Statistical Analysis Plan for Interventional Studies

Sponsor Name: Galderma Research & Development, LLC

Protocol Number: RD.06.SPR.115230

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

Clinical Trial Phase: III

Protocol Version and Date: 3.0 Amendment 2 (07-Jan-2021)

Syneos Health Project Code: 7007743

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
Draft 1.1	15-Jan-2021	PPD	Changes due to protocol amendment 2
final 2.0	27-Sep-2021	PPD	Change of Lead Biostatistician and Senior Reviewing Biostatistician

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD, Principal Biostatistician	PPD	PPD
Name, Title	Signature	Date (DD-Mmm-YYYY)
Lead Biostatistician		

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Senior Reviewing Biostatistician		

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Principal Biostatistician		

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AK	Actinic Keratosis
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
DL-PDT	Daylight Photodynamic Therapy
eCRF	Electronic Case Report Form
ET	Early Termination
FST	Fitzpatrick Skin Type
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IRC	Independent Review Committees
LTFU	Long-term Follow-up
MAL	Methyl Aminolevinulate Hydrochloride
MedDRA	Medical Dictionary for Regulatory Activities
PDT	Photodynamic Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
UPT	Urine Pregnancy Test
WHO	World Health Organization

2. Introduction

This Statistical Analysis Plan (SAP) is based on the study protocol final version 3.0 dated 07-JAN-2021. This document describes all the analyses and reporting that will be required for a clinical report purpose and any resulting publications. This SAP has been developed prior to any examination of study data. The analyses and reporting will be performed after the completion of study. Any post hoc, or unplanned, exploratory analyses performed, if included, will be clearly identified as such in the final Clinical Study Report (CSR).

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to assess recurrence of lesions treated in RD.06.SPR.112199 for subjects who achieved Complete Response (CR) of treated Actinic Keratosis (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.

3.2. 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 CR of treated AK lesions in study RD.06.SPR.112199.

4. Study Design

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 throughout 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 (26 weeks after the last DL-PDT) for efficacy and safety assessments. The investigative site staff will contact the subject via telephone at Week 26 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).

