16.1.9 Documentation of Statistical Methods

M-14867-32 Statistical Analysis Plan Version 1.0, 17-JAN-2023

ALMIRALL, S.A.

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Clinical Trial Protocol Title:

A PHASE 3, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF TIRBANIBULIN OINTMENT 1% APPLIED TO A FIELD OF APPROXIMATELY 100 CM^2 ON THE FACE OR BALDING SCALP IN ADULT PATIENTS WITH ACTINIC KERATOSIS

Statistical Analysis Plan for Clinical Trial M-14867-32

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SAP REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Final v1.0	17-Jan-2023	PPD	Initial version

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1 ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AK	Actinic keratosis
ATC	anatomical therapeutic chemical
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRO	Clinical Research Organization
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End of Study
EoT	End of Treatment
ESI	Event of special interest
ET	Early termination
ICF	Informed Consent Form
PE	Physical examination
PT	preferred term
Q1	first quantile
Q3	third quantile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®
SE	standard error
SD	standard deviation
SOC	system organ class
TF(s)	Treatment Field(s)
TEAE	Treatment-emergent adverse event
TESAE	treatment emergent serious adverse events

TLF	tables, listings, and figures
WHO-DD	World Health Organization Drug Dictionary

2 CLINICAL TRIAL PERSONNEL

A detailed list of team members with respective role and contact information is maintained separately in the main study contact list.

3 INTRODUCTION

3.1 Description of this Document

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for sponsor clinical protocol M-14867-32. The analyses described in the SAP are based upon the protocol Version 2.0 dated 21-Mar-2022. In case of discrepancies between the protocol and the SAP, the SAP will be used to guide the statistical analysis.

This SAP has been developed prior to database lock and final analyses. All final analyses will be performed after the clinical trial data are entered into the database, any discrepancies in the data are resolved, the database is locked, and following the signature of the SAP.

The signature of this SAP will act as the assignment of each patient within the populations.

3.2 Trial Design

This is a Phase 3, multicenter, open-label, single-arm trial to evaluate safety and local tolerability of tirbanibulin ointment 1% administered topically for 5 days over a field of approximately 100 cm^2 on the face or balding scalp in adult patients with actinic keratosis (AK). The study consists of a 4-week (28-day) Screening Period, a 5-day Treatment Period, and a Response Assessment Period of approximately 7 weeks (see Table 1, Schedule of Assessments):

- During the Treatment Period, patients will apply tirbanibulin ointment 1% once daily for 5 days beginning on Day 1.
- All patients will be evaluated for safety, tolerability, and the presence of AK lesions in the treatment field (TF) until completion of the Response Assessment Period at Day 57.

Enrollment will be controlled such that the trial population is representative of the population expected to use the product in terms of age and treated area. A minimum of 50% of patients older than 65 years old will be included and approximately two-thirds of the patients will be treated for AK lesions on the face and one-third on the scalp.

Table 1 Schedule of Assessments

Period	Screening*	Treatment		Response Assessment				
Visit(s)	**1**	**2**	**At home, once-daily self-administration[m]**	**3**	**4**	**5**	**6**	**7 ET/EoS**
Day(s)	**-28 to -1**	**1 (Baseline)**	**2 to 5**	**5**	**8**	**15**	**29**	**57**
Visit Time Window (days)	**None**	**None**		**None**	**±2**	**±2**	**±3**	**±3**
Informed consent	X							
Inclusion & exclusion criteria	X	X[a]						
Demographics	X							
Medical/surgical history	X							
AK history/AK treatment history	X							
Prior and concomitant medications/therapies	X	X[a]		X	X	X	X	X
Fitzpatrick skin type	X							
Treatment field identification[k]	X	X[a]						
Vital signs[i]	X	X[a]						X

Period	**Screening***	**Treatment**		**Response Assessment**				
Visit(s)	**1**	**2**	**At home, once-daily self-administration[m]**	**3**	**4**	**5**	**6**	**7 ET/EoS**
Day(s)	**-28 to -1**	**1 (Baseline)**	**2 to 5**	**5**	**8**	**15**	**29**	**57**
Visit Time Window (days)	**None**	**None**		**None**	**±2**	**±2**	**±3**	**±3**
Physical examination[d]	X							X
Clinical chemistry, hematology, urinalysis	X							X
ECG[b]	X							X
Pregnancy test for WOCBP[c]	X	X[a]						X
Study App installation and instructions		X[a]						
Study App review by Investigator[j]				X				
Study drug application		X	X					
Instructions for self-administration and study drug dispensing		X						
Study drug return				X[e]				
Weight of study drug packets[f]		X		X				
Standardized photography of the treatment field	X	X[a,l]		X	X	X	X	X
AEs[g]	X	X	X	X	X	X	X	X[h]

