CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Assess the Efficacy and Safety of Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) versus vehicle cream in the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratosis of the face and scalp when using daylight photodynamic therapy (DL-PDT)

Protocol Number:	RD.06.SPR.112199
EudraCT Number:	Not Applicable
Syneos Health Study Number:	7004981
Investigational Product:	Methyl aminolevulinate hydrochloride 16.8% cream (CD06809-41)
IND Number:	132978
Phase:	3
Sponsor:	Galderma Research &Development, LLC 14501 North Freeway Fort Worth, TX 76177
Contract Research Organization:	Syneos Health 1030 Sync Street Morrisville, NC 27560 United States
Protocol Date:	12JUL2020
Protocol Version:	Version 3.0 FINAL

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A randomized, double-blind, vehicle-controlled, multicenter study evaluating the efficacy and safety of Methyl aminolevulinate hydrochloride (MAL) 16.8% (CD06809-41) cream versus vehicle cream in the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratosis of the face and scalp when using daylight photodynamic therapy (DL-PDT)

Protocol Number: RD.06.SPR.112199

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

PPD
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3 SYNOPSIS

Protocol Number: RD.06.SPR.112199

Title:

A Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Assess the Efficacy and Safety of Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) versus vehicle cream in the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratosis of the face and scalp when using daylight photodynamic therapy (DL-PDT)

Investigational Product: Methyl aminolevinulate cream 16.8% (CD06809-41)

IND Number: 132978

Study Centers: Approximately 60 study centers are planned in the United States

Phase: 3

Objectives:

Primary objective: The primary objective is to evaluate the safety and efficacy of MAL DL-PDT in adult subjects with mild to moderate actinic keratoses on the face and scalp over a 14-week period, and to show superiority in efficacy of MAL cream over vehicle cream at 12 weeks after the last DL-PDT session (Visit 6)

Secondary objectives:

- Compare the lesion response between MAL DL-PDT and vehicle DL-PDT
- Compare partial clearance of actinic keratoses (AKs) between MAL DL-PDT and vehicle DL-PDT :
- Compare subject assessment of pain (by NRS) between MAL DL-PDT and vehicle DL-PDT
- Assess safety, including adverse events
- Document the estimated PpIX effective dose for each subject DL-PDT exposure through satellite image data

Study Design:

This is a randomized, double-blind, vehicle-controlled, multicenter, parallel-group study in adult subjects with clinically-confirmed mild to moderate AKs on the face and the balding scalp, to be conducted at approximately 60 clinical sites in the United States. Sites will be selected to ensure that diverse daylight conditions will be represented in the study to understand the effects of latitude, elevation, and climate.

After a screening visit, approximately 570 subjects will be randomized in a 2:1 ratio to receive 2 treatments of daylight photodynamic therapy (DL-PDT) with either MAL cream 16.8% (CD06809-41) or a vehicle cream. The 2 treatments will occur at least 2 weeks up to 4 weeks apart, Visit 2 (first DL-PDT) and Visit 4 (second DL-PDT). Other study visits will occur 1 week after each of the PDT treatments (Visits 3 and 5) for safety assessments and 12 weeks after the last PDT treatment (Visit 6) for efficacy and safety assessments.

A subject will be considered to have a CR if all AK lesions treated with the study drug and then illuminated by daylight PDT are clear at Visit 6 (Final Visit).

Those subjects who have a CR at Visit 6 will be followed in the long-term follow-up study for recurrence of the treated AKs.

Number of Subjects:

Approximately 570 subjects will be randomized to receive 2 treatments of daylight photodynamic therapy (DL-PDT) with either MAL cream 16.8% (CD06809-41) (380 subjects) or a vehicle cream (190 subjects).

Treatment:

Methyl aminolevinulate hydrochloride 16.8% cream (CD06809-41) or vehicle cream will be provided in 2 g aluminum tubes. The tubes will be identical to ensure that the site and the subject are masked to the subject's treatment.

Eligible subjects will be randomized to receive treatment with daylight photodynamic therapy (DL-PDT) with either MAL 16.8% or vehicle cream.

- Prior to randomization/initiating treatment, the investigator must assess local weather conditions to determine if the subject will be able to remain outdoors comfortably for 2 hours, and confirm it is not raining and estimate it will not rain for the next 3 hours. If the subject is not able to go outdoors, the treatment is to be postponed for no more than two weeks.
- Actinic keratoses in the treatment 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 and scalp being treated in order to mark the location and severity of AKs. Other anatomical landmarks will also be marked on this sheet. The sheet "map" used at Visit 2 will be used as the reference to the ones created at Visits 4 and 6, to evaluate efficacy.
- A sunscreen with chemical filters of at least SPF 30 will be applied to the entire treatment area of the face and the balding scalp and to all other sun-exposed areas approximately 15 minutes before lesion preparation, to prevent further UVA and UVB exposure while outdoors.
- Scales and crusts should be carefully removed from lesions of the face and balding scalp to be treated with a sharp curette. The curette should be used gently, in order to not induce bleeding. The extent of the preparation will depend on the thickness of the lesion.
- MAL cream or vehicle cream will be applied as a thin layer to each lesion and the surrounding 5 to 10 mm of normal skin.
- Thirty minutes after application of study medication, subjects will be instructed to go outside for 2 hours and avoid coming indoors.
- On sunny days, should the subject feel uncomfortable in direct sunlight, shelter in the shade may be taken until the subject feels comfortable to return to be in direct sunlight. After 2 hours, subjects will return inside and site staff will remove the study cream.with gentle cleanser. Subjects will be instructed to avoid sun exposure and to use sunscreen for the next 48 hours.
- There will be 2 treatment sessions at least 2 weeks up to 4 weeks apart
- During illumination, the subject will be geolocalized and satellite data corresponding to the time and place of the subject will be used to calculate the PpIX effective dose
- If significant precipitation begins during the 2-hour daylight exposure, the subject will be instructed to goinside and the study cream will be removed. The treatment will be considered incomplete and will be repeated after a minimum of 2 weeks. There will be only one repeat allowed for an incomplete treatment. If this attempt should be imcomplete also, the subject will continue in the study for all assessments and be considered a major protocol violation.

Study Duration:

The expected duration for each subject's participation in the study will be approximately 14 weeks. With potential visit rescheduling due to weather issues and incomplete visits, the duration of a subject's participation could take up to 20 weeks.

The planned duration of recruitment is approximately 9 months.

The planned duration of the clinical study is approximately 12 to 15 months.

Study Population:

Inclusion Criteria: To be eligible for study entry, subjects must satisfy all of the following inclusion criteria:

1. Subjects aged ≥ 18 years at the Screening visit
2. Subjects have at least 4, but no more than 12, clinically-confirmed thin or moderately thick (Grade I and II in the Olsen scale, respectively), non-hyperkeratotic, non-pigmented AKs located on the face, excluding eyelids, lips and mucosa (e.g., forehead, cheek, chin), and balding scalp
3. A: Female subjects of non-childbearing potential: postmenopausal (absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason), hysterectomy or bilateral oophorectomy.

   B: Female subjects of child-bearing potential: negative urine pregnancy tests at Screening and Baseline visits. Female subjects of childbearing potential must agree either to be strictly abstinent for for one completed menstrual cycle after the last DL-PDT session, or to use an effective and approved method of contraception for one completed menstrual cycle after the last DL-PDT session. Effective and approved methods of contraception applicable for the subject and/or his/her partner include:

   - Progestogen-only oral hormonal contraception
   - Cap, diaphragm, or sponge with spermicide
   - Combination of male or female condom with cap, diaphragm, or sponge with spermicide
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
   - Injectable or implanted hormonal contraception
   - Intrauterine devices
   - Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
   - Vasectomy at least 3 months before the study
4. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol
5. Fully understands and signs an informed consent form before any investigational procedure(s) are performed

Exclusion Criteria: Subjects will be excluded from the study if 1 or more of the following exclusion criteria are applicable:

1. Subjects with clinical diagnosis of at least one severe (very thick actinic keratosis) AK in treatment areas
2. Subjects with pigmented AK in the treatment areas
3. Subjects with a clinical diagnosis of a skin disease other than AK (including non-melanoma skin cancer) in the target area(s), if these diagnoses interfere with the investigative treatment or interpretation of the clinical results
4. Immunocompromised subjects such as organ transplant reccipients or HIV+ persons
5. Subjects with porphyria
6. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to the Investigator's judgment) if he/she participates in the clinical study
7. Female subjects who are pregnant, nursing, or planning a pregnancy during the study
8. Subjects with known or suspected hypersensitivity to the active substance or to any excipients of MAL cream 16.8% or any prior exposure to MAL cream
9. Subjects having received any of the treatments in Table 1 within the specified timeframe before the Baseline visit:

Table 1: Prior treatments (Synopsis)

Treatment(s)	***Timeframe****
Topical: 5-fluorouracil, diclofenac, imiquimod, retinoids, alpha-hydroxy acid, salicylic acid ointment, ingenol mebutate	12 weeks
Surgical: elliptical excision, excision and reconstructive surgery, Mohs' micrographic surgery, chemical peels/chemosurgery, cryosurgery, dermabrasion	12 weeks
Photodynamic therapy	12 weeks
Radiotherapy of the skin	12 weeks
Investigative therapies for actinic keratosis	12 weeks
Systemic retinoids	12 weeks
Immunosuppressive agents such as glucocorticoids, cytostatic agents, antibodies, drugs acting on immunophilins, interferon, TNF binding proteins, mycophenolate mofetil, or biologics	12 weeks

*minimum washout period prior to Baseline

10. Planned or expected major surgical procedure during the clinical study
11. Currently participating or participated in any other study of a drug or device, within the past 12 weeks before the screening visit, or is in an exclusion period (if verifiable) from a previous study
12. Subjects with any condition that may be associated with a risk of poor protocol compliance
13. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limted to elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN), at the screening or baseline visit that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (e.g., poor venous access or needle-phobia)
14. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.7)

Primary Endpoint:

- The primary efficacy endpoint is the subject complete response, defined as the proportion of subjects with complete clearance of all AK lesions treated, at 12 weeks after the last DL-PDT (Visit 6), comparing MAL cream with vehicle cream

Secondary Endpoints:

- Lesion complete response, defined as the percent reduction from baseline in the number of cleared treated lesions, at 12 weeks after the last DL-PDT treatment (Visit 6), comparing MAL cream with vehicle cream
- Subject partial response, defined as the proportion of subjects with 75% or greater reduction from baseline in the number of cleared treated lesions, at 12 weeks after the last DL-PDT treatment (Visit 6), comparing MAL cream with vehicle cream

Safety Assessments:

The following safety assessments are planned according to the schedule of assessments (see Section 8.1.2):

- Subject's assessment of pain after each DL-PDT treatment (Visits 2 and 4), comparing MAL cream with vehicle cream
- Safety Visit Question

- Adverse events (AEs), treatment-emergent AEs (TEAEs), and serious AEs (SAEs)
- Physical examination and vital signs
- Clinical laboratory tests
- Electrocardiogram

Other Assessments:

- Subject satisfaction questionnaires at Visit 4 (2nd DL-PDT) and at Visit 6 (Final Visit)
- The Clinical Assessment of the Subject's Skin Aspect at Visit 6 (Final Visit)
- Weather conditions
  - The Investigator is to assess weather conditions at the time of randomization/commencing treatment and consult local weather forecasts to determine the likelihood of rain in the next 3 hours, and the temperature should be be suitable for the subject to stay comfortably outdoors for 2 hours. If the weather is rainy, or is likely to become so, the treatment should be postponed.
- Document the calculated PpIX effective dose using geolocalized weather satellite data during 2-hour daylight illumination

Clinical Photographs:

- Optional standardized clinical photographs of AK lesions will be captured for subjects who consent at selected sites, according to the schedule of assessments in Section 8.1.2 and the photographic manual.

Statistical Analysis:

Principal Statistical Method

Populations: The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population is defined as all randomized subjects to whom study drug has been applied at least once; and the per protocol (PP) population is defined as all ITT subjects without major protocol violations that would have a significant effect on the efficacy of the study treatment. The ITT population will be used for the analyses of efficacy endpoints; and the safety population (SAF) will be used for the analyses of safety data. The PP population will be used for the sensitivity analyses of the primary endpoint.

Analysis centers: Original or pooled clinical centers that will be used as stratification factor in the statistical analysis.

Primary Endpoint:

The proportion of subjects with complete clearance of all AK lesions treated at 12 weeks after the last DL-PDT (Visit 6) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The p-value for the treatment comparison (MAL DL-PDT vs. vehicle DL-PDT) will be calculated from the general association statistic of the stratified CMH test. Difference in proportions between treatment groups and the 99.875% confidence interval of the difference will be based on the large sample approximation method for binary data. Efficacy will be claimed if the between treatment difference on the primary endpoint is significant with a p-value < 0.00125. This result will provide an acceptable level of evidence of efficacy, in presence of good internal consistency across primary and secondary endpoints in the absence of a second pivotal study.

For the primary analysis all subjects in the ITT population with missing data for the primary endpoint will be classified as non-responders regardless of treatment allocation.

To assess the robustness of the primary efficacy results, sensitivity analyses will be conducted on the ITT population using different methods for replacing missing data and by performing a tipping-point analysis in order to explore the plausibility of missing data assumptions under which the conclusions change (i.e. under which there is no longer evidence of efficacy) and the primary efficacy analysis will be repeated on the PP population.

Secondary Endpoints:

The percent reduction from baseline in the number of cleared treated lesions at 12 weeks after the last DL-PDT treatment (Visit 6) will be analyzed using an ANCOVA with treatment, analysis center and baseline AKs count as fixed effects; the difference in percent reduction between MAL DL-PDT and vehicle DL-PDT, the 99.875% confidence interval of the difference and the p-value will be generated from the ANCOVA model.

For analysis of percent reduction from baseline in the number of treated AK lesions, missing counts of cleared treated lesions for subjects on the ITT population will be imputed using MI (Multiple Imputation) under the Missing At Random (MAR) assumption.