Figure 1 - Study Schema

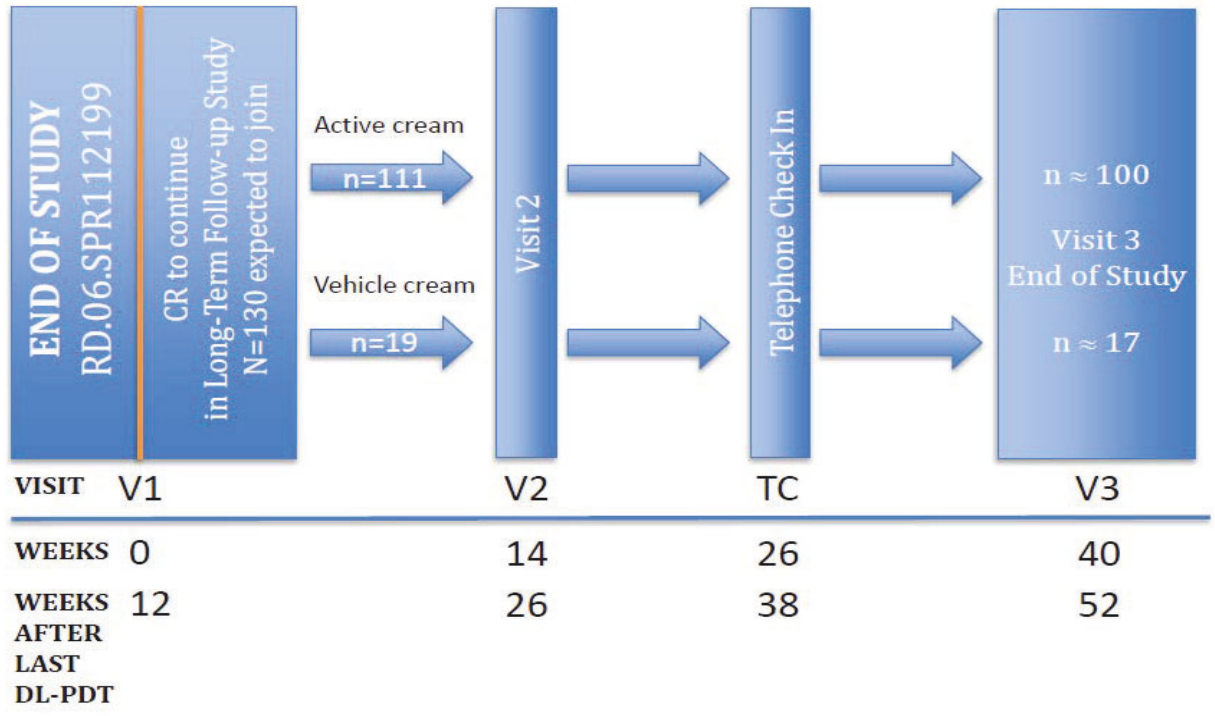

Table 1 - Schedule of Assesments of Efficacy and Safety Variables

	RD.06.SPR.112199								RD.06.SPR.1152300			
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]**		**Week14 Week 28**	**Week26 Week 40**	**Week40/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

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]		Week14 Week 28	Week26 Week 40	Week40/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			
Weather assessment		X	X		X	X						
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AK mapping + counting + grading[d]		X	X		X	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 [d]					X	X		X[d]				

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]		Week14 Week 28	Week26 Week 40	Week40/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			
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

Abbreviations: FST=Fitzpatrick Skin Type.

a) 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.
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. 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.
c) Only for females of childbearing potential, UPT at Visits 1,2, and 3 of this study
d) Should be performed earlier if subject discontinues before Visit 3 of this study

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

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.

5. Efficacy and Safety Assessments

5.1. Efficacy Variables

5.1.1. 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 2.

Table 2 - 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 (26 weeks after the last DL-PDT) and Visit 3/Final Visit (52 weeks after the last DL-PDT) to identify each lesion treated previously, and the lesion response as a CR or a non-CR, as described in Table 3.

Table 3 - Lesion Response Score

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

5.2. Safety Variables

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

5.2.1. Adverse Events

Adverse events (AEs) will be recorded during each visit (Visits 1, 2 and 3) and during telephone call.

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.

Refer to the study protocol for further details about AEs definition and management.

5.2.2. Pregancy Testing

All women of childbearing potential will have a urine pregnancy test at Visits 1, 2 and 3.

If the result of a urine pregnancy test (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.

6. Efficacy Endpoints

6.1. 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.

6.2. 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.

7. Populations Analyzed

7.1. Intent-to-Treat Population

Not applicable.

7.2. Safety Population

The safety population will consist of all enrolled subjects and will be used for all the efficacy and safety analyses. Screen failures will not be included into the Safety Population.

7.3. Per Protocol Population

Not applicable.

8. Sample Size Consideration

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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9. Statistical Methods and Data Considerations

9.1. General Considerations

9.1.1. Baseline

Baseline analysis visit is based on study RD.06.SPR.112199. For statistical analyses purpose, baseline is defined as the last measurement prior to the first DL-PDT treatment of study RD.06.SPR.112199 (regardless of treatment completion status). CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.1.3. Reference Start Date and Analysis Day

The first treatment date of study RD.06.SPR.112199 will be the reference start date.

Analysis day will be calculated from the first treatment date of study RD.06.SPR.112199 and will be used to show start/end day of assessments, events, therapies or procedures.

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[redacted]

9.1.4. Analysis Visits Definition

Analysis visit will be calculated according to the following table (see Table 5) to summarize the data by proper visit.