Period	**Screening***	**Treatment**		**Response Assessment**				
Visit(s)	**1**	**2**	**At home, once-daily self-administration[m]**	**3**	**4**	**5**	**6**	**7 ET/EoS**
Day(s)	**-28 to -1**	**1 (Baseline)**	**2 to 5**	**5**	**8**	**15**	**29**	**57**
Visit Time Window (days)	**None**	**None**		**None**	**±2**	**±2**	**±3**	**±3**
Treatment Field location		X[a]	X	X	X	X	X	X
Focused dermatological exam of treatment field								
Local tolerability		X[a]		X	X	X	X	X[h]
Hypo- and hyperpigmentation and scarring		X[a]		X	X	X	X	X[h]
AK Lesion count in the TF	X	X		X	X	X	X	X

Abbreviations: AE=adverse event; AK=actinic keratosis; ECG=electrocardiogram; ET=Early Termination; EoS=End of Study; ICF=informed consent form; TF=treatment field; WOCBP=women of child-bearing potential.

* Patients who require a washout period from prohibited concomitant treatments should be seen and sign the ICF prior to the Screening visit, to ensure the necessary washout before starting treatment. No trial assessments will be performed on that date and the Screening visit will be scheduled according to the washout length required for the specific medication stopped.

[a] Assessments/procedures performed before treatment administration. Day 1 evaluation will serve as a Baseline for these assessments.

[b] Patients must be in a supine position for 5 minutes prior to ECG.

[c] Highly sensitive urinary pregnancy test performed at the clinical trial site.

[d] Physical examination to include height, weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, neurological systems, and an expanded dermatological examination to cover the sun-exposed areas, where photo-damage is likely. Height is measured only at screening.

[e] On Day 5 patients are to bring all 5 study drug packets back to the site (used and unused) with their respective torn parts in the individual closed zipper storage bag provided in the study kit.

[f] All study drug packets will be weighed together in their respective closed zipper storage bag before and after use (including the torn opening part).

[g] At each study visit, patients will be asked a general question e.g. “How have you been since the last visit?” AEs will be recorded before assessments of local tolerability, hypo- and hyperpigmentation, and scarring in the TF. AEs will be reported separately from local tolerability signs.

[h] All patients who have unresolved local tolerability signs, hypo- or hyperpigmentation, scarring in the TF, or treatment-related AEs at Day 57 will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

[i] Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and body temperature. Measurements of systolic and diastolic blood pressure will be performed after at least 5 minutes of rest in a supine position and preferably on the same arm.

[j] Patients will complete a diary (Study App) to record daily dates and times of study treatment application. The diary (Study App) will be checked by the Investigator (or designee) at Visit 3.

[k] TF identification (face/scalp)

[l] Baseline photo is only required in case of any significant change from Screening is detected in the TF as per the Investigator judgement or if the quality of the image captured at Screening is not appropriate. If no photo is needed at baseline, then the screening photo will be considered the baseline assessment.

[m] Study drug will be applied by the patient at home before study Visit 3 on Day 5, which will take place at the clinical site.

4 OBJECTIVES

4.1 Objectives

The primary objective of the trial is to evaluate the safety and tolerability of tirbanibulin ointment 1% when applied to a field of approximately 100 cm^2 on the face or balding scalp.

Additionally, the treatment effect of tirbanibulin ointment 1% when applied to a field of approximately 100 cm^2 on the face or balding scalp will be explored.