The proportion of subjects with 75% or greater reduction from baseline in the number of cleared treated lesions at 12 weeks after the last DL-PDT treatment (Visit 6) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The p-value for the treatment comparison (MAL DL-PDT vs. vehicle DL-PDT) will be calculated from the general association statistic of the stratified CMH test. Difference in proportions between treatment groups and the 99.875% confidence interval of the difference will be based on the large sample approximation method for binary data.

For the analysis of proportion of subjects achieving a partial response, all subjects of the ITT population with missing data will be classified as non-responders regardless of treatment allocation.

In order to maintain the overall type I error rate at 0.00125, a predefined hierarchal testing procedure will be implemented to test the MAL cream against vehicle.

Testing will start from primary endpoint and descend in the order described as below until the null hypothesis fails to be rejected at 0.00125 level of significance.

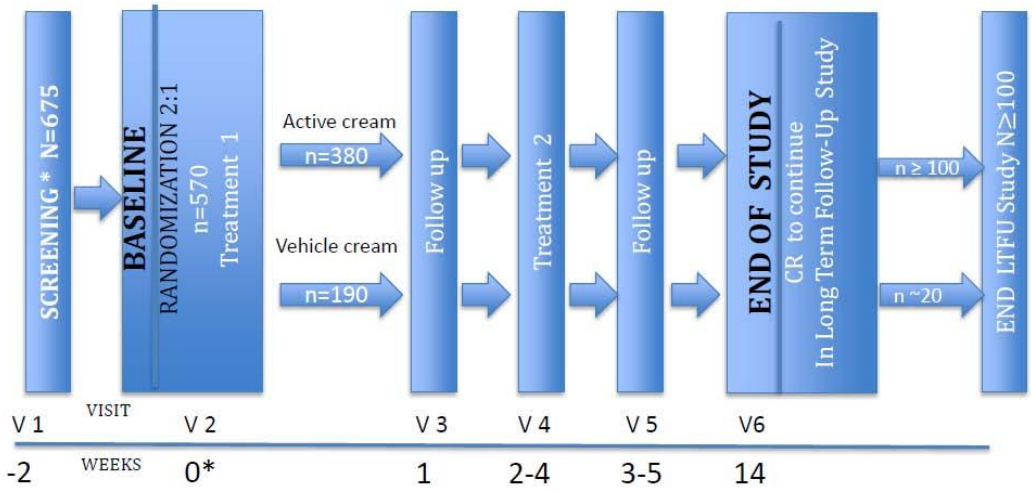
1) Lesion complete response at 12 weeks after the last DL-PDT treatment (Week 14), defined as the percent reduction from Baseline in the number of treated lesions, comparing MAL cream with vehicle cream.

2) Partial clearance of AKs, defined as the proportion of subjects with 75% or greater reduction from Baseline in the number of treated AK lesions, at 12 weeks after the last DL-PDT treatment (Week 14) comparing MAL cream with vehicle cream.

Sample Size

Subjects who achieve a CR at Visit 6, 12 weeks after the last DL-PDT, will be offered the opportunity to continue in the long-term follow-up study. The sample size calculation is based on providing enough subjects to enable the detection of a treatment difference in the primary endpoint and ensuring approximately 100 subjects complete the long-term follow-up study. Approximately 675 subjects will be screened for a total of 570 subjects to be randomized (380 in the MAL DL-PDT arm and 190 in the vehicle DL-PDT arm, using a 2:1 randomization ratio) in order for enough subjects who had CR at Visit 6 to complete a long-term follow-up with 100 subjects at one year. This study will have more than 90% power to detect a 30% difference between MAL DL-PDT (45% CR rate) and vehicle DL-PDT (15% CR rate) and with a type I error of 0.00125 assuming 7% subjects will be non-evaluable at 12 weeks after the last PDT for the primary endpoint, 70% of subjects achieving a complete response at 12 weeks after the last DL-PDT will be enrolled in the LT follow-up study, and a dropout rate of 10% during the long-term follow-up study.

Figure 1: Study Schema (Synopsis)



*At Visit 6 (Week 14 or Final Visit), 12 weeks after the last DL-PDT treatment those subjects who achieve Complete Response (CR) of treated lesions will be offered the opportunity to continue in the long-term follow-up study to evaluate recurrence of the treated lesions

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5 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Evemt of Special Interest
AK	Actinic keratosis
ALA	5-aminolevulinic acid
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the curve from 0 to 24 hours
BCC	Basal cell carcinoma
BL	Baseline
CI	Confidence interval
C_{max}	Observed peak drug concentration
CR	Complete response
CRO	Contract research organization
CS	Clinically significant
c-PDT	Conventional PDT
DL	Daylight
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ET	Early termination
FDA	Food and Drug Administration
FST	Fitzpatrick Skin Type
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
LOCF	Last observation carried forward
LTFU	Long-term follow-up
MAL	Methyl aminolevinulate hydrochloride
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
mL	millilitre
MNAR	Missing not at Random
MRHD	Maximum Recommended Human Dose

MUsT	Maximal Use Trial
NCS	Not clinically significant
NDA	New drug application
ng	nanogram
nM	nanomolar
NOAEL	No observed adverse event limit
NRS	Numeric rating scale
OC	Observed case
PDT	Photodynamic Therapy
PK	Pharmacokinetics
PpIX	Protoporphyrin IX
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Squamous cell carninoma
SIN	Subject identification number
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TA	Treatment area
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States
UV	Ultraviolet

6 INTRODUCTION

6.1 Background & Rationale

Actinic keratosis (AK) is a common epithelial non-infiltrative lesion caused by prolonged exposure to ultraviolet (UV) radiation, which damages cell cycle regulators and leads to the proliferation of epidermal keratinocytes. Actinic keratoses are premalignant skin lesions that are characteristically distributed on sun-exposed areas such as face, bald scalp, neck, chest, back of the hands, and forearms. Individuals often present with multiple actinic keratosis.

Actinic keratosis is a global condition and it is the second most frequent diagnosis made by dermatologists in the US (Uhlenhake 2013) with prevalence between 11% and 26% (Salasche 2000). Actinic keratoses themselves are deemed not serious, but they are very common, highly widespread, and recurrent. Actinic keratosis is considered the earliest, clinically recognizable manifestation of squamous cell carcinoma (SCC) that is capable of transforming into SCC (*in situ* and invasive) (Feldman 2011 p201). Between 60-80% of SCC cases begin as AK (Feldman 2011). The rate of progression of AK to invasive SCC has been estimated to be from less than 0.025% to 16% per year (Werner 2013). However, there is no reliable way to measure this rate and predict which lesions will transform, meaning that it is necessary to treat AK lesions to avoid progression.

The etiology of AK is multifactorial, and risk factors include increased age, male gender, a fair skin Fitzpatrick skin type, and extensive outdoor activities (Goldberg 2010). Moreover, AK is an indicator of chronic ultraviolet (UV) damage and thus, of increased risk for UV-related skin cancer. A review of epidemiological studies showed that the prevalence and incidence of AK are highly variable according to the population studied, world location, age, and gender (Frost 1994). For example, prevalence rates near 60% have been reported in Australia, and even up to 64% in women and 83% in men aged 60 to 69 years (Frost 1998; Frost 2000), in contrast to the prevalence rate reported in England in 2000 of 15.4% in men and 5.9% in women older than 40 years (Memon 2000). These rates increased to 34.1% and 18.2%, respectively, at 70 years of age, when prevalence was most strongly related to 2 objective signs of sun exposure, solar elastosis and lentigines. The South Wales Skin Cancer Study reported an AK prevalence of 23% (Harvey 1996). Studies in the United States have reported prevalence rates of 55% in individuals aged 65 to 75 years with high sun exposure, but only 12% to 19% in those with low sun exposure (Engel 1988).

Various treatment options are available for AK lesions, including destructive therapies such as cryosurgery or excisional surgery, topical therapies such as 5-fluorouracil, imiquimod, diclofenac, ingenol mebutate, and non-approved topical or oral retinoids (Gold 2006; Fenske 2010). However, patient satisfaction with many of these treatments, especially the destructive therapies, can be affected by considerable treatment discomfort and residual scarring. Photodynamic therapy (PDT) is a highly efficacious therapy recommended as a

first-line treatment for individual, or multiple and/or confluent AK lesions (de Berker 2007; Braathen 2007). Photodynamic therapy has been associated with a better cosmetic outcome than other treatments, and it can also be used to treat multiple AK lesions over large areas (Lehmann 2007; Sidoroff 2010).

Metvixia® cream 168 mg/g (methyl aminolevulinate) was approved in the USA in 2008 (NDA 021415) in combination with LED red light illumination using the Aktilite® CL128 lamp for the treatment of thin and moderately thick, non-hyperkeratotic, and non-pigmented AK of the face and scalp (it was initially approved in 2004 with the Curelight lamp), and was marketed for more than 4 years until it was withdrawn in the United States in 2012 for commercial reasons. The product, used in combination with red light illumination, is also named Metvix or Metvixia in other countries worldwide.

Galderma has developed a new treatment regimen for the face and scalp, in which natural daylight (DL) may replace the previously-approved red light as the means of activating the PpIX formed after application of the cream during PDT.

Given that the area to be treated is no longer limited by the size or configuration of the lamp, the DL-PDT procedure is simplified compared to conventional PDT (c-PDT). In addition, significantly less pain is experienced during illumination as shown in 2 randomized, Phase 3 clinical studies recently conducted by Galderma. These studies, performed in Australia (N=100) and Europe (N=108), confirmed that methyl aminolevulinate hydrochloride (MAL) DL-PDT has similar efficacy as MAL with c-PDT, leads to fewer related adverse events, is nearly painless, and more convenient for subjects (Rubel 2014, Lacour 2015). It is known that the use of the red lamp results in discomfort and pain for subjects, as all produced PpIX is photobleached in a short period of time. With 2 hours of DL exposure, PpIX will be continuously produced at a very low level and immediately photobleached with no or almost no pain.

The use of DL-PDT, as opposed to the use of blue or red light sources c-PDT, has many benefits. In particular, the use of DL will treat whole fields of cancerization to target visible and subclinical AK lesions, and is not limited to clinically apparent lesions. In 2015, an European consensus on DL-PDT (Morton 2015 p1) recommended DL-PDT as a first-line treatment option for immunocompetent patients with Grade I (thin) or II (moderately thick) AKs or fields of actinic damage on the face and scalp, due to its efficacy, tolerability, and simplicity. More recently, a structured Expert Consensus on Actinic Keratosis has confirmed DL-PDT as a valuable option for subjects with multiple AKs in small or large fields (Calzavara-Pinton, 2017).

Galderma is developing MAL DL-PDT in the United States for lesion treatment, but may consider field treatment as a secondary indication for life cycle management.

Methyl aminolevulinate hydrochloride is marketed under various trade names: Metvix / Metvixia / Mexvivia 160 mg/g or 168 mg/g. The products are identical but are labelled

differently, depending on the various country specific approvals. As of 30 June 2019, the product is approved in 39 countries for the treatment of AK, basal cell carcinoma (BCC), and Bowen's disease (individual country approvals vary) with a red lamp. As of 30 June 2019, Metvix® Cream with DL activation for the treatment of AK has been approved as a variation to the current Metvix Aktilite authorization in Europe and outside Europe (Argentina, Australia, New Zealand, Singapore, Switzerland, Russian Federation, Colombia, Mexico, Brazil, Costa Rica, Venezuela, Chile, and Canada). In addition, Luxera, Luxerm, and Lumexia are other commercial names for the same product, which is approved for the treatment of AKs with daylight only, approved in Austria, Germany, Italy, Portugal, Spain, and Sweden.

6.2 Clinical and Pharmacokinetic Studies

The Investigator's Brochure (IB) contains detailed information on clinical and non-clinical studies. Results of the Phase 3 MAL cream DL-PDT studies are summarized below. A PK study has been recently conducted in the United States.

6.2.1 Phase 3 MAL cream DL-PDT studies

The efficacy and safety of MAL 16.8% cream DL-PDT were compared with MAL 16.8% cream c-PDT in 2 randomized, investigator-blinded, comparative, intra-individual clinical studies conducted in Australia and Europe, in 231 subjects. Subjects were treated on 1 side of the face or scalp with MAL 16.8% cream DL-PDT and on the contralateral side with MAL 16.8% cream c-PDT.

The results of both Phase 3 studies demonstrated that the efficacy of MAL 16.8% cream DL-PDT is similar (noninferior) to MAL 16.8% cream c-PDT for treatment of AK lesions (on the percentage change from Baseline in the number of treated lesions per side at 12 weeks after 1 treatment), and is significantly less painful.

In the Australian study, the percentage change from Baseline in the number of mild treated lesions was 89.2% for DL-PDT versus 92.8% for c-PDT (95% confidence interval [CI] of the mean treatment difference: [-6.8; -0.3], PP population). In the European study, the percentage change from Baseline in the number of total (mild and moderate) treated lesions was 70.1% for DL-PDT versus 73.6% for c-PDT (95% CI of the mean treatment difference: [-9.5; 2.4], PP population).

Methyl aminolevulinate hydrochloride 16.8% cream DL-PDT was almost painless compared with MAL 16.8% cream c-PDT, with a pain score (on an 11-point scale ranging from 0 to 10) of 0.8 versus 5.7 ($p<0.001$) in the Australian study, and 0.7 versus 4.4 ($p<0.001$) in the European study.

In both studies, regardless of whether the weather was sunny or cloudy, similar efficacy was demonstrated.

The maintenance of lesion response rate assessed in the Australian study was high with both treatments for subjects presenting at Week 24 (96% for DL-PDT lesions and 96.6% for c-PDT lesions).

In these two Phase 3 studies, in 231 subjects, local related adverse events (AEs) were reported less frequently on MAL cream DL-PDT than on MAL cream c-PDT treated sides (45.0% and 60.1% of subjects, respectively).

No new local adverse reactions were reported in the 2 MAL DL-PDT Phase 3 studies compared with the already known local adverse reactions with MAL c-PDT. Methyl aminolevulinate hydrochloride DL-PDT was almost painless compared with MAL c-PDT.

