CLINICAL STUDY PROTOCOL

A double-blind, multicenter, long-term follow-up study to assess recurrence of Actinic Keratosis in subjects treated with Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) or 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), for subjects achieving complete response of treated lesions at Final Visit in Study RD.06.SPR.112199

Protocol Number:	RD.06.SPR.115230
EudraCT Number:	Not Applicable
PPD :	PPD
Investigational Product:	None
IND Number:	CCI
Phase:	3
Sponsor:	Galderma Research & Development, LLC 14501 North Freeway Fort Worth, TX 76177
Contract Research Organization:	PPD
Protocol Date:	07JAN2021
Protocol Version:	Version 3.0 Amendment 2

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A double-blind, multicenter, long-term follow-up study to assess recurrence of Actinic Keratosis in subjects treated with Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) or 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), for subjects achieving complete response of treated lesions at Final Visit in Study RD.06.SPR.112199

Protocol Number: RD.06.SPR.115230

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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Fort Worth, TX 76177
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PPD

Signature

Date

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Principal Investigator Signatory:

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2 STUDY PERSONNEL CONTACTS

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3 SYNOPSIS

Protocol Number: RD.06.SPR.115230

Title: A double-blind, multicenter, long-term follow-up study to assess recurrence of Actinic Keratosis in subjects treated with Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) or 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), for subjects achieving complete response of treated lesions at Final Visit in Study RD.06.SPR.112199

Investigational Product: none

IND Number: CCI [redacted]

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

Phase: 3

Objectives:

Primary objective: The primary objective of this study is to assess recurrence of lesions treated in RD.06.SPR.112199 for those subjects who achieved Complete Response (CR) of treated AK lesions. They will be offered the opportunity to participate in this 9-month long-term follow-up study (i.e., 52 weeks after the last DL-PDT), continuing the double-blind conduct of this study.

Secondary objective: The secondary objective of this study is to evaluate the long-term safety of MAL DL-PDT and vehicle cream DL-PDT for 52 weeks after the last DL-PDT for those subjects who achieved Complete Response (CR) of treated AK lesions in study RD.06.SPR.112199

Study Design: This is a double-blind, multicenter, parallel group, vehicle-controlled long-term follow-up study to evaluate recurrence of AKs in subjects who completed study RD.06.SPR.112199. Only those subjects who achieved CR of treated AK lesions at the Final Visit (12 weeks after the last DL-PDT session) will be offered the opportunity to continue to be followed in the current study for 9 months to assess recurrence. After obtaining informed consent for this follow-up study, the subjects will return at Weeks 14 and 40, which correspond to 26 and 52 weeks after the last DL-PDT session, respectively to assess the lesions treated in the previous study for recurrence of AK. Recurrence will be determined by reappearance of those lesions completely cleared by 2 DL-PDT sessions, i.e., subjects whose lesions are evaluated to be non-CR at the visits in this study will be deemed to have recurrence. If the percentage of subjects maintaining complete response would be 60% at Visit 3 (52 weeks after the last DL-PDT), 40% of subjects would have experienced recurrence (subject recurrence response). The same calculation will be done for lesion complete response, to assess the lesion recurrence. There will be a telephone check-in with the subjects by the clinical site at Week 40 to help retain the subject's participation for the entire duration of the study. CCI [redacted]

Number of Subjects:

Approximately 111 subjects from the MAL cream arm and 19 subjects from the vehicle cream arm from the previous study are expected to enroll in the follow-up study.

Treatment:

Neither investigational product nor intervention will be part of this study.

Study Duration:

The expected duration for each subject's participation in the study will be approximately 40 weeks from the completion of study RD.06.SPR.112199.

Study Population:

The study population will consist of adult male and female subjects with clinically confirmed mild to moderate actinic keratosis on the face and balding scalp, who have completed study RD.06.SPR.112199 with a Complete Response at Final Visit of that study, meaning those subjects, whose treated AKs were all cleared at 12 weeks after the last DL-PDT session.