4.2 Endpoints

4.2.1 Safety Endpoints

Safety Endpoints

- Local Tolerability Assessment:
    - Number and proportion of patients with each local tolerability score by visit (0-3) for each individual sign (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration)
    - Maximum local tolerability score post baseline through all the visits for each individual sign
    - Time to maximum local tolerability score for each individual sign
    - Local tolerability signs composite score (0-18) by visit, defined as the sum of the scores graded from 0 to 3 on all six individual tolerability sign categories
    - Maximum local tolerability signs composite score post baseline through all the visits
    - Time to maximum local tolerability composite score
    - Proportion of patients with pigmentation and scarring in the TF through all the visits
- Number and proportion of patients with treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs), adverse events of special

interest (AESIs), and change from baseline in clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])

4.2.2 Exploratory Endpoints

- Absolute number, change from baseline, and percent change from baseline in AK lesion count from total lesions in the TF at each visit
- Absolute number, change from baseline, and percent change from baseline in AK lesion count, for lesions that were already present at baseline, from total lesions in the TF at each visit
- Absolute number and percent change of new lesions from total lesions in the TF at each visit

5 SAMPLE SIZE JUSTIFICATION

Approximately 125 patients will be screened to initiate treatment in approximately 100 patients.

With 100 patients and assuming an expected percentage of patients with at least one local tolerability sign of approximately 90%, the precision in the estimation of that percentage will be approximately 11%. The precision is defined as the width of the 95% confidence interval.

Furthermore, 100 patients will provide approximately 10% and 13% precision in the estimation of the percentage of patients with the local tolerability events of particular interest, specifically vesiculation/pustulation (assuming an expected percentage of 8%) and erosion/ulceration (assuming an expected percentage of 12%), respectively.

6 STRUCTURE AND METHODOLOGY OF STATISTICAL ANALYSIS

6.1 Descriptive Statistics

Categorical variables will be summarized with counts (n) and percentages (%). For continuous variables, the number of non-missing observations (n), mean, standard deviation (SD), standard error (SE) of the mean, 95% confidence interval (CI) of the mean, median, first (Q1) and third (Q3) quartiles, minimum (min) and maximum (max) will be tabulated.

The 95% confidence interval for continuous data will be calculated using the normal approximation. If less than 30 patients with non-missing data are available (in a sub-group, if applicable) for a specific continuous data point, no confidence interval will be reported for this data point.

The 95% confidence interval for proportions will be calculated using the exact Clopper-Pearson method.

When applicable, summaries will be provided by visit of assessment.

6.2 Level of Statistical Significance

No statistical inferences will be performed for this study. Confidence intervals (CIs) will be two-sided with 95% coverage.

6.3 Baseline

Unless otherwise specified, baseline value will be defined as the last non-missing assessment prior to the first study treatment dose dosing on Day 1 (including unscheduled and repeat assessments). If the last non-missing assessment is performed on the same date as the first study treatment administration and time is not available, the assessment will be considered as baseline, except for adverse events (AEs) not related to a pre-dose assessment and medications starting on the first study treatment dose administration date which will be considered post-baseline.

6.4 Interim Analysis

No interim analyses are planned.

6.5 Reference Start Date and Analysis Day

Analysis day will be calculated from the first study treatment dose administration date and will be used to show start/end day of assessments or events.

Analysis day = (Date of event – Date of first dose administration) + 1 if date of event is on or after the date of first dose administration of study treatment;

= (Date of event – Date of first dose administration) if date of event is before the date of first dose administration of study treatment.

In the situation where the assessment/event date is partial or missing, analysis day will be missing.

6.6 Software Version

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

7 DATA HANDLING

7.1 Missing Data

No imputation will be made for missing data. See Appendix 2 for handling of completely or partially missing dates and time for prior and concomitant medications and adverse events.

7.2 Computation of Derived Variables

Change from baseline will be calculated as:

Assessment value at post-baseline Visit X – Baseline value.

Percent change from baseline (%) will be calculated as:

(Assessment value at post-baseline Visit X – Baseline value) / Baseline value * 100.

Percent change from baseline will be missing in situation where baseline value equals to 0.

7.3 Windowing Conventions

Windowing conventions will apply to all local tolerability, hypopigmentation, hyperpigmentation and scarring, and AK lesions count assessments.

Visits will be analyzed as scheduled. Scheduled, unscheduled, and early termination visits measurements will only be included if the scheduled, early termination, or unscheduled measurement falls within the analysis visit windows as described in Table 2.

Table 2 Analysis Visit Windows

Analysis Visit	Target Study Day	Local tolerability, Hypopigmentation, hyperpigmentation and Scarring, AK lesions count
Baseline	Refer to Baseline definition	Refer to Baseline definition
Day 5	5	[1 post-dose; 5]
Day 8	8	[6; 11]
Day 15	15	[12; 22]
Day 29	29	[23; 43]
Day 57	57	[44; EOS]

If there is more than one assessment for a given analysis visit, the assessment closest to the target day will be considered. If two assessments fall at the same distance from the target day for a given analysis visit and one of them is a scheduled assessment, the scheduled assessment will be considered. If two assessments fall at the same distance from the target day for a given analysis visit and none of them is a scheduled assessment, the first assessment will be considered.