6.2.2 PK Study (MUsT)

The PK profiles of MAL and its metabolites, ALA and PpIX, were assessed in 23 subjects with AK lesions following two topical applications at least 2 weeks apart, of the to-be marketed formulation under maximal use conditions. The study was an open- label study of adult men and women with at least 10 mild to moderate actinic keratosis of the face or balding scalp.

The purpose of this maximal use trial (MUsT) was to assess systemic exposure at the upper range of disease severity of the population that will be enrolled in the proposed pivotal phase 3 study [RD.06.SPR.112199]. The mean number of treated lesions reported in the MUsT (i.e., N=14.5 ± 6.56 lesions, range 10 to 30 AK lesions) exceed the maximum number of lesions that will be treated in the Phase 3 study (i.e., N=12 lesions)

Subjects received two separate single-dose applications of MAL cream on the face or on the balding scalp with a 2-week washout period between the two applications. A total of 24 adult subjects with AK lesions on the face or balding scalp received lesion-directed treatment, and then had 2 hours of daylight under 3 different conditions: full shade, full sunlight, and full sunlight with physical exercise.

After two topical application of MAL cream, the systemic exposure to the unchanged compound (MAL) was very low, i.e. no more than 3 times the LOQ (2 ng/mL) and transient in time with MAL systemic exposure limited to no more than a 3-hour duration after the first treatment only. Given the limited systemic exposure of MAL and its quick methyl ester hydrolysis in its acid from ALA, no drug accumulation is expected and hence the parent drug potential for systemic toxicity or drug-drug interaction is unlikely.

The two MAL metabolites, ALA and PpIX, are endogenous substances and exogenous application of MAL cream on lesions resulted in a non-significant increase of ALA systemic exposure and in a negligible increase of PpIX systemic exposure (up to a maximum of 34% of the 24-hour PpIX endogenous level).

Of note, the increase in PpIX exposure from baseline and presence of quantifiable MAL concentrations were observed mainly in subjects presenting with a number of AK lesions (at least 30) that greatly exceed the maximum number of AK lesions that will be treated in the proposed Phase 3 study.

There were no clinically significant changes in ECG findings, nor changes in tolerability or new types of AEs found in the study.

6.3 Risk/Benefit Assessment

Metvix® cream (methyl aminolevulinate 16.8%) is currently marketed worldwide by Galderma for the treatment of thin or non-hyperkeratotic and non-pigmented AK of the face and scalp, and in some countries for the treatment of superficial and nodular BCC and the treatment of SCC *in situ* (Bowen's disease) in adults.

The cumulative post-marketing patient exposure to MAL cream is estimated to be 2,213,42 patient treatments, calculated on the basis of number of tubes sold worldwide and the assumption that a single 2-g tube is used for 2 patient treatments. In the near future, the 2-g tube will be a unidose tube, intended for one use only.

Galderma has developed a new treatment regimen of the product in which DL is used in place of the previously authorized red light-emitting diode (LED) for the illumination in the treatment of AKs. This has been approved in various countries and Galderma is now developing methyl aminolevinulate cream 16.8% (CD06809-41) DL-PDT in the United States for the treatment of AK.

With regards to safety, in clinical studies conducted with MAL c-PDT in subjects with AKs, BCC, or Bowen's disease, approximately 60% of subjects experienced reactions localized to the treatment site, attributable to toxic effects of the photodynamic therapy (phototoxicity) or to preparation of the lesion. The most frequent symptoms were painful and burning skin sensation, typically beginning during illumination or soon after and lasting for a few hours with resolution on the day of treatment. The symptoms were usually of mild or moderate severity and rarely required early termination of illumination. The most frequent signs of phototoxicity were erythema and scab. The majority were of mild or moderate severity and persisted for 1 to 2 weeks, or occasionally longer. Repeated treatment with Metvix was associated with a reduced frequency and severity of local phototoxic reactions.

In the post-marketing experience, the following adverse drug reactions were the more relevant ones reported with Metvix cream: eyelid edema, angioedema, face edema (swelling face), application site eczema, allergic contact dermatitis, and rash pustular (application site pustule). In addition, hypertension and transient global amnesia were reported with Metvix cream used with c-PDT (refer to the Investigators' Brochure).

In the two Phase 3 MAL DL-PDT studies conducted in subjects with AKs to compare MAL DL-PDT with MAL c-PDT, no new local adverse reactions were reported compared with the already known local adverse reactions with MAL c-PDT. Methyl aminolevulinate hydrochloride DL-PDT was almost painless compared with MAL c-PDT.

As a conservative approach, the calculation presented below considers the treatment conditions expected to maximize the MAL hydrochloride 16.8% cream (CD06809-41) penetration, i.e., the field treatment after preparation of the lesional skin with a pad (sterile gauze).

The *in vitro* total penetration through the skin of MAL 16.8% cream (CD06809-41) in humans, after a 2.5-hour contact on skin pretreated with preparation pad (sterile gauze), corresponded to up to 6.853% of the applied dose after 10 passages with the preparation pad (study RDS.03.SRE.105070). Thus, after an administration of 2 g of CD06809-41 cream, a theoretical maximum up to 23.03 mg of MAL could be absorbed systematically (336 mg x 6.85/100), which would represent 0.46 mg/kg for a 50 kg subject (23.03 mg/50 kg). Using a conversion factor of 37 for humans, the maximum recommended human dose (MRHD) for each application is 17.02 mg/m^2 (0.46 x 37).

For comparison, the MUsT PK study RD.06.SPR.108431, performed in subjects with mild to moderate AKs, demonstrated that between 0.11 and 0.54 g of MAL cream was sufficient to cover between 10 and 37 AKs on skin surface area, measuring between 12 and 67 cm^2. After cream administration, the systemic MAL exposure was mainly non-quantifiable, with few subjects having very low MAL plasma concentrations (C_{max} between 2.14 and 6.19 ng/mL) limited to about 3 hours after the first treatment. Therefore, the safety profile of MAL 16.8% cream can be considered well established.

All nonclinical animal studies were performed with the MAL-HCl salt, and consequently, NOAEL expressed as MAL are to be divided by a 1.251-fold factor, as MAL-HCl has a formula weight of 181.62 g and MAL of 145.17 (difference for HCl of 35.45 g).

The safety margins based on the NOAELs at MAL 160 mg/kg/day (200 mg/kg/day MAL-HCl), determined based on systemic toxicity (liver cholangitis/pericholangitis) after IV administration in rats for 2 weeks and on the NOAELs based on reproduction toxicity studies are summarized in Table 2:. These safety margins consider comparisons on an mg/m^2 basis with the maximum recommended human dose (MRHD) for each application being 17.02 mg/m^2. The conversion factor for rats is 6 and it is 12 for rabbits. With this method of

calculation, the lowest estimated safety margin for the study is 35 (based on pre/postnatal toxicity in a rat study).

Therefore, based on the extensive pre- and post-marketing safety data available for the product, MAL cream remains effective and safe with a favorable benefit/risk ratio.

With regards to efficacy, MAL DL-PDT has been demonstrated to be as effective as MAL c-PDT for the treatment of AKs, and has already been approved in several countries for this indication.

Overall, the cumulative post-marketing experience, as well as the information from the clinical studies and literature, confirm that the benefit-risk ratio remains positive for the use of MAL in the approved indications in the various countries in which it is approved, and supports the conduct of the proposed study.

Table 2: Safety Margins for MAL comparing NOAEL and MRHD expressed as mg/m^2

Study type (Study number)	**Species**	**NOAEL (expressed as MAL)**	**Safety margin versus MRHD (17.02mg/m^2)[a]**
14-day IV administration (1555/7-D6144)	Rat	160 mg/kg/day = 960 mg/m^2/day	56
Male and female fertility (494190)	Rat	400 mg/kg/day = 2400 mg/m^2/day	141
Embryo-fetal development (494054)	Rat	280 mg/kg/day = 1680 mg/m^2/day	98
Embryo-fetal development (494080)	Rabbit	80 mg/kg/day = 960 mg/m^2/day	56
Pre/postnatal toxicity (494274)	Rat	100 mg/kg/day = 600 mg/m^2/day	35

a) conservative approach, assuming a human body weight of 50 kg and a 2 g application

6.4 Drug Profile

Methyl aminolevulinate cream contains 16.8% of methyl aminolevulinate hydrochloride; each gram of cream contains 168 mg of MAL in a cream base. It is a patented derivative of ALA. Methyl aminolevulinate is not a photosensitizing agent itself, but its topical application results in the formation of photoreactive PpIX. Light activation of accumulated PpIX leads to a photochemical reaction and thereby, phototoxicity to the light-exposed target cells.

7 STUDY OBJECTIVES & ENDPOINTS

7.1 Primary Objective

The primary objective is to evaluate the safety and efficacy of MAL DL-PDT in adult subjects with mild to moderate actinic keratoses on the face and scalp over a 14-week period, and to show superiority in efficacy of MAL cream over vehicle cream at 12 weeks after the last DL-PDT session (Visit 6).

7.2 Secondary Objectives

- Compare the lesion response between MAL DL-PDT and vehicle DL-PDT
- Compare partial clearance of actinic keratoses (AKs) between MAL DL-PDT and vehicle DL-PDT
- Compare subject assessment of pain (by NRS) between MAL DL-PDT and vehicle DL-PDT
- Assess safety, including adverse events
- Document the estimated PpIX effective dose for each subject DL-PDT exposure through satellite image data

7.3 Primary Endpoint

The primary efficacy endpoint is the subject complete response, defined as the proportion of subjects with complete clearance of all AK lesions treated, at 12 weeks after the last DL-PDT (Visit 6), comparing MAL cream with vehicle cream.

7.4 Secondary Endpoints

- Lesion complete response, defined as the percent reduction from baseline in the number of cleared treated lesions, at 12 weeks after the last DL-PDT treatment (Visit 6), comparing MAL cream with vehicle cream
- Subject partial response, defined as the proportion of subjects with 75% or greater reduction from baseline in the number of cleared treated lesions, at 12 weeks after the last DL-PDT treatment (Visit 6), comparing MAL cream with vehicle cream

7.5 Safety Assesments

- Subject's assessment of pain after each DL-PDT treatment (Visit 2 and Visit 4), comparing MAL cream with vehicle cream
- Safety Visit Question

- Assess safety, including adverse events (AEs), treatment-emergent AEs (TEAEs), and serious AEs (SAEs)
- Physical examination and vital signs
- Clinical laboratory tests
- Electrocardiogram

7.6 Other Assessments

- Subject satisfaction questionnaires at Visit 4 (2nd DL-PDT) and at Visit 6 (Final Visit)
- The Clinical Asssessment of the Subject's Skin Aspect at Visit 6
- Weather conditions
  - The Investigator is to assess weather conditions at the time of randomization/commencing treatment and consult local weather forecasts to determine the likelihood of rain in the next 3 hours,and the temperature should be be suitable for the subject to stay comfortably outdoors for 2 hours. If the weather is rainy, or is likely to become so, the treatment should be postponed.
- Document the calculated PpIX effective dose using geolocalized weather satellite data during 2-hour daylight illumination for each DL-PDT (Visit 2 and Visit 4)

7.7 Clinical Photographs

- Clinical photographs of AK lesions are optional and will be captured only for subjects who consent at selected sites. Refer to Section 9.3 for further details.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This is a randomized, double-blind, vehicle-controlled, multicenter, parallel-group study in adult subjects with a clinical diagnosis of mild and moderate actinic keratosis on the face and scalp.

In this study, the results of DL-PDT with MAL 16.8% cream or a vehicle cream will be compared.

It is planned to enroll male and female subjects, at least 18 years old, with mild and moderate actinic keratoses on the face and scalp, meeting specific inclusion and exclusion criteria.

All subjects will provide written informed consent prior to any study-related procedure.

A total of 570 subjects will be randomized to either MAL 16.8% cream or vehicle cream in a 2:1 ratio, at approximately 60 sites in the United States with diverse latitude, altitude, and climate characterisitics.

- 380 subjects will receive MAL 16.8% cream applied to 4 to 12 AK lesions on the face and scalp, and then go outdoors for 2 hours of daylight illumination
- 190 subjects will receive vehicle cream applied to 4 to 12 AK lesions on the face and scalp, and then go outdoors for 2 hours of daylight illumination

Eligible subjects will be screened (Visit 1) and then have randomized treatment at Baseline (Visit 2). They are to return to the study center for safety assessment at Visit 3 and then return for another treatment at Visit 4 (Weeks 2-4), and evaluations at Visit 5 (Weeks 3-5) and Visit 6 (Week 14 or Final Visit). Subjects who have CR of all treated lesions at Week 14 (Final Visit) or 12 weeks after the last DL-PDT visit, will be offered the opportunity to continue in the long-term follow-up study to assess recurrence of the treated lesions.

The primary endpoint of the study occurs at Visit 6, the Week 14 or Final Visit, 12 weeks after the last DL-PDT visit.

