dechallenge or rechallenge, relevant medical history, and confounding factors such as co-medication or co-concurrent diseases.

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

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all adverse events 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) and the AE,
- The clinical trial protocol procedure (e.g., skin preparation, skin pad, daylight exposure, such as moisturizers or sunscreen, 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 investigational product or the clinical trial protocol procedure and the AE.

8.2 Reporting procedures

8.2.1 Procedures for reporting adverse events

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

At each post-baseline visit, the investigator (or sub-investigator) will enquire about adverse events using an open question taking care not to influence the subject's answer (e.g., "Have you noticed any change in your health since the last visit?"). Direct 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 or not, will be recorded immediately in the source document, and described in the Adverse Event Form of the eCRF along with the date of onset, severity, relationship to the study drug, 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 will be monitored until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

Adverse events assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition. The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details. For SAEs (see section 8.2.2) and pregnancies (see section 8.3), the Sponsor is to be informed immediately by e-mail/fax. The event must be reported by fax or sent by e-mail to the Sponsor within 24 hours of receipt of the information (contact details in section 8.2.2).

8.2.2 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:

11. **Take prompt and appropriate medical action**, if necessary. The safety of subject is the first priority.
12. Ensure that the event is classified as an SAE. **Immediately (no later than 24 hours) inform *the Sponsor*** of the event by email/ fax/, and discuss further actions to be taken:

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Email	pharmacovigilance@galderma.com

13. Print and complete the Serious Adverse Event form (available in the EDC system as PDF document). Fax or send by email the completed form, accompanied any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours of receipt of this information to the sponsor (see contact details above). The demographics, medical history, drugs/therapies forms, and adverse event pages of the eCRF must be completed and available for review in the EDC system at the time of the report.

14. **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 sponsor (see contact details above) within 24 hours of receipt of the updated information. SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
15. 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.
16. **Inform the sponsor of the final outcome of the event**. Send a revised or updated SAE form and AE form, if appropriate.
17. 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, IRBs/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 IRB/IEC, if appropriate according to local requirements.

18. Comply with the applicable regulatory requirements related to the reporting of SAEs to your IRB/EC.

8.3 Procedure for suspected allergic contact reaction

This is a general procedure and further details can 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**, email/fax the Sponsor immediately, and report the event within 24 hours of receipt of the information as described in section 8.2.2.

In case of suspicion of allergic contact dermatitis

1. After all signs and symptoms have resolved and after a minimum of two weeks from last dose application, a re-challenge test with the assigned study product will be performed.
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 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 will 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 may be performed 96 to 120 hours later (i.e. 6 to 7 days after application of the patch) if the overall assessment so far 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 edema 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 sponsor 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.

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.

8.4 Procedures for reporting pregnancies

Any pregnancy occurring during clinical trials, where the foetus could have been exposed to the investigational product(s), must be followed-up until outcome in order to ensure the complete collection of safety data on *GALDERMA* product.

If a subject becomes pregnant, the Investigator is to do the following:

1. **Withdraw the subject from the clinical trial**
2. Complete all appropriate visit evaluations and CRF pages.
3. **Immediately (no later than 24 hours) contact the Sponsor** to inform them of the pregnancy occurrence and discuss further steps to be taken.
4. **Complete, as fully as possible, the pregnancy surveillance form – Part I:** History and start of pregnancy - provided by the CRA at the beginning of the clinical trial, as fully as possible. Fax or send by email this pregnancy form along with the Exit form within 24 hours of receipt of the information to the Sponsor.

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

6. **Inform the Sponsor of the progress by tri-monthly updates up** to the final outcome of the pregnancy. For all the additional follow-up evaluations, fax or send by e-mail the additional follow-up information to the sponsor within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.

   At outcome of pregnancy, complete as fully as possible the pregnancy surveillance form – Part II: Course and outcome of pregnancy, as full as possible. Inform the Sponsor by email/ fax, then fax or send by e-mail this pregnancy form to the Sponsor within 24 hours of receipt of the information.

7. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 8.2.2).

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical trial protocol below. The SAP will be finalized prior to database lock.

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

The purpose of this clinical trial is to evaluate the subject reported outcome with Luxerm® Daylight field procedure after one session. Also the efficacy and safety of Luxerm® in terms of subject complete response rate will be assessed.