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

1. Subjects who have participated in study RD.06.SPR.112199 and have achieved a complete response at the Final Visit of that study, defined as complete clearance of all treated lesions at 12 weeks after the last DL-PDT
2. Written Informed Consent before any assessment related to the LTFU study is performed
3. Willing and capable of complying with requirements of the protocol

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

1. Subjects, who develop or experience a condition that my compromise subject safety or compliance, interfere with evaluation or preclude completion of the study. In particular, these conditions include, but are not limited to malignancy or other life threatening diseases.
2. Pertinent non-compliance with the conditions for this study or instructions by the investigator during RD.06.SPR.112199

Primary Endpoint:

- Subject recurrence, defined as the proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 3, 52 weeks after the last DL-PDT treatment.

Secondary Endpoints:

- Subject recurrence, defined as the proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 2, 26 weeks after the last DL-PDT treatment;
- Lesion recurrence, defined as the percent recurrence of cleared treated lesions at Visits 2 and 3, 26 and 52 weeks after the last DL-PDT treatment.

The recurrence results will be conveyed in the opposite sense of clearance, i.e., those subjects or lesions that are not CR at Visits 2 and 3 will be deemed to have recurrence.

Safety Assessments:

The following safety assessments are planned according to the schedule of assessments (see Table 1):

- Adverse events (AEs), Treatment-emergent AEs (TEAEs), and serious AEs (SAEs)

CCI [redacted]

Statistical Analysis:

Principal Statistical Method

Populations: The safety population will consist of all enrolled subjects and will be used for all the efficacy and safety analyses.

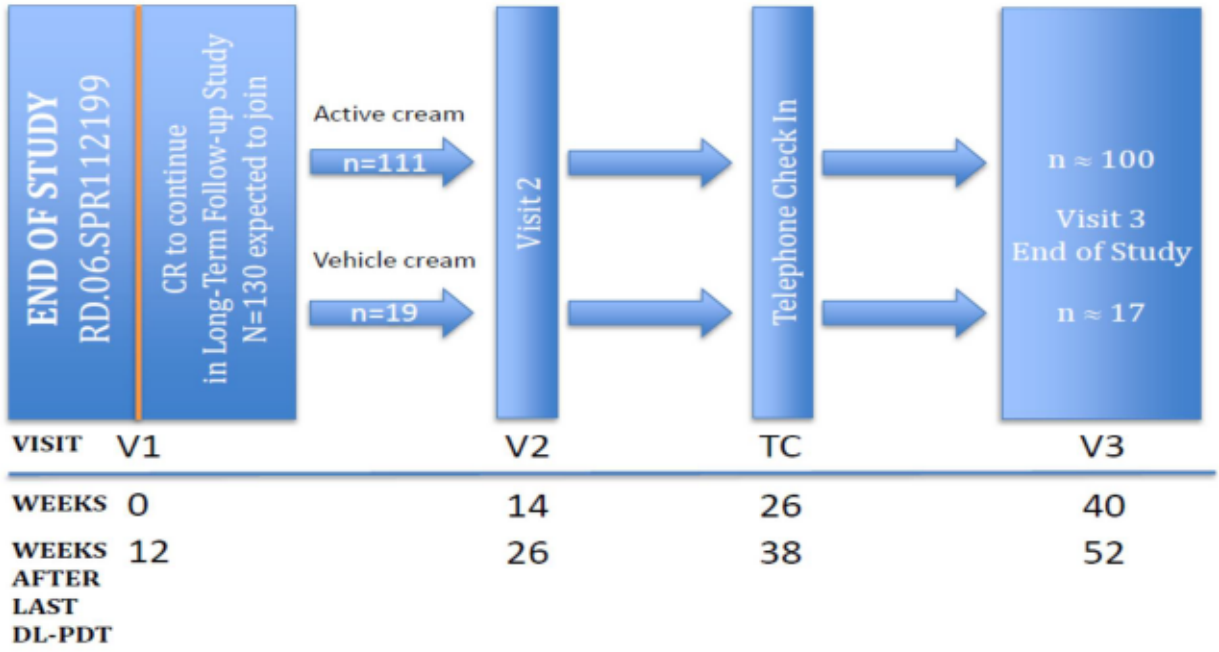
Primary Endpoint: The proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at 52 weeks after the last DL-PDT will be summarized using tables of frequency. All subjects in the safety population with missing data will be classified as non-responders regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