The 6 planned visits are:

Visit 1	Screening
Visit 2	Baseline; randomization, first DL-PDT treatment and safety assessments
Visit 3	Week 1; safety assessments
Visit 4	Weeks 2-4; second DL-PDT treatment and safety assessments
Visit 5	Weeks 3-5; safety assessments
Visit 6	Week 14 or Final Visit; 12 weeks after the last DL-PDT treatment; primary and secondary efficacy assessments, and safety assessments; subjects with CR will continue in a long-term follow-up study

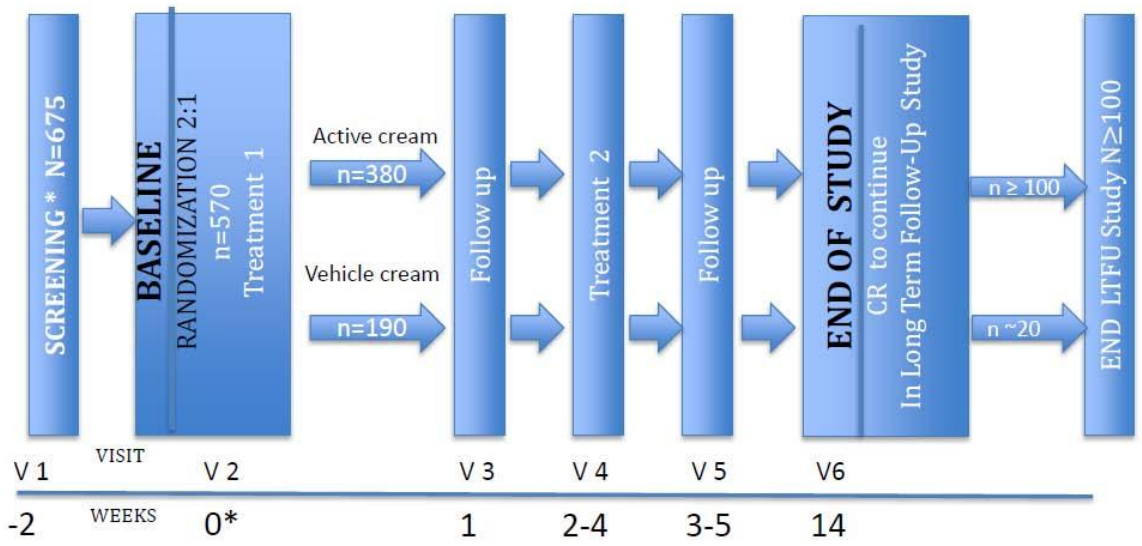
The Investigator will determine the suitability of weather conditions at randomization/treatment outset to undertake DL-PDT at the time the subject is in the clinc. Visits 2 and 4 may be postponed for up to 2 weeks in case of unsuitable weather conditions at each visit; postponements will be automatically added to the time of scheduled Visits 3, 4, 5, and 6.

If subjects experience rain during the 2 hours of daylight exposure during either DL-PDT visit, they will be instructed to go indoors at the investigative site and the study drug will be washed off. The treatment will be considered incomplete and should be repeated at a minimum interval of 2 weeks, and a maximum interval of 4 weeks. There will be only one attempt at retreatment of an incomplete treatment. If the attempt at retreatment is also incomplete, the subject will continue in the study and will undergo all the interventions and assessments according to the protocol. The additional time for repeat visits will be added to the time of scheduled Visits 3, 4, and 5. The timing for Visit 6 will be recalculated according to the formula of 12 weeks after the last DL-PDT treatment.

Data collected for this study will be recorded on an electronic case report form (eCRF), Procedure Log, and subject questionnaires.

8.1.1 Study Schema

Figure 2: Study Schema



*At Visit 6 (Week 14 or Final Visit), 12 weeks after the last DL-PDT treatment those subjects who achieve Complete Response (CR) of treated lesions will be offered the opportunity to continue in the long-term follow-up study to evaluate recurrence of the treated lesions

8.1.2 Schedule of Assessments

Table 3: Schedule of Assessments

Visit	1	2 [a]	2b [b]	3	4 [a]	4b [b]	5 [a,b]	6 [a,b]
Purpose	**Medical history and labs**	**First DL-PDT session**	**If required**	**Follow-up** 1 wk after 1st DL-PDT (visit 2 or 2b)	**Second DL-PDT session**	**If required**	**Follow-up** 1 wk after 2nd DL-PDT (visit 3 or 3b)	**Final** 12 weeks after last DL-PDT
Week	**Screening**	**Baseline**		**Week 1**	**Week 2**		**Week 3**	**Week 14/ET[f]**
Visit window	-14 to-5 days	0+14 days		-2 to+14days	0 to+14days		-2 to+14days	-2 to+28days
Informed Consent (IC for photography as needed)	X							
Demographics (including FST)	X							
Medical History	X							
Previous Therapies/Procedures	X							
Vital Signs/Physical Examination	X							X
Inclusion/Exclusion Criteria	X	X						X
Hematology/ Blood Chemistry/ UA/ECG	X							X
Pregnancy Test[c]	X	X	X		X	X		X
Weather assessment		X	X		X	X		
Photography (Selected sites) [d]		X						X
AK mapping + counting + grading[d]		X	X		X	X		X
Sunscreen application		X	X		X	X		
Lesion débridement and treatment application		X	X		X	X		
Geolocalized Satellite data and exposure time		X	X		X	X		

Study drug(s) Dispensing (D) and Accountability (A)		X	X		X	X		
Subject Assessment of Pain		X	X		X	X		
Subject Skin Aspect Assessment[d]								X
Subject satisfaction questionnaire					X	X		X [d]
Safety visit question				X			X	
Adverse Events[e]	X	X	X	X	X	X	X	X
Concomitant Therapies/Procedures [d]		X	X	X	X	X	X	X
Subjects with Complete Response evaluation and IC for continuation into long-term follow-up study								X
Exit Form[f]								X

a) Visits 2 and 4 may be delayed for up to 2 weeks in case of unsuitable weather conditions at randomization/treatment outset. These postponements will be automatically added to the time of scheduled Visits 5 and 6
b) If subjects experience rain during the 2 hours of daylight exposure of either DL-PDT visit, they will be instructed to go indoors at the investigative site and the study drug will be washed off. The treatment will be considered incomplete and should be repeated at a minimum interval of 2 weeks, with a maximum interval of 4 weeks. There will be only one attempt at retreatment of an incomplete treatment. These visits will be Visits 2b and 4b. If the attempt at retreatment is also incomplete, the subject will continue in the study.. Likewise these repeat visits will be added to the time of scheduled Visits 5 and 6.
c) Only for females of childbearing potential, urine at Visits 1, 2, 2b (if applicable), 4, 4b (if applicable) and 6
d) Should be performed earlier if subject discontinues before Visit 6
e) Adverse Events have to be collected from the time of the Informed Consent signature
f) Exit form should be completed after subject data collection has been completed for subjects in the study,
Unscheduled visits – see Section 8.6

8.2 Discussion of Study Design

8.2.1 Study Design

This study will evaluate the safety and efficacy of MAL 16.8% cream in adult subjects with mild to moderate actinic keratoses on the face and scalp, illuminated with a standardized time of 2 hours of daylight exposure. The comparator group will be treated with the vehicle cream using the same treatment protocol. This study will confirm the use of daylight as the energy source for MAL PDT, with demonstation of a positive clinical outcome with a known safety profile. The use of daylight activation of MAL PDT has been shown to be effective and safe in 2 clinical studies conducted in Australia and the European Union, in which subjects had lesion clearance rates non-inferior to MAL PDT with illumination with a narrow band LED red lamp. The subjects who underwent treatment wih daylight illumination experienced no to almost no pain compared with those subjects who underwent red lamp illumination. Adverse events in both groups were similar in nature and incidence, and no new types of AEs were identified. For these reasons, MAL PDT activated by daylight illumination is being developed in the United States.

Before undertaking MAL DL-PDT with a given subject for this study, the investigator is asked to determine if ambient weather conditions for daylight PDT will be adequate for the next 3 hours. This should be done by consulting an internet weather app, such as weather.gov, to understand the likely expected local meteorologic conditions. After assessments and lesion preparation, subjects should be able to remain outdoors comfortably for 2 hours. If it is raining at the time of the weather condition assessment, or if there is significant likelihood of precipitation, treatment is to be postponed.

The selection of approximately 60 clinical sites at which this study is to be conducted, will be undertaken with thought to represent latitude, altitude, and climate diversity. The quality and quantity of the visible light during daylight exposures may vary considerably because of these factors The conditions in which subjects are to receive daylight exposure are set forth simply: 2 hours outdoors in a comfortable temperature without imminent precipitation. These directions are easily understood by all. For this pivotal study, the geolocalized daylight exposure time will be recorded to estimate a PpIX effective dose for each treatment, using satellite data. The concept of standardized, timed daylight exposure works based on previous clinical study experience in both Australia and the EU, and in a recent PK MUsT conducted in the United States. The evidence of similar clinical outcomes of daylight PDT compared with quantified light exposures from a LED lamp confirms the utility of using daylight. Light measurements recorded from ground measuring devices correlated highly with data from satellites geolocalized to the time of daylight exposure. Moreover, non-inferior (similar) clinical response rates with less pain offer a better treatment experience for subjects.

The study plan is to conduct the study from autumn through winter and spring to allow investigative sites to enroll seasonally. There is less concern about adequacy of light dose in the summer months in most of the continental US. Thus, the study provides the means to assess the applicability of the directions for daylight exposure in less favorable conditions. Analysis of the

results from different investigative sights will determine the applicability of DL-PDT in the more northern regions of the United States.

The 2:1 randomization scheme of MAL 16.8% cream to vehicle cream with the planned subject numbers will ensure that 90% power will remain should efficacy estimates move from the values assumed for the powering of the study; 45% subject CR for MAL cream and 15% for vehicle cream.

After completing Visit 6, at which the primary efficacy endpoint is measured, those subjects who achieve CR of the lesions treated by DL-PDT will continue in a long-term follow-up study to assess recurrence of treated lesions.

8.3 Selection of the Study Population

8.3.1 Number of Planned Subjects

Approximately 570 subjects.

Refer to Section 10.2 for the statistical considerations on which the sample size is based.

8.3.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following inclusion criteria:

1. Male or female subjects age 18 years or older
2. Subjects have at least 4 but no more than 12 clinically confirmed thin and moderately thick (Grade I and II in the Olsen scale, respectively), non-hyperkeratotic, non-pigmented AK lesions located in on the face (e.g., forehead, cheek, chin), and balding scalp (excluding eyelids, lips and mucosa~~)~~
3. A: Female subjects of non-childbearing potential: postmenopausal (absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason), hysterectomy or bilateral oophorectomy.

   B: Female subjects of child-bearing potential: negative urine pregnancy tests at Screening and Baseline visits. Female subjects of childbearing potential must agree either to be strictly abstinent until one completed menstrual cycle after the last DL-PDT, or to use an effective and approved method of contraception until one completed menstrual cycle after the last DL-PDT. This criterion also applies to a prepubertal female subject who begins menses during the study.

   Effective and approved methods of contraception applicable for the subject and/or her/his partner are defined below:

   - Progestogen-only oral hormonal contraception
   - Cap, diaphragm, or sponge with spermicide
   - Combination of male or female condom with cap, diaphragm, or sponge with spermicide

- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Vasectomy at least 3 months before the study

4. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol
5. Fully understands and signs an informed consent form before any investigational procedure(s) are performed

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable

1. Severe AKs (Grade III, very thick) in the treatmentareas
2. Pigmented or hyperkeratotic AK lesions in the treatment areas
3. Subjects with a clinical diagnosis of a skin disease other than AK (including non-melanoma skin cancer) in the target area(s) if these diagnoses interfere with the investigative treatment or interpretation of the clinical results
4. Immunocompromised subjects such as organ transplant receipts or HIV+ persons
5. Subjects with porphyria
6. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the participation in the clinical trial, and/or put the subject at significant risk (according to Investigator's judgment) if the subject participates in the clinical trial
7. Female subjects who are pregnant, nursing or planning a pregnancy during the study
8. Subjects with known or suspected hypersensitivity to the active substance or to any excipients of MAL cream or prior exposure to MAL cream
9. Having received any of the treatments in Table 4 within the specified timeframe before the baseline visit:

Table 4: Prior treatments

Treatment(s)	***Timeframe****
Topical : 5-fluorouracil, diclofenac, imiquimod, retinoids, alpha-hydroxy acid, salicylic acid ointment, ingenol mebutate	12 weeks
Surgical: elliptical excision, excision and reconstructive surgery, Mohs' micrographic surgery, chemical peels/chemosurgery, cryosurgery, dermabrasion	12 weeks
Photodynamic therapy	12 weeks

Laser therapy	12 weeks
Electrocoagulation therapy	12 weeks
Radiotherapy	12 weeks
Investigative therapies for actinic keratosis	12 weeks
Systemic retinoids	12 weeks
Immunosuppressive agents such as glucocorticoids, cytostatic agents, antibodies, drugs acting on immunophilins, interferon, TNF binding proteins, mycophenolate mofetil, or biologics	12 weeks

*minimum washout period prior to baseline

10. Planned or expected major surgical procedure during the clinical study
11. Currently participating or participated in any other study of a drug or device, within the past 12 weeks before the screening visit, or is in an exclusion period (if verifiable) from a previous study
12. Subjects with any condition that may be associated with a risk of poor protocol compliance
13. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limted to elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN), at the screening or baseline visit that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (e.g., poor venous access or needle-phobia).
14. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.7)

8.3.4 Removal of Subjects From Therapy or Assessments

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

Reasons for discontinuing study drug include:

- WITHDRAWAL BY SUBJECT

  Subject request (i.e., consent withdrawal)
- PROTOCOL VIOLATION

  Use of non-permitted concurrent therapy (unless discussed and agreed upon with the Investigator and medical monitor)
- NON-COMPLIANCE WITH STUDY DRUG

Non-compliance with the study drug or study schedule

- LOST TO FOLLOW-UP
- ADVERSE EVENT

  Occurrence of AEs not compatible with the continuation of subject participation in the study, in the Investigator's opinion, or unacceptable to the subject to continue, such as serious immediate-type allergic manifestations, including anaphylactic reaction.
- PREGNANCY
- PHYSICIAN DECISION
- LACK OF EFFICACY
- OTHER
- INTERCURRENT ILLNESS
  - Diagnosis of a malignancy (except curatively treated *in situ* cervical carcinoma or BCC in areas outside of treatment areas studied in this protocol)
  - Any opportunistic infection (such as active TB and other infections whose nature or course suggest an immune-compromised status)

The reason(s) for withdrawal will be documented in the eCRF. Subjects who have been enrolled and treated will not be replaced by another subject.

Subjects who prematurely discontinue study drug will be encouraged to complete the scheduled study visits.

When a subject discontinues study drug, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 8.5.1 (Early Termination Visit).

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the Investigator(s) will be informed of the reason for study termination.

8.3.4.1 Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator. **If a subject becomes pregnant, the Investigator must withdraw the subject from the study without delay. The subject must not receive any further study drug.** Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 9.2.4.4.

The Investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 9.2.4.3) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 9.2.4.3)
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide tri-monthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), *in utero* death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 9.2.4.3).

The investigator should also be notified of pregnancy occurring during the study (and within 12 weeks [± 5 days] after the last dose of study drug) but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study.

8.4 Investigational Products

"Study drug" refers to methyl aminolevinlulate hydrochloride 16.8% cream (CD06809-41) or vehicle cream for the purpose of this double-blind study.

8.4.1 Investigational Products Administered

Study drug will be supplied as a cream, which is cream to pale yellow in color in a 2 g aluminum tube.

Vehicle cream will be supplied as a cream, which is cream to pale yellow in color in a 2 g aluminum tube.

Health care professionals should wear nitrile gloves when applying and removing MAL 16.8% cream.

8.4.1.1 Study Drug Dosing

Subjects should not be randomized by the Investigator when outdoor conditions do not allow outdoor exposure:

- When raining or when there is a significant possibility of rain in the 3 hours after beginning the DL-PDT.
- When in the Investigator's opinion, the subject is unable to stay outdoors in direct light or shade for 2 hours (e.g., the temperature is too cold or too hot).

- No subject should be randomized less than 3 hours before sunset.

After mapping and counting the AK lesions and noting their severity, the Investigator will select 4 to 12 AKs of mild and moderate severity for the investigative treatment and record which lesions are being treated. On treatment visits, which occur at Visit 2 and Visit 4, a sunscreen with chemical filters of at least SPF 30 will be applied on all areas to be sun-exposed, including the treatment area. Application will occur approximately 15 minutes before lesion preparation, to prevent further UVA and UVB exposure when the subject is outside. Scales and crusts should be carefully removed from the AKs to be treated on the face and balding scalp with a sharp curette. The extent of the preparation will depend on the thickness of the lesion. The site will register the subject in the randomization database and request the subjects treatment assignement. The site will select the tube assigned to the patient. Methyl aminolevulinate cream or its vehicle cream will be applied as a thin layer to each lesion and the surrounding 5 to 10 mm of normal skin. Nitrile gloves should be worn when applying and removing the cream. At 30 minutes following study medication application, subjects will be instructed to go outside for 2 hours and avoid going indoors. The exact times the subjects goes outdoors and returns in side are to be noted in the eCRF. On sunny days, should the subject feel uncomfortable in direct sunlight, shelter in the shade may be taken. After 2 hours, subjects will return inside the investigative site and they will complete the Subject Assessment of Pain (see Table 8) which will assess the the pain the subjects experienced during the PDT session, before site staff will remove the cream. Subjects will complete the survey questionnaire at Visit 4 (see Appendix 1), and will be instructed to avoid sun exposure and use sunscreen for the next 48 hours. There will be 2 treatment sessions at least 2 weeks up to 4 weeks apart. At Visit 4, the same lesions should be treated as at Visit 2.

In case of unexpected rain that occurs during the 2 hours that the subject is outdoors, the subject should be instructed to go indoors and have the study drug washed off. The reason for premature treatment procedure discontinuation and the information about the treatment procedure received will be recorded. That treatment will be considered incomplete and should be repeated at a minimum interval of 2 weeks, and a maximum interval of 4 weeks There will be only one attempt at retreatment of an incomplete treatment. If the attempt at retreatment is also incomplete, the subject will continue in the study and will undergo all the interventions and assessments according to the protocol. The additional time for repeat visits will be added to the time of scheduled Visits 3, 4, and 5. The timing for Visit 6 will be recalculated according to the formula of 12 weeks after the last PDT treatment.

8.4.1.2 Non Investigational Product

As subjects will be staying outdoors for 2 hours for illumination of the study drug or vehicle cream, the investigative site will provide each subject with a bottle of sunscreen with a SPF value of ≥30 with only chemical filters. The use of sunscreens containing physical filters such as titanium dioxide or zinc oxide is not permitted. As part of the procedure, the subject will have sunscreen applied by investigative site personnel to the target area on the face and scalp to be treated with the study product. The subject can then continue applying sunscreen to areas not in the target area that will be exposed to sunlight during the 2-hour illumination, such as ears, neck, chest, arms, hands, legs, and feet depending on the apparel chosen by the subject on the days of

treatment. A list of sunsceens rated by different organizations is included in Appendix 3, the Sponsor or CRO designee will provide the option to supply sunscreen to investigational sites upon request. After 15 minutes, the Investigator can begin débridement of the AK lesions to be treated, with a sharp curette.

8.4.2 Identification of Investigatonal Products

Table 5: Description and Usage of Investigational Product

Investigational Product:	
Name	Methyl aminolevulinate hydrochloride
Internal code*:*	CD06809-41
Pharmaceutical Form:	Cream
***[Strength/Concentration]*:**	16.8%
Storage:	2 to 8°C
Dosage (total daily dose):	There will be 2 treatment sessions at least 2 weeks up to 4 weeks apart. The investigator will apply a thin layer of MAL cream to each lesion during each treatment. A total of 4 to 12 lesions will be treated.
Route:	Topical
Duration of administration:	Two treatment sessions at least 2 weeks apart. At 30 minutes after cream application, subjects will go outside in daylight for 2 hours. After this time, the cream will be removed by investigative site personnel washing the skin with gentle skin cleanser.
Dose Regimen:	Thin layer on each AK lesion and surrounding 5 to 10 mm of normal skin
Location of treated area:	Face and balding scalp
Manufactured by:	GALDERMA PRODUCTION INC 19400 Route Transcanadienne, Baie-d'Urfé, Québec, Canada H9X 3S4

Comparator Product :	
Name	Methyl aminolevulinate hydrochloride Vehicle
Internal code [*if applicable*]*:*	
Pharmaceutical Form:	Cream
***[Strength/Concentration]*:**	N/A
Storage:	2 to 8°C
Dosage (total daily dose):	There will be two treatment sessions at least 2 weeks up to 4 weeks apart. The PI will apply a thin layer of MAL cream to each lesion during each treatment. A total of 4-12 lesions will be treated.
Route:	Topical
Duration of administration:	Two treatment sessions at least 2 weeks up to 4 weeks apart. At 30 minutes after cream application, subjects will go outside in daylight for 2 hours. After this time the cream will be removed by investigative site personnel washing the skin with gentle skin cleanser.

Dose Regimen:	Thin layer on each AK lesion and surrounding 5 to 10 mm of normal skin
Location of treated area:	Face and balding scalp
Manufactured by:	GALDERMA PRODUCTION INC 19400 Route Transcanadienne, Baie-d'Urfé, Québec, Canada H9X 3S4

8.4.3 Packaging and Labeling

Each subject kit will be appropriately labeled by adding the subject's initials and SIN and will contain two 2-g tubes of MAL cream or vehicle cream for Visit 2 (first DL-PDT) and Visit 4 (second DL-PDT)) to be stored at 2° to 8°C.

All boxes and tubes will bear an affixed label detailing the investigational treatment, and the visit (Visit 2 or Visit 4).

Each label on tubes of the study drug will also bear a tear-off portion.

For treatment documentation, the affixed portion of the label will remain on the tube. The tear-off portion of the label is to be removed from the tubes at the time of dispensation and attached to the appropriate drug accounting record form.

The same kit number will be printed on each investigational product tube.

Treatment identification for emergency purpose will be possible with unblinding via RTSM/IRT, stating the randomization number, investigational treatment, study drug identification, batch number and expiration date, as applicable.

The labels (including tear-off part) will contain a unique tracking number as well as information required by Good Manufacturing Practice (GMP), GCP, and local regulations, and will be printed in the local language.

8.4.4 Study Drug Management

8.4.4.1 Storage of Study Drug

The investigator must 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, between 2° and 8°C (see Section 8.4.2). Temperature excursions greater than 24 hours must be reported to the Sponsor.

8.4.4.2 Study Drug Accountability

Upon receipt of the clinical supplies, the site personnel responsible for managing the supplies must conduct a complete inventory of all study drugs.

The investigator or designee will maintain accurate records of supplies received, inventoried at the clinical trial site and used per subject.

All unused ancillary products will be appropriately inventoried by the monitor and returned to the Sponsor or designee as instructed by Syneos Health or a designated contractor.

All supplies sent to the investigational site will be accounted for and in no case used in any unauthorized situations. All used and unused clinical supplies will be appropriately inventoried by the CRA (Clinical Research Associate) and returned to the assigned clinical packager for further storage, weighing, reconciliation, accounttng, and destruction as instructed by Syneos Health or a designated contractor.

8.4.4.3 Dispensing of Study Drug

All investigational and non-investigational products will be allocated only to subjects enrolled in the study at no cost and in accordance with the conditions specified in the protocol. Treatment kits will be dispensed according to the chronological order of inclusion of subjects into the study (see Section 8.4.5)

The application of the study cream to the subjects' lesions will be performed at the investigational site by the Investigator or qualified staff members. Therefore there will be no direct dispensation of the study product to the subject.

The treatment procedure will be performed at Visit 2 (first DL-PDT) and Visit 4 (second DL-PDT). Dispensations should be appropriately documented by the Investigator or designee in the Procedure Log at each DL-PDT visit.

At the beginning of treatment, the Investigator will apply sunscreen on the face and balding scalp, where the lesions are being treated. The sunscreen must have chemical filters only that provide a SPF ≥30. Physical filters such as zinc or titanium oxide are not permitted. The subject can continue applying sunscreen to other exposed areas of the skin away from the treatment area, depending on clothing worn to the study visit. A sunscreen bottle will be provided to the subject after the procedure is complete, in order for the subject to continue application of the sunscreen to protect the skin from further sun exposure.

After 15 minutes, the AK lesions to be treated will be débrided lightly with a curette to remove crusts and scales, while not causing any bleeding. The Investigator then can apply the study product to the subject's AK lesions. A thin layer of cream is applied on each AK lesion to be treated and the surrounding 5 to 10 mm of normal skin. Nitrile gloves should be worn when applying and removing the cream. After 30 minutes, the subject is instructed to go outside and remain outdoors for 2 hours. See Section 9.4.3.

8.4.4.4 Treatment Compliance

Since the subjects will receive MAL cream or vehicle cream at the investigational site, treatment compliance will be assessed through the actual treatment sessions and adherence to the different steps of the procedure and timing.

8.4.5 Method of Assigning Subject to Treatment Groups: Randomization

Upon an ICF signature by a given subject, a unique subject identification number (SIN) for that subject will be assigned via Electronic Data Capture (eDC).The eDC will be accessed immediately after ICF signature has been recorded by study center personnel. The SIN will be used for the whole duration of the study. This SIN will be allocated in ascending sequential order to each subject. Once a SIN has been assigned, that number must not be used again for any other subject (e.g., when a subject is withdrawn from the study, that subject's SIN must not be reused for any other subject, including rescreens).

Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number will be assigned to that subject via Interactive Response Technology (IRT). The randomization number for a given subject will be used to identify the treatment arm the subject will be assigned to.

Subjects will be randomized in a 2:1 ratio to receive 2 treatments of daylight photodynamic therapy (DL-PDT) with either MAL cream 16.8% (CD06809-41) or a vehicle cream. Randomization will be stratified by study centers using the Interactive Response Technology (IRT) System.

8.4.6 Blinding

All attempts will be made to keep the investigative site staff and subjects blinded throughout the study. Members of the study center staff, including the procedure operator, will not have access to the randomized treatment assignment.

To ensure double-blind administration of study drug, the qualified personnel will dispense all MAL 16.8% cream or vehicle cream treatments, according to the current version of the pharmacy manual provided by the IRT system.

The qualified personnel who dispense the study drug should not be involved with any study assessments, and should not discuss any aspects of study drug dispensation with the subject/caregiver or study staff involved in subject interviews or study assessments.

At the initiation of the study, the study center will be instructed on the method to follow for emergency breaking of the blind. The randomization information for any particular subject may be made available to the Investigator, only in the event of a medical emergency or an AE that necessitates identification of the study drug for the welfare of that participant. Whenever possible, the Investigator or sub-investigator should consult with the medical monitor and the sponsor before breaking the blind.

When the blinding code is broken, the reason must be fully documented. If the code is broken by the Investigator, the subject must be withdrawn from the study and must also be appropriately followed for a minimum of 12 weeks after the last dose of study drug. The reporting requirements for unblinding are the same for reporting an SAE. See also Section 9.2.4.3.

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked. Initial treatment period results will be analyzed after all subjects have either completed Visit 6 , or have withdrawn or been discontinued from the study before Visit 6 . However, personnel from sponsor, CRO, and investigational sites directly involved with the ongoing conduct of the study will not have access to any information that may lead to unblinding for the ongoing recurrence evaluation during the follow-up study.

8.4.7 Prior and Concomitant Therapy

Prior therapies are defined as therapies that have been stopped within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, prior therapies for AK should be documented.

Concomitant therapies/medications are defined as follows:

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

The following 2 categories are to be considered for prior and concomitant therapies:

- Drugs/Therapies include but are not limited to prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures (e.g., phototherapy, exodontia). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

Prior and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate eCRF.

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

At each visit, Investigators should also confirm concomitant therapies for contraception. Contraceptive counseling should occur at Screening.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE form should be completed to account for the new therapy or change in therapy, in which case the medication will be linked to an item in the subject's medical history.

The therapies listed in Table 4 are also considered prohibited because they may interfere with the

efficacy and/or safety assessments of the study drug.

In addition, administration of antalgics (including anti-inflammatory and corticosteroids at doses that relieve pain) should be avoided from the day preceding the treatment procedure until the subject self -assessment of pain is completed, in order for subjects to not underestimate any pain that may be experienced. For the same reason, use of local treatment on treatment areas such as xylocaine spray, nerve blocks, and cooling procedures (such as cold-water spray or a cooling fan) are not allowed before and during the treatment procedures until the subject's self-assessment of pain is completed. Cooling procedure may be used after the subject's self-assessment of pain is completed, if this is current practice at the site.

In case the subject is using topical therapy listed in Table 4 or treatment listed above on other area than TAs, the Investigator will remind him/her to pay strict attention to not apply any of these therapies on the TA.