9.1.1 Analysed Variables

The following variables will be analysed:

9.1.1.1 Efficacy variable

- Patient Reported Outcomes: subject questionnaire at treatment day after daylight session and at last visit (week 12 or early termination).
- Lesion complete response rate, defined as the percentage of preexisting and treated lesions in the anatomical area at baseline assessed as clear at week 12

- Subject complete response rate defined as the percentage of subjects with all treated lesions clear in the anatomical area at Week 12.
- Subject partially clear defined as the percentage of subjects with at least 75% lesion complete response in the anatomical area at week 12.
- Number of new AK lesions in the anatomical area.
- Subject's skin aspect at week12: mean score on anatomical area at week12.

9.1.1.2 Safety variables

- Subject's self-assessment of maximal pain after daylight exposure.
- Incidence and severity of adverse events.

9.1.1.3 Other variables

- Photodamage score with Dover's scale at baseline visit and week 12.
- Physician questionnaire at study end once all subjects in the study center have completed the study.

9.1.2 Populations analysed, evaluability and limitations / evaluation of Bias

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

9.1.2.1 The Intent-to-Treat efficacy population (ITT)

This population will consist of the entire population enrolled (i.e. treatment dispensed). The ITT population will be used for all variables except the safety variables.

9.1.2.2 The Safety population (All subject treated [APT])

This population will consist of the Intent-to-Treat population, after exclusion of subjects who never used the treatment with certainty based on monitoring report. The APT population will be only used for the safety variables (AEs).

9.1.2.3 Missing values

In order to evaluate the effect of major deviations or of data exclusions, lesion response endpoint will be analysed using a worst case approach, in which the lesions with missing lesion response assessment will be considered as having not responded.

9.1.3 Data presentation and graphics

All continuous data will be summarized using usual statistics: number of values, mean, median, standard deviation, minimum and maximum, and by frequency distribution (n, %) for qualitative data. For ordinal data, both frequency distribution and usual statistics will be presented. All tables will be presented by clinical trial treatment and by visit (when applicable).

Therapies that have been stopped before the baseline visit will be presented as prior therapies. Those reported at screening or starting between screening and baseline visits and still continuing after baseline will be classified as concomitant therapies.

The adverse events will be descriptively summarized (n, %) for the safety population (APT). The adverse events will be descriptively summarized (n, %) by relationship to clinical trial treatments within System Organ Class (SOC) and preferred term (MedDRA). Subjects will be descriptively summarized (n, %) by intensity (i.e. mild, moderate and severe) of adverse events, SOC and preferred terms. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events. A subject will be counted only once per System Organ Class (SOC) and only once per preferred term even if more than one occurrence of an event was reported within a SOC or preferred term. In the summary by categories of intensity, the adverse event with the highest intensity will be used. The subject will be counted only once per SOC (highest intensity whatever the AE within the SOC) and once per preferred term (highest intensity whatever the AE within the preferred term).

9.1.4 Statistical analyses

The objective of this trial is to evaluate the subject reported outcome with Luxerm® Daylight field procedure after one treatment session. Also the efficacy and safety of Luxerm® in terms of subject complete response rate will be assessed.

No inferential statistics will be performed. All variables will be descriptively summarized on ITT population and on APT population for the safety variables.

Any changes of the statistical analyses decided after the database lock will be justified and documented.

9.2 Sample size determination

9.2.1 Historical data and assumptions

As no inferential statistics will be performed and as this study is of exploratory nature, no statistical rationale of sample size can be used.

9.2.2 Sample size calculation

However, concerning the satisfaction survey, assuming an overall satisfaction around 85%, with total of 50 subjects included in the study, the precision is 10%, which is sufficient.

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for monitoring the clinical trial and the sponsor may perform co-monitoring visits at selected sites.

10.1 Personnel training

Clinical Research Associates (CRA) will be trained prior to clinical trial initiation. During this training, an overview of the disease of interest and treatment will be presented. Training on safety reporting sponsor procedures will be done. Specific monitoring guidelines and procedures to be followed during monitoring visits will be discussed.

Initiation visits will be conducted with all Principal Investigators and site teams. During these visits, an extensive review and discussion of the protocol, procedures and CRF will be conducted. Evaluation scales will also be reviewed.

A trial reference monitoring manual will be provided to each CRA as an additional reference tool.

An eCRF completion guideline will be provided to each CRA and site. These guidelines will contain instructions on how to fill-in the eCRF with some examples in order to standardize the eCRF completion as much as possible.

A trial reference manual will be provided to each site as an additional reference tool. These guidelines will contain key CRO and Sponsor contacts and phone numbers and specific instructions for site, including specific instruction detailing use of the study treatment, in order to standardize as much as possible the assessments performed during the clinical trial.
During the Investigator meeting this document will be discussed and reviewed thoroughly.

