16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol, Protocol Amendments and Clarification Letters

M-14867-32 Clinical Trial Protocol Version 1.0, 23-JAN-2022

M-14867-32 Clinical Trial Protocol Amendment Version 2.0, 21-MAR-2022

M-14867-32 Protocol Clarification Letter – Contraception, 08-AUG-2022

M-14867-32 Protocol Clarification Letter – Paper Diary, 03-JAN-2023

ALMIRALL, S.A.

Clinical Trial Protocol M-14867-32

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
Investigational Medicinal Product(s):	Tirbanibulin ointment 1% (Klisyri®)
Indication:	Actinic keratosis (AK)
Development Phase:	Phase 3
Final Protocol Version Date:	Version 1.0, 23 January 2022
Amendment(s)	**Number:** None **Date:** N/A
IND Number:	122464
Sponsor:	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona, Spain

Protocol Amendment Summary of Changes

There have been no amendments to the trial protocol.

Sponsor Signatures

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
Trial Code:	M-14867-32

The individuals signing this clinical trial protocol declare that they have reviewed it for completeness, accuracy. They are responsible for the trial and agree to conduct it in adherence to the present document, any amendments, to International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, and to local regulatory requirements, wherever applicable.

Sponsor

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona, Spain

Functional Role	Name	Signature	Date
PPD	PPD		
PPD	PPD		
PPD	PPD		

This document was electronically signed in the eDMS R&D system.
Manifestation of the e-signatures are available at the end of this document which are the equivalent of handwritten signatures, in compliance with 21CFR Part 11

Principal Investigator Signature

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
Trial Code:	M-14867-32

The individual signing this clinical trial protocol declares that he/she has reviewed it for completeness, accuracy. He/she is responsible for the trial and agrees to conduct it in adherence to the present document, any amendments, to International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, and to local regulatory requirements, wherever applicable.

Principal Investigator

Role	Name	Signature	Date
Principal Investigator			

1 Protocol Synopsis

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

Investigators:

A Principal Investigator will be designated at each participating clinical trial center and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical study report (CSR).

Trial Center(s):

The trial is planned to be conducted at approximately 20 centers in the United States (US).

Trial Duration:

The duration of the entire study from first patient, first visit to last patient, last visit is anticipated to be approximately 8 months.

Phase of Development:

This is a Phase 3 trial.

Rationale:

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well-controlled Phase 3 clinical trials, tirbanibulin ointment 1% was demonstrated to be an effective and safe treatment for actinic keratosis (AK) of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

On the basis of the Phase 3 trial results, tirbanibulin ointment 1% was approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of ultraviolet (UV) light-damaged skin; thus, there is a need for a product to treat AK patients with affected fields larger than 25 cm^2.

This study will assess the safety and tolerability of tirbanibulin ointment 1% administered under the same posology (once daily for 5 days) to a field of approximately 100 cm^2 on the face or balding scalp containing 4 to 12 clinically typical, visible, and discrete AK lesions.

Objectives:

The primary objective 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.

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 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.

Number of Patients:

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

Trial Population:

Male and female AK patients, aged 18 years or older, having 4 to 12 clinically typical, visible, and discrete AK lesions over a field of approximately 100 cm^2 on the face or the balding scalp. A minimum of 50% of patients will be older than 65 years old and approximately two-thirds of the patients will be treated for AK lesions on the face and one-third on the scalp.

Test Investigational Medicinal Product, Dosage, and Mode of Administration:

Substance code/name:	Tirbanibulin
Administration route:	Topical
Strength:	1%
Dosage form:	Ointment

Tirbanibulin ointment 1% will be applied once daily for one 5-day treatment course. On Day 1, treatment application will occur at the investigational site in the morning under the supervision of clinical trial site staff. Between Days 2 and 5, the treatment will be self-administered once daily at home.

Reference Investigational Medicinal Product, Dosage, and Mode of Administration:

Not applicable. No control arm will be included in this study.

Methodology:

Study visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1).

Duration of Treatment:

The duration of each patient's treatment is 5 days.

Duration of Patients' Participation in the Trial:

The total duration of each patient's participation in the trial, including screening, treatment, and response assessment is estimated to be approximately 3 months.

Statistical Methods

Sample Size Calculation

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.

Endpoints

Safety Endpoints

- Local Tolerability Assessment:
  - 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
  - Pigmentation and scarring in the TF through all the visits
- Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])

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

Statistical Analysis

All analyses will be performed on the Safety population, defined as all patients who have received at least one dose of study treatment.

Safety Endpoints

Descriptive statistics will be provided for all safety endpoints.

Local tolerability signs composite score, and specific local tolerability scores will be analyzed by means of descriptive statistics and provided by visit. The maximum local tolerability scores and maximum local tolerability composite score will be presented. The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by visit as well as the number and percentage of patients with changes from baseline in pigmentation and scarring in the TF.

TEAEs and TESAEs recorded during the study will be presented, including the total number of events and the number and percentage of patients with events. Summaries of the number and percentage of patients with TEAEs (and number and percentage of events), study drug-related TEAEs, TEAEs by severity, TESAEs, TESAEs with an outcome of death, and TEAEs leading to temporary or definite discontinuation of the study treatment will be provided. Specific tables describing AESIs will be also provided. The number and percentage of patients who experience one or more AESI will be tabulated by AESI.

For PEs, ECGs, vital signs, and clinical laboratory parameters, the number and percentage of patients with normal or abnormal results will be presented at scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. Shift tables will be provided when appropriate.

Exploratory Endpoints

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

Interim Analysis

No interim analysis is planned for this trial.

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
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						

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**
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]
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 hyper-pigmentation, 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 5.

[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 subject at home before study Visit 3 on Day 5, which will take place at the clinical site.

2 Table of Contents

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3 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AK	Actinic keratosis
ALCOA	Attributable, legible, contemporaneous, original, and accurate
BCC	Basal cell carcinoma
CDISC	Clinical Data Interchange Standards Consortium
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CROOP	Clinical Research Organization Oversight Plan
CSR	Clinical Study Report
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of Study
ET	Early termination
eTMF	Electronic Trial Master File
FDA	Food & Drug Administration (United States)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MUsT	Maximum usage trial
OTC	Over-the-counter
PDF	Portable document format
PE	Physical examination
PIS	Patient Information Sheet
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma

SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TF	Treatment field
TMF	Trial Master File
US	United States
UV	Ultraviolet
WOCBP	Women of child-bearing potential

4 Sponsor, Investigator(s) and Trial Administrative Structure

4.1 Sponsor

Almirall, S.A. (Legal entity)
General Mitre, 151
08022 Barcelona, Spain

Almirall Research and Development Centre:
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
Barcelona, Spain

4.2 Investigator(s)

A Principal Investigator will be designated at each participating clinical trial center and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical study report (CSR).

4.3 Administrative Structure

Medical Expert appointed by the Sponsor for this trial:

PPD MD, PhD
Almirall Research and Development Centre
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
Barcelona, Spain
Telephone: PPD
Email: PPD

This study will be conducted by a Contract Research Organization (CRO) on behalf of the Sponsor; the Sponsor will maintain oversight of the CRO. Refer to the CRO Oversight Plan (CROOP) for details and see Section 10.7.4 for Serious Adverse Event (SAE) and Adverse Event of Special Interest (AESI) reporting.

5 Introduction

A summary on the indication, mechanism of action, and completed nonclinical and clinical studies is provided below. A detailed description of the chemistry, pharmacology, efficacy, and safety of tirbanibulin ointment 1% is provided in the Athenex KX2-391 (tirbanibulin) Investigator's Brochure.

5.1 Background Information

5.1.1 Indication

Actinic keratosis (AK) is an ultra-violet (UV) light-induced pre-cancerous lesion of the skin that represents the initial clinical manifestation of intra-epidermal abnormal keratinocyte

proliferation (Röwert-Huber, 2007; Fernandez Figueras, 2017). Given the demonstrated potential for progression to invasive squamous cell carcinoma (SCC), dermatologists encourage and actively pursue treatment, as recommended in current national and international guidelines (Hofbauer, 2014; Werner, 2015; de Berker, 2017; Leitlinienprogramm Onkologie, 2019).

Actinic keratosis presents as erythematous, scaly patches on the skin of sun-exposed areas and so particularly affecting the face, scalp, and extremities, either as a single lesion or multiple lesions and may present in as an entire field ("field cancerization") with widespread actinic damage, such as in areas on the forehead or the back of the hand (Dodds, 2014; Figueras Nart, 2018). Actinic keratosis is common in older, fair-skinned populations of European ancestry, and is more frequently observed in men (Flohil, 2013).

Precise estimates of AK prevalence are difficult, owing to its strong association with increased age. The prevalence of AK in the US has been reported to range from 11% to 26% (Salasche, 2000). Recent studies in Europe suggest that AK prevalence there ranges from 33% to 49% for men and 14% to 28% for women (Eder, 2014, Tizek, 2019, Flohil, 2013, Ferrándiz, 2016, Fargnoli, 2017, Dziunycz, 2018).

In some cases, AK represents a carcinoma *in situ* of the skin, and when left untreated, AK can progress to invasive SCC (Röwert-Huber, 2007; Werner, 2013; Fernandez Figueras, 2017). Cutaneous SCC represents 20% to 50% of skin cancers (Que, 2018) and poses a significant threat due to its ability to metastasize to any organ in the body (Burton, 2016). Up to 65% of SCCs arise from pre-existing AK; however, the risk of progression to SCC of a single AK lesion per year has been reported to be very low, 0% to 0.075% in patients without a previous history of non-melanoma skin cancer (Marks, 1988), and up 0.53% per lesion in patients with a prior history of non-melanoma skin cancer (Werner, 2013; Green, 2017).

5.1.2 Unmet Medical Need

Tirbanibulin ointment 1% is approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of UV light-damaged skin; thus, there is a need for a product to treat AK patients over fields larger than 25 cm^2.

Although a limited number of AK field-directed therapies are currently available that target areas larger than 25 cm^2, there remain unmet needs for patients with AK in terms of tolerability and treatment convenience/adherence. Topical therapies, such as 5-fluorouracil and imiquimod, frequently present safety and tolerability events during treatment that may lead to treatment discontinuation. While diclofenac sodium 3%, which is also used over larger fields, has a good safety and tolerability profile, it is administered over a longer treatment period (60 to 90 days) and drugs with shorter treatment durations are desirable, as they are associated with better adherence (Goldenberg, 2017). In a survey of 40 dermatologists in France, short treatment duration was the primary consideration in selecting a field-directed topical treatment (Savary, 2019). Thus, there is a need in the current armamentarium for well-tolerated, short-duration therapies targeted to areas larger than 25 cm^2.

5.1.3 Mechanism of Action

Tirbanibulin has potent anti-proliferative and anti-tumor activities *in vitro* and *in vivo* by virtue of its ability to induce cell cycle arrest and apoptotic cell death by disrupting the cellular

microtubule network via direct binding to tubulins. Furthermore, it is associated with disruption of Src tyrosine kinase signaling.

5.1.4 Nonclinical Studies

CCI

5.1.5 Clinical Studies

The clinical development program on topical tirbanibulin includes 10 completed clinical trials that enrolled a total of 1338 subjects, 989 subjects who received tirbanibulin ointment 1% and 349 subjects who received vehicle ointment. Of the 989 subjects treated with tirbanibulin ointment 1%, 597 were patients with AK and 392 were healthy adults.

Pharmacokinetics

Pharmacokinetic studies showed that tirbanibulin ointment 1% was minimally absorbed in patients with AK after topical application to 25 cm^2 on the face or balding scalp once daily for 5 consecutive days. Exposure (C_{max}, AUC_{0-24}) was higher when tirbanibulin ointment 1% was applied to the face versus the scalp. A proportional increase in systemic exposure (C_{max}, AUC_{0-24}) was observed when tirbanibulin ointment 1% was applied to an area measuring 100 cm^2 on the face or balding scalp.

Efficacy and Safety

The efficacy and safety studies included two Phase 3 double-blind, vehicle-controlled, randomized trials, KX01-AK-003 (N=351) and KX01-AK-004 (N=351), that were conducted in the US to evaluate the efficacy and safety of tirbanibulin ointment 1% compared to vehicle ointment in patients with AK on face or balding scalp. Tirbanibulin ointment 1% once daily for 5 days was effective in the treatment of AK on either the face or balding scalp, with statistically significantly higher rates of complete and partial clearance at Day 57 in the treated field as compared to control vehicle (complete clearance, 49% vs 9%, respectively). Treatment-related adverse events (AEs) were few (16% vs 10%, respectively) and consisted of mostly transient mild to moderate application site pruritus and pain that required no treatment; there were no treatment-related SAEs. Signs assessing local tolerability were mostly mild to moderate erythema and flaking/scaling. Mean composite scores for local tolerability signs peaked at Day 8 and were mostly resolved by Day 29.

The safety of treating larger AK fields (>25 cm^2) was evaluated in a Phase 1, maximal usage trial (MUsT), in which tirbanibulin ointment 1% was applied to an area measuring 100 cm^2 on the face or balding scalp in 28 patients with AK. The most frequently reported treatment-related AEs were application site pruritus and application site pain. All AEs were mild or moderate in intensity; no severe AEs were reported. The most frequently reported local tolerability signs were erythema and flaking/scaling. Most local tolerability signs were mild or moderate, with severe erythema and flaking/scaling reported in 14.3% of patients each. Local tolerability sign composite scores peaked around Day 7 to 8 and were mostly resolved by Day 29.