Secondary Endpoints: The proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at 26 weeks after the last DL-PDT will be summarized using tables of frequency. All subjects in the safety population with missing data will be classified as non-responders regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

The percent recurrence of cleared treated AK lesions at 26 and 52 weeks after the last DL-PDT treatment will be summarized using descriptive statistics. Missing counts of cleared treated AK lesions for subjects in the safety population will be imputed assuming that all baseline AK lesions had recurred regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

Sample Size: There is no formal hypothesis to be tested. The number of 100 completers in the MAL cream arm is deemed sufficient for the descriptive purposes of this study.

Figure 1: Study Schema (Synopsis)



TC=telephone call

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5 LIST OF ABBREVIATIONS

AE	Adverse Event
AK	Actinic keratosis
BCC	Basal cell carcinoma
BL	Baseline
CI	Confidence interval
CR	Complete response
CRO	Contract research organization
CS	Clinically significant
c-PDT	Conventional PDT
DL	Daylight
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
HIPAA	Health Insurance Portability and Accountability Act
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
LTFU	Long-term follow-up
MAL	Methyl aminolevinulate hydrochloride
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
PDT	Photodynamic Therapy
PpIX	Protoporphyrin IX
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
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).

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.

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. This study serves as a follow-up study to RD.06.SPR.112199 to evaluate recurrences of lesions that achieved CR in both MAL cream DL-PDT and vehicle cream DL-PDT treated groups.

7 STUDY OBJECTIVES & ENDPOINTS

7.1 Primary Objective

The primary objective of this study is to assess recurrence of AKs treated in RD.06.SPR.112199 for those subjects who achieved Complete Response (CR) of treated AK lesions. They will be offered the opportunity to participate in this 9-month long-term follow-up study (i.e., 52 weeks after the last DL-PDT), continuing the double-blind conduct of this study.

7.2 Secondary Objective

The secondary objective of this study is to evaluate the long-term safety of MAL DL-PDT and vehicle cream DL-PDT for 52 weeks after the last DL-PDT for those subjects who achieved Complete Response (CR) of treated AK lesions in study RD.06.SPR.112199.

7.3 Primary Endpoint

- The primary efficacy endpoint is the subject recurrence, defined as the proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 3, 52 weeks after the last DL-PDT treatment.

7.4 Secondary Endpoints

- Lesion recurrence, defined as the percent recurrence of cleared treated lesions at Visits 2 and 3, 26 and 52 weeks after the last DL-PDT treatment.

- Subject recurrence, defined as the proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 2, 26 weeks after the last DL-PDT treatment.

7.5 Safety Assessments

- Assess safety, including adverse events (AEs), Treatment-emergent AEs (TEAEs), related to the study drug administered in study RD.06.SPR.112199 and serious AEs (SAEs)

CCI [redacted]

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a double-blind, vehicle-controlled, multicenter, parallel-group long-term follow-up study to evaluate recurrence of AKs in subjects who completed study RD.06.SPR.112199. Only those subjects who achieved CR of treated AK lesions at the Final Visit of that study will be offered the opportunity to continue to be followed in the current study for 9 months to assess recurrence.

In this study, the results of DL-PDT with MAL 16.8% cream or a vehicle cream will be compared; no intervention occurs in this study.

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

A total of approximately 130 subjects will continue from the study RD.06.SPR.112199 to be followed for another 40 weeks, which corresponds to 52 weeks after the last DL-PDT. It is anticipated that approximately 111 subjects will continue from the MAL cream arm, and 19 subjects will continue from the vehicle cream arm. Blinding will be maintained through this study.