10.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by representatives of CRO/*GALDERMA R&D* to verify the adherence to the clinical trial protocol, ICH-GCP regulations, applicable SOPs, guidelines, and all local regulations.

The investigator will allow representatives of *GALDERMA R&D/CRO* to have direct access to all clinical trial records, eCRFs, corresponding subject medical records, investigational product dispensing records and investigational product storage area, site facilities and any other documents considered as source documentation.

The investigator also agrees to assist the *GALDERMA R&D/* CRO representatives, if required.

10.3 Data management

A CRO will be responsible for data management in connection with the sponsor's data manager.

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

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect and validate data. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data discrepancies are resolved.

After all data discrepancies are resolved, coding is approved, and subject evaluability has been determined, the data will be exported to SAS datasets and will be locked.

The locked SAS database will be used to generate subject listings, tabulations and analyses.

The data may be audited by the sponsor and/or CRO Quality Assurance department before or after the first statistical analysis results on the primary criteria.

10.4 Quality assurance / audit / inspection

The clinical trial will be conducted under the sponsorship of *GALDERMA R&D* in compliance with all appropriate local and local regulations as well as ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from *GALDERMA R&D* and/or the Contract Research Organization (CRO).

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

The investigator will allow and assist the CRO/Sponsor's representatives, IRBs/ECs 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 R&D* auditors, audit certificate(s) will be provided by Quality Assurance.

11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Institutional review board (IRB) or ethics committee (EC)

This clinical trial protocol will be reviewed and approved by IRBs/ECs prior to clinical trial initiation.

This protocol may be modified at any time for ethical, medical or scientific reasons. Such modifications will be documented by a clinical protocol amendment and, if deemed necessary, an amended protocol will be issued.

Before implementation, the amendment should be submitted and approved by applicable IRBs/ECs and, if required by the Regulatory Authority(ies).

No amendment will be required for modification(s) due to a change in logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers). In such a case, the appropriate institution(s) and/or person(s) will be directly notified of the changes.

11.2 Ethical conduct of the clinical trial

This clinical trial will be conducted in accordance with the ethical principles originating from the Declaration of HELSINKI declaration (1964) and subsequent amendments, the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and in compliance with local regulatory requirements.

11.3 Subject information sheet / informed consent

All subjects who participate in this trial will have to be fully informed about the clinical trial in accordance with the applicable regulations and GCP guidelines and in accordance with local legal requirements.

The informed consent form approved by an IRB/EC, will be fully explained to the subject during the baseline visit.

Prior to any clinical trial procedures, the subject will sign and date the informed consent form(s) which is written in the local language. A copy of the signed and dated form(s) will be given to the subject. The investigator is responsible for maintaining each subject's consent form(s) in the investigator's site file (ISF) and providing each subject with a copy of the consent form.

As photographs will be taken during the clinical trial, a specific photograph release consent form approved by an IRB/EC will be fully explained to the subject. Subjects willing to be photographed will sign and date the photograph release consent form before any to take any photograph.

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 required records on all clinical trial subjects.

Data for this clinical trial will be recorded in the subject's source documents and in the eCRF, the product dispensation logs, the subject questionnaires and the investigator questionnaire provided by *GALDERMA R&D*.

All data recorded in the documents described above should be recorded completely, promptly, and legibly using black ink.

The appropriate pages will be collected upon clinical trial completion or at any other time specified by CRO CRA/sponsor.

A complete set of copies will remain at the investigational site.

11.5.2 Source documentation

Investigators must keep accurate separate records of all subjects' visits, and all procedures done, being sure to include all pertinent clinical trial related information from which CRF data will be recorded.

A statement should be made on subject's medical notes indicating that the **subject has been enrolled in GALDERMA R&D protocol RD.03.SPR.114384 and has provided dated and signed informed consent.**

All adverse events with the associated concomitant therapies must be thoroughly documented. Results of any diagnostic tests conducted during the clinical trial will be included in the source documentation.

Subject questionnaires completed after the study treatment and at week 12 are considered as source documents and must be kept by the investigator with other study records.

Telephone conversations with the subjects and/or CRO/ *GALDERMA R&D* concerning the clinical trial may be recorded and kept on file.

11.5.3 Archives

All pertinent data, samples, photos, questionnaires, correspondence, original or amended protocol, all reports and all other material relating to the clinical trial will be maintained securely in *GALDERMA R&D* / Investigator/Institution archives for the legally-required duration of archiving.