A detailed description of the completed clinical studies is provided in the Athenex KX2-391 Ointment 1% (tirbanibulin) Investigator's Brochure.

5.2 Summary of the Known Potential Risks and Benefits

Actinic keratosis is a UV light–induced pre-cancerous lesion of the skin that represents the initial clinical manifestation of intra-epidermal abnormal keratinocyte proliferation. Given the demonstrated potential for progression to SCC, dermatologists generally encourage and actively pursue treatment, with a goal of completely eliminating AK lesions, thereby reducing the risk of progression to invasive SCC.

Data from the two pivotal Phase 3 studies demonstrate that treatment with tirbanibulin ointment 1% once-daily for 5 days is effective in the treatment of AK of the face or balding scalp.

In the pivotal studies, the safety profile of tirbanibulin ointment 1% showed a low rate of treatment-emergent AEs and no unexpected or unanticipated safety findings. The overall incidence of treatment-emergent AEs (TEAEs) was similar between the tirbanibulin ointment 1% and vehicle groups, and there were no treatment-related treatment-emergent serious AEs (TESAEs) or discontinuations due to a TEAE. There were also no long-term safety concerns related to tirbanibulin ointment 1% in patients followed up to 1 year after Day 57.

The most frequently reported local tolerability signs were transient, mild to moderate erythema and flaking/scaling. Treatment-related AEs were mostly transient, mild to moderate application-site pruritus or pain, and most did not require treatment.

The safety profile of tirbanibulin ointment 1% observed in the Phase 1 maximal-use trial M-14687-01, in which study drug was applied to 100 cm^2 on the face or balding scalp, was consistent with that observed in the pivotal studies.

Based on the available efficacy and safety data from the completed clinical and nonclinical studies, the benefit-risk assessment is positive and supports the evaluation of tirbanibulin ointment 1% in this Phase 3 study of patients with AK of the face or scalp.

Further information regarding the nonclinical and clinical characteristics, summaries of the known and potential risks, as well as reasonably expected adverse reactions of the product under investigation, is provided in the Athenex KX2-391 (tirbanibulin) Investigator's Brochure.

5.3 Scientific Rationale for the Trial

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well-controlled Phase 3 clinical trials, tirbanibulin ointment 1% was demonstrated to be an effective and safe treatment for AK of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

On the basis of the Phase 3 trial results, tirbanibulin ointment 1% was approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of UV light-damaged skin; thus, there is a need for a product to treat AK patients with affected fields larger than 25 cm^2.

This study will assess the safety and tolerability of tirbanibulin ointment 1% administered under the same posology (once daily for 5 days) to a field of approximately 100 cm^2 on the face or balding scalp containing 4 to 12 clinically typical, visible, and discrete AK lesions.

6 Objectives and Endpoints

6.1 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.

6.2 Endpoints

6.2.1 Safety Endpoints

Safety Endpoints

- Local Tolerability Assessment:
  - 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
- Pigmentation and scarring in the TF through all the visits

- TEAEs, TESAEs, adverse events of special interest (AESIs), clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])

6.2.2 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

7 Trial Design and Rationale

7.1 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 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 TF until completion of the Response Assessment Period at Day 57.

7.2 Trial Rationale

7.2.1 Rationale for Trial Design

Since tirbanibulin ointment 1% is an approved product and there is no change in the formulation or posology, the main objective of this study is to evaluate the safety and tolerability of tirbanibulin ointment 1% applied over an extended field (100 cm^2) in adult patients with AK on the face or balding scalp.

The duration of the study considers both safety and efficacy. From a local tolerability perspective, most of the local signs are expected to be resolved by Day 29. However, the study duration is extended up to Day 57, in order to assess the treatment effect as exploratory endpoints.

In addition to the overall incidence of local tolerability events, the sample size considers detection of local tolerability signs of particular interest, specifically, vesiculation/pustulation and erosion/ulceration (see Section 11.1). When severe, these local tolerability signs can lead to permanent local events such as dyspigmentation or scarring.

7.2.2 Rationale for Trial Population

The study will be conducted in male and female AK patients, aged 18 years or older, having 4 to 12 clinically typical, non-hypertrophic, non-hyperkeratotic, visible, and discrete AK lesions over a field of approximately 100 cm^2 on the face or the balding scalp.

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.

7.2.3 Rationale for Trial Dose and Regimen

In this study patients will be treated with tirbanibulin ointment 1% daily for 5 consecutive days beginning on Day 1. Treatment will be applied to a field measuring approximately 100 cm^2 on the face or balding scalp. There are no changes in treatment duration or posology. Tirbanibulin ointment 1% has shown effectiveness in the treatment of AK lesions and the good safety and tolerability profile supports the field extension to a higher area to satisfy medical needs.

In a Phase 2 trial (KX01-AK-002), efficacy and safety results of 3 and 5-day treatment regimens over 25 cm^2 were compared. The 5-day regimen showed substantial clinical activity and acceptable local tolerability. The 5-day treatment regimen showed a higher proportion of patients with 100% clearance at Day 57 compared with the 3-day regimen (43% vs 32%, respectively), as well as a higher proportion of patients maintaining their treatment response at 12 months (43% vs 30%, respectively). Patients in the 5-day regimen experienced slightly more mild/moderate erythema and flaking/scaling, but local signs were self-limited with both regimens and by Day 29 had essentially returned to baseline values.

7.2.4 Rationale for Trial Assessments

In prior studies, mild to moderate erythema and flaking/scaling were the most frequently observed signs when assessing local tolerability. Local tolerability signs following treatment will be characterized and assessed throughout this study and reported separately from AEs.

Standard safety assessments will be performed throughout the study including the capture of AEs, SAEs, concomitant medications, laboratory testing for hematology, blood chemistry, and urinalysis, PEs and vital signs measures, and ECGs.

Lesion counts in the TF will be performed at Screening, Day 1/Baseline (predose), and at every visit from Day 5 up to Day 57 to evaluate the treatment effect of tirbanibulin ointment 1%, when applied to an area measuring 100 cm^2 on the face or balding scalp.

8 Selection of Trial Population and Withdrawal of Patients

8.1 Number of Patients

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

8.2 Inclusion Criteria

All of the following criteria must be met for inclusion of a patient in the trial:

1. Male or female and ≥18 years old at the time of consent
2. Having a TF on the face or balding scalp (excluding lips, eyelids, and inside nostrils and ears) that
   - measures approximately 100 cm^2 (eg, mid face) and
   - contains 4 to 12 clinically typical, visible, and discrete AK lesions within the TF
3. If a woman of childbearing potential (WOCBP), ie, fertile, defined as a female in the life period from menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (with hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months prior to Screening), she must:
   - have a negative urine pregnancy test using a highly sensitive method at screening and on Day 1 prior to treatment administration
   - be using highly effective methods of birth control (defined in Appendix 1) for at least 30 days or 1 menstrual cycle, whichever is longer, prior to the study treatment and must agree to continue use during the study period and until at least 30 days or 1 menstrual period, whichever is longer, after the last dose of investigational product
   - agree to have pregnancy tests while in the study and at the end of the study (according to the Schedule of Assessments in Table 1)
4. Willing to avoid excessive sunlight or UV light exposure, including the use of tanning beds, to the face or scalp during the study
5. Ability to understand the purpose and risks of the trial, willingness and ability to comply with the protocol, and provided written informed consent in accordance with institutional and regulatory guidelines

8.3 Exclusion Criteria

Patients will be excluded from trial enrollment if they meet any of the following criteria:

1. Presence in the TF of:
   a) Clinically atypical and/or rapidly changing AK lesions in the TF
   b) Hyperkeratotic or hypertrophic lesions, recalcitrant disease (had cryosurgery on 2 previous occasions) and/or cutaneous horn
   c) Confluent AK lesions (ie, non-discrete lesions defined as per inclusion criteria)
   d) History of invasive SCC, Bowen's disease, basal cell carcinoma (BCC), or other malignant tumors in the TF

e) Any other dermatological disease that causes difficulty with examination

2. Location of the TF is:
   - On any location other than the face or balding scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected BCC or other neoplasia
   - Periorbital, lips, or nostrils
3. Previous treatment with tirbanibulin ointment 1%.
4. Anticipated need for inpatient hospitalization or inpatient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil, imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the TF or within 2 cm of the TF, within 8 weeks prior to the Screening visit
6. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the TF or within 2 cm of the selected TF
   - Treatment with cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate).
   - Treatment with systemic medications that modulate and/or suppress the immune system (eg, cyclosporine, azathioprine, methotrexate, prednisone, alefacept, infliximab, interferons/interferon inducers).
   - Therapy/treatment with UV-A or UV-B light.
8. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the TF or within 2 cm of the selected TF
   - Topical steroids within the TF or within 2 cm of the selected TF
   - Artificial tanners within the TF or within 5 cm of the selected TF
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication
10. Patients with significant abnormalities on the medical history, PE findings, vital signs, ECG, clinical chemistry, hematology, and urinalysis results that in the judgment of the Investigator may interfere with the interpretation of the results.
11. A skin disease (eg, atopic dermatitis, psoriasis, seborrheic dermatitis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the patient to unacceptable risk by study participation

12. Significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the patient to unacceptable risk by study participation
13. Females who are pregnant or nursing or seeking to become pregnant
14. Participated in an investigational drug trial during which an investigational study medication was administered within 30 days or 5 half-lives of the investigational product, whichever is longer, before dosing in the current study
15. Patient who is employee or relative to employees at the research site or Almirall

8.4 Treatment Discontinuation Criteria

Any patient may discontinue from study treatment at any time during the trial at the discretion of the Investigator or at the request of the patient. For patients who discontinue treatment, efforts should be made to encourage the patient to remain in the trial and complete the trial-related assessments. The main reason for such a premature treatment discontinuation must be documented in the electronic case report form (eCRF), as follows:

- Adverse event: If a patient experiences an AE, treatment discontinuation will be at the discretion of either the Investigator or the patient regardless of the causal relationship to the investigational medical product (IMP).
- Protocol deviation: Any protocol deviation detected should be corrected when possible and the patient should be allowed to continue. ONLY the following deviations should lead to treatment discontinuation: those which could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor] might invalidate the trial by interfering with the IMP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected
- Lost to follow-up: Non-attendance. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure patient’s attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the patient and documented in the medical records. If patient cannot be reached after that, a registered mail letter will be sent to the patient and documented in the medical records
- Patient's personal request: The patient is permitted to stop his/her treatment at any time during the trial without incurring any loss in his/her medical care. The Investigator should ensure that such discontinuation is not due to an AE or disease exacerbation, in which case the corresponding reason should be recorded
- Pregnancy

8.5 Trial Withdrawal Criteria

Any patient may withdraw from the trial at any time during the trial at the discretion of the Investigator or at the request of the patient. The main reason for such a premature study withdrawal must be documented in the eCRF, as follows:

- Adverse event: If a patient experiences an AE, study withdrawal will be at the discretion of either the Investigator or the patient regardless of the causal relationship to the IMP.
- Death

- Protocol deviation: Any protocol deviation detected should be corrected when possible and the patient should be allowed to continue. ONLY the following deviations should lead to patient withdrawal: those which could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor might invalidate the trial by interfering with the IMP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected
- Lost to follow-up: Non-attendance. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure patient's attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the patient and documented in the medical records. If patient cannot be reached after that, a registered mail letter will be sent to the patient and documented in the medical records
- Patient's personal request: The patient is permitted to stop his/her participation at any time during the trial without incurring any loss in his/her medical care. The Investigator should ensure that such withdrawal is not due to an AE or disease exacerbation, in which case the corresponding reason should be selected
- Trial terminated by Sponsor

8.6 Screening Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently treated in the study. A minimal set of screen failure information is required to be entered into the database to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Competent Authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failures) will not be rescreened.

8.7 Patient Replacement Criteria

Patients who withdraw from the trial at any time will not be replaced.

8.8 Termination of the Trial

8.8.1 End of Trial Definition

The "end of trial" is defined as the date of the last visit of the last patient, either at Day 57 or earlier, if the last patient discontinues prematurely. The end of trial will be communicated to the Competent Authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) according to local regulations.

8.8.2 Completed Patient Definition

Patients who complete all the phases of the study, including the last visit as described in the Schedule of Assessments (Table 1), will be considered to be completed patients.

8.8.3 Premature Trial Termination

Almirall reserves the right to prematurely terminate (ie, suspend) the trial.

Certain circumstances may require the premature termination of the trial including:

- The Investigator/Coordinating Investigator and the Sponsor feel that the type, number, and/or severity of AEs justify discontinuation of the trial.
- The Sponsor considers the applied doses of the trial drug to be no longer relevant.
- Data not known before becoming available and that raise concerns about the safety of the trial drug so that continuation would pose potential risks to the patient

If the trial is terminated or suspended, the Sponsor/CRO will promptly inform the Investigators. The IRBs/IECs should be promptly informed and provided the reason(s) for the termination or suspension by the Investigator, as specified by the applicable regulatory requirement(s).

The Investigator will inform the patients and will collect and keep all the data up to the date of discontinuation. Samples retrieved up to the date of trial termination will be analyzed as per protocol.

If the trial is prematurely terminated or suspended, trial results will be reported according to the requirements outlined in this protocol, as far as applicable.

The Clinical Data Interchange Standards Consortium (CDISC) criteria should be followed while recording the patient trial discontinuation reasons.