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, the medical monitor should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the medical monitor should be notified to discuss the pertinence and the modalities to be used for the subject to continue in the clinical study.

8.5 Duration of Subject Participation

The expected duration for each subject's participation in the study will be approximately 14 weeks, depending on the completion of the 2-hour outdoor daylight exposure after the initiation of the DL-PDT for each of the 2 treatments. If a treatment is considered incomplete, that visit can be repeated at a minimum interval of 2 weeks. Only 1 attempt at repeat of an incomplete treatment is permitted. The duration of subject participation in the study could extend up to 20 weeks, if both treatments were incomplete and were subsequently repeated successfully.

Those subjects who have CR at Visit 6 will be offered the opportunity to be followed in a 9-month long-term follow-up study to have treated lesions assessed for recurrence.

8.5.1 Early Termination Visit

Subjects may discontinue from the study at any time.

Subjects who prematurely discontinue from the study should undergo final study assessments.

8.6 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results or for follow-up of AEs. Visits occurring outside of the visit window are not considered unscheduled visits.

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit and will be conducted at the discretion of the principal investigator. Any of the procedures/assessments listed in Section 8.1.2 may be conducted, but not all are required.

9 STUDY ASSESSMENTS

A written, signed Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) authorization is required before any study-related procedures are performed.

Upon provision of the signed ICF, each subject will be assigned a unique SIN. For the duration of the clinical study, the subject will be identified using the SIN in all documentations and discussion.

The planned study assessments are in Table 3: Schedule of Assessments. At each visit, assessments/procedures should be performed in the following order:

1. Investigator assessments (weather assessment first, then proceed to study visit only if suitable, then proceed with assessments including efficacy and safety)
2. Electrocardiogram (ECG) should be done before vital signs measurements (and blood draws). See Section 9.2.9.
3. Sample collections for laboratory assessments at Visits 1 and 6.
4. In selected sites clinical photographs are taken of the treatment areas at Visits 2 and 6.
5. The AKs in the treatment area are counted, mapped, and graded at Visits 2, 4, and 6. The maps from Visits 4 and 6 are compared to the map from Visit 2. For the treatment visits (Visits 2 and 4) steps 5-13 are followed.
6. Sunscreen is applied to the target area by site personnel, subject applies sunscreen to other areas which will be exposed during outdoor daylight exposure.
7. Removal of crusts and scales with a sharp curette of the AK lesions to be treated
8. Application of study drug to AK lesions on face and scalp
9. After 30 minutes, the subject moves outdoors for exposure to daylight.
10. The subject remains outdoors for 2 hours and then comes inside the investigative site.
11. The subject assesses pain on the NRS form at Visit 2 and 4
12. The study drug is washed off after the daylight exposure has been completed.
13. The subject applies sunscreen to the treatment areas and other sun-exposed areas (before leaving the investigative site).
14. The subject fills out the questionnaire at Visits 4 and 6.
15. The Investigator asks the subject the Safety Visit Question at Visits 3 and 5.
16. The Investigator assesses the Subject Skin Aspect Assessment at Visit 6.

9.1 Efficacy Assessments

Evalutations are to be performed by the same Investigator for a given subject throughout the study, whenever possible. The Investigator is to be blinded to the randomization.

9.1.1 Lesion Response

At Visit 2 (before treatment), the Investigator will map the subject's lesions, count them, and report their severity according to criteria based on Olsen (1991) (see Table 6).

At Visits 2b (if applicable), 4, 4b (if applicable) before treatment and at Visit 6/ET, the severity of pre-existing, treated AK lesions that had been identified and treated previously will be recorded. If new AKs develop in the treatment area, they will be recorded, but not treated nor included into the efficacy evaluations.

Table 6: Lesion Severity Grade Scale

Grade	Severity	Description
Grade 1	Mild	slightly palpable, better felt than seen
Grade 2	Moderate	moderately thick, easily felt and seen
Grade 3	Severe	very thick and/or obvious actinic keratoses

The Investigator will be asked at Visits 2b (if applicable), 4, 4b (if applicable) and 6/ET to identify each lesion treated previously, and the lesion response as a CR or a non-CR, as described in Table 7.

Table 7: Lesion Response

Response	Score	Description
Complete response (CR)	1	Complete disappearance of the lesion, visually and by palpation
Non complete reponse (non-CR)	0	Non-complete disappearance of the lesion

If all of the treated lesions in the treatment area are assessed to be CR at 12 weeks after the last DL-PDT session (Visit 6), the subject will be assessed as a subject CR. If any of the treated lesions in the treatment area are assessed to be non-CR, the subject will be assessed as a non-complete responder. Those subjects who are assessed to be CR, i.e., all treated lesions cleared, at

Visit 6 (Final Visit) will be offered the opportunity to continue in the long-term follow-up study, to assess recurrence of lesions treated.

9.2 Safety Assessments

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

9.2.1 Subject Assessment of Pain

At Visit 2, 2b (if applicable), and Visit 4, 4b (if applicable), after the treatment session (once illumination in daylight isterminated), the subject will assess the maximal pain felt during daylight exposure. The subject will complete this assessment for all DL-PDT exposures, both complete and incomplete. The pain sensation will be assessed on an 11-point Numerical Rating Scale (NRS), where 0 is no pain at all and 10 is extreme pain as shown in Table 8. The site personnel will collect and report the subject's self-assessment of pain in the Procedure Log. In the event that a subject requires an intervention for pain such as medication, it will then be recorded as an AE in the eCRF.

Table 8: Scale for Subject Self-Asssesment of Pain

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

9.2.2 Safety Visit Question

At Visits 3 and 5, particular attention is paid to AEs and events which can be sequelae of treatment.

The Investigator will answer the following question at each of Visit 3 and Visit 5:

Does the subject exhibit signs and symptoms of possible contact sensitization?

☐ YES	☐**NO**

If YES, then see Sections 9.2.4.2 and 9.4.4 of this protocol.

If the Investigator recognizes signs and symptoms of possible contact sensitization at other visits during the study, he/she should report these as an Adverse Event of Special Interest proceed to those sections of the protocol.

9.2.3 Clinical Assessment of the Subject's Skin Aspect

At Visit 6, for each lesion that has responded completely (see Table 7), the Investigator will assess the subject's skin aspect on the following signs: scarring, atrophy, induration, redness or change in pigmentation. (see Table 9)

The clinical assessment of skin aspect will be graded as:

Table 9: Scale for Clinical Assessment of Subject's Skin Aspect

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

In the event of the score of 2 or less for the clinical assessment of subject's skin aspect, it will be recorded as an AE in the eCRF**.**

9.2.4 Adverse Events

Adverse events will be recorded during each visit (Visits 1, 2, 3, 4, 5, and 6) and at other visits caused by postponement of treatment or incomplete treatment.

All medical events, whether observed by the Investigator or reported by the subject, and whether or not thought to be treatment-related, will be considered AEs and recorded on the appropriate AE form.

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study, in which a subject is administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation, that is not recorded elsewhere in the eCRF under specific efficacy assessments.

Note(s):

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms, or abnormal laboratory values.
- Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 9.2.4.4.
- Each new episode of a chronic disease (e.g., hay fever, allergy) from the screening visit should be reported as a new AE.

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

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

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

Adverse events 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 all pertinent medical records in the subject’s files, 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.

Assessment of Severity

Each AE will be assigned a category by the Investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

The Investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug (i.e., MAL cream or vehicle cream) and/or study procedure (e.g., illumination, blood sample collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

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

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during this clinical study:

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 (methyl aminolevinulate hydrocholide 16.8% cream or vehicle cream) and the AE, and/or
- Between the clinical study protocol procedure (e.g., topical background therapy, blood sample collection) and the AE

No Reasonable Possibility:

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

Action Taken with Study Drug

The investigator will describe the action taken with study drug due to the adverse event in the appropriate section of the eCRF, as follows:

- Dose Not Changed
- Drug Interrupted – cream applied, no DL exposure, then removed
- Drug Withdrawn – cream not applied

Other Action Taken

The investigator will describe the other actions taken (i.e. the ones not related to the study drug) in the appropriate section of the eCRF, as follows:

- None

- Concomitant medication (any additions or discontinuations)
- Other, specify

Follow-up of Adverse Events

All Investigators should follow-up with subjects with related AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed up for 12 weeks (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom/event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with study drug
- Other action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2.4.1 Serious Adverse Events

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it includes a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and SAEs, if they cause prolongation of the current hospitalization. Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE, if it is solely for the purpose of diagnostic tests [even if related to an AE], elective hospitalization for an intervention that was already planned before subject enrollment in the clinical study, 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]. The details of such hospitalizations must be recorded on the medical history or physical examination eCRF.)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Results in a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent 1 of the outcomes listed above 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.

9.2.4.2 Adverse Events of Special Interest (AESIs)

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

The AESIs for this protocol have been predefined as follows:

- Contact sensitization see Section 9.4.4

At each visit, particularly Visits 3 and 5, the Investigator should examine the treatment area(s) carefully and be aware of the potential for contact irritation and contact sensitization. Contact sensitization is an AESI. For AESIs, the Investigator is required to complete the Adverse Event Form in the eCRF, within 72 hours of the event, otherwise follow the SAE reporting procedures in Section 9.2.4.3, even if the event is considered non-serious according to the usual regulatory criteria.

9.2.4.3 Procedure for Reporting a Serious Adverse Event

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

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

2. Ensure that the event is evaluated as an SAE. Immediately notify (**within 24 hours of receipt of the event**) the Syneos Health Safety and Pharmacovigilance group of an SAE report, by email or fax:

   Fax Number: 1-877-464-7787
   Safety email: SafetyReporting@SyneosHealth.com

   Note: Immediate SAE reporting is required by the Investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in the eCRF, at that time.

3. Send any relevant information or anonymized medical records (e.g., laboratory test results) to the Syneos Health Safety and Pharmacovigilance group (see contact details above), within 24 hours of receipt of this relevant information.

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

5. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, complete an updated SAE report, if appropriate.

7. Prompt notification of SAEs by the Investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor or its delegate (i.e., the CRO) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements, 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 the Sponsor or its delegate (i.e., the CRO) will file it accordingly (i.e., within the Trial Master File [TMF]), and will notify the IRB/IEC, if appropriate according to local requirements.

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

9.2.4.4 Procedure for Reporting Pregnancies

Any pregnancy occurring during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome, in order to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Withdraw the subject from the clinical study. The subject must not receive any further study drug.

2. Complete as fully as possible the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy. Send by email or fax along with the exit form within 24 hours of receipt of the

information, to the Syneos Health Safety and Pharmacovigilance group. Refer to Section 9.2.4.3.

Note: Immediate pregnancy reporting is required by the Investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

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

4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, send the form by email or fax to the Syneos Health Safety and Pharmacovigilance group within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete as fully as possible the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. Print and send the form by email or fax to the Syneos Health Safety and Pharmacovigilance group within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), *in utero* death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 9.2.4.3).

9.2.4.5 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose, the nature or severity of which is not consistent with the applicable product information (e.g., reference safety information in the IB for MAL 16.8% cream, study protocol).

The Sponsor or its delegate (i.e., Syneos Health) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, IRB/IEC, and Investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and sponsor 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 the Sponsor or its delegate (i.e., Syneos Health) will file it accordingly (i.e., with the TMF), and will notify the IRB/IEC, if appropriate, according to local requirements.

9.2.5 Clinical Laboratory Evaluation

The hematology laboratory analyses, clinical chemistry laboratory analyses, and urinalyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

The Investigator or medically-qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the Investigator or designee will evaluate whether he/she considers it to be clinically significant (CS), defined as meeting at least 1 of the following conditions:

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

If the Investigator observes a CS laboratory result, the test will be repeated as soon as possible and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where he/she suspects an inaccuracy or false result, and which may impact the safety of the subject or the interpretation of the study results; only after discussion with the medical monitor.

All CS out-of-range laboratory values at the screening visit will be recorded (report a diagnosis rather than the laboratory value, whenever possible). All CS out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the screening visit (i.e., changed significantly from the screening visit). Whenever possible, the Investigator should provide a diagnosis of an AE when reporting the abnormal laboratory value.

Subjects should be reminded to be well hydrated before all visits for phlebotomy purposes. Subjects should fast for at least 8 hours before the visits when blood chemistry testing is planned, except for the screening visit. The screening visit laboratory values must be available before the baseline visit. Laboratory testing conducted in a nonfasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual. Additional samples may be required if medically indicated (e.g., at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

See Section 9.2.6 for details about pregnancy testing

The following laboratory safety tests will be performed as specified in Section 8.1.2:

9.2.5.1 Hematology

Hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, mean cell volume, and INR.

9.2.5.2 Clinical Chemistry

Creatinine, AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), creatinine phosphokinase (CPK). Creatinine phosphokinase isoenzyme test will be performed only if CPK is elevated to >2.5 × ULN. The Investigator should also contact the medical monitor in such situations.

For postmenopausal subjects (i.e., no menses for 12 consecutive months), postmenopausal status will be confirmed with a high follicle-stimulating hormone level in the postmenopausal range.

9.2.5.3 Urinalysis

pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity

9.2.6 Pregnancy Testing

All women of childbearing potential will have a urine pregnancy test at Visit 1 and UPTs at subsequent visits at Visits 2, 4, and 6 according to Section 8.1.2. Pregnancy test results must be available prior to the administration of the study drug.

Subjects with a positive serum pregnancy test result at Screening must not be enrolled.

Urine pregnancy tests with a sensitivity < 25 IU/L will be provided to the study centers for use in the study.

Urine pregnancy tests will be performed at the study centers, and all other samples will be sent to the central laboratory for analysis.

If the result of a UPT is positive, it must be confirmed with a serum pregnancy test, and no study drug should be administered pending the serum pregnancy test result. Subjects with a positive serum pregnancy test result during the study must discontinue treatment and be withdrawn from the study.