If the investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the clinical trial records, custody must be transferred to a person who will accept the responsibility. The sponsor 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/*GALDERMA R&D* will be provided upon request.

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13 ATTACHMENTS

Appendix 1: Subject questionnaire – Treatment day after daylight exposure

This questionnaire aims to collect information on your feelings and opinions regarding the treatments for your actinic keratoses. There is no "right" or "wrong" answer. Your feedback will help us to better understand your needs and expectations, and they will not affect your future care.

Thank you for taking the time to complete this questionnaire.

Instructions:

- This questionnaire is to be completed immediately after the 2 hours of daylight exposure
- Use a black pen to complete the questionnaire and make sure your answer is legible;
- Tick one box only per question unless otherwise indicated; if you need to change your answer, draw a line through the previous answer and then record the new answer;
- Check for completeness of the questionnaire and give it back to the study doctor at the end of the procedure

1. Date of treatment: ____/____ / ____/____

2. Have you received detailed instructions by your doctor on how to use the study treatment?
   ❒ Yes ❒No

3. How convenient do you find the study treatment instructions?
   - ❒$_1$ Very convenient
   - ❒$_2$ Convenient
   - ❒$_3$ Inconvenient
   - ❒$_4$ Highly inconvenient

4. Was Actinica applied to protect from sunburn during daylight exposure? ❒ Yes ❒No

   ↳Time of sunscreen application *(hr/hr : min/min- use 24 hour clock):* ____/____ **:** ____/____

5. Did you use the provided abrasive skin pad to prepare your skin? ❒ Yes ❒ No

6. Which anatomical area identified by your doctor did you prepare *(check one)?*
   a. ❒Scalp
   b. ❒ Forehead
   c. ❒ Right cheek
   d. ❒ Left cheek
   e. ❒ Chin

7. Were the scales and crusts removed on the whole anatomical area? ❒ Yes ❒ No

8. Did you roughen the surface of the anatomical area with the skin pad? ❒Yes ❒ No

9. Time of Luxerm® application (hr/hr : min/min- use 24 hour clock): ____/____ : ____/____

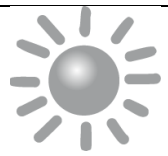
10. At what time did you go outside for 2 hours of daylight exposure (hr/hr : min/min- use 24-hour clock): ___/___:___/___

11. At what time did you complete the 2 hours of daylight exposure (hr/hr : min/min- use 24 hour clock): ___/___:___/___

12. Did you spend time in the shade during the time you had to stay outdoors? ❒ Yes ❒ No

    ↳If yes, how much time? _____ min

13. Please indicate below how was the overall weather during the daylight exposure?

			
□1	□2	□3	□4

14. What was the overall temperature during the daylight exposure? ❒1 10-15°C
    ❒2 15-20°C
    ❒3 20-25°C
    ❒4 25-30°C
    ❒5 >30°C

15. Was the Luxerm® cream removed after the 2 hours daylight exposure? ❒Yes ❒No

16. What was the maximal pain you felt during the duration of the daylight exposure? report below

To be completed after the end of the 2 hours Daylight exposure												
No pain at all	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8	□ 9	□ 10	Extreme pain

17. How bothered were you by this pain?

    ❒1 Not bothered at all
    ❒2 Bothered somewhat
    ❒3 Bothered a little
    ❒4 Bothered
    ❒5 Bothered a great deal

18. How convenient do you find Luxerm® daylight illumination (staying outside)?

- ❒1 Very convenient
- ❒2 Convenient
- ❒3 Inconvenient
- ❒4 Highly inconvenient

19. Globally, how satisfied are you with Luxerm® daylight procedure?

- ❒1 Very satisfied
- ❒2 Satisfied
- ❒3 Somewhat satisfied
- ❒4 Not satisfied

20. If you are dissatisfied with Luxerm® daylight procedure, what are the reasons (more than one answer may be chosen)?

- ❒1 Treatment not effective
- ❒1 Side effects of the treatment.
- ❒1 Treatment not easy/convenient to use
- ❒1 Other. Please specify:_____

Appendix 2: Subject questionnaire–Week 12 / early termination

This questionnaire aims to collect information on your feelings and opinions regarding the treatments for your actinic keratosis performed 3 months ago. There is no "right" or "wrong" answer. Your feedback will help us to better understand your needs and expectations, and they will not affect your future care.

Thank you for taking the time to complete this questionnaire.