9 Treatments

9.1 Identity of Trial Investigational Medicinal Products

Investigational medicinal product manufacturing, labelling, packaging, and release will be done following Good Manufacturing Practice (GMP).

Tirbanibulin is a white to off-white ointment containing tirbanibulin freebase active drug substance. For a full product description, refer to the KX2-391 Ointment 1% (tirbanibulin) Investigator's Brochure.

Test Investigational Medicinal Product

Substance Code/Name	Tirbanibulin
Route of Administration	Topical
Dosage Form	Ointment
Strength	1%

Reference Investigational Medicinal Product

This is single arm study; no reference IMP will be used.

9.2 Packaging and Labelling

Study drug will be packed and labeled in accordance with local regulations by the Sponsor according to GMP conditions, including but not limited to the Sponsor contact details, protocol number, drug identification, storage conditions, and content of study drug. A sample label will be filed in the Investigator file.

On Day 1, patients will be dispensed a study kit containing 5 zipper bags each with a single-dose packet containing 350 mg tirbanibulin ointment 1%.

Local regulatory requirements will be fulfilled for packaging and labelling (US 21 Code of Federal Regulations 312.6).

9.3 Shipment, Storage, and Accountability

Only participants enrolled in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All drug supplies must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Tirbanibulin ointment 1% must be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Do not refrigerate or freeze tirbanibulin ointment 1%. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and ensure that any discrepancies are reported and resolved before use of the study medication.

The Investigator, the trial staff, institution, or the head of the medical institution (where applicable) is responsible for clinical supplies accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study.

Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused investigational products are provided in the Study Reference or equivalent manual.

Empty packages and unused medication will be returned to Almirall or a designated depot, where the remaining medication will be destroyed according to regulatory requirements. Retention drug samples will be kept by the Sponsor or designee, during the trial and until it is legally required after trial completion.

The Investigator and trial staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional requirements.

9.4 Treatment Administration

Treatment will begin on Day 1, following confirmation of patient eligibility and collection of all pre-dose samples and assessments.

At Baseline (Day 1 pre-dose), the Investigator will confirm the TF on the face or balding scalp that was identified at Screening and the patients will receive instructions on how to apply the topical medication and how to care for the TF.

Patients will be provided with 5 single-dose packets containing tirbanibulin ointment 1%.

The first dose will be administered by the patient under the supervision of study personnel on Day 1 at the site. The patient will self-administer the remaining single-dose packets once daily at home for the next 4 consecutive days. The fifth dose should be applied by the patient at home before the Day 5 site visit.

Tirbanibulin ointment 1% will be applied to cover the treatment field of approximately 100 cm^2, corresponding to approximately 0.5% of the body surface area. Study medication should be applied each day at approximately the same time. The treatment field should not be wet, should be kept dry for approximately 8 hours after application, and should not be touched or covered with dressing. The ointment should not be applied near the eyes, mouth, or lips.

Patients will return the used medication packaging (all parts of each packet, including the torn opening part) and any unused study medication back to the clinical site at the next visit to check compliance and for drug reconciliation purposes. Further details will be given in the study manuals (see Section 9.5).

9.5 Treatment Compliance

Compliance with the study treatment will be assessed by site personnel on Day 5. Compliance will be assessed by counting the dispensed and returned used tirbanibulin ointment 1% single-use packets. Patients will be instructed to return both the used and unused study treatment back to the clinical site. This information will be recorded in the eCRF.

Deviations from the prescribed dosage regimen should be also recorded in the eCRF.

Patients will record dates and times of study treatment application, including dates for study treatment delays in the electronic diary of the study mobile application (Study App).

The amount of study drug applied will be determined based on weight. The site will record the weight, as a whole, of the 5 packets each one in their respective closed zipper storage bags before and after dosing to quantify the amount used by the patient. Patients will be required to bring back to the site the respective two torn parts of each packet in their respective closed zipper storage bags. The weighing of the 5 packets will be performed on a balance with sufficient precision to calculate the weight by difference of tirbanibulin administered daily with high accuracy. To avoid losing any study drug by leakage issues, the total weight of 5 packets will be measured as a whole in their respective re-sealable zipper storage bags. Additional details for this process are provided in the study manuals.

The dosing logs for each patient will be kept during the study. The Clinical Research Associate (CRA) will review treatment compliance during monitoring site visits.

9.6 Methods for Assigning Patients to Treatment Groups

9.6.1 Patient Identification

In order to protect the patient identity and data confidentiality, each patient will be identified in the trial with one unique patient number. The unique patient number is a combination of his/her site number and a sequential number assigned by the Investigator.

The site number will be predetermined, but the sequential number is assigned by the Investigator upon signing the informed consent form (ICF). At each site, the first patient is assigned patient number 001, and subsequent patients are assigned the next consecutive number.

Once assigned to a patient, the patient number will not be reused. The patient number will be used to identify the patient throughout the trial.

9.6.2 Randomization

This is single-arm study in which all patients are treated with tirbanibulin ointment 1%; no randomization is performed.

9.7 Blinding

This is an open-label study with no active or placebo comparator; no study blind will be applied.

9.8 Unblinding by the Investigator

Not applicable.

9.9 Pre-trial, Concomitant, and Post-trial Medications/Therapy

9.9.1 Pre-trial Medications

Patients must not have received any other IMP within 30 days or 5 half-lives of the IMP, whichever is longer, before the first trial drug administration.

All medications, including over-the-counter (OTC) drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to screening will be recorded at Screening. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria to ensure proper washout is followed. Thereafter, a record of all medications taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be captured in the patient's eCRF.

A complete study disease treatment history will be recorded in the eCRF.

Any medication taken for medical reasons (mainly diseases concomitant with studied disease) prior to trial entry, will be continued at the same dose and conditions during the entire experimental phase of the trial.

9.9.2 Concomitant Medications

No concomitant therapy will be allowed during the entire duration of the trial, other than the prior allowed medication or any other required for the treatment of AEs or local tolerability. In such cases, the drug will need to be prescribed by the Investigator and recorded in the Concomitant Medication eCRF. The following items should be specified: trade name, dose and frequency of dosing, route, indication, date and time of first dose, and date and time of last dose, when applicable.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used. The use of non-medicated therapies (eg, sunscreen and moisturizers) will also be recorded in the Concomitant Medication eCRF. The use of or change in the dose of any of the concomitant medications, either prescription or OTC, during the study will be recorded. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE.

Patients must be instructed to inform the Investigator of plans to take any new treatment during the participation in the trial, including OTC medicinal and herbal products.

9.9.3 Prohibited Concomitant Medications

The use of any non-study drug on the TF is prohibited during the study.

The use of moisturizers and sunscreens in the TF is prohibited during the study, but can be applied outside of the TF, as needed.

Patients will be reminded that AK lesions located outside the treatment field may be treated by physical lesion-directed treatment only (eg, cryotherapy) at the Investigator's discretion.

All medications requiring wash-out (see Exclusion Criteria, Section 8.3) are prohibited during the patient's participation in the study.

9.9.4 Post-trial Medications

Once study treatment and all visits and related study measurements are complete, patients should continue to take their usual medications allowed during the study and may resume other medications interrupted prior to study enrolment, as deemed appropriate by the Investigator. It is not planned to treat patients with tirbanibulin ointment 1% any further than scheduled in this study. No intervention or additional care is planned to follow the end of the study.

10 Trial Procedures and Assessments

10.1 General Conditions of the Trial

Informed consent will be obtained after the study has been fully explained to each patient and before the conduct of any screening procedures or assessments. Documentation will be required (documented in the patient's medical records) to confirm that the Investigator has ensured the informed consent process was done correctly, and that the patient understood what to expect, he/she had the opportunity to ask any questions and consider other treatment options and agreed to participate.

The ICF can be either in paper or electronic form. Patients will be able to download the signed ICF (in case of completing the electronic ICF) or will be given a hard copy (in case of completing the paper ICF).

Trial visits must be scheduled with respect to Baseline/Day 1. In order to adapt appointments to local holidays, patients´ availability or site internal organization needs, time windows are allowed as indicated in Table 1. The CRA or CRO Medical Monitor should be contacted for advice in case of exceptional situations.

As applicable, laboratory tests and other assessments will be performed using supplies or equipment provided by the Sponsor for this trial through a specialized provider who will perform centralized assessment and reporting.

Optimally, the evaluations for each patient (lesion counts, review of trial drug compliance, etc.) should be performed by the same Investigator (or other suitably qualified and experienced designee) throughout the trial to avoid inter-assessor bias.

Unless specified otherwise, the study assessments scheduled during the study visits must be performed before the study product administration, except on Day 5, when the study product application will be done by the patient at home prior to the site visit. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. Vital signs
2. ECG
3. Blood draw for laboratory tests

Table 1 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in the following sections.

10.2 Patient's General Conditions During the Trial

After the screening evaluation and while not at the research site, patients will maintain normal daily activities, following the instructions of the Investigator. Any event likely to interfere with the objectives of the trial will be communicated to the Investigator and reported without delay to the Sponsor.

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

All screening assessments will be performed after the patient provides informed consent. The Screening Visit (Visit 1) will occur between Day -28 and Day -1. Patient screening numbers will be assigned at Visit 1.

Prior to signature of the ICF, Investigators will evaluate eligibility of patients for entry in the trial by comparing past and current medical status, as documented in the patient's medical history, to the inclusion/exclusion criteria of the trial.

Eligible patients will receive a detailed description of all activities and requirements before signing the ICF to ensure their understanding and compliance with sample collection and clinical examinations.

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. 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.

The Screening visit and assessments will be performed in accordance with schedule detailed in Table 1.

Demographics and Baseline Characteristics

Data on demographic (sex, age, race, ethnicity) and baseline characteristics (body weight, height, smoking and alcohol habits) will be collected during Screening. Height will be measured at Screening only.

Skin type will be recorded according to the Fitzpatrick scale (Table 2).

Table 2 Fitzpatrick Skin Type

Skin Type	Description*
I	Always burns easily, never tans (sensitive)
II	Always burns easily, tans minimally (sensitive)
III	Burns moderately, tans gradually (light brown) (normal)
IV	Burns minimally, always tans well (moderate brown) (normal)
V	Rarely burns, tans very well (dark brown) (intensive)
VI	Never burns, deeply pigmented (intensive)

*Sunburn and tanning history based on first 30 to 45 minutes of sun exposure after winter season of non-sun exposure.

Medical and Actinic Keratosis History

Medical history at Screening will include:

- Significant medical and surgical history during the last 5 years (eg, a common cold would not be captured unless it was ongoing at Screening)
- The initial diagnosis date of AK on the face or balding scalp and on any other part of the body
- Any AK treatment history of the face or balding scalp including all commercial and investigational products and surgical modalities dating back to the initial diagnosis
- History of and location of cancers including skin cancers, eg, BCC, SCC, melanoma

Prior Medications

All medications, including OTC drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to screening will be recorded at the Screening visit (see Section 9.9.1).

Physical Examination

A complete Physical Examination includes 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 sun-exposed areas where photo-damage is likely. Height is measured at Screening only. Physician examinations will be conducted in accordance with schedule detailed in Table 1.

Treatment Field Identification

The size of the TF must be approximately 100 cm^2.

At Screening, the Investigator will select and measure the anatomical area (eg, approximately mid face or an area on the scalp) and will outline the TF with a marker pen over the skin. Each AK lesion within the TF will be also 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 the number and location of lesions inside it will be confirmed. A baseline photograph 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 photograph is needed at baseline, then the screening photograph will be considered the baseline assessment. The same field will be located during the study with the aid of imaging software before performing the study assessments. Study Manuals will be provided to describe the image procedures in detail. The number of AK lesions in the TF will be recorded in the eCRF and photographs will be taken according to the schedule in Table 1.

Pregnancy Testing

In females of childbearing potential, a highly sensitive urine pregnancy test will be performed at the Screening visit and according to the Schedule of Assessments (Table 1). Urine pregnancy test kits will be provided by the Sponsor.

Any pregnancy, whether occurring in a female patient or in the female partner of a male patient, for which the estimated date of conception was during the patient's study participation must be reported. In addition, pregnancies in female partners of male patients for which the estimated date of conception was within 90 days of the last study treatment must be reported.

10.3.2 Response Assessment Period

Response Assessment Period visits and assessments will be performed in accordance with the schedule detailed in Table 1. See Sections 10.4 and 10.5 for details on the lesion and safety assessments, respectively.

The trial visit at Day 5 cannot be repeated nor skipped. The trial visits at Day 8, Day 15, Day 29, and Day 57 may be rescheduled within the time windows allowed in this protocol, in case of:

- scheduling conflicts (weekends or holidays),
- technical problems with the equipment necessary for the visit (eg, ECG),
- any AEs that impede conduct of the visit,
- restrictions related to the coronavirus 2019 disease (COVID-19) pandemic.

10.3.3 Unscheduled and Repeated Tests

Unscheduled Tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the trial in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc. These additional tests outside of the initial schedule of the trial will be considered "unscheduled tests" and will not be associated with any trial visit.

Repeated Tests

Any safety test may be repeated at the Investigator's discretion under either of the following situations:

- When there is any kind of problem with the first test (ie, technical problem with the ECG machine, blood sample hemolyzed, presence of artifacts, etc.). The Investigator should repeat the individual test as soon as possible.
- At the screening visit any individual test(s) may be reasonably repeated during the screening window to confirm the eligibility criteria (eg, laboratory sample when there is any clinically significant abnormality, etc.).