Subjects will have a combined visit which includes the final visit for the RD.06.SPR.112199 study and the initial visit for this study. Data from the previous study will be pulled into the database for this study. Subjects will return to the study center for another visit at Visit 2 (Week 14, 26 weeks after the last DL-PDT treatment) for efficacy and safety assessments. The investigative site staff will contact the subject via telephone at Week 26 (38 weeks after the last DL-PDT treatment) to determine if the subject is experiencing any treatment-related safety issues.

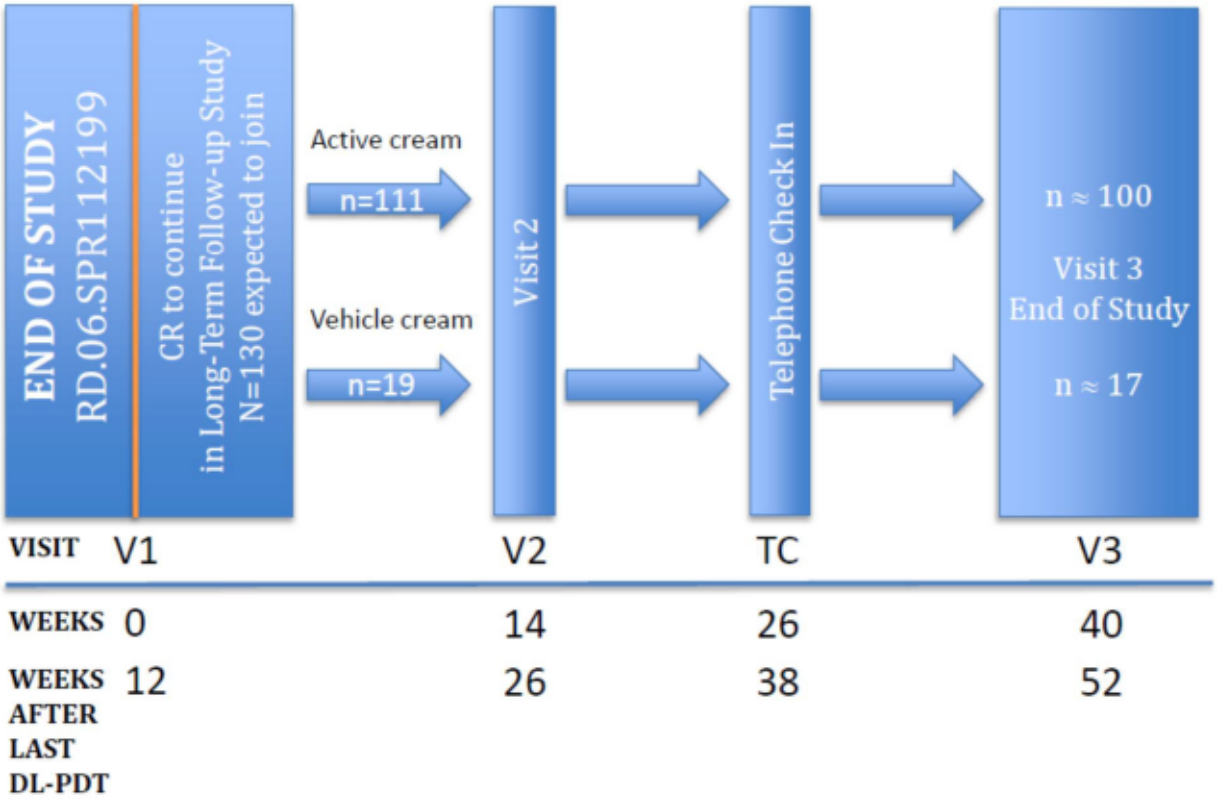
The primary endpoint of this study occurs at Visit 3; Final Visit, Week 40 (52 weeks after the last DL-PDT visit).