9.2.7 Vital Signs

Vital signs will be evaluated at the screening visit and at the final visit according to Section 8.1.2 before blood sampling. Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least 15 minutes), and body temperature. All abnormal values at the screening visit, identified as CS by the Investigator will be recorded. Any CS changes from the screening visit will be recorded as an AE.

9.2.8 Physical Examination

A complete physical examination should be performed at the screening and final visits, according to Section 8.1.2. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system.

Investigators should assess all abnormal findings for clinical significance. All CS abnormal findings at the screening visit will be recorded in the medical history form. Any CS changes from the screening visit will be recorded as an AE.

9.2.9 Electrocardiogram

A 12-lead ECG will be performed and read centrally according to visits specified in Section 8.1.2 using the ECG machine provided. Electrocardiograms for each subject should be obtained using the same electrocardiograph machine whenever possible. Electrocardiograms will be performed in the supine position at the time points described in the schedule of assessments and before any scheduled vital sign measurements and blood draws. Subjects should be monitored for potentially CS ECG results (refer to the current version of the central laboratory manual). Tests with abnormal results that are deemed CS should be repeated to ensure reproducibility of the abnormality. Any abnormalities considered to be CS by the Investigator are to be recorded as AEs and discussed with the medical monitor, as needed.

9.3 Optional Clinical Photographs

Clinical photographs are optional for this study and will apply only to subjects who provide written consent at selected sites. Photographs of AK lesions at Baseline and at Visit 6 or Final Visit will be captured from approximately 30 subjects using standardized photographic methods. Subjects are not required to provide photographs in order to enroll in the main study. Additional details will be provided in the photographic manual.

9.4 Other Assessments

9.4.1 Subject Questionnaires

At Visit 4 (4b if applicable, last DL-PDT) and Visit 6 (Final Visit)or early termination, the subject will be asked to complete a questionnaire [see Appendices 1 (see Section 15.1) and 2 (see Section 15.2)].

9.4.2 Weather Assessment

At Visit 2 (2b if applicable), and Visit 4 (4b if applicable), the visits at which the DL-PDT sessions are performed, the Investigator should ensure that the weather conditions are appropriate to begin the process of DL-PDT. Before randomizing/treating the subject, the Investigator should determine that subjects will be able to spend 2 hours comfortably outdoors in ambient conditions, after the AKs have been prepared for DL-PDT. The Investigator should also

assess the likelihood of rain over the next 3 hours by consulting the local weather forecast using the internet (e.g., weather.gov). If it is raining or there is a significant probability of rain in the ensuing 3 hours, treatment should be postponed.

9.4.3 Subject Exposure Time and PpIX effective light dose

The subject will be asked to stay outside under direct light exposure or shade for 2 consecutive hours.

The exposure should not start less than 2 hours before sunset. Trained personnel from the investigational site will be asked to note all changes in exposure conditions and their duration (Start/End) in order to be able to determine the effective duration of the daylight exposure for a given subject (Subject Exposure Time) (see Section 8.4.4.3). The location of the subject will be geolocalized during the Subject Exposure Time. Records of all assessments linked to Weather assessment and Subject Exposure Time will be reported in the Procedure Log.

From the geolocalization and time of the subject's daylight illumination, satellite data will be used to determine estimated irradiance during the subject exposure time. The PpIX effective dose for each subject's daylight exposure will be calculated using these parameters.

9.4.4 Procedures for Suspected Sensitization (Rechallenge and Patch Ingredient Test)

If a subject experiences suspected skin sensitization (contact allergy), the following actions should be taken to characterize the event:

- Stop the study drug
- Take a photo of the affected area and the non-affected surrounding skin
- Document the event as an AESI report the event to the Syneos Health Safety and Pharmacovigilance group within 72 hours as described for SAE in Section 9.2.4.3.

a) In case of suspicion of allergic contact dermatitis

- After all signs and symptoms have resolved (after a minimum of 2 weeks), perform a rechallenge test with the assigned study drug. Patch tests will be supplied by Galderma
- Ensure the subject has not been under any treatment with corticosteroids or antihistamines of any route of administration the week before testing
- Ensure that the skin on the back has not been exposed to the sun or artificial ultraviolet sources the week before testing.
- Apply an appropriate quantity of the assigned study product to fill in the cupule of the test chamber to a naïve zone on the back 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. The use of semi-occlusive conditions can be preferred depending on the irritant potential of the study product and the intensity of the reaction that was observed. The method to be used should be discussed with the Sponsor, see **Table 10**

Choose a skin site that was not previously involved in the inflammatory skin reaction on the back. Cover the test chamber for 48 hours with a hypoallergenic tape.

- Patient should be informed about avoiding exercise, showers, application of toiletries products, to keep the test system dry

- After 48 hours, remove the test chamber and evaluate the site and take photos after each reading:
  −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)
  −if the result of the second reading is equivocal, the Investigator or at the Sponsor'srequest, may perform an optional 3rd reading at 96 to 120 hours later (i.e., 6 to 7 days after application of the patch)
  −Pictures of each reading and the reading results should be sent to the Syneos Health and Pharmacovigilance

Table 10: Patch Test Procedure

Duration of study product application	1st reading + Photographs	2nd reading + Photographs	3rd reading (optional) + Photographs
48 hours	48 hours after study product application (30 minutes after patch test removal)	72 to 96 hours after studyproduct application (24 to 48 hours after patch test removal)	6 or 7 days after study product application (96 to 120 hours after patch removal)

- Use the following scoring system (Spiewak 2008) used by the International Contact Dermatitis Research Group (ICDRG) at each reading, see **Table 11**:

Table 11: Suspected Sensitization - Challenge Reaction Grading Scale

Score	Morphology	Interpretation
-	No reaction	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

- At the last reading, the Investigator will provide an assessment regarding a possible sensitization reaction using the following scale (see Table 12):

Table 12: Suspected Sensitization - Challenge Conclusion Scale

Score	Sensitization Reaction
0	Negative, might include an irritant reaction
1	Equivocal
2	Positive

- In case of absence of reaction after quotation with the International Contact Dermatitis Research Group (ICDRG scale), the subject may resume treatment if appropriate

- If the rechallenge is positive or equivocal after quotation with the ICDRG scale, notify Syneos Health immediately. Except specific situations, a new series of patch tests 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 an additional two weeks (but not later than 6 months) and after all signs and symptoms have resolved.If a rechallenge test is required, repeat this process above beginning with the test chamber step

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

A case-by-case approach will be applied and the procedure to follow will be discussed with the Sponsor.

10 STATISTICAL METHODS

A statistical analysis plan (SAP) will be developed as a separate document. The SAP will contain detailed and technical descriptions of specific data conventions, calculations, and statistical procedures for executing the analyses that are specified in this Section 10 of the clinical study protocol.

10.1 Statistical and Analytical Plans

10.1.1 Data sets or Populations Analyzed

10.1.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will comprise all randomized subjects. All primary and secondary efficacy endpoints will be analyzed based on the ITT population. The ITT population will be the primary population for all efficacy analyses.

10.1.1.2 Safety Population

The safety population will consist of all randomized subjects who receive at least 1 application of study drug. All safety data will be summarized based on the safety population.

10.1.1.3 Per Protocol Population

The per protocol (PP) population will comprise all subjects in the ITT population who have no major protocol deviations, that would have a significant effect on the efficacy of the study treatment. The PP population will be used for the sensitivity analyses of primary endpoint to assess the robustness of study conclusion.

10.1.2 Demographic and Other Baseline Characteristics

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

10.1.3 Efficacy Analysis

Both primary and secondary endpoints will be evaluated for the ITT population.

The PP analysis will be carried out as sensitivity analyses for the primary endpoint.

All efficacy variables will be summarized by treatment at each visit.

The categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using descriptive statistics (number of observations, mean, median, minimum, maximum, and standard deviation) for the data collected at each visit.

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

10.1.3.1 Primary Endpoint Analysis

The proportion of subjects with complete clearance of all AK lesions treated at 12 weeks after the last DL-PDT (Visit 6) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The p-value for the treatment comparison (MAL DL-PDT vs. vehicle DL-PDT) will be calculated from the general association statistic of the stratified CMH test. Difference in proportions between treatment groups and the 99.875% confidence interval of the difference will be based on the large sample approximation method for binary data.

The hypothesis test for the primary efficacy endpoint will be evaluated on the ITT population at the two-sided significance level $\alpha = 0.00125$.

Efficacy will be claimed if the between treatment difference on the primary endpoint is statistically significant with a p-value < 0.00125.

This result will provide an acceptable level of evidence of efficacy, in presence of good internal consistency across primary and secondary endpoints in the absence of a second pivotal study.

For the primary analysis all subjects on the ITT population with missing data for the primary endpoint will be classified as non-responders regardless of treatment allocation.

10.1.3.2 Primary Endpoint Sensitivity Analysis

To assess the robustness of the primary efficacy results, the following sensitivity analyses will be conducted:

1. Missing data of the ITT population will be imputed using MI (Multiple Imputation) under the Missing At Random (MAR) assumption. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points.
2. Missing data of the ITT population will be imputed using MI (Multiple Imputation) based on the Pattern-Mixture Model under the missing not at random (MNAR) assumption, by using the profiles from vehicle DL-PDT subjects with observed data to impute missing data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with non-missing data from earlier time points included as covariate in the imputation model.
3. Missing data of the ITT population will be imputed using MI (Multiple Imputation) based on the Pattern-Mixture Model under the missing not at random (MNAR) assumption in order to perform a tipping-point analysis by varying independently the assumptions about the missing outcomes on the two arms and including scenarios where dropouts on MALcream DL-PDT arm have worse outcomes than dropouts on vehicle cream DL-PDT arm with the aim of exploring the plausibility of missing data assumptions under which the conclusions change (i.e. under which there is no longer evidence of efficacy). It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with non-missing data from earlier time points included as covariate in the imputation model.
4. Missing data of the ITT population will be imputed using Last Observation Carried Forward (LOCF).
5. Observed Case (OC) analysis on the ITT population.
6. The primary analysis will be repeated on the PP population.

10.1.3.3 Secondary Endpoints Analysis

The percent reduction from baseline in the number of cleared treated lesions at 12 weeks after the last DL-PDT treatment (Visit 6) will be analyzed using an ANCOVA with treatment, analysis center and baseline AKs count as fixed effects; the difference in percent reduction between MAL DL-PDT and vehicle DL-PDT, the 99.875% confidence interval of the difference and the p-value will be generated from the ANCOVA model.

For analysis of percent reduction from baseline in the number of treated AK lesions, missing counts of cleared treated lesions for subjects on the ITT population will be imputed using MI (Multiple Imputation) under the Missing At Random (MAR) assumption. It is expected that the pattern of

missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing lesion count data, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points.

The proportion of subjects with 75% or greater reduction from baseline in the number of cleared treated lesions at 12 weeks after the last DL-PDT treatment (Visit 6) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The p-value for the treatment comparison (MAL DL-PDT vs. vehicle DL-PDT) will be calculated from the general association statistic of the stratified CMH test. Difference in proportions between treatment groups and the 99.875% confidence interval of the difference will be based on the large sample approximation method for binary data.

For the analysis of proportion of subjects achieving a partial response, all subjects of the ITT population with missing data will be classified as non-responders regardless of treatment allocation.

10.1.3.4 Subgroup Analysis

Descriptive summary and analysis for primary and secondary endpoints will be produced for the following subgroups and others as appropriate:

- AK lesions location
  - ✓ Face
  - ✓ Balding scalp
- Baseline AK grade
  - ✓ Grade 1 (mild) AK
  - ✓ Grade 2 (moderate) AK
- Sex
  - ✓ Male
  - ✓ Female
- Number of baseline AK lesions
  - ✓ 4-8 AK lesions
  - ✓ 9-12 AK lesions
- Fitzpatrick skin type
  - ✓ Type I, II and III
  - ✓ Type IV, V and VI

10.1.3.5 Other Assessments Analysis

The subject questionnaires at Visit 4 (second DL-PDT) and Visit 6 (Final Visit) will only be descriptively summarized. The Clincal Assessment of the Subject's Skin Aspect evaluated by the investigator at Visit 6 will only be descriptively summarized. The subject exposure time and PpIX effective dose at Visit 2 and Visit 4 will only be descriptively summarized.

10.1.4 Safety Analysis

All safety analyses will be based on the safety population.

Summaries of all safety endpoints will be presented.

10.1.4.1 Subject Assessment of Pain

Pain data will be summarized by treatment using descriptive statistics (number of observation, mean, median, minimum, maximum, and standard deviation) and tables of frequency. Missing pain data will not be imputed. The Hodges-Lehmann estimator of the median difference in pain scores between treatment groups and the related nominal 95% Moses distribution-free confidence interval will be presented by visit for descriptive purposes only.

10.1.4.2 Adverse Events

Treatment-emergent AEs, defined as those AEs occurring after the first administration of study treatment until the last study visit, will be tabulated in frequency tables by system organ class and preferred term based on the Medical Dictionary for Regulatory Activities for each study phase. Additional summary tables will be provided for SAEs, AESIs, AEs related to the study drug(s) (defined as the ones with a reasonable possibility of causal relationship with the study drug), AEs related to the study procedures (defined as the ones with a reasonable possibility of causal relationship with the study procedures), and AEs leading to treatment discontinuation and study withdrawal. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

Pretreatment AEs will be listed separately.

10.1.4.3 Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized by visit and treatment group for each study phase. In addition, the number and percentage of subjects below, within, and above the laboratory reference ranges, the number and percent of subjects with CS abnormal values (of clinical concern as identified by the Investigator) and the number and percentage of subjects who meet criteria of potential CS abnormal values will be summarized by treatment group. Shift tables will be generated using the reference ranges. Reference ranges will be provided in the laboratory manual.

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

10.1.4.4 Vital Signs

All vital signs data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percent of subjects with CS abnormal values (of clinical concern as identified by the Investigator) and the number and percentage of subjects who meet criteria of potential CS abnormal values will be summarized by treatment group.

10.1.4.5 Physical Examination

The number and percentage of subjects who are normal, abnormal ([CS), and abnormal (not CS [NCS]) will be displayed by treatment at each visit.

10.1.4.6 Electrocardiogram

The number and percentage of subjects who have ECGs that are abnormal/CS and normal/NCS will be displayed by treatment at each visit.

10.1.4.7 Safety Visit Question

The answers Yes/No to the question "Does the subject exhibit signs and symptoms of possible contact sensitization?" at Visit 3 and Visit 5 will be listed.

10.1.5 Interim Analyses

No interim analysis is planned.

10.1.6 Handling of Missing Data

For the primary analysis all subjects on the ITT population with missing data for the primary endpoint will be classified as non-responders regardless of treatment allocation

To assess the robustness of the primary efficacy results, the following sensitivity analyses will be conducted:

1. Missing data of the ITT population will be imputed using MI (Multiple Imputation) under the Missing At Random (MAR) assumption. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points.
2. Missing data of the ITT population will be imputed using MI (Multiple Imputation) based on the Pattern-Mixture Model under the missing not at random (MNAR) assumption, by using the profiles from vehicle cream DL-PDT subjects with observed data to impute missing data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with non-missing data from earlier time points included as covariate in the imputation model.
3. Missing data of the ITT population will be imputed using MI (Multiple Imputation) based on the Pattern-Mixture Model under the missing not at random (MNAR) assumption in order to perform a tipping-point analysis by varying independently the assumptions about the missing outcomes on the two arms and including scenarios where dropouts on MAL cream DL-PDT arm have worse outcomes than dropouts on vehicle cream DL-PDT arm with the aim of exploring the plausibility of missing data assumptions under which the conclusions change

(i.e. under which there is no longer evidence of efficacy). It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Logistic regression will be employed to model the missing subject complete response binary outcome, with non-missing data from earlier time points included as covariate in the imputation model.

4. Missing data of the ITT population will be imputed using Last Observation Carried Forward (LOCF).

For analysis of percent reduction from baseline in the number of treated AK lesions, missing counts of cleared treated lesions for subjects on the ITT population will be imputed using MI (Multiple Imputation) under the Missing At Random (MAR) assumption. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing lesion count data, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points.

For the analysis of proportion of subjects achieving a partial response, all subjects of the ITT population with missing data will be classified as non-responders regardless of treatment allocation.

10.2 Determination of Sample Size

A long-term follow up study is planned to gather data about recurrences at around the 1 year time point after the DL- PDT treatments.

Subjects who achieve a complete response at Visit 6, 12 weeks after the last DL-PDT treatment, will be offered the opportunity to be followed in a 9-month long-term follow-up study to have treated lesions assessed for recurrence. The sample size calculation is based on providing enough subjects to enable the detection of a treatment difference in the primary endpoint and ensuring approximately 100 subjects complete the long-term follow-up study.

Approximately 675 subjects will be screened for a total of 570 subjects to be randomized (380 in the MAL DL-PDT arm and 190 in the vehicle cream DL-PDT arm using a 2:1 randomization ratio) to have approximately 100 subjects complete the long-term follow-up study. This study will have more than 90% power to detect a 30% difference between MAL cream DL-PDT (45% complete response rate) and vehicle cream DL-PDT (15% complete response rate) and with a type I error of 0.00125 assuming 7% subjects will be non-evaluable at 12 weeks after the last DL-PDT for the primary endpoint, 70% of subjects achieving a complete response at 12 weeks after the last DL-PDT will be enrolled in the LT follow-up study and dropout rate of 10% during LT follow-up study.

10.3 Protocol Deviations

Major deviations include the following categories:

- Eligibility deviations (inclusion/exclusion criteria)

- Improper administration of study medication
- Noncompliance with study medication due to 2 consecutive incomplete treatments or per the Investigator's discretion
- Noncompliance with study procedures if the consequence of noncompliance would compromise either the subject's safety and/or the study integrity, primary endpoint, and/or is not in line with Good Clinical Practice (GCP)/ICH guidelines
- Use of prohibited concomitant therapies
- Administrative error
  - ✓ Accidental unblinding
  - ✓ Medication dispensing errors
  - ✓ AK lesion counts and evaluation performed by a non-approved evaluator

The final list of major protocol deviation criteria, subjects who have any major protocol deviations and subjects excluded from the per protocol (PP) population will be documented in the blind review memo before database lock and in the clinical study report.

Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to database lock and unblinding and will be documented in blind review memo and in the clinical study report.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on eCRFs. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3 Personnel Training

Study monitors and all relevant personnel will be trained before study initiation on the condition to be treated, the standard operating procedures to be used in this clinical study, the protocol, and all study-specific procedures. Team organization, communication, and operational issues will also be discussed and agreed upon.

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

It is the principal investigator's responsibility to ensure that all personnel involved in the study conduct receive training before participating in any procedure and/or evaluation. Each study center will have a training record as part of the site file and TMF.

11.4 Data Management

The designated CRO will be responsible for activities associated with the data management of this study. This will include, but is not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. All data management activities will be detailed in the data management plan.

Study centers will record all study information in an appropriate source document. The data will then be entered directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source

documents at the study center. Any changes to the data entered into the EDC system will be recorded in the audit trail.

11.5 Clinical Study Conduct

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

The investigator should document and explain any deviation from the clinical study protocol.

11.6 Amendments

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

11.7 Quality Management and Risk Evaluation

Details will be provided in a separate Integrated Quality Risk Management Plan.

12 ETHICS

12.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the nvestigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The nvestigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

12.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

12.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

12.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks, and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points she/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the Investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits, to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

12.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identities will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations (HIPAA for the United States) on personal data protection.

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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15 APPENDICES

15.1 Appendix 1: Subject Questionnaire at Visit 4 (second DL-PDT)

INTRODUCTION:

The purpose of this questionnaire is to record your feelings and opinions concerning the treatments you just received. This questionnaire must be completed after daylight illumination. Your answers will help us to better understand your needs and expectations.

This questionnaire has been designed so that it can be completed quickly and easily. Please use **black pen** to complete this questionnaire. Please check the box corresponding to your preferred answer; only ONE box should be ticked by question, unless otherwise specified. There are no "Right" or "Wrong" answers.

If you are unsure how to answer a question, please give the best answer you can.
If you need to make a change, draw a line through the answer you would like to change, and then record your next response with a checkmark, put your initial and a date next to your correction.

Your answers will not affect your participation in the study and no prejudice will be shown towards you for completing this document.

1. How convenient do you find the treatment?
   - Very convenient
   - Convenient
   - Inconvenient
   - Inconvenient a great deal

2. Did you feel any pain during the treatment?
   - ☐ Yes
   - ☐ No

   2b. If yes, how bothered were you by this pain?

   - ☐ Not bothered at all
   - ☐ Bothered somewhat
   - ☐ Bothered
   - ☐ Bothered a great deal

3. Globally are you satisfied with the treatment?
   - ☐ Very satisfied
   - ☐ Satisfied
   - ☐ Dissatisfied
   - ☐ Very dissatisfied

15.2 Appendix 2: Subject Questionnaire at Visit 6 (Final Visit)

INTRODUCTION:

The purpose of this questionnaire is to record your feelings and opinions (efficacy, safety, visual aspect of the skin, convenience, etc.) concerning the treatments you received during the study. This questionnaire must be completed when you end the study. Your answers will help us to better understand your needs and expectations.

This questionnaire has been designed so that it can be completed quickly and easily. Please use **black pen** to complete this questionnaire. Please check the box corresponding to your preferred answer; only ONE box should be ticked by question, unless otherwise specified. There are no "Right" or "Wrong" answers.

If you are unsure how to answer a question, please give the best answer you can.
If you need to make a change, draw a line through the answer you would like to change, and then record your next response with a checkmark, put your initial and a date next to your correction.

Your answers will not affect your participation in the study and no prejudice will be shown towards you for completing this document.

1. How satisfied were you with the effectiveness of the treatment?

   ☐ Very satisfied
   ☐ Satisfied
   ☐ Dissatisfied
   ☐ Very dissatisfied

2. How bothered were you by treatment side effects?

   ☐ Not bothered at all
   ☐ Bothered somewhat
   ☐ Bothered
   ☐ Bothered a great deal

3. Overall, are you satisfied with the treatment?

   ☐ Very satisfied
   ☐ Satisfied
   ☐ Dissatisfied
   ☐ Very dissatisfied

4. Would you consider having the treatment again?

   ☐ Yes ☐ No

15.3 Appendix 3: List of Sunscreens

Table 13: List of Sunscreens

SUNSCREENS Consumer Reports Recommended May 2019 ***denotes spray sunscreen which is flammable**	Score	Price†	Ingredients
La Roche-Posay Anthelios 60 Melt-in Sunscreen Milk	100	$36	Avobenzone 3%, Homosalate 10.72%, Octisalate 3.21%, Octocrylene 6%, Oxybenzone 3.86%
BullFrog Land Sport Quik Gel SPF 50	95	$13	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Ocotocrylene 10%, Oxybenzone 6%
Coppertone Ultra Guard Lotion SPF 70 Sunscreen	94	$8	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 10%, Oxybenzone 6%
Equate (Walmart) Ultra Lotion SPF 50 Sunscreen	94	$7	Avobenzone 3%, Homosalate 13%, Octisalate 5%, Octocrylene 7%, Oxybenzone 4%
Trader Joe's Spray SPF 50+ Sunscreen*	100	$6	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Oxybenzone 6%
Banana Boat Suncomfort Clear Ultramist Spray SPF 50+ Sunscreen*	96	$13	Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octocrylene 3%, Oxybenzone 4%
CVS Health Beach Guard Clear Spray SPF 70 Sunscreen*	90	$10	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%
Neutrogena CoolDry Sport Spray SPF 50 Sunscreen*	87	$11	Avobenzone 2.7%, Homosalate 9%, Octisalate 4.5%, Octocrylene 6%, Oxybenzone 4.5%

Neutrogena Beach Defense Water + Sun Protection Spray SPF 70 Sunscreen*	82	$13	Avobenzone 3%, Homosalate 15%, Octisalate 5%, Octocrylene 4%, Oxybenzone 6%
GOOD HOUSEKEEPING **Best sunscreens recommended by dermatologists, May 2019** https://www.goodhousekeeping.com/beauty/anti-aging/g1288/best-sunscreens/	Rating	Price†	Ingredients
X-treme Sport Spray Gel Sunscreen SPF 50 Australian Gold	"Best Value"	$10	Avobenzone 3% Homosalate 10% Octisalate 5% Octocrylene 2.75% Oxybenzone 4%
Activated Sun Protector™ Water-Light Lotion For Face & Body Sunscreen Broad Spectrum SPF 50	"Best Overall"	$29	Avobenzone 2.24%, Homosalate 8%, Octisalate 2.40%, Octocrylene 4.48%, Oxybenzone 2.88%
CoolDry Sport Sunscreen Lotion SPF 50 Neutrogena	"Most effective"	$9	Avobenzone 2.7%, Homosalate 9%, Octisalate 4.5%, Octocrylene 8%, Oxybenzone 4.5%
SunComfort Sunscreen SPF 50+ Banana Boat Lotion	"Best non-sticky formula"	$10.50	Avobenzone (3.0%), Homosalate (9.0%), Octocrylene (5.0%)
Everyday Sunscreen SPF 50 Supergoop!	"Crowd Pleaser"	$19	Avobenzone 3%, Homosalate 10%, Octinoxate 7.5%, Octisalate 5%
Moisturizing Sunscreen Lotion SPF 50+ Sun Bum	"Best for sensitive skin"	$16	Avobenzone (3%), Homosalate (10%), Octisalate (5%), Octocrylene (10%)
Sunscreen Water Sport SPF 50 Bull Frog	"Most water-resistant sunscreen"	$8	Avobenzone 2%, Homosalate 10%, Octisalate 5%, Octocrylene 2%, Oxybenzone 5%

From Environmental Working Group's 2018 guide to sunscreens https://www.ewg.org/sunscreen/best-sunscreens/best-beach-sport-sunscreens-non-mineral-options/ The Environmental Working Group takes a very different view of sunscreens and rates them according to the "hazard" they could potentially cause. Their controversial view is not mainstream. Included to allow people with a different view to choose among their recommended chemical based sunscreens. Scores 0-2 low hazard Scores 3-6 moderate hazard Scores 7-10 high hazard	Score	Price†	Ingredients
Supergoop! Super Power Sunscreen Mousse, SPF 50	3	$34	Avobenzone 3%, Homosalate 10%, Octinoxate 7.5%, Octisalate 5%
JASON Sport Sunscreen, SPF 45	3	$10	Avobenzone 3%, Homosalate 10%, Octocrylene 10%, Octyl Salicylate 5%
Coppertone Defend & Care Face Sunscreen Lotion, SPF 30	2	$10	Avobenzone 3.0%, Homosalate 8.0%, Octisalate 4.5%, Octocrylene 6.0%
Coppertone Defend & Care Face Sunscreen Lotion, SPF 50	3	$19	Avobenzone 3.0%, Homosalate 10.0%, Octisalate 4.5%, Octocrylene 8.0%
COOLA Suncare Sport Classic Sunscreen, Unscented, SPF 50	3	$32	Avobenzone 2.8%, Octinoxate 4.7%, Octisalate 4.9%, Octocrylene 7.7%
Bare Republic Clearscreen Sport Sunscreen Gel, SPF 30	2	$15	Avobenzone 2.9%, Homosalate 10.8%, Octisalate 4.9%
Alba Botanica Sport Sunscreen, Fragrance Free, SPF 45	3	$11.20	Avobenzone 3.0%, Homosalate 10.0%, Octocrylene 10.0%, Octyl Salicylate 5.0%

*sprays are flammable
†prices presented were presented in the original lists, are not exact and are shown only to show relative pricing

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, vehicle-controlled, multicenter study to assess the efficacy and safety of Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) versus vehicle cream in the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratosis of the face and scalp when using daylight photodynamic therapy (DL-PDT)

Protocol Number: RD.06.SPR.112199

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Galderma Research & Development, LLC and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Galderma Research & Development, LLC and the IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Galderma Research & Development, LLC to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature	Date
Printed Name	Title
Institution	Study Center Number