10.4 Lesion Assessments

To the extent possible, the Investigator who conducts the lesion count at Baseline/Day 1 and through the study visits according to the Schedule of Assessments (see Table 1) **must** be the same for an individual patient. All other intermediate assessment visits **should** be conducted by the same Investigator, to the extent possible.

A dermatologist (Investigator or Subinvestigator) will count all lesions in the TF for all subjects, according to the Schedule of Assessments (see Table 1). Details on whether the lesion present in the TF is new or an existing lesion at baseline will be recorded at each visit in the eCRF.

Lesions identified at baseline will be followed during the study using appropriate tools such as imaging software, where baseline lesions will be identified and new lesions appearing along the study recognized.

10.5 Safety and Tolerability Assessments

Safety will be assessed periodically during the study by recording AEs, including SAEs, local tolerability, pigmentation and scarring, and AESIs. Safety assessments also include PEs and vital signs measures, ECGs, clinical laboratory evaluations and pregnancy testing for WOCBP (see Table 1).

10.5.1 Adverse Events

10.5.1.1 Adverse Events

At each study visit, patients will be asked a general question "How have you been since the last visit?" before assessment of local tolerability, pigmentation, and scarring in the TF.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, vital sign measurements), including those that worsen from baseline which are determined to be clinically significant in the medical and scientific judgment of the Investigator, are to be recorded as AEs or SAEs.

Local tolerability signs will be reported separately from AEs (see Section 10.5.2). The Investigator, or designee, may report an AE based on his or her judgement. See Section 10.5.1.2 for definitions and reporting of AESIs.

All patients who have unresolved treatment-related AEs at Day 57/Early Termination (ET) 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.

Adverse event and SAE definitions and reporting requirements are detailed in Section 10.7.

10.5.1.2 Adverse Events of Special Interest

The following have been identified as AESIs based on their relevance for the current intended use:

Skin Cancers

Skin cancers (including BCC, SCC, and melanoma) appearing within or outside the TF during the study will be reported as AESIs. Details of the skin cancer and any other associated AE will be recorded in the AE form in the eCRF and by using the Skin Cancer Report Form. The location and treatment will be recorded. In the case of an SCC arising within the TF, it will be recorded if an AK had been present at the same location at baseline. See Section 10.7.4 for reporting requirements for AESIs.

If the skin cancer meets seriousness criteria, an SAE Report Form must also be completed and sent along with Skin Cancer Report Form, as specified in Section 10.7.4.

10.5.2 Focused Dermatological Examination of the Treatment Field

The focused dermatological examination will include evaluations for local tolerability signs, pigmentation, and scarring in the TF.

10.5.2.1 Local Tolerability

Local tolerability assessments in the TF will be recorded per the schedule in Table 1. The assessment for local tolerability is to be done after the assessment for AEs. The evaluation of local tolerability is done by the Investigator (or an appropriate trained designee). The local tolerability signs to be assessed and the corresponding grading scale for each sign are provided in Table 3.

Table 3 Local Tolerability Signs and Grading Scale

Local Tolerability Signs	Local Tolerability Score
Erythema Flaking/scaling Crusting Swelling Vesiculation/pustulation Erosion/ulceration	0=absent 1=mild (slightly, barely perceptible) 2=moderate (distinct presence) 3=severe (marked, intense)

Application site symptoms such as itching, burning, stinging, tenderness, pain etc., are not classified as local tolerability signs and will be reported as AEs.

All patients who have unresolved local tolerability signs in the TF at Day 57/ET 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 Investigator.

Any sign of local tolerability leading to temporary or permanent discontinuation of the study drug application or requiring the use of concomitant medications should be reported as an AE. If a sign of local tolerability leads to an AE meeting the criteria of seriousness (ie, an SAE), the SAE form will be completed with all the available information and reported within the same timeframe and following the same routing as for an SAE (see Section 10.7.4).

In case of occurrence of possible contact dermatitis in the TF, an evaluation (patch test) will be made to confirm or rule out the diagnosis (see Appendix 2).

10.5.2.2 Pigmentation Changes and Scarring

Hypo- and hyperpigmentation and scarring in the TF will be assessed as being present or absent in accordance with the Schedule of Assessments (Table 1). The assessment of pigmentation and scarring is to be done after the assessment for AEs.

All patients who have unresolved hypo- or hyperpigmentation or scarring in the TF at Day 57/ET 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 Investigator.

10.5.3 Physical Examinations and Vital Signs

Physical Examinations

A complete PE includes 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 sun-exposed areas where photo-damage is likely. Height is measured at Screening only.

Vital Signs

Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and body temperature. Measurements of systolic and diastolic blood pressure will be conducted after at least 5 minutes resting in the supine position and preferably on the same arm. If there is any suspicion of unreliable measurement, blood pressure will be measured again. The value obtained this time will be considered as definitive and should be recorded in the eCRF.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded in the AE form in the eCRF.

10.5.4 Electrocardiograms

Electrocardiogram training, equipment, and a procedural manual will be provided to the sites by a central ECG vendor. Refer to the procedural manual for details.

Electrocardiograms will be performed according to the schedule in Table 1. Patients must be in a supine position for 5 minutes prior to ECG and ECG is to be done prior to any blood sampling.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded on the AE form in the eCRF.

10.5.5 Laboratory Testing

Routine laboratory assessments will be performed at a designated central laboratory (refer to the laboratory manual). Tests to be performed at the central laboratory are detailed in Table 4.

Table 4 Laboratory Testing Parameters

Assessment	Specific Tests
Hematology	Red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood chemistry	Electrolytes: Chloride, potassium, sodium, bicarbonate (HCO3) Liver Function Tests: alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, direct bilirubin Renal Function Tests: Blood urea/blood urea nitrogen, creatinine Other: Total protein, albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, triglycerides, uric acid
Urinalysis	Hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood.

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes according to the Schedule of Assessments (Table 1). Blood samples are to be collected before administration of concomitant medications (if any), and after vital signs measures and ECGs are performed. Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded on the AE form in the eCRF.

Urine pregnancy testing for WOCBP will be performed at the study site in accordance with the Schedule of Assessments (Table 1).

10.6 Other

Standardized Photography

Standardized photography of each patient's TF will be performed prior to dosing while on treatment (see Table 1) for illustrative purposes and to support the TF and AK lesion identification within the TF. Each AK lesion within the TF will be identified at the screening/baseline visit with a label placed over the skin, a photo will be captured as a reference to support AK lesion follow up during the study. Refer to the study manuals for detailed instructions.

Care must be taken to ensure that the same lighting, background, subject positioning relative to the camera, and camera settings are used for each photograph. Equipment, supplies, and detailed instructions for obtaining and managing the photographs will be provided to the clinical study site prior to the initiation of patient enrollment.

10.7 Adverse Events

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the patient.

10.7.1 Definitions

Adverse Event

An AE is defined as any untoward medical occurrence in a clinical trial participant, regardless of the administration of the IMP and its causal relationship to it.

An AE can therefore be any unfavorable and unintended medical occurrence during the patient's participation in the trial, including deterioration of a pre-existing medical condition, an abnormal value in a laboratory assessment, ECG abnormality, or an abnormal finding in the physical examination.

Adverse events must be temporally associated with the patient's participation in the trial, ie, occur after signing the ICF. At the time of the occurrence of an AE, the administration of the IMP does not need to have already been initiated. If initiated, it does not necessarily need to have a positive causal relationship to the event.

Serious Adverse Event

An SAE is an adverse event, which falls into one or more of the following categories:

- results in death
- is life-threatening (ie, an event which, in the view of the Investigator, places the patient at immediate risk of death from the event as it occurred.) It does not mean that the event might hypothetically have caused death if it was more severe or lasted longer
- requires in-patient hospitalization or prolongs existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

- is any other medically important event that may jeopardize the patient or may require intervention to prevent one of the other above outcomes.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. These are considered "other important medical events."

Hospitalization is defined as an overnight stay at the hospital or emergency room.

Prolongation of hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician.

10.7.2 Reporting of Adverse Events

Adverse events either reported by the patient or observed by the Investigator must be recorded in the AE page of the eCRF and should be described in the following manner:

- The nature of the AE will be described in precise, standard medical terminology (ie, not necessarily the exact words used by the patient). If known, a specific diagnosis should be recorded instead of listing signs and symptoms (eg, allergic contact dermatitis)
- The duration of the AE will be described by the start date and end date
- The location for cutaneous adverse events will be described as at or just around the TF (≤2 cm from the TF) or distant (>2 cm from the TF)
- The intensity of the AE will be described in terms of mild, moderate, or severe according to the Investigator's clinical judgment, using the following definitions:
  - **Mild**: Awareness of event, symptoms, or signs, but easily tolerated (acceptable)
  - **Moderate**: Sufficient discomfort and interferes with usual activity (disturbing)
  - **Severe**: Incapacitating with inability to do normal daily living activities or significantly affects clinical status and warrants intervention (unacceptable)
- The causal relationship of the event to use of the IMP will be described in terms of:
  - **Not related**: Event or laboratory test abnormality, definitely not related to trial drug, as related to other drug, chemicals, or underlying disease
  - **Unlikely related**: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable; disease or other drugs, chemicals or underlying disease provide plausible explanations
  - **Possibly related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake; could also be explained by underlying disease or other drugs or chemicals; information on drug withdrawal may be lacking or unclear
  - **Related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake, unlikely to be attributed to underlying disease or other drugs or chemicals; response to withdrawal clinically reasonable (positive dechallenge)

'Possibly related' and 'related' will be considered as 'related' terms for reporting purposes. If the events are assessed as 'unlikely related' or 'not related' to the suspect IMP, the event does not qualify for reporting purposes. In the absence of information on causality from the reporting Investigator, the CRO will immediately contact the reporting Investigator to request a causality assessment. The case will be updated with the follow-up information and reported accordingly. If no causality is provided by the Investigator, the Sponsor assessment will be considered for submission purposes.

- The outcome of the event will be described in terms of:
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal
  - Unknown
- The action taken on the IMP will be captured as:
  - Drug withdrawn
  - Dose not changed
  - Not applicable

An AE will be collected only once with its maximum severity, except when the AE started before first IMP administration and persisted after it and worsened in severity any time after first IMP application. In this latter case, the AE will be collected with each respective severity. The AE term recorded must be exactly the same at the different time points where this AE is reported again in the eCRF.

10.7.3 Recording of Adverse Events

Adverse events will be collected from signature of the ICF up to Day 57/ET. Any AE reported by the patient up to 30 days after the last study contact (Day 57/ET) should also be captured in the eCRF.

Medical disorders present at the time of signing the informed consent that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Abnormalities detected before IMP administration in the PE, laboratory tests, ECGs, or other safety assessments will not be considered AEs if already known as part of the medical history or in relation to prior medical conditions and will be recorded in the eCRF/CRF Medical History/physical examination form/page. However, abnormalities detected in screening/baseline tests, thought to be due to a trial procedure, will be considered AEs.

Abnormalities (newly occurring or worsening of previously known abnormalities) detected after IMP administration in physical exam, laboratory tests, ECGs, or other safety assessments, which are considered clinically relevant by the Investigator, or which require an intervention or a diagnosis test, or may result in the IMP discontinuation, should be reported as AEs.

Reported terms should accurately characterize the adverse event. When a patient experiences an unspecified injury, signs or symptoms, active investigation should be conducted to reach a final diagnosis. If reached, then the disease diagnosis is the preferred reported term.

Adverse events will be elicited by asking the patients non-leading questions (eg, "How do/did you feel?") and by collecting AEs spontaneously reported by the patient to the Investigator or a designee.

All AEs elicited by the Investigator during the defined AE collection period must be recorded in the eCRF. In addition, when an AE meets the criteria of seriousness (ie, an SAE), it must also be recorded on the SAE form and reported following the defined timelines in Section 10.7.4.

10.7.4 Reporting of Serious Adverse Events and Adverse Events of Special Interest

Serious adverse events and AESIs will be collected from signature of the ICF up to Day 57/ET. Any SAE or AESI reported by the patient up to 30 days after the last study contact (Day 57/ET) should be collected in the eCRF.

The Investigator must report any SAE or AESI within 24 hours from the moment she/he first learns of it to the CRO pharmacovigilance unit on a SAE report form. This reporting will take place regardless of whether the Investigator considers the event to be causally related to the IMP(s), to any other medicinal product(s), to the clinical trial procedure or to any intervention undergone by the patient.

Original reports are to be kept by the Investigator in the Investigator's File.

Contact details and specific instructions on the flow of SAE and AESI reports will be provided to all sites by the CRO.

The minimum information that must be included in the initial report is:

- An event meeting the criteria of SAE or AESI.
- A qualifiable reporter, defined as an Investigator of this trial or his/her delegate.
- A qualified patient, defined as a patient who has consented to this trial.
- A suspect medicinal product.
- The Investigator's causality assessment.

Unless the SAE or AESI has been sufficiently documented in the initial report, the Investigator will provide all available additional information in follow-up reports by using a new form and adhering to the same routing and time frames as defined for the initial report. This will be continued until the event has been fully documented and reported.

An event reported to the CRO pharmacovigilance unit which does not meet the SAE or AESI criteria shall be nullified by the Investigator by forwarding a follow up report.

Depending on the local requirements, a regulatory report of the SAE or AESI (if serious) will be produced by the CRO pharmacovigilance unit and submitted to relevant Competent Authorities and Investigators, when applicable according to local regulations.