7.4 Repeated or Unscheduled Assessments

When repeated measurements are done, the repeated measurement will be considered for the windowing and analysis in lieu of the original measurement.

For local tolerability, hypopigmentation, hyperpigmentation and scarring, and AK lesions count assessments, unscheduled and early termination assessments will be remapped as mentioned in section 7.3. All data from visits will be listed under the nominal visit, and the analysis visit will also be presented if it differs from the nominal visit.

For other assessments, unscheduled measurements will not be summarized in by-visit summary tables or figures. Early Termination (ET) visit assessments will be summarized as part of the Day 57/ET visit. All data from unscheduled and early termination visits will be listed.

8 ANALYSIS POPULATIONS

There will be one analysis population in this trial:

Safety population: The safety population will include all patients who have received at least one dose of study treatment.

9 STUDY PATIENT

9.1 Patient Disposition

All patients who provide informed consent will be accounted for in this study. The number of patients screened and number and percentage who failed screening (screen failures) will be presented. The reason for screen failure (count and percentage) will be presented for all screened patients who failed screening, if applicable. Moreover, the number of patients enrolled (patients will be considered as enrolled if they started Day 1) and included in the safety population will be presented. Study completion status and the reason for study discontinuation, including if related to COVID-19 or not, will also be presented both as count and percentages. The percentage of patients with screen failures will be calculated using the number of patients screened as denominator. The percentage of screen failure by reasons will be calculated using the number of screen failures as denominator. The percentage of patients with study discontinuation and reasons for discontinuation, including if related to COVID-19 or not, will be calculated by reasons using the number of enrolled patients who did not complete study as denominator. Otherwise, percentages will be calculated using the number of patients enrolled as denominator.

Number of days in the study will be calculated as follows and summarized using descriptive statistics based on the safety population:

Number of days in study = Date of completion/discontinuation – first study drug dose date +1.

A listing of patients' disposition will be provided. A listing of patients excluded from the safety population and associated reason, and a listing of missed visits due to the COVID-19 pandemic will also be provided.

9.2 Protocol Deviation

All protocol deviations will be reported based on Almirall protocol deviations categories. Important vs. not important classification of protocol deviations will be conducted prior to the database lock.

The number of events and the number and percentage of patients with at least one important protocol deviation will be summarized by deviation category and sub-category using the safety population. In case of a site-level protocol deviation, one protocol deviation for each patient for that site will be accounted for in the tables and listings. The number of events and the number

and percentage of patients with at least one protocol deviation related to COVID-19 will be summarized similarly.

A listing of all protocol deviations will also be provided.

10 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

10.1 Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age as collected at the time of Informed Consent Form, sex, Fitzpatrick skin type, race, and ethnicity) and baseline characteristics (height, body weight, area of face or scalp treated, number of AK lesions in the treatment field, presence of scarring, hypopigmentation and hyperpigmentation in the treatment field, and smoking and alcohol habits usage [never, current or former for smoking; consumption yes vs no for alcohol]), based on the safety population. Patients who reported more than one race will be summarized as 'Multiple' races in the table, and all races selected will be displayed in the listing.

A listing of all demographics and baseline characteristics will be provided.

10.2 Medical History

Surgical and medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.0.

Non-AK surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) using the safety population. A patient who experienced the same non-AK surgical and medical history event multiple times will be counted only once for the corresponding PT. Similarly, if a patient experienced multiple non-AK surgical and medical history events within the same SOC, the patient will be counted only once for that SOC. Non-AK surgical and medical history events will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

A listing of all non-AK surgical and medical history events will be provided.

AK disease history, including body parts and sides affected, will be summarized based on the safety population. The time since first AK diagnostic (in years) will be calculated as:

Time since first AK diagnostic (years) = {[First study treatment dose date – first AK diagnostic date] + 1} / 365.25.

Should any AK diagnostic date be partially or completely missing, the time since first AK diagnostic will be left as missing.

A listing of AK disease history will be provided.