Table 5 - Analysis Visits Definition

Clinical Visit	Analysis Visit	Analysis Visit Number	Target Study Day	Visit Window
Visit 1 (12 weeks after the last DL-PDT)	Week 14	11	Day of Visit 6 of study RD.06.SPR.112199	<= Target Study Day + 14 days
Visit 2 (26 weeks after the last DL-PDT)	Week 28	12	Day of last DL-PDT + 182 days	>= Target Study Day - 21 days <= Target Study Day + 21 days
Telephone Contact (38 weeks after the last DL-PDT)	Week 40	13	Day of last DL-PDT + 266 days	>= Target Study Day - 21 days <= Target Study Day + 21 days
Visit 3 (52 weeks after the last DL-PDT)	Week 54	14	Day of last DL-PDT + 364 days	>= Target Study Day - 28 days

Early termination visit will be managed as a stand-alone visit. The assessments performed at early termination visit will be windowed based on the analysis visit windows.

Unscheduled visits will be windowed based on the analysis visit windows.

If multiple assessments are performed within the same window, all assessments will be listed and the ones taken closest to the target study day will be used for the analysis.

9.1.5. Missing Data Management

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.

9.1.6. Descriptive Statistics

For the descriptive statistics, unless otherwise noted, the categorical variables will be summarized by frequency and percentage (n, %) for each response category, CCI [redacted].

9.1.7. Statistical Tests and Confidence Intervals

No formal hypothesis test will be performed in this study for the primary and the secondary endpoints. CCI [redacted]

CCI [redacted]

9.1.9. Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

9.2. Study Subjects

9.2.1. Disposition of Subjects

The number and percentage of subjects (n, %) will be summarized by treatment group and overall (all subjects) for the following categories:

- Subjects screened;
- Subjects eligible;

- Screen failures;
  - Reasons for screen failure;
- Screen failures due to COVID-19;
  - Reasons for screen failure due to COVID-19;
- Subjects enrolled;
- Subjects enrolled who completed the study;
- Subjects enrolled who discontinued the study;
  - Reasons for study discontinuation;
- Subjects enrolled who discontinued the study due to COVID-19;
  - Reasons for study discontinuation due to COVID-19;
- Subjects enrolled affected by COVID-19 related study disruptions;
- Subjects enrolled affected by COVID-19 related study disruptions impacting efficacy;
- Subjects enrolled affected by COVID-19 related study disruptions impacting safety.

All disposition data will be listed. A listing of all subjects affected by the COVID-19 related study disruptions inclusive of the description of how the individual's participation was altered will be provided.

9.2.2. Demographic and Baseline Characteristics

Descriptive summaries of the following demographic data and baseline characteristics will be presented by treatment group and overall using the Safety population.

- Age
- Age group
  - ≤ 39 years old
  - 40-64 years old
  - ≥ 65 years old
- Sex
  - Male
  - Female
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
  - Unknown
- Race
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Hawaiian Native or Other Pacific Islander
  - Other
  - Multiple
- Fitzpatrick skin type
  - Type I
  - Type II
  - Type III

  - Type IV
  - Type V
  - Type VI
- Number of baseline AK lesions of grade 1 and grade 2 and total number of baseline AK lesions
- Classified number of baseline AK lesions
  - 4-8 AK lesions
  - 9-12 AK lesions
- Baseline AK grade
  - Grade 1 (mild) AK
  - Grade 2 (moderate) AK

All demographic data and baseline characteristics will be listed.

9.2.3. Accounting of Subjects

Number and percentage (n, %) of subjects for each clinical visit and each analysis visit will be presented by treatment group and overall using the Safety Population.

9.3. Protocol Deviations

Potential major protocol deviations may include but are not limited to:

- 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;
- Administrative error:
  - Accidental unblinding;
  - AK lesion counts and evaluation performed by a non-approved evaluator.

Major protocol deviations and major protocol deviations due to COVID-19 will be summarized using frequency and percentage (n, %) for each deviation coded term by treatment group and overall using the Safety Population. All protocol deviations will be listed.