The 4 planned interactions are:

Visit 1	Rollover visit from study RD.06.SPR.112199; corresponds to Visit 6 in that study. Only those subjects who achieve CR will be given the opportunity to continue in this long-term follow-up study. All assessments captured are transferred to this study
Visit 2	Week 14 (26 weeks after the last DL-PDT treatment) - Efficacy and safety assessments; CCI [redacted]
Telephone check in	Week 26 (38 weeks after the last DL-PDT treatment) - Safety assessments
Visit 3	Week 40 Final Visit (52 weeks after the last DL-PDT treatment) - Efficacy and safety assessments; CCI [redacted]

8.1.1 Study Schema

Figure 2: Study Schema



TC=telephone call

8.1.2 Schedule of Assessments

Table 1: Schedule of Assessments

RD.06.SPR.112199 → RD.06.SPR.115230

Visit	1	2	2b [a,b]	3	4	4b [a,b]	5 [a,b]	6[a,b]	1	2 (7)	TC	3 (8)
Purpose	Medical history and labs	First DL-PDT session	If required	Follow-up 1 week after 1st DL-PDT	Second DL-PDT session	If required	Follow-up 1 week after 2nd DL-PDT	Final 12 weeks after last DL-PDT	Visit 6 is Visit 1 of LTFU study	26 weeks after last DL-PDT	Telephone call to check on subject	Final 52 weeks after last DL-PDT
Week	Screening	Baseline			Week 2		Week 3	Week 14/ET[f]		Week 14 Week 28	Week 26 Week 40	Week 40/ET Week 54
Visit window	-14 to -5 days	0 to +14 days			0 to +14 days		-2 to +14 days	-2 to +28 days		+/- 5 days	+/- 5 days	+/- 5 days
									LONG-TERM FOLLOW-UP STUDY			
Informed Consent CCI [redacted]	X								X			
Demographics (including FST)	X								X			
Medical History	X								X			
Previous Therapies/Procedures	X								X			
Vital Signs/Physical Examination	X							X[g] →	X			
Inclusion/Exclusion Criteria	X	X						X →	X			
Hematology/ Blood Chemistry/ UA/ECG	X							X				
Pregnancy Test[c]	X	X	X		X	X		X →	X	X		X
Weather assessment		X	X		X	X						
CCI [redacted]												
AK mapping + counting + grading[d]		X	X		X	X		X →	X	X		X
Sunscreen application		X	X		X	X						

Visit	1	2	2b [a,b]	3	4	4b [a,b]	5 [a,b]	6[a,b]	1	2 (7)	TC	3 (8)
Purpose	Medical history and labs	First DL-PDT session	If required	Follow-up 1 week after 1st DL-PDT	Second DL-PDT session	If required	Follow-up 1 week after 2nd DL-PDT	Final 12 weeks after last DL-PDT	Visit 6 is Visit 1 of LTFU study	26 weeks after last DL-PDT	Telephone call to check on subject	Final 52 weeks after last DL-PDT
Week	Screening	Baseline			Week 2		Week 3	Week 14/ET[f]		Week 14 Week 28	Week 26 Week 40	Week 40/ET Week 54
Visit window	-14 to -5 days	0 to +14 days			0 to +14 days		-2 to +14 days	-2 to +28 days		+/- 5 days	+/- 5 days	+/- 5 days
									LONG-TERM FOLLOW-UP STUDY			
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 [d]					X	X		X[d]				
Safety Visit Question				X			X					
Adverse Events[e]	X	X	X	X	X	X	X	X→	X	X	X	X
Concomitant Therapies/Procedures [d]		X	X	X	X	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				X

Visits 2 and 4 may be delayed for up to 2 weeks in case of unsuitable weather conditions at randomization/treatment outset; these visits will be Visits 2b and 4b. These postponements will be automatically added to the time of scheduled Visits 5 and 6

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. 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 not be excluded from the study. Likewise, these repeat visits will be added to the time of scheduled Visits 5 and 6. If a subject has two incomplete visits in a row, ther subject will continue with assessment in this study.