11 EXPOSURE AND COMPLIANCE

11.1 Exposure to Study Medication

Duration of exposure to study treatment, in days, will be computed as follows:

[(Date of last dose of study treatment – Date of first dose of study treatment) + 1].

Descriptive statistics for the duration of exposure to study treatment will be presented based on the safety population. Duration of exposure will also be presented by treatment area (scalp or face) sub-groups.

A summary of amount of product applied will be presented based on the safety population. Amount of product applied will be derived based on the information on the pre-dose packets weight and post-dose packets weight captured in the eCRF. Amount applied (in grams) will be computed as follows:

(Sum of packets weight pre-dose on Day 1 – Sum of packets weight post-dose on Day 5).

If the information on packet weight is missing for a dispensed packet (i.e., the number of packets returned is not equal to the number of packets dispensed), the amount applied will be missing.

A listing of study treatment amount applied, number of packets dispensed, returned and used will be provided.

11.2 Compliance with Study Medication

Compliance with study treatment (%) will be calculated based on used packets as follows:

$$\frac{\text{Total number of used packets per the eCRF}}{\text{Total duration of exposure (days) x Planned number of dose per day (i.e., 1)}} \text{x} 100$$

Descriptive statistics for the compliance to study treatment will be presented based on the safety population. Frequency distribution will also be presented for the following compliance categories: <80%, 80% to 120%, >120%. Compliance will also be presented by treatment area (scalp or face) sub-groups.

If a patient did not return the full number of packets dispensed, his compliance will be left as missing.

A listing of patient exposure, compliance and drug interruption will be provided.

12 ANALYSES OF PRIOR AND CONCOMITANT MEDICATION

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) B3, March 2022.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dosing. Concomitant medications are defined as any medication started on the same day than or after the first study treatment dosing, including those who started prior to the first study treatment date and continued past that date. See Appendix 2 for handling of completely or partially missing dates and time for prior and concomitant medications.

Incidence of prior and concomitant medications will be tabulated by anatomical therapeutic chemical (ATC) Level 3 and standardized drug name using the safety population. A patient with the same medication taken multiple times will be counted only once for the corresponding standardized drug name. Similarly, if a patient has taken more than one medication within the same ATC level, then the patient will be counted only once for that ATC. Prior and concomitant medications will be sorted alphabetically by ATC level and within each ATC level, the standardized drug name will be presented by decreasing order.

Prior and concomitant medication information will be presented in a by-patient listing using the Safety population.

Actinic keratosis treatment non-drug therapies and procedures during the study will be provided in a listing.

13 ANALYSES OF EXPLORATORY ENDPOINTS

The analyses of exploratory endpoints will be performed on the safety population. No statistical inferences will be performed.

13.1 AK Lesions Count

At screening, the Investigator will select and measure the TF (e.g., approximately mid face or an area on the scalp). Each AK lesion within the TF will also been identified with a label. A photograph will be captured using imaging devices to be used to support the location of the same TF identified at screening during the follow-up study visits assessments. At baseline (Day 1), the area of the TF and location of AK lesions in the TF will be confirmed. A baseline photograph is only required in case of any significant change from screening is detected in the TF as per Investigator's judgement or if the quality of the image captured at screening is not appropriate. If no photograph is needed at baseline, then the screening photograph, TF, and AK lesions count will be considered the baseline assessment. At each post-baseline visit, all lesions in the TF will be counted and details on whether the lesion present in the TF is new or an existing lesion at baseline will be recorded in the eCRF.

The absolute number, change from baseline, and percent change from baseline in total number of AK lesions in the TF (i.e., already present at baseline *AND* new) will be analysed descriptively at each visit.

The absolute number, change from baseline and percent change from baseline in AK lesion count for lesions that were already present at baseline in the TF will be summarized at each post-baseline visit using descriptive statistics.

The absolute number and percent change in new AK lesions since baseline in the TF will also be summarized at each post-baseline visit using descriptive statistics. The percent change in new AK lesions since baseline in the TF is defined as:

$$\frac{\text{Number of new AK lesions in the TF}}{\text{Number of AK lesions at baseline}} \text{ x } 100$$

A listing of AK lesions count will be provided. Figures of the AK lesions counts (total lesions, lesions that were already present at baseline, and new lesions from baseline) by visit will also be provided.

14 ANALYSES OF SAFETY AND TOLERABILITY ENDPOINTS

The analyses of safety and tolerability endpoints will be performed on the safety population.