9.4. Medical History, Prior and Concomitant Therapies and Procedures

For statistical analysis purposes, prior therapies/procedures are defined as those ending before the day of first treatment of study RD.06.SPR.112199; concomitant therapies/procedures are defined as those starting before the day of first treatment of study RD.06.SPR.112199 and ongoing on the day of first treatment and as those starting on the day of first treatment of study RD.06.SPR.112199 or after. Previous and concomitant therapies/medications will be coded using WHO Drug Dictionary (March 1, 2019, B3/C3 format). Medical history and prior and concomitant medical/surgical procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 22.0).

A summary table will be provided for each of the following using Safety population by treatment group and overall:

- Number and percentage (n, %) of subjects who had medical history by System Organ Class and Preferred Term.

- Number and percentage (n, %) of subjects who had prior therapies/medications by ATC levels 2, 3 and Preferred Term.
- Number and percentage (n, %) of subjects who had concomitant therapies/medications by ATC levels 2, 3 and Preferred Term.
- Number and percentage (n, %) of subjects who had prior medical/surgical procedures by System Organ Class and Preferred Term.
- Number and percentage (n, %) of subjects who had concomitant medical/surgical procedures by System Organ Class and Preferred Term.

Listings of all medical history, prior and concomitant therapies/medications and medical/surgical procedures will be provided.

9.5. Vital Signs

Descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment group and overall will be presented for vital signs at Visit 1 (Week 14 analysis visit, 12 weeks after the last DL-PDT).

Number and percentage (n, %) of subjects with Clinically Significant Abnormal Values (as identified by the Investigator) will be summarized by treatment group and overall at Visit 1 (Week 14 analysis visit, 12 weeks after the last DL-PDT).

A listing of all vital signs will be provided.

9.6. Physical Examination

Physical examination assessments will be summarized in terms of number and percentage (n, %) of subjects with 'normal', 'abnormal/not clinically significant' and 'abnormal/clinically significant' results for each body system.

Summaries will be presented by treatment group and overall at Visit 1 (Week 14 analysis visit, 12 weeks after the last DL-PDT).

A listing of all physical examination assessments will be provided.

9.7. Study Duration

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Follow-up study duration and pivotal and follow-up study duration of each subject will be listed.

9.8. Efficacy Analysis

All efficacy analyses will be based on the Safety population. Subjects will be analyzed according to the treatment they were randomized to in study RD.06.SPR.112199.

Primary summary for efficacy analysis will be based on the Safety population at Visit 3 (Week 54 analysis visit, 52 weeks after the last DL-PDT).

All efficacy data will be listed.

9.8.1. Analysis of the Primary Endpoint

The proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 3 (Week 54 analysis visit, 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]

9.8.2. Sensitivity Analyses of Primary Endpoint

No sensitivity analysis is planned.

9.8.3. Analysis of Secondary Endpoints

The proportion of subjects with recurrence of any (≥1) cleared treated AK lesions at Visit 2 (Week 28 analysis visit, 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]

CCI [redacted]

9.9. Interim Analyses and Data Monitoring

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.

9.10. Examination of Subgroups

No subgroup analysis is planned.

9.11. Safety Analysis

All safety analyses will be based on the Safety population. Subjects will be analyzed according to the treatment they actually received in study RD.06.SPR.112199. Summaries of all safety endpoints will be presented.

9.11.1. Adverse Events Analysis

Treatment-emergent AEs are defined as those AEs occurring after the first administration of study treatment until the last study visit from study RD.06.SPR.112199 and as all AEs in this study RD.06.SPR.115230.

All treatment-emergent AEs will be listed in a by-subject listing which will include both the term reported on the eCRF (verbatim term) and the MedDRA System Organ Class and Preferred Term. Relative start and stop days will be included along with the actual onset and resolution dates.

If relationship is missing the closest relationship, i.e. “Related” will be imputed. If severity is missing the greatest severity, i.e. “Severe”, will be imputed.