Serious adverse events NOT considered to require reporting to the CRO pharmacovigilance unit will be:

- Hospitalization for a treatment/surgical procedure which was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the trial.

10.7.5 Follow-up of Adverse Events / Serious Adverse Events

Those AEs and SAEs, including AESIs, recorded for Screening failure patients will be followed-up until resolution or until otherwise agreed between the Sponsor and the Investigator.

All AEs and SAEs, including AESIs, that are still present after the last study visit (including AEs that have led to premature discontinuation), will be followed-up at least 2 weeks for AEs and 4 weeks for SAEs after the last trial drug administration, by means of a follow-up contact or visit (whichever is considered more appropriate by the Investigator). In case the AE/SAE is still ongoing after that time point, this will be followed-up until its resolution or until otherwise agreed between the Sponsor and the Investigator. The same timeframes will apply for AEs from screening failures which are ongoing at the time the patient is withdrawn from the trial.

Additional safety data collected at a contact/visit to follow-up the ongoing AE will not be included into the clinical database, if this was already locked; therefore, the clinical database lock will not be delayed due to this situation. Any SAE will be followed up if needed after clinical database lock and the information will be only stored in the safety database.

10.8 Pregnancies

There is no information about effects that tirbanibulin could have on the development of the fetus in humans. However, consistent with its mode of action, tirbanibulin was embryo- and fetotoxic in preclinical studies.

Any pregnancy, whether occurring in a female patient or in the female partner of a male patient, for which the estimated date of conception was during the patient's study participation must be reported. In addition, pregnancies in female partners of male patients for which the estimated date of conception was within 90 days of the last study treatment must be reported.

In case of pregnancy during the participation in the trial, the patient will be immediately discontinued.

The Sponsor will be informed according to the safety reporting procedure: the Investigator must complete a study specific pregnancy form upon confirmation of a pregnancy and send it to the CRO Safety Contact within 24 hours of confirmation of the pregnancy. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate.

The Investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, the follow-up period will be deemed to have ended when the health status of the child has been determined on its birth or after an appropriate period post-delivery considered necessary to monitor the development of the new-born is completed.

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriage, developmental delay, fetal death, SAE in a neonate, and congenital abnormalities will be reported as SAEs. The Investigator will inform the CRO Safety Contact of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

10.9 Unblinding for Safety Reasons

Not applicable.

11 Statistics

The statistical analyses described below will be supplemented by a comprehensive Statistical Analysis Plan (SAP) that will be finalized before the database is locked. Any changes to the statistical plans will be described and justified in the final report. All statistical processing will be performed using the SAS® system.

11.1 Sample Size Calculation

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.

11.2 Structure and Methodology of the Statistical Analysis

Statistical analyses of demographic, baseline characteristics, safety, tolerability, and lesion count data will be performed by the CRO Biostatistics department.

The SAP will be prepared by the CRO statistician under Almirall Standard Operating Procedures (SOPs) prior to database lock. SAS will be the statistical software used to analyze the data sets. A complete set of raw data listings will be appended to the Statistical Report. All tables, figures, and listings will be presented in portable document format (PDF) documents without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

Tables, figures, and listings will be compiled in the statistical report and appended to the CSR.

11.3 Analysis Populations

There will be one analysis population in this trial:

- Safety population, defined as all patients who have received at least one dose of study treatment.

11.4 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. When applicable, these summaries will be provided by visit and time-point of assessment.

11.5 Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics.

11.6 Study and Treatment Compliance

Descriptive statistics will be used to summarize study and treatment compliance.

11.7 Prior and Concomitant Medications

The number and percentage of the patients with concomitant medications during the study will be summarized by anatomical therapeutic chemical class, standardized drug name.

11.8 Statistical Methods

The statistical approach for the analysis of safety and other endpoints is described below. A more detailed description of the statistical methods to be used will be provided in the SAP.

11.8.1 Analysis of Safety Endpoints

Descriptive statistics will be provided for all safety endpoints.

Local tolerability signs composite score, and specific local tolerability scores will be analyzed by means of descriptive statistics and provided by visit. The maximum local tolerability score and maximum local tolerability composite score will be presented. The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by visit as well as the number and percentage of patients with change from baseline in hypo- or hyperpigmentation and scarring in the TF.

An AE will be considered to be a TEAE, if it was not present prior to the first dose of trial drug or was present prior to the first dose of trial drug but increased in severity after the date of the first dose of study treatment. An AE that occurs more than 57 days after the last IMP application will not be counted as a TEAE.

TEAEs and TESAEs recorded during the study will be presented, including the total number of events and the number and percentage of patients with events. Summaries of the number and percentage of patients with TEAEs (and number and percentage of events), study drug-related TEAEs, TEAEs by severity, TESAEs, TESAEs with an outcome of death, and TEAEs leading to temporary or definite discontinuation of the study treatment will be provided. Specific tables describing AESIs will be also provided. The number and percentage of patients who experience one or more AESI will be tabulated by AESI.

For PEs, ECGs, vital signs, and clinical laboratory parameters, the number and percentage of patients with normal or abnormal results will be presented at scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. Shift tables will be provided when appropriate.

11.8.2 Analysis of Exploratory Endpoints

Descriptive statistics will be provided for exploratory endpoints overall and by subgroup (see Section 11.11). An Observed Cases approach will be used for handling missing data, as the main analysis (see Section 11.9). Any other sensitivity analyses will be defined in the SAP.

11.9 Handling of Missing Data

No imputation will be made for missing data.

11.10 Multiplicity Strategy

Not applicable.

11.11 Subgroup Analyses

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

11.12 Interim Analysis

No interim analysis is planned for this trial.

12 Data Handling, Processing, and Record Keeping

The Investigator will conduct the trial in accordance with the protocol and ICH E6 GCP guidelines. In addition to the routine monitoring procedures, training records should be in place to ensure investigators and CROs understand the data processing in any of the computerized systems to be used to ensure the confidence in the reliability, quality, and integrity of the patient data.

Sponsors, CROs, data safety monitoring boards, and other authorized personnel can view the trial data elements in the eCRF before and after the clinical Investigator(s) has electronically signed the completed eCRF. Reviewing trial data dynamically will allow early detection of trial-related problems (eg, safety concerns, protocol deviations) and problems with conducting the trial (eg, missing data, data discrepancies).

According to the eCRF entry guidelines, eCRFs must be completed for each patient by qualified and authorized personnel. Any data entry and corrections made in the eCRF must have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the trial should be collected.

A list of all authorized data originators (ie, persons, systems, devices, and instruments) should be developed and maintained by the CRO and made available at each clinical site.

The eCRF is an auditable electronic record of information reported to the Sponsor on each trial patient, according to this clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.

12.1 Data Collection

12.1.1 Identification of the Trial Data Sources

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.

When a device or instrument is the data originator (eg, blood pressure monitoring device or glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is the source.

Access to source data is critical to the review and inspections of clinical investigations. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.

The trial data sources are outlined below:

- Signed informed consent forms
- Patient medical history records will include trial diagnosis and inclusion/exclusion criteria age, sex, demographics, physical examination, medical history, vital signs, previous medication, original or certified copy of a laboratory reports, instrument printout, trial progress notes of the physician
- Laboratory test results reports (hematology, clinical chemistry, urinalysis, etc)
- Digital photographs
- ePatient diary (Study App)
- eCRF

12.1.2 Electronic Case Report Forms

To comply with the requirement to maintain accurate case histories Investigators should review and electronically sign the completed eCRF for each patient before the data are archived or submitted. Use of electronic signatures must comply with US Title 21 Code of Federal Regulations part 11.

For trial data elements transcribed from paper or electronic to the eCRF, the electronic or paper documents from which the data elements are transcribed are the source.

These data must be maintained by the Investigators and available to the monitor or inspector if requested (eg, an original or certified copy of a laboratory report, instrument printout, progress notes of the physician, the trial patient's hospital chart(s), nurses' notes).

Direct Entry of Data Into the eCRF

The direct entry of data can eliminate errors by not using a paper transcription step before entry in the eCRF. For the following data elements, the eCRF may be the source:

- Date of ICF signature (in the case of a paper ICF; in the case of an electronic ICF the eConsent will be the source)
- Inclusion and exclusion criteria confirmation (checking)
- Patient demographics and physical examination, including. age, gender, race, ethnicity height, weight, and Fitzpatrick skin type
- Relevant previous and concomitant therapies
- Up-to-date relevant medical history, including trial diagnosis
- TF measurements and location (face or scalp)
- Number of lesions in the TF and identification of whether each lesion is new or existed at baseline
- Vital signs (blood pressure, pulse, body temperature, and respiratory rate)
- Pregnancy test results
- Trial/visit dates
- Visit assessment (checking compliance, trial diary data, drug application, blood sample collection, tolerability score, end of treatment)
- Drug accountability (medication given and returned and product weight before and after application)
- Adverse events

For the above trial data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for monitoring or inspection.

Direct data entry should meet ALCOA+ principles for data integrity in life sciences. In case trial data cannot be entered at the time of the patient visit, eg, laboratory tests results, then Investigators are requested to make their entries at the time when the report with the results is received.

All non-CRF entered external data (ie, images) will not be loaded into the eCRF, but it will be integrated in SAS datasets and reconciled frequently with the eCRF data by CRO Data Management.

The information directly collected in the eCRF must match the source documents. The source data verification will be performed by the CRO Clinical Research Associate (monitor) according to the requirements specified in the Monitoring Plan.

At the trial end, the CRO will generate a PDF copy of the completed CRFs which will be sent to the Investigator(s) for all patients enrolled at his or her location.

12.1.3 Patient Diary

During the study, patients will use a mobile application. Clinical personnel will be instructed on the use of the Study App in order that they further instruct the patients at the Day1/Baseline visit, and as many times as deemed necessary. Patients will also receive written instructions on the Study App use. The Study App will be installed onto the patient's own mobile phone, and there will also be the possibility to provide patients with a mobile phone, if necessary. The Study App will be installed onto the mobile phone during the baseline visit. Clinical personnel will check and confirm the correct installation of the Study App during the visit.

On the Study App, patients will:

- Receive notifications, communications, and reminders through the patient retention tool
- Complete the eDiary: Patients, and assisted by caregivers, as needed, will complete a diary to record daily the study treatment application dates and times of application. The eDiary will be completed by the patient and will be checked by the Investigator (or designee) in accordance with the Schedule of Assessments (Table 1).

At the study end, the Investigator will receive a CD/DVD with the mobile application data (in PDF) from the patients enrolled at his/her location. The Investigator will keep this CD/DVD with the rest of the original data for as long as required by local regulations. The mobile application files are relevant documentation for registration.

The mobile application data is the sole property of the Sponsor and should not be available in any form to third parties without the written permission of the Sponsor, except to authorized representatives of appropriate Competent Authorities.

12.2 Data Management and Quality Control

Data Management of the trial will be performed by the CRO Data Management department according to the CRO SOPs and supervised by Data Management at Almirall, according to Almirall SOPs.

In order to facilitate the collection of accurate and complete data, the CRO will target the risks associated with critical trial data and these will be documented into the Data Management Plan (DMP) and the Monitoring Plan.

Investigators will respond to any query generated by the Data Management group or any data risk indicator reported.

Main Data Management activities and procedures will be accurately described in the DMP, created by the CRO and approved by Almirall.

Database checks will be programmed by the CRO, based on the Data Validation Plan. The listings will be documented in the DMP. The checks and listings programming will be appropriately validated by the CRO.

Reconciliation of trial data and SAEs between Clinical and Drug Safety databases will be performed by the CRO on an ongoing basis and before database lock. Procedures to be followed will be detailed in the DMP.

Encoding of specific data will be conducted by the CRO. For this trial, medical history, AEs, and concomitant medications (including rescue medications) will be coded; Medical Dictionary for Regulatory Activities (MedDRA) and WHO-DRUG Enhanced dictionaries will be used, version number of each dictionary will be documented in the DMP.

A Quality Control check to ensure the accuracy of the data will be done by the CRO, when data are cleaned on an ongoing basis and just before the database lock. Specifications of the Quality Control check will be found in the DMP.

An audit trail will be maintained in order to protect the authenticity and integrity of the clinical data.

12.3 Investigator and Trial Master Files

The Investigator's file and Sponsor Trial Master File (TMF) will contain all trial documents indicated in the ICH GCP guidelines and local regulations.

At the trial end the Investigator will receive one CD/DVD/USB key with the electronic data capture (EDC) data, as well as one CD/DVD with the tablet PC and electronic Patient Diary data from the patients enrolled at his/her location. The Investigator will keep these in the Investigator’s file.

The CRO will provide Almirall with an electronic TMF (eTMF). Almirall will have on-line access to the eTMF during the study and study documents will be reviewed, approved, and managed within the system. At the end of the study the eTMF and complete audit trail will be transferred to the TMF-dedicated Sponsor server for long-term storage. Information about eTMF contents, index, structure, nomenclature, metadata, and oversight metrics will be detailed in other documents (ie, eTMF Management Plan, CROOP, etc.).

All records must be stored in a secure facility protected from fire, flood, and unauthorized access where they may be readily accessed in the event of an audit or inspection.

12.4 Documents and Record Keeping

The Investigator should retain control of the records (ie, completed and signed eCRF or certified copy of the eCRF). The Investigator maybe requested by inspectors with access to the records that serve as the electronic source data.