14.1 Local Tolerability Assessment

Local tolerability is assessed based on the review of the following signs in the treatment field: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration and will be evaluated both individually and as a composite score (total of the 6 individual scores ranging from 0 to 18). These signs will be graded as: 0=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). If one or more individual score is missing, the composite score will be set as missing.

The maximum local tolerability signs composite score across visits will be derived as the maximum local tolerability assessment (LTA) composite score observed post-baseline for a patient. The maximum local tolerability of individual signs across visits will be derived as the maximum LTA of an individual sign observed postbaseline for a patient.

Descriptive statistics will be presented for local tolerability signs composite score by visit, and for maximum local tolerability signs composite score across post-baseline visits. Frequency and percentages by visit of patients presenting any individual and composite local tolerability signs and associated CI based on exact Clopper-Pearson method will be presented. The presence of any individual and composite local tolerability sign is defined by a score of >0. Frequency and percentages by visit for specific local tolerability individual signs results and maximum local tolerability of individual signs across post-baseline visits will also be provided.

The 95% CI will be presented for the median of the maximum local tolerability composite score.

Figures presenting the number of patients with each local tolerability individual sign (absent/mild/moderate/severe) by visit, and a figure presenting the mean local tolerability composite score by visit will be produced.

The time to maximum LTA score for each individual sign and the time to maximum LTA composite score will be calculated as the time (in days) from the first dose of study treatment to the time of the first occurrence of the maximum LTA score observed post-baseline for each individual sign and composite score, respectively. That is, for each individual sign, time to maximum LTA, in days, will be calculated as follows:

(Date of first post-baseline occurrence of maximum LTA score for an individual sign – Date of first dose)

Time to maximum composite LTA, in days, will be calculated as follows:

(Date of first post-baseline occurrence of maximum composite LTA score – Date of first dose)

If a patient's maximum composite/individual sign LTA score stays at 0 throughout the study, the patient will be considered censored at his last LTA score observation. The time to maximum composite/individual sign LTA will be analyzed using Kaplan Meier estimation, overall and by strata as applicable. The Kaplan Meier estimates will include the 25th, 50th (median), and 75th percentiles along with their 95% CIs. The standard errors (SE) will be computed using the Greenwood's formula. The CI for the median will be calculated as per Brookmeyer and Crowley and the CIs for the 25th and 75th percentiles will be calculated using the log-log transformation.

Survival curves will also be presented and all local tolerability assessments will be listed.

14.2 Scarring, Hypopigmentation and Hyperpigmentation

The number and percentage of patients with absence or presence of scarring, hypopigmentation, and hyperpigmentation in the TF and associated 95% CIs will be presented separately at scheduled visits.

Shift tables representing the change from baseline in scarring, hypopigmentation, and hyperpigmentation in the TF will be provided separately as well. Only patients with a baseline result and a result at the specified post-baseline visit for the parameter will be considered in the shift tables.

Scarring, hypopigmentation and hyperpigmentation evaluations will be presented in a listing.

14.3 Adverse Events

AEs will be coded according to the MedDRA, Version 25.0.

TEAEs will be defined as any AEs with onset date/time on or after the first study treatment dosing and prior to the last date of study treatment dosing + 57 days (inclusive), or as any AE that was present prior to the first dose of trial drug but increased in severity on or after the first study treatment dosing and prior to the last date of study treatment dosing + 57 days (inclusive). AEs starting on the first study treatment dosing date and related to a pre-dose study assessment will not be considered as TEAE. See Appendix 2 for handling of completely or partially missing dates and time for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

Overall summaries of AEs will be presented by number and percentages of patients with and number of events of AEs, TEAEs, study treatment-related TEAEs, TESAEs, TEAEs by worst severity, TEAEs leading to study treatment discontinuation, TEAEs leading to study discontinuation, application site TEAEs, AESIs, and TEAEs with an outcome of death.

Frequency and percentage of patients who experience TEAE will be summarized by SOC and PT within SOC. Unless otherwise specified, a patient experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a patient experiences multiple TEAEs within the same SOC, the patient will be counted only once for that SOC. TEAEs will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order. Treatment-emergent SAEs, TEAEs leading to study treatment discontinuation, TEAEs with an outcome of death and TEAEs leading to study discontinuation will be summarized similarly.