A summary table of TEAEs will be provided for each of the following for the safety population by treatment group and overall:

- Number and percentage (n, %) of subjects with any TEAE and frequency of TEAEs overall and by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any TEAE by closest relationship to study drug and frequency of TEAEs by closest relationship to study drug;
- Number and percentage (n, %) of subjects with any TEAE by closest relationship to study procedures and frequency of TEAEs by closest relationship to study procedures;
- Number and percentage (n, %) of subjects with any TEAE related to the study drug and frequency of TEAEs related to the study drug by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any TEAE related to the study procedures and frequency of TEAEs related to the study procedures by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any TEAE by greatest severity and frequency of TEAEs by greatest severity overall and by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any TEAE leading to study discontinuation and frequency of TEAEs leading to study discontinuation.

A summary table of serious TEAEs will be provided for each of the following in the safety population by treatment group and overall:

- Number and percentage (n, %) of subjects with any Serious TEAE and frequency of Serious TEAEs overall and by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any Serious TEAE by closest relationship to study drug and frequency of Serious TEAEs by closest relationship to study drug;
- Number and percentage (n, %) of subjects with any Serious TEAE by closest relationship to study procedures and frequency of Serious TEAEs by closest relationship to study procedures;
- Number and percentage (n, %) of subjects with any Serious TEAE related to the study drug and frequency of Serious TEAEs related to the study drug by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any Serious TEAE related to the study procedures and frequency of Serious TEAEs related to the study procedures by System Organ Class and Preferred Term;
- Number and percentage (n, %) of subjects with any Serious TEAE leading to study discontinuation and frequency of Serious TEAEs leading to study discontinuation;

- Number and percentage (n, %) of subjects with any Serious TEAE leading to death and frequency of Serious TEAEs leading to death.

In order to evaluate the impact of COVID-19 on the safety of the subjects, a summary table of TEAEs and serious TEAEs will be provided for each of the following for the safety population by treatment group and overall:

- Number and percentage (n, %) of subjects with any TEAE related to COVID-19 and frequency of TEAEs related to COVID-19 by System Organ Class and Preferred Term.
- Number and percentage (n, %) of subjects with any Serious TEAE related to COVID-19 and frequency of Serious TEAEs related to COVID-19 by System Organ Class and Preferred Term.

Listings of all AEs leading to death, all serious AEs, all TEAEs leading to study discontinuation and all AEs due to COVID-19 will be provided.

9.11.2. Pregnancy Testing

All women of childbearing potential will have a urine pregnancy test at Visit 1 (Week 14 analysis visit, 12 weeks after the last DL-PDT), Visit 2 (Week 28 analysis visit, 26 weeks after the last DL-PDT) and Visit 3 (Week 54 analysis visit, 52 weeks after the last DL-PDT).

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 (Week 14 analysis visit, 12 weeks after the last DL-PDT) will be followed in this study.

A listing of all pregnancy test results will be provided.

10. Changes from the Protocol Analysis Plan

Any change from the protocol will be justified and fully documented.

If the blind review suggests changes to the principal features stated in the protocol, these have to be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review.

11. Shells of Tables, Figures and Listings and Reporting Output (General Features)

Tables, figures and listings will be generated using SAS® and will be displayed on A4 size paper with landscape orientation, 2 cm for top and bottom margins, 0.8 cm for left and right margins and 8pt Courier New font.

The header section will comprise the sponsor's name, the protocol number, the delivery description, the TFL number, the TFL title, the population and the page number (Page X of Y). The footer section will include the TFL footnotes, the data extract date (if applicable), the date and time of the execution of the program, and the name of the program.

A clear, accurate and complete programming code will be developed to generate the statistical analyses, summary tables, figures and listings to be integrated in the report. Fluent use of precise titles and footnotes will be made to improve the understanding of summaries and document any assumption. Details of analysis specifications including but not limited to the SAS code will be documented on the shells.

12. Appendices

12.1.1. Shells for Table, Figure and Listings

The final list of tables, figures and listings and their shells for the reporting of this study is available in a separate document that is developed and is finalized before database lock.