When data elements are transcribed from paper sources into an eCRF, the Investigator must also retain the paper sources, or certified copies, for later review. Other records (electronic and paper) required to corroborate data in the eCRF may also be requested during an inspection.

All trial data (including electronic data), all hard copies including protocol, consent forms, CRFs, queries and printouts, and all essential documents relating to the conduct of the clinical trial will be stored at the research site for a period of 25 years after completion of the trial, unless otherwise communicated in writing by the Sponsor.

CROs/vendors will store the databases, including audit trails and related documentation, for a period of 25 years after completion of the trial, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period

without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13 Quality Control and Quality Assurance

13.1 Training of Staff

During the set-up phase of the trial, appropriate kick-off meetings will be performed between Almirall and the CRO and/ or vendors (eg, eCRF, laboratories, central ECG), in order to train CRO staff on trial procedures.

An Investigators' meeting will be performed, including training on GCP procedures, trial protocol, efficacy and safety assessments, laboratory procedures, eCRF completion, usage of any specific device and any other applicable process/procedure/method, as applicable.

An initiation visit will be performed at each site by the trial CRA designated by the CRO to assess if all the material and supplies (eg, eCRF, IMP) arrived in good conditions and to train the site staff for protocol compliance.

Appropriate study manuals will be provided to the research sites as written help to support all trainings on all trial procedures (eg, laboratory samples, eCRF).

13.2 Monitoring

The trial will be monitored by CRO CRA/Monitors according to the details specified in the Monitoring Plan.

The trial CRA/Monitor will conduct monitoring visits according to a pre-agreed schedule and with enough frequency to perform source data verification, check the accuracy of entries in the CRFs, the adherence to the protocol and to GCP, the progress of enrollment and to ensure that trial medication is being stored, dispensed, and accounted for, according to specifications and report any deviation as soon as possible to the Clinical Trial Manager.

Standard monitoring reports will be produced by the trial CRA/Monitor after each visit and filed in the TMF. Key trial personnel must be available to assist the field CRA/Monitor during these visits.

The Investigator must also keep the original informed consent form signed by the patient and maintain source documents for each patient in the trial, case and visit notes medical records, all information in eCRFs must be traceable to these source documents in the patient´s file.

A close out visit to solve pending issues and to agree on the shipment of remaining trial materials to the Sponsor (eCRF and other data source, medication) will be performed by the trial CRA/Monitor once all patients have completed the trial.

13.3 Inspections and Audits

The trial site, trial processes, CRO, providers and/or trial documents may be subject to Quality Assurance audits by Almirall (or authorized partner companies) as well as to inspection by competent authorities, as applicable, during the trial or after trial completion. Audits and inspections may include, but are not limited to, drug supply, presence of required documents,

informed consent process, medical records, general protocol compliance and comparison of data recorded in the eCRF and queries against source documents. Investigator will ensure direct access to source medical records for inspection and audit purposes.

14 Ethics

This trial will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly of Helsinki (1964), as amended in Fortaleza, Brazil (2013) (World Medical Association, 2013), as well as in compliance with ICH GCP guidelines, and local laws of the Countries in which the trial centers are located.

14.1 Responsibilities

The Investigator is responsible for conducting the trial in accordance with the procedures described in this protocol. All the personnel involved in the clinical trial will be fully informed about the drug and the nature of the trial and will be patient to protocol procedures concerning their duties in the trial.

The Investigator, the CRO/vendors and the Sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted according to the highest standards of Good Clinical Practice (ICH GCP guidelines) and local regulations.

The Investigator, the CRO and the Sponsor will work according to the ICH guidelines, EU Clinical Trials Directive 2001/20/EC and/or Clinical Trials Regulation No 536/2014, and Title 21 of the US Code of Federal Regulations (US Food and Drug Administration [FDA]).

The Investigator shall administer the trial medication to patients under his or her personal supervision or under the supervision of any co-Investigator reporting to him/her who are identified in the delegation of responsibilities and signatures log. The Investigator and designees will be responsible for the patient's compliance throughout the trial.

Refer to Section 9.9.4, for details on post-trial medications.

14.2 Patient Information and Informed Consent

Patients will be informed by the Investigator in detail of the characteristics of the drug to be administered, the nature of the clinical investigation, the risks and the discomfort that can reasonably be expected as a result of their participation and the uses of the data, as described in the Patient Information Sheet (PIS).

The patients will be informed that they are free to withdraw their consent and suspend their participation in the trial at any time with no penalty or loss of benefits to which the patient is otherwise entitled. Administration of the drug may be interrupted, and a patient withdrawn from the trial at the discretion of the Investigator. The Investigator should justify his decision in the patient's eCRF.

Any patient considered by the Investigator to be suitable for inclusion must document his or her willingness to participate in the trial by giving his or her informed consent in writing before starting any trial procedure by signing the ICF, which must be signed and dated by the patient

and the Investigator. Explicit consent to participate in the standardized photography procedure will also have to be given by patient.

At such time the patient must be given adequate time to understand the information provided and ask questions, if required. Any new relevant information that becomes available during the trial will be provided to the patient.

The PIS and ICF will include all elements required according to the applicable legislation. These documents or any modification will have been authorized by Almirall, S.A. and approved by the relevant IRB/IEC before use.

Patients will have access to the written PIS and ICF in paper or electronic format, preferably but not exclusively through a web system (eConsent). When using the eConsent process, the system will allow for on-line meetings between the patient and Investigator to facilitate answering patient questions and recording the responses. Patients will give their consent by signing electronically the ICF (eConsent). Patients will be requested to download the signed ICF, and/or ask the Investigator for a printed version. While they are in the study, patients will always have access to the PIS and ICF through eConsent. When eConsent cannot be used, the patient will sign a paper ICF.

14.3 Institutional Review Board/Independent Ethics Committee

This protocol, PIS and the ICF should be submitted to an IRB/IEC for review and approval. Notification in writing of approval must be obtained from the IRB/IEC by the Investigator before initiation of patient enrolment.

The Investigator must promptly report to the IRB/IEC all changes in the implementation of the research (protocol amendments) and will not make such changes without IRB/IEC approval except where necessary to eliminate apparent immediate hazards to the trial patients or administrative changes.

Serious adverse events reasonably related to the trial drug will be communicated by the Investigator/CRO to the IRB/IEC.

The Investigator is required to maintain accurate and complete records of all written correspondence sent to and received from the IRB/IEC and must agree to share these documents and any reports with the Sponsor.

14.4 Patient Data Protection

The trial patients shall be informed by the Investigator that complete confidentiality will be maintained concerning their identity. On eCRFs/EDC and all trial data records (eg, electronic patient diary) patients will be identified only by the assigned patient identification number.

A signed written ICF signifies the explicit acceptance by the individual that data from the trial will be available to the Investigator and his/her staff, the authorized representatives of the Sponsor and, if required, by the IRB/IEC and Competent Authorities. However, all data contained in the patient's medical history will be considered as confidential. Almirall will treat data according to personal data regulations (Health Insurance Portability and Accountability Act [HIPAA]), and any other applicable national and international regulation.

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

15 Financing and Insurance

Almirall will set up a contract with the CRO with the economic aspects for trial funding.

All patients recruited will have an insurance policy provided by Almirall to cover any possible risk resulting from their participation in the clinical trial.

Except in the proven case of clinical malpractice, the insurance company will indemnify against any claim or claims made by patients or their dependents which may result from administration of the IMP.

16 Publication Policy

Almirall will disclose clinical trials in a manner consistent with applicable national laws and rules governing personal data privacy and protection of intellectual property rights. Clinical trials will be registered, and results disclosed by means of recognized public databases, such as clinicaltrials.gov in the US and EudraCT in the European Union.

The Investigator understands and accepts that his/her name and trial center may be disclosed in the context of this national or international legislation.

All the information related to this clinical trial is considered strictly confidential and is the property of Almirall. This information will not be given to a third party without the written consent of Almirall.

By signing this trial protocol, the Investigator affirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her in relation to or resulting from this trial. The Investigator will only divulge such information as may be necessary to the IRB/IEC, the members of the staff and the patients who are involved in this trial.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and CRO.

In all cases, the trial results shall be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations of the trial. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication.

Publication and/or presentation whether complete or partial, of any part of the data or results of this trial will not be allowed until global publication and trial results disclosure by the Sponsor as per US FDA regulatory compliance obligations, and only after mutual agreement between the Investigator and Almirall.

17 Other Practical Considerations

17.1 Investigator's Brochure

The Investigator's Brochure contains a summary of the pre-clinical and clinical data. The same confidentiality procedures apply for the Investigator's Brochure as for the protocol.

The Investigator's Brochure will be included in the Investigator file. The Investigator will sign a receipt form.

17.2 Final Clinical Trial Report

The CSR will be written by the CRO following the ICH guidelines requirements. It will be approved and signed by the Coordinating Investigator and Almirall representatives according to internal SOPs.

The CSR will be audited by the CRO and/or Almirall before issuing the final version.

The final version of the electronic CSR will be e-published (hyperlink, bookmarks, etc.) including all appendices according to ICH Guidelines.

The summary of the CSR will be sent to all the Investigators participating in the clinical trial.

17.3 Protocol Amendments

Modifications of the original protocol are referred to as "amendments" to the trial protocol. Modifications of the original protocol may only be made with Almirall approval. Two types of amendment maybe produced:

- Substantial Amendments (related to the safety or physical or mental integrity of the patients, scientific value of the trial, conduct or management of the trial or the quality or safety of any IMP used) must be notified to the IRB and/or Competent Authorities and approved by them before implementation.
- Non-substantial Amendments do not require notification but should be recorded and be available on request for inspection at the trial site and/or Sponsor premises as appropriate.

17.4 Protocol Deviations

Any protocol deviations during the conduct of the trial will be recorded by the CRA/Monitors as detected or derived from data collected in the clinical database.

Relevant deviations will be promptly reported to Almirall after detection. Major protocol deviations will be included in the corresponding listing of the CSR.

Additionally, protocol deviations will be reported to the IRBs/IECs and/or Competent Authorities according to the local regulation in each country.

18 References

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19 Appendices

1. Highly Effective Methods of Birth Control
2. Patch test for the Assessment of Contact Dermatitis

Appendix 1, Highly Effective Methods of Birth Control

Highly effective methods or birth control (ref. CTFG 2014 guidance document):

- Intrauterine device, intrauterine hormone-releasing system or bilateral tubal occlusion or ligation (1)
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable (1))
- Vasectomized partner (2). Female patient must agree to implement one of the other highly effective methods of birth control if her lifestyle/partner changes
- Sexual abstinence (3)

Notes

(1) Low user dependency methods from at least 3 months before trial screening

(2) Only provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

(3) Only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments (from Day1 to at least 30 days after the last dose of the investigations product).

Appendix 2, Patch Test for the Assessment of Contact Dermatitis

In the event the patient experiences a skin reaction of such nature or severity that an allergic contact dermatitis is suspected, the patient can be treated with topical treatment with corticosteroids (eg, betamethasone) and oral antihistamines and should temporally discontinue the study medication. The event should be documented as an adverse event and the medication given recorded. The patient should be re-challenged using the assigned study medication (patch test in the back) to confirm or rule out contact dermatitis. If the diagnosis of allergic contact dermatitis is confirmed the patient may have an additional patch test with both the tirbanibulin-containing ointment and the vehicle base.

The patch test will be performed at least 2 weeks after last treatment or discontinuation of the study medication. Patches will be applied to untreated areas on the back for 48 hours. Readings will be performed approximately 15 to 30 minutes and 48 hours following the removal of the patches. At the investigator's discretion, a facultative additional reading might be performed at 96 or 120 hours after removal of the patches if an equivocal reaction is observed at the previous reading. If allergic contact dermatitis is confirmed the patient will discontinue permanently the study medication, on the contrary the patient can be treated with the study medication if necessary.

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 cm2 on the Face or Balding Scalp in Adult Patients with Actinic Keratosis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical Approval	26-Jan-2022 18:01 GMT+01
PPD	Clinical Approval	27-Jan-2022 08:55 GMT+01
PPD	Clinical Statistics Approval	27-Jan-2022 11:04 GMT+01

eDMS R&D Object_ID: CCI [redacted]

ALMIRALL, S.A.

Clinical Trial Protocol M-14867-32

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
Investigational Medicinal Product(s):	Tirbanibulin ointment 1% (Klisyri®)
Indication:	Actinic keratosis (AK)
Development Phase:	Phase 3
Final Protocol Version Date:	Version 2.0, 21 March 2022
Amendment(s)	**Number:** 1 **Date:** N/A
IND Number:	122464
Sponsor:	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona, Spain

Protocol Amendment Summary of Changes

DOCUMENT HISTORY			
Document	**Date**	**Description of changes**	**Rationale**
Clinical Trial Protocol final Version 1.0	23-Jan-2022	Initial version	Not applicable
Clinical Trial Protocol final Version 2.0	21-Mar-2022	Section 1 Protocol Synopsis Table 1 Schedule of Assessments The footnote: [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 5." has been updated to replace "Visit 5" by "Visit 3".	This text has been updated to correct a typographical error.
		Section 8.2 Inclusion Criteria Number 4 has been added: "4. Sexually active males with partners who are WOCBP must agree to use two forms of contraception, one of which must be barrier contraception, from Screening through 90 days after their last dose of study treatment. All male patients must agree not to donate sperm or attempt conception from Screening through 90 days following their last dose of study treatment."	This section was updated to add language regarding birth control measures for males and their female partners and sperm donation.