Frequency and percentage of patients who experience TEAE will also be summarized by SOC, PT and worst severity (mild/moderate/severe). TEAE with an unknown severity will be considered as severe. If a patient experiences more than one TEAE within different severity categories within the same SOC/PT, the patient will be counted only once under each SOC/PT under the worst severity.

Frequency and percentage of patients who experience study treatment-related TEAE will be summarized by SOC and PT. A study treatment-related TEAE is defined as any TEAE that is assessed by the Investigator as possibly related or related to study treatment. A not study treatment-related TEAE is defined as any TEAE that is assessed by the Investigator as unlikely or not related to study treatment. TEAE with an unknown relationship will be considered as treatment-related.

Frequency and percentage of patients who experience application site TEAE will be summarized by PT. AESIs will be summarized similarly.

Frequency and percentage of patients who experience TEAE in the application site pain preferred term will be summarized by PT and lowest level term (LLT). Unless otherwise specified, a patient experiencing the same TEAE multiple times will be counted only once for the corresponding PT/LLT.

All AEs will be listed. Separate listings will also be provided for AEs leading to death, all SAEs, all TEAEs leading to study discontinuation, and all AESIs.

14.4 Clinical Laboratory Parameters

Laboratory parameters of hematology, blood chemistry, and urinalysis will be summarized using descriptive statistics at baseline and at subsequent visits. Change from baseline values will be presented for each post-baseline assessment. Frequencies and percentages for each result will be provided for qualitative urinalysis data.

In addition, shift tables (for hematology, blood chemistry, and quantitative urinalysis: low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table; for qualitative urinalysis: normal-abnormal at baseline versus normal-abnormal at follow-up in a 2-by-2 contingency table) will be provided to assess changes in laboratory values from baseline. Only patients with a baseline result and a result at the specified post-baseline visit for the parameter will be considered in the shift tables.

Separate listings of all data for hematology, blood chemistry, and urinalysis will be provided. In addition, separate listings of data for hematology, blood chemistry, and urinalysis will be provided for each parameter where a patient had at least one clinically significant or not clinically significant abnormal result.

A listing will be provided for Pregnancy test results.

14.5 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature) and weight will be summarized using descriptive statistics at baseline and at each subsequent visit. Change from baseline values will also be presented for each post-baseline assessment.

For each vital sign, shift table from baseline to each post-baseline assessments describing shifts to abnormality (normal-abnormal not clinically significant [NCS]-abnormal clinically significant [CS] at baseline versus normal-abnormal NCS-abnormal CS at post-baseline visit in a 3-by-3 contingency table) will be provided as well. Only patients with a baseline result and a result at the specified post-baseline visit for the parameter will be considered in the shift tables.

A listing of all vital sign assessments, including height and weight, will be provided. In addition, a separate listing will be provided for each parameter where a patient had at least one clinically significant or not clinically significant abnormal result.

14.6 ECGs

Descriptive statistics will be presented for data related to ECGs (HR, RR, PR, QRS, QT

interval, QTcB interval and QTcF interval) at each scheduled visit, with change from baseline values presented for post-baseline assessments.

Shift tables from baseline to each post-baseline assessments describing shifts to abnormality (normal-abnormal NCS-abnormal CS at baseline versus normal-abnormal NCS-abnormal CS at post-baseline visit) will be provided for overall interpretation (based on Investigator interpretation). Only patients with a baseline result and a result at the specified post-baseline visit will be considered in the shift tables.

A listing of all ECG assessments will be provided. In addition, a separate listing will be provided for overall interpretation where a patient had at least one clinically significant or not clinically significant abnormal result.

14.7 Physical Examinations

All physical examinations will be listed.

15 ADDITIONAL ANALYSES

15.1 Subgroup Analyses

Descriptive statistics will be provided for exploratory endpoints by subgroups: age (<65 and ≥65), sex (male/female), number of AK lesions in the TF at baseline (≤8 and >8), treatment area (face/scalp), history of skin cancer (yes/no), and Fitzpatrick skin type (I/II and III/IV/V/IV). Figures for exploratory endpoints will only be provided for overall and by subgroup of treatment area (face/scalp).

Additionally, exposure, compliance and local tolerability assessments will be provided by subgroup of treatment area (face/scalp).

No other subgroup analysis is planned for this study.

15.2 Other Analyses

No other analyses are planned for this study.

16 CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

The changes made to analyses specified in the protocol are presented in Table 3.