a) Only for females of childbearing potential, UPT at Visits 1,2, and 3 of this study

b) Should be performed earlier if subject discontinues before Visit 3 of this study

c) Adverse Events have to be collected from the time of the Informed Consent signature

d) Exit form should be completed after subject data collection has been completed for subjects in the study; FST=Fitzpatrick Skin Type

e) Red arrows signify that pertinent data obtained at Visit 6 of RD.06.SPR.112199 will be transcribed as this visit as Visit 1 of RD.06.SPR.115230

8.2 Discussion of Study Design

8.2.1 Study Design

This study will evaluate recurrence of AKs treated in study RD.06.SPR.112199. In this study, investigators will review the condition of lesions mapped and treated in that study, over a 9-month follow-up. Only those subjects who achieve a Complete Response at the Final Visit from the vehicle and active cream groups in that study, are eligible to continue in this long-term follow-up study.

In study RD.06.SPR.112199, approximately 570 subjects with mild to moderate actinic keratoses of the face and scalp, meeting specific criteria, will receive 2 sessions of DL-PDT, randomized to receive either MAL 16.8% cream (CD06809-41) or vehicle cream in a CCI ratio. It is estimated that 380 subjects would receive MAL DL-PT and 190 subjects would receive vehicle cream DL-PDT at 2 treatment sessions 2 to 4 weeks apart. The endpoint of study RD.06.SPR.112199 occurs at Visit 6, 12 weeks after the last DL-PDT treatment, when the treated AK lesions are assessed for complete response. The subject complete response, defined as the proportion of subjects with complete clearance of all AK lesions treated, will compare MAL cream with vehicle cream. In the powering of the study, the assumptions of a 45% subject complete response for MAL 16.8% cream (CD06809-41) and 15% subject complete response for vehicle cream were used. Because there will be subjects enrolling in the long-term follow-up study from both treatment arms, it is essential to keep the subjects and the site personnel blinded to the treatment, in order to not bias the evaluations of recurrence scheduled at Visits 2 and 3 of this study, occurring 26 and 52 weeks after the last DL-PDT.

Approximately 130 subjects who completed the study RD.06.SPR.112199 and achieve complete response of all treated lesions (estimated to be 111 randomized to MAL DL-PDT and 19 randomized to Vehicle DL-PDT) will be enrolled in this study in order to have approximately 100 subjects randomized to MAL DL-PDT who complete the long-term follow-up.

8.3 Selection of the Study Population

8.3.1 Number of Planned Subjects

Approximately 130 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. Subjects who have participated in study RD.06.SPR.112199 and have achieved a complete response at Final Visit of that study, complete clearance of treated lesions at 12 weeks after the last DL-PDT.
2. Written Informed Consent before any assessment related to the LTFU study is performed.

3. Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol.

8.3.3 Exclusion Criteria

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

1. Subjects, who develop or experience a condition that may compromise subject safety or compliance, interfere with evaluation or preclude completion of the study. In particular, these conditions include, but are not limited to malignancy or other life threatening diseases.
2. Pertinent non-compliance with the conditions for this study or instructions by the investigator during RD.06.SPR.112199.

8.3.4 Removal of Subjects From 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 the study 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) see Section 8.3.7
- NON-COMPLIANCE WITH 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
- PHYSICIAN DECISION
- OTHER

The reason(s) for withdrawal will be documented in the eCRF.

Subjects who prematurely discontinue the study will be encouraged to complete the Final/ETstudy 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 the company itself occur. In this event, the Investigator(s) will be informed of the reason for study termination.

8.3.5 Method of Continuing already Randomized Subject from Previous study

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). See Section 9.

8.3.6 Blinding

All attempts will be made to keep the investigative site staff and subjects blinded to the study treatment from study RD.06.SPR.112199 throughout the study. Members of the study center staff, including the procedure operator, will not have access to the randomized treatment assignment of subjects in RD.06.SPR.112199. It would be extremely unlikely for a situation to occur in which the blind would need to be broken during this study. The Investigator or sub-investigator should consult with the medical monitor and the Sponsor in cases where it be required to break 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. The reporting requirements for unblinding are the same for reporting an SAE. See also Section 9.2.1.3

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.