Sponsor Signatures

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
Trial Code:	M-14867-32

The individuals signing this clinical trial protocol declare that they have reviewed it for completeness, accuracy. They are responsible for the trial and agree to conduct it in adherence to the present document, any amendments, to International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, and to local regulatory requirements, wherever applicable.

Sponsor

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona, Spain

Functional Role	Name	Signature	Date
PPD	PPD		
PPD	PPD		
PPD	PPD		

This document was electronically signed in the eDMS R&D system.
Manifestation of the e-signatures are available at the end of this document which are the equivalent of handwritten signatures, in compliance with 21CFR Part 11

Principal Investigator Signature

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
Trial Code:	M-14867-32

The individual signing this clinical trial protocol declares that he/she has reviewed it for completeness, accuracy. He/she is responsible for the trial and agrees to conduct it in adherence to the present document, any amendments, to International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, and to local regulatory requirements, wherever applicable.

Principal Investigator

Role	Name	Signature	Date
Principal Investigator			

1 Protocol Synopsis

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

Investigators:

A Principal Investigator will be designated at each participating clinical trial center and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical study report (CSR).

Trial Center(s):

The trial is planned to be conducted at approximately 20 centers in the United States (US).

Trial Duration:

The duration of the entire study from first patient, first visit to last patient, last visit is anticipated to be approximately 8 months.

Phase of Development:

This is a Phase 3 trial.

Rationale:

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well-controlled Phase 3 clinical trials, tirbanibulin ointment 1% was demonstrated to be an effective and safe treatment for actinic keratosis (AK) of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

On the basis of the Phase 3 trial results, tirbanibulin ointment 1% was approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of ultraviolet (UV) light-damaged skin; thus, there is a need for a product to treat AK patients with affected fields larger than 25 cm^2.

This study will assess the safety and tolerability of tirbanibulin ointment 1% administered under the same posology (once daily for 5 days) to a field of approximately 100 cm^2 on the face or balding scalp containing 4 to 12 clinically typical, visible, and discrete AK lesions.

Objectives:

The primary objective 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.

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 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.

Number of Patients:

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

Trial Population:

Male and female AK patients, aged 18 years or older, having 4 to 12 clinically typical, visible, and discrete AK lesions over a field of approximately 100 cm^2 on the face or the balding scalp. A minimum of 50% of patients will be older than 65 years old and approximately two-thirds of the patients will be treated for AK lesions on the face and one-third on the scalp.

Test Investigational Medicinal Product, Dosage, and Mode of Administration:

Substance code/name:	Tirbanibulin
Administration route:	Topical
Strength:	1%
Dosage form:	Ointment

Tirbanibulin ointment 1% will be applied once daily for one 5-day treatment course. On Day 1, treatment application will occur at the investigational site in the morning under the supervision of clinical trial site staff. Between Days 2 and 5, the treatment will be self-administered once daily at home.

Reference Investigational Medicinal Product, Dosage, and Mode of Administration:

Not applicable. No control arm will be included in this study.

Methodology:

Study visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1).

Duration of Treatment:

The duration of each patient's treatment is 5 days.

Duration of Patients' Participation in the Trial:

The total duration of each patient's participation in the trial, including screening, treatment, and response assessment is estimated to be approximately 3 months.

Statistical Methods

Sample Size Calculation

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.

Endpoints

Safety Endpoints

- Local Tolerability Assessment:
  - 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
  - Pigmentation and scarring in the TF through all the visits
- Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])

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

Statistical Analysis

All analyses will be performed on the Safety population, defined as all patients who have received at least one dose of study treatment.

Safety Endpoints

Descriptive statistics will be provided for all safety endpoints.

Local tolerability signs composite score, and specific local tolerability scores will be analyzed by means of descriptive statistics and provided by visit. The maximum local tolerability scores and maximum local tolerability composite score will be presented. The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by visit as well as the number and percentage of patients with changes from baseline in pigmentation and scarring in the TF.

TEAEs and TESAEs recorded during the study will be presented, including the total number of events and the number and percentage of patients with events. Summaries of the number and percentage of patients with TEAEs (and number and percentage of events), study drug-related TEAEs, TEAEs by severity, TESAEs, TESAEs with an outcome of death, and TEAEs leading to temporary or definite discontinuation of the study treatment will be provided. Specific tables describing AESIs will be also provided. The number and percentage of patients who experience one or more AESI will be tabulated by AESI.

For PEs, ECGs, vital signs, and clinical laboratory parameters, the number and percentage of patients with normal or abnormal results will be presented at scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. Shift tables will be provided when appropriate.

Exploratory Endpoints

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

Interim Analysis

No interim analysis is planned for this trial.

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
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						

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**
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]
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 hyper-pigmentation, 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 subject at home before study Visit 3 on Day 5, which will take place at the clinical site.

2 Table of Contents

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3 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AK	Actinic keratosis
ALCOA	Attributable, legible, contemporaneous, original, and accurate
BCC	Basal cell carcinoma
CDISC	Clinical Data Interchange Standards Consortium
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CROOP	Clinical Research Organization Oversight Plan
CSR	Clinical Study Report
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of Study
ET	Early termination
eTMF	Electronic Trial Master File
FDA	Food & Drug Administration (United States)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MUsT	Maximum usage trial
OTC	Over-the-counter
PDF	Portable document format
PE	Physical examination
PIS	Patient Information Sheet
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma

SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TF	Treatment field
TMF	Trial Master File
US	United States
UV	Ultraviolet
WOCBP	Women of child-bearing potential

4 Sponsor, Investigator(s) and Trial Administrative Structure

4.1 Sponsor

Almirall, S.A. (Legal entity)
General Mitre, 151
08022 Barcelona, Spain

Almirall Research and Development Centre:
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
Barcelona, Spain

4.2 Investigator(s)

A Principal Investigator will be designated at each participating clinical trial center and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical study report (CSR).

4.3 Administrative Structure

Medical Expert appointed by the Sponsor for this trial:

PPD , MD, PhD
Almirall Research and Development Centre
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
Barcelona, Spain
Telephone: PPD
Email: PPD

This study will be conducted by a Contract Research Organization (CRO) on behalf of the Sponsor; the Sponsor will maintain oversight of the CRO. Refer to the CRO Oversight Plan (CROOP) for details and see Section 10.7.4 for Serious Adverse Event (SAE) and Adverse Event of Special Interest (AESI) reporting.

5 Introduction

A summary on the indication, mechanism of action, and completed nonclinical and clinical studies is provided below. A detailed description of the chemistry, pharmacology, efficacy, and safety of tirbanibulin ointment 1% is provided in the Athenex KX2-391 (tirbanibulin) Investigator's Brochure.

5.1 Background Information

5.1.1 Indication

Actinic keratosis (AK) is an ultra-violet (UV) light-induced pre-cancerous lesion of the skin that represents the initial clinical manifestation of intra-epidermal abnormal keratinocyte

proliferation (Röwert-Huber, 2007; Fernandez Figueras, 2017). Given the demonstrated potential for progression to invasive squamous cell carcinoma (SCC), dermatologists encourage and actively pursue treatment, as recommended in current national and international guidelines (Hofbauer, 2014; Werner, 2015; de Berker, 2017; Leitlinienprogramm Onkologie, 2019).

Actinic keratosis presents as erythematous, scaly patches on the skin of sun-exposed areas and so particularly affecting the face, scalp, and extremities, either as a single lesion or multiple lesions and may present in as an entire field ("field cancerization") with widespread actinic damage, such as in areas on the forehead or the back of the hand (Dodds, 2014; Figueras Nart, 2018). Actinic keratosis is common in older, fair-skinned populations of European ancestry, and is more frequently observed in men (Flohil, 2013).

Precise estimates of AK prevalence are difficult, owing to its strong association with increased age. The prevalence of AK in the US has been reported to range from 11% to 26% (Salasche, 2000). Recent studies in Europe suggest that AK prevalence there ranges from 33% to 49% for men and 14% to 28% for women (Eder, 2014, Tizek, 2019, Flohil, 2013, Ferrándiz, 2016, Fargnoli, 2017, Dziunycz, 2018).

In some cases, AK represents a carcinoma *in situ* of the skin, and when left untreated, AK can progress to invasive SCC (Röwert-Huber, 2007; Werner, 2013; Fernandez Figueras, 2017). Cutaneous SCC represents 20% to 50% of skin cancers (Que, 2018) and poses a significant threat due to its ability to metastasize to any organ in the body (Burton, 2016). Up to 65% of SCCs arise from pre-existing AK; however, the risk of progression to SCC of a single AK lesion per year has been reported to be very low, 0% to 0.075% in patients without a previous history of non-melanoma skin cancer (Marks, 1988), and up 0.53% per lesion in patients with a prior history of non-melanoma skin cancer (Werner, 2013; Green, 2017).

5.1.2 Unmet Medical Need

Tirbanibulin ointment 1% is approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of UV light-damaged skin; thus, there is a need for a product to treat AK patients over fields larger than 25 cm^2.

Although a limited number of AK field-directed therapies are currently available that target areas larger than 25 cm^2, there remain unmet needs for patients with AK in terms of tolerability and treatment convenience/adherence. Topical therapies, such as 5-fluorouracil and imiquimod, frequently present safety and tolerability events during treatment that may lead to treatment discontinuation. While diclofenac sodium 3%, which is also used over larger fields, has a good safety and tolerability profile, it is administered over a longer treatment period (60 to 90 days) and drugs with shorter treatment durations are desirable, as they are associated with better adherence (Goldenberg, 2017). In a survey of 40 dermatologists in France, short treatment duration was the primary consideration in selecting a field-directed topical treatment (Savary, 2019). Thus, there is a need in the current armamentarium for well-tolerated, short-duration therapies targeted to areas larger than 25 cm^2.

5.1.3 Mechanism of Action

Tirbanibulin has potent anti-proliferative and anti-tumor activities *in vitro* and *in vivo* by virtue of its ability to induce cell cycle arrest and apoptotic cell death by disrupting the cellular

microtubule network via direct binding to tubulins. Furthermore, it is associated with disruption of Src tyrosine kinase signaling.

5.1.4 Nonclinical Studies

CCI

5.1.5 Clinical Studies

The clinical development program on topical tirbanibulin includes 10 completed clinical trials that enrolled a total of 1338 subjects, 989 subjects who received tirbanibulin ointment 1% and 349 subjects who received vehicle ointment. Of the 989 subjects treated with tirbanibulin ointment 1%, 597 were patients with AK and 392 were healthy adults.

Pharmacokinetics

Pharmacokinetic studies showed that tirbanibulin ointment 1% was minimally absorbed in patients with AK after topical application to 25 cm^2 on the face or balding scalp once daily for 5 consecutive days. Exposure (C_{max}, AUC_{0-24}) was higher when tirbanibulin ointment 1% was applied to the face versus the scalp. A proportional increase in systemic exposure (C_{max}, AUC_{0-24}) was observed when tirbanibulin ointment 1% was applied to an area measuring 100 cm^2 on the face or balding scalp.

Efficacy and Safety

The efficacy and safety studies included two Phase 3 double-blind, vehicle-controlled, randomized trials, KX01-AK-003 (N=351) and KX01-AK-004 (N=351), that were conducted in the US to evaluate the efficacy and safety of tirbanibulin ointment 1% compared to vehicle ointment in patients with AK on face or balding scalp. Tirbanibulin ointment 1% once daily for 5 days was effective in the treatment of AK on either the face or balding scalp, with statistically significantly higher rates of complete and partial clearance at Day 57 in the treated field as compared to control vehicle (complete clearance, 49% vs 9%, respectively). Treatment-related adverse events (AEs) were few (16% vs 10%, respectively) and consisted of mostly transient mild to moderate application site pruritus and pain that required no treatment; there were no treatment-related SAEs. Signs assessing local tolerability were mostly mild to moderate erythema and flaking/scaling. Mean composite scores for local tolerability signs peaked at Day 8 and were mostly resolved by Day 29.

The safety of treating larger AK fields (>25 cm^2) was evaluated in a Phase 1, maximal usage trial (MUsT), in which tirbanibulin ointment 1% was applied to an area measuring 100 cm^2 on the face or balding scalp in 28 patients with AK. The most frequently reported treatment-related AEs were application site pruritus and application site pain. All AEs were mild or moderate in intensity; no severe AEs were reported. The most frequently reported local tolerability signs were erythema and flaking/scaling. Most local tolerability signs were mild or moderate, with severe erythema and flaking/scaling reported in 14.3% of patients each. Local tolerability sign composite scores peaked around Day 7 to 8 and were mostly resolved by Day 29.

A detailed description of the completed clinical studies is provided in the Athenex KX2-391 Ointment 1% (tirbanibulin) Investigator's Brochure.

5.2 Summary of the Known Potential Risks and Benefits

Actinic keratosis is a UV light–induced pre-cancerous lesion of the skin that represents the initial clinical manifestation of intra-epidermal abnormal keratinocyte proliferation. Given the demonstrated potential for progression to SCC, dermatologists generally encourage and actively pursue treatment, with a goal of completely eliminating AK lesions, thereby reducing the risk of progression to invasive SCC.

Data from the two pivotal Phase 3 studies demonstrate that treatment with tirbanibulin ointment 1% once-daily for 5 days is effective in the treatment of AK of the face or balding scalp.