Table 3 Changes to Analyses Specified in the Protocol

Description of the Change	Rationale
Protocol states that Unscheduled tests will not be associated with any trial visit. However assessments performed at each study visit will be remapped based on windowing conventions specified in Section 7.3.	To minimize missing data in table reporting.
Protocol states that the number and percentage of patients who experience one or more AESI will be tabulated by AESI. However the number and percentage of patients who experience one or more AESI will rather be tabulated by SOC and PT.	The only type of AESI considered in this study is skin cancer.

Protocol states the number and percentages of patients with events, and number and percentage of events will be presented for TEAEs.	Only the number and percentages of patients with events, and the number of events will be reported. Percentages of events will not be reported.
Protocol states subgroup analyses for exploratory endpoints only.	Exposure, compliance and local tolerability assessments will also be provided by subgroup of treatment area (face/scalp).

17 REFERENCES

Not applicable.

18 APPENDICES

18.1 Appendix 1

Output Conventions

Tables, listings, and figures (TLFs) will be generated using SAS® and will be displayed on letter size paper with landscape orientation. A margin of 2.1, 2.5, 2.5, 2.1 cm should be on the top, right, left, and bottom, respectively, and 8 pt Courier New Bold font.

The header section will comprise the drug name or code, the protocol number (Almirall code for the trial), the page number (Page X of Y), the TLF number, the TLF titles (left aligned), the population. The footer section will include the TLF footnotes, the name of the program, and the date of the execution of the program. Please refer to the Almirall Statistical TLFs Generation Process for details.

Mean, median and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1". The denominator for each percentage will be the number of patients within the population per group, unless otherwise specified.

Listings will be ordered by patient number, date, visit (where applicable) and timepoint (where applicable). Imputed dates and imputed missing data will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format DDMMMYYYY/HH:MM.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

Study Treatment Full Names	Study Treatment Output Names
Tirbanibulin 1%	Tirbanibulin

18.2 Appendix 2

Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- Completely missing: Impute to the first study treatment date.
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event Start Time Imputation

- Imputation of event end time should be done before imputation of event start date.
- If the event date (imputed or not) is not the same as the first dose date or time part of the first dose date is missing, impute to 00:00.
- If the event date (imputed or not) is the same as the first dose date, impute to time part of first dose date.
- If the event start date (imputed or not) is equal to event end date and imputed event start time is after event end time (imputed or not), set the event start time to the imputed event end time.

Event End Date Imputation

- Completely Missing (not flagged as "ongoing"): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

Event End Time Imputation

- Impute to 23:59.

DocuSign

Certificate Of Completion

Envelope Id: 318AF1C6E01848C48C0C1ACEA6D58ADA
Status: Completed
Subject: Your electronic signature is required by Innovaderm Research- M14867-32_SAP_Final_v1.0_20230117
Source Envelope:
Document Pages: 36
Signatures: 4
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
PPD
3530 boul. Saint-Laurent
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Montréal, QC h2x2v1
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17-Jan-2023 | 11:55

Holder: PPD
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Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 26-Jul-2022 | 10:21 ID: PPD	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 17-Jan-2023 | 12:00 Viewed: 17-Jan-2023 | 12:02 Signed: 17-Jan-2023 | 12:03
PPD Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 19-Jan-2023 | 07:56 ID: PPD	DocuSigned by: PPD Nombre del firmante: PPD Motivo de la firma: Apruebo este documento Hora de firma: 19-Jan-2023 | 13:57:35 CET PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Apruebo este documento	Sent: 17-Jan-2023 | 12:03 Viewed: 19-Jan-2023 | 07:56 Signed: 19-Jan-2023 | 07:57

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Jan-2023 | 07:57 Viewed: 20-Jan-2023 | 08:56 Signed: 20-Jan-2023 | 08:57
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Apruebo este documento	Sent: 20-Jan-2023 | 08:57 Viewed: 20-Jan-2023 | 09:26 Signed: 20-Jan-2023 | 09:26
Electronic Record and Signature Disclosure: Accepted: 20-Jan-2023 | 09:26 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17-Jan-2023 | 12:00
Certified Delivered	Security Checked	20-Jan-2023 | 09:26
Signing Complete	Security Checked	20-Jan-2023 | 09:26
Completed	Security Checked	20-Jan-2023 | 09:26

Payment Events	Status	Timestamps

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