8.3.7 Prior and Concomitant Therapy

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.

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 2 are considered prohibited in the treatment areas because they may interfere with the lesion assessments.

Table 2: Forbidden Treatments in Treatment Area

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

In case the subject is using topical therapy listed in Table 2 on other areas than on the documented lesions, the Investigator will remind him/her to pay strict attention to not apply any of these therapies on the treatment areas.

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. It is also possible that the use of prohibited therapies may result in early termination of a subject.

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

8.4 Duration of Subject Participation

The expected duration for each subject's participation in the study will be approximately 40 weeks.

8.4.1 Early Termination Visit

Subjects may discontinue from the study at any time.

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

8.5 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits occurring outside of the visit window.

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 different SIN from the SIN in protocol RD.06.SPR.112199. For the duration of the clinical study, the subject will be identified using the new SIN in all documentation and discussion for this protocol.

9.1 Efficacy Assessments

Evaluations are to be performed by the same Investigator for a given subject throughout the study, whenever possible. The Investigator is to remain blinded to the study treatment from study RD.06.SPR.112199.

9.1.1 Lesion Response

The lesions treated in the pivotal trial will be evaluated for reoccurrence. Any lesions that have recurred will be evaluated for severity according to the grading scale in Table 3

Table 3: 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 2 and 3/ET to identify each lesion treated previously, and the lesion response as a CR or a non-CR, as described in Table 4.

Table 4: 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 Visits 2 and 3 of this study (26 and 52 weeks after the last DL-PDT session), the subject will be assessed as a subject CR and will be deemed to have no recurrence. If any of the treated lesions in the treatment area are assessed to be non-CR, those lesions are recurrences; the subject will be assessed as a non-complete responder or deemed as a subject recurrence.

9.2 Safety Assessments

Safety assessments will be conducted for all subjects at Visit 1 (upon signing of the ICF) and at every subsequent visit.

Adverse events (AEs), Treatment-emergent AEs (TEAEs), related to the study treatment in study RD.06.SPR.112199. and serious AEs (SAEs) will be recorded during each visit, should they occur.

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 product, whether or not it is related to the medicinal 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
- Each new episode of a chronic disease (e.g., hay fever, allergy) from the time the ICF is signed 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 related to the study treatment of study RD.06.SPR.112199, 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 will be recorded immediately in the source document and described on the Adverse Event Form (“AE Form”) along with the date of onset, seriousness, severity, relatedness or causality and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

Adverse events assessed as related to the study treatment from the previous study 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. If not resolved at time of LTFU study completion, sites will continue to contact patient on a regular basis until resolved or stable.

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 subject's oversight. 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 will have determined that 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) in study RD.06.SPR.112199.

For AEs arising during this study, 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.

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.

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)
- Other action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2.1.1 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.

9.2.1.2 Adverse Events of Special Interest (AESIs)

There are no AESIs in this study as there is no treatment or intervention.

9.2.1.3 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 PPD Safety and Pharmacovigilance group of an SAE report, by email or fax:

   Fax Number: PPD
   Safety email: PPD

Note: Immediate SAE reporting is required by the Investigator if it occurs during the clinical study, 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 to the PPD 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.

9.2.1.4 Procedure for Reporting Pregnancies

A pregnancy occurring during this clinical study, where the fetus would not have been exposed to the study drug because of the temporal gap from study drug exposure to the beginning of this study (12 weeks and > 7 half lifes) will be monitored nonetheless, in order to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Continue to follow the subject in the clinical study. The subject will not be receiving any intervention in this study.

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 PPD Safety and Pharmacovigilance group. Refer to Section 9.2.1.3.

Note: Immediate pregnancy reporting is required by the Investigator if it occurs during the clinical study.

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 PPD 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 PPD 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 9.2.1.3).