In the pivotal studies, the safety profile of tirbanibulin ointment 1% showed a low rate of treatment-emergent AEs and no unexpected or unanticipated safety findings. The overall incidence of treatment-emergent AEs (TEAEs) was similar between the tirbanibulin ointment 1% and vehicle groups, and there were no treatment-related treatment-emergent serious AEs (TESAEs) or discontinuations due to a TEAE. There were also no long-term safety concerns related to tirbanibulin ointment 1% in patients followed up to 1 year after Day 57.

The most frequently reported local tolerability signs were transient, mild to moderate erythema and flaking/scaling. Treatment-related AEs were mostly transient, mild to moderate application-site pruritus or pain, and most did not require treatment.

The safety profile of tirbanibulin ointment 1% observed in the Phase 1 maximal-use trial M-14687-01, in which study drug was applied to 100 cm^2 on the face or balding scalp, was consistent with that observed in the pivotal studies.

Based on the available efficacy and safety data from the completed clinical and nonclinical studies, the benefit-risk assessment is positive and supports the evaluation of tirbanibulin ointment 1% in this Phase 3 study of patients with AK of the face or scalp.

Further information regarding the nonclinical and clinical characteristics, summaries of the known and potential risks, as well as reasonably expected adverse reactions of the product under investigation, is provided in the Athenex KX2-391 (tirbanibulin) Investigator's Brochure.

5.3 Scientific Rationale for the Trial

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well-controlled Phase 3 clinical trials, tirbanibulin ointment 1% was demonstrated to be an effective and safe treatment for AK of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

On the basis of the Phase 3 trial results, tirbanibulin ointment 1% was approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects larger areas of UV light-damaged skin; thus, there is a need for a product to treat AK patients with affected fields larger than 25 cm^2.

This study will assess the safety and tolerability of tirbanibulin ointment 1% administered under the same posology (once daily for 5 days) to a field of approximately 100 cm^2 on the face or balding scalp containing 4 to 12 clinically typical, visible, and discrete AK lesions.

6 Objectives and Endpoints

6.1 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.

6.2 Endpoints

6.2.1 Safety Endpoints

Safety Endpoints

- Local Tolerability Assessment:
  - 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
- Pigmentation and scarring in the TF through all the visits

- TEAEs, TESAEs, adverse events of special interest (AESIs), clinical laboratory data, and other safety assessments (vital signs, physical examinations [PEs], electrocardiograms [ECGs])

6.2.2 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

7 Trial Design and Rationale

7.1 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 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 TF until completion of the Response Assessment Period at Day 57.

7.2 Trial Rationale

7.2.1 Rationale for Trial Design

Since tirbanibulin ointment 1% is an approved product and there is no change in the formulation or posology, the main objective of this study is to evaluate the safety and tolerability of tirbanibulin ointment 1% applied over an extended field (100 cm^2) in adult patients with AK on the face or balding scalp.

The duration of the study considers both safety and efficacy. From a local tolerability perspective, most of the local signs are expected to be resolved by Day 29. However, the study duration is extended up to Day 57, in order to assess the treatment effect as exploratory endpoints.

In addition to the overall incidence of local tolerability events, the sample size considers detection of local tolerability signs of particular interest, specifically, vesiculation/pustulation and erosion/ulceration (see Section 11.1). When severe, these local tolerability signs can lead to permanent local events such as dyspigmentation or scarring.

7.2.2 Rationale for Trial Population

The study will be conducted in male and female AK patients, aged 18 years or older, having 4 to 12 clinically typical, non-hypertrophic, non-hyperkeratotic, visible, and discrete AK lesions over a field of approximately 100 cm^2 on the face or the balding scalp.

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.

7.2.3 Rationale for Trial Dose and Regimen

In this study patients will be treated with tirbanibulin ointment 1% daily for 5 consecutive days beginning on Day 1. Treatment will be applied to a field measuring approximately 100 cm^2 on the face or balding scalp. There are no changes in treatment duration or posology. Tirbanibulin ointment 1% has shown effectiveness in the treatment of AK lesions and the good safety and tolerability profile supports the field extension to a higher area to satisfy medical needs.

In a Phase 2 trial (KX01-AK-002), efficacy and safety results of 3 and 5-day treatment regimens over 25 cm^2 were compared. The 5-day regimen showed substantial clinical activity and acceptable local tolerability. The 5-day treatment regimen showed a higher proportion of patients with 100% clearance at Day 57 compared with the 3-day regimen (43% vs 32%, respectively), as well as a higher proportion of patients maintaining their treatment response at 12 months (43% vs 30%, respectively). Patients in the 5-day regimen experienced slightly more mild/moderate erythema and flaking/scaling, but local signs were self-limited with both regimens and by Day 29 had essentially returned to baseline values.

7.2.4 Rationale for Trial Assessments

In prior studies, mild to moderate erythema and flaking/scaling were the most frequently observed signs when assessing local tolerability. Local tolerability signs following treatment will be characterized and assessed throughout this study and reported separately from AEs.

Standard safety assessments will be performed throughout the study including the capture of AEs, SAEs, concomitant medications, laboratory testing for hematology, blood chemistry, and urinalysis, PEs and vital signs measures, and ECGs.

Lesion counts in the TF will be performed at Screening, Day 1/Baseline (predose), and at every visit from Day 5 up to Day 57 to evaluate the treatment effect of tirbanibulin ointment 1%, when applied to an area measuring 100 cm^2 on the face or balding scalp.

8 Selection of Trial Population and Withdrawal of Patients

8.1 Number of Patients

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

8.2 Inclusion Criteria

All of the following criteria must be met for inclusion of a patient in the trial:

1. Male or female and ≥18 years old at the time of consent
2. Having a TF on the face or balding scalp (excluding lips, eyelids, and inside nostrils and ears) that
   - measures approximately 100 cm^2 (eg, mid face) and
   - contains 4 to 12 clinically typical, visible, and discrete AK lesions within the TF
3. If a woman of childbearing potential (WOCBP), ie, fertile, defined as a female in the life period from menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (with hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months prior to Screening), she must:
   - have a negative urine pregnancy test using a highly sensitive method at screening and on Day 1 prior to treatment administration
   - be using highly effective methods of birth control (defined in Appendix 1) for at least 30 days or 1 menstrual cycle, whichever is longer, prior to the study treatment and must agree to continue use during the study period and until at least 30 days or 1 menstrual period, whichever is longer, after the last dose of investigational product
   - agree to have pregnancy tests while in the study and at the end of the study (according to the Schedule of Assessments in Table 1)
4. Sexually active males with partners who are WOCBP must agree to use two forms of contraception, one of which must be barrier contraception, from Screening through 90 days after their last dose of study treatment. All male patients must agree not to donate sperm or attempt conception from Screening through 90 days following their last dose of study treatment.
5. Willing to avoid excessive sunlight or UV light exposure, including the use of tanning beds, to the face or scalp during the study
6. Ability to understand the purpose and risks of the trial, willingness and ability to comply with the protocol, and provided written informed consent in accordance with institutional and regulatory guidelines

8.3 Exclusion Criteria

Patients will be excluded from trial enrollment if they meet any of the following criteria:

1. Presence in the TF of:
   a) Clinically atypical and/or rapidly changing AK lesions in the TF

b) Hyperkeratotic or hypertrophic lesions, recalcitrant disease (had cryosurgery on 2 previous occasions) and/or cutaneous horn

c) Confluent AK lesions (ie, non-discrete lesions defined as per inclusion criteria)

d) History of invasive SCC, Bowen's disease, basal cell carcinoma (BCC), or other malignant tumors in the TF

e) Any other dermatological disease that causes difficulty with examination

2. Location of the TF is:
   - On any location other than the face or balding scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected BCC or other neoplasia
   - Periorbital, lips, or nostrils
3. Previous treatment with tirbanibulin ointment 1%.
4. Anticipated need for inpatient hospitalization or inpatient surgery from Day 1 to Day 57
5. Treatment with 5-fluorouracil, imiquimod, ingenol mebutate, diclofenac, photodynamic therapy, or other treatments for AK within the TF or within 2 cm of the TF, within 8 weeks prior to the Screening visit
6. Use of systemic retinoids (eg, isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit
7. Use of the following therapies and/or medications within 4 weeks prior to the Screening visit:
   - Cosmetic or therapeutic procedures (eg, use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the TF or within 2 cm of the selected TF
   - Treatment with cytotoxic drugs (eg, cyclophosphamide, vinblastine, chlorambucil, methotrexate).
   - Treatment with systemic medications that modulate and/or suppress the immune system (eg, cyclosporine, azathioprine, methotrexate, prednisone, alefacept, infliximab, interferons/interferon inducers).
   - Therapy/treatment with UV-A or UV-B light.
8. Use of the following therapies and/or medications within 2 weeks prior to the Screening visit:
   - Acid-containing therapeutic products (eg, salicylic acid or fruit acids, such as alpha and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the TF or within 2 cm of the selected TF
   - Topical steroids within the TF or within 2 cm of the selected TF
   - Artificial tanners within the TF or within 5 cm of the selected TF
9. A history of sensitivity and/or allergy to any of the ingredients in the study medication

10. Patients with significant abnormalities on the medical history, PE findings, vital signs, ECG, clinical chemistry, hematology, and urinalysis results that in the judgment of the Investigator may interfere with the interpretation of the results.
11. A skin disease (eg, atopic dermatitis, psoriasis, seborrheic dermatitis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the patient to unacceptable risk by study participation
12. Significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the patient to unacceptable risk by study participation
13. Females who are pregnant or nursing or seeking to become pregnant
14. Participated in an investigational drug trial during which an investigational study medication was administered within 30 days or 5 half-lives of the investigational product, whichever is longer, before dosing in the current study
15. Patient who is employee or relative to employees at the research site or Almirall

8.4 Treatment Discontinuation Criteria

Any patient may discontinue from study treatment at any time during the trial at the discretion of the Investigator or at the request of the patient. For patients who discontinue treatment, efforts should be made to encourage the patient to remain in the trial and complete the trial-related assessments. The main reason for such a premature treatment discontinuation must be documented in the electronic case report form (eCRF), as follows:

- Adverse event: If a patient experiences an AE, treatment discontinuation will be at the discretion of either the Investigator or the patient regardless of the causal relationship to the investigational medical product (IMP).
- Protocol deviation: Any protocol deviation detected should be corrected when possible and the patient should be allowed to continue. ONLY the following deviations should lead to treatment discontinuation: those which could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor] might invalidate the trial by interfering with the IMP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected
- Lost to follow-up: Non-attendance. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure patient’s attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the patient and documented in the medical records. If patient cannot be reached after that, a registered mail letter will be sent to the patient and documented in the medical records
- Patient's personal request: The patient is permitted to stop his/her treatment at any time during the trial without incurring any loss in his/her medical care. The Investigator should ensure that such discontinuation is not due to an AE or disease exacerbation, in which case the corresponding reason should be recorded
- Pregnancy

8.5 Trial Withdrawal Criteria

Any patient may withdraw from the trial at any time during the trial at the discretion of the Investigator or at the request of the patient. The main reason for such a premature study withdrawal must be documented in the eCRF, as follows:

- Adverse event: If a patient experiences an AE, study withdrawal will be at the discretion of either the Investigator or the patient regardless of the causal relationship to the IMP.
- Death
- Protocol deviation: Any protocol deviation detected should be corrected when possible and the patient should be allowed to continue. ONLY the following deviations should lead to patient withdrawal: those which could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor might invalidate the trial by interfering with the IMP) or which are due to patient unwillingness to comply with the trial activities or those violations of inclusion and/or exclusion criteria detected
- Lost to follow-up: Non-attendance. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure patient’s attendance as soon as possible. Every effort (at least three documented attempts) should be made to contact the patient and documented in the medical records. If patient cannot be reached after that, a registered mail letter will be sent to the patient and documented in the medical records
- Patient's personal request: The patient is permitted to stop his/her participation at any time during the trial without incurring any loss in his/her medical care. The Investigator should ensure that such withdrawal is not due to an AE or disease exacerbation, in which case the corresponding reason should be selected
- Trial terminated by Sponsor

8.6 Screening Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently treated in the study. A minimal set of screen failure information is required to be entered into the database to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Competent Authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failures) will not be rescreened.

8.7 Patient Replacement Criteria

Patients who withdraw from the trial at any time will not be replaced.

8.8 Termination of the Trial

8.8.1 End of Trial Definition

The "end of trial" is defined as the date of the last visit of the last patient, either at Day 57 or earlier, if the last patient discontinues prematurely. The end of trial will be communicated to the Competent Authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) according to local regulations.

8.8.2 Completed Patient Definition

Patients who complete all the phases of the study, including the last visit as described in the Schedule of Assessments (Table 1), will be considered to be completed patients.

8.8.3 Premature Trial Termination

Almirall reserves the right to prematurely terminate (ie, suspend) the trial.

Certain circumstances may require the premature termination of the trial including:

- The Investigator/Coordinating Investigator and the Sponsor feel that the type, number, and/or severity of AEs justify discontinuation of the trial.
- The Sponsor considers the applied doses of the trial drug to be no longer relevant.
- Data not known before becoming available and that raise concerns about the safety of the trial drug so that continuation would pose potential risks to the patient

If the trial is terminated or suspended, the Sponsor/CRO will promptly inform the Investigators. The IRBs/IECs should be promptly informed and provided the reason(s) for the termination or suspension by the Investigator, as specified by the applicable regulatory requirement(s).

The Investigator will inform the patients and will collect and keep all the data up