Instructions:

- This questionnaire is to be completed 3 months after the treatment of Actinic Keratosis you have received.
- Use a black pen to complete the questionnaire and make sure your answer is legible;
- Tick one box only per question unless otherwise indicated; If you need to change your answer, draw a line through the previous answer and then record the new answer;
- Check for completeness of the questionnaire

1. How satisfied are you with the effectiveness of this treatment to clear AKs?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied
   - ❒4 Not satisfied

2. How much have you been bothered by any side effects of this treatment (skin reactions)
   - ❒1 Not bothered at all
   - ❒2 Bothered somewhat
   - ❒3 Bothered a little
   - ❒4 Bothered
   - ❒5 Bothered a great deal

3. How satisfied are you with the skin aspect of the treated area?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied
   - ❒4 Not satisfied

4. How long after treatment was the duration of social embarrassment due to skin reactions?
   ------- (days)

5. What was the last treatment you received prior to your treatment with Luxerm® and daylight illumination?

   - ❒1 None
   - ❒2 Cryotherapy
   - ❒3 Efudix, efurix (5% cream)
   - ❒4 Aldara, Almiq, Aldiq, Soldara, APO-imiquimod, Terry White Chemist Imiquimod, Chemmart Imiquimod, Imiquad, Apotex-imiquimod, Imiquad, Ixium
   - ❒5 Solaraze

❒$_6$ Picato
❒$_7$ Photodynamic Therapy with a red lamp or a blue lamp (PDT)
❒$_8$ Photodynamic Therapy with daylight
❒$_9$ Peelings
❒$_{10}$ Laser

6. How did you find Luxerm® with daylight exposure compared to your last treatment ticked in question 5 (except if it was option 8 "PDT with Daylight")?
   ❒$_1$ Better
   ❒2 Similar
   ❒3 Worse
   ❒4 Never treated with previous treatment

7. Would you consider using Luxerm® with daylight illumination again if needed in future?
   ❒$_0$ No
   ❒$_1$ Yes

8. Overall, how satisfied are you with this treatment (regarding the procedure, effectiveness, side effects, skin aspect)?
   ❒$_1$ Very satisfied
   ❒$_2$ Satisfied
   ❒$_3$ Somewhat satisfied
   ❒$_4$ Not satisfied

9. If you are dissatisfied with Luxerm® daylight procedure, what are the reasons (more than one answer may be chosen)?
   ❒$_1$ Treatment not effective
   ❒$_1$ Side effects of the treatment
   ❒$_1$ Luxerm® daylight procedure not easy/convenient to use
   ❒$_1$ Skin aspect of the treated area
   ❒$_1$ Other. Please specify:_____

Appendix 3: physician satisfaction questionnaire when all subjects have completed the study

1. Overall, are you satisfied with Luxerm® DL-PDT?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied *(please specify in the comments section below)*
   - ❒4 Not satisfied *(please specify the reason in question 2)*

2. If you are dissatisfied with Luxerm® daylight procedure, what are the reasons (more than one answer may be chosen)?
   - ❒1 Treatment not effective
   - ❒1 Side effects of the treatment
   - ❒1 Luxerm® daylight procedure not easy/convenient to use
   - ❒1 Skin aspect of the treated area
   - ❒1 Other. Please specify:_____

3. How satisfied are you with the effectiveness of Luxerm® DL-PDT on clearing AKs?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied *(please specify in the comments section below)*
   - ❒4 Not satisfied *(please specify in the comments section below)*

4. How satisfied are you with the tolerability of Luxerm® DL-PDT?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied *(please specify in the comments section below)*
   - ❒4 Not satisfied *(please specify in the comments section below)*

5. How satisfied are you with the cosmetic aspect of the treated area?
   - ❒1 Very satisfied
   - ❒2 Satisfied
   - ❒3 Somewhat satisfied *(please specify in the comments section below)*
   - ❒4 Not satisfied *(please specify in the comments section below)*

6. Did you think the instructions provided to the patients were adequate to perform the treatment at home with Luxerm® DL-PDT?
   - ❒1 Yes
   - ❒0 No
     - ⇨ If no, please specify _____

7. Would you consider using Luxerm® again for future patients?
   - ❒1 Yes
   - ❒0 No
     - ⇨ If no, please check all the reasons that apply
       - ❒ Issues on safety
       - ❒ Issues on effectiveness
       - ❒ Issues on treatment price

❒ Other, please specify:_____

Additional Comments (please write legibly):