9.2.1.5 Unexpected Adverse Reactions

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., PPD) 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., PPD) will file it accordingly (i.e., with the TMF), and will notify the IRB/IEC, if appropriate, according to local requirements.

9.2.2 Pregancy Testing

All women of childbearing potential will have a urine pregnancy test at Visit 1 and UPTs at subsequent visits at Visits 2 and 3, according to Section 8.1.2.

If the result of a UPT is positive, it must be confirmed with a serum pregnancy test.

Subjects with a positive serum pregnancy test result at Visit 1 will be followed in this study.

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.

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[redacted]

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

Not applicable.

10.1.1.2 Safety Population

The safety population will consist of all enrolled subjects and will be used for all the efficacy and safety analyses.

10.1.1.3 Per Protocol Population

Not applicable.

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 safety population.

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 recurrence of any (≥1) cleared treated AK lesions at 52 weeks after the last DL-PDT will be summarized using tables of frequency. All subjects in the safety population with missing data will be classified as non-responders regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

CCI [redacted]

10.1.3.2 Primary Endpoint Sensitivity Analysis

No sensitivity analysis is planned.

10.1.3.3 Secondary Endpoints Analysis

The proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at 26 weeks after the last DL-PDT will be summarized using tables of frequency. All subjects in the safety population with missing data will be classified as non-responders regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

The percent recurrence of cleared treated AK lesions at 26 and 52 weeks after the last DL-PDT treatment will be summarized using descriptive statistics. Missing counts of cleared treated AK lesions for subjects in the safety population will be imputed assuming that all baseline AK lesions had recurred regardless of treatment allocation. Summaries by treatment group will be presented for both the imputed data and the observed cases. CCI [redacted]

10.1.3.4 Subgroup Analysis

No subgroup analysis is planned.

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 Adverse Events

Treatment-emergent AEs, defined as those AEs occurring after the first administration of study treatment until the last study visit, from study RD.06.SPR.112199 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, 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.

10.1.5 Interim Analyses

An interim analysis is planned of all available data from this study, RD.06.SPR.115230, at the time of regulatory submission for marketing approval for MAL cream.

10.1.6 Handling of Missing Data

For the proportion of subjects with recurrence at 26 and 52 weeks after the last DL-PDT treatment, all subjects in the safety population with missing data will be classified as non-responders regardless of treatment allocation.

For the recurrence of cleared treated AK lesions at 26 and 52 weeks after the last DL-PDT treatment, missing counts of cleared treated AK lesions for subjects in the safety population will be imputed assuming that all baseline AK lesions had recurred regardless of treatment allocation.

10.2 Determination of Sample Size

This 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 Final Visit of study RD.06.SPR.112199, 12 weeks after the last DL-PDT treatment, will be offered the opportunity to be followed in this 9-month long-term follow-up study to have treated lesions assessed for recurrence. The sample size calculation of study RD.06.SPR.112199 was based on providing enough subjects to enable the detection of a treatment difference in the primary endpoint of that study and ensuring approximately 100 subjects randomized to MAL DL-PDT complete the long-term follow-up study.

Approximately 675 subjects are 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 CCI randomization ratio) in the study RD.06.SPR.112199 to have approximately 100 subjects randomized to MAL DL-PDT complete this long-term follow-up study. CCI

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10.3 Protocol Deviations

Major deviations are categorized into the following categories:

- Eligibility deviations (inclusion/exclusion criteria)
- 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

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be described in the final SAP and 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 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, and study coordinators will be trained at the Site Initiation Visit by the site clinical research associate.

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. 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.

14 REFERENCES

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Investigator Signature Page

Protocol Title: A double-blind, multicenter, long-term follow-up study to assess recurrence of Actinic Keratosis in subjects treated with Methyl aminolevulinate hydrochloride (MAL) 16.8% cream (CD06809-41) or 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), for subjects achieving complete response of treated lesions at Final Visit in Study RD.06.SPR.112199

Protocol Number: RD.06.SPR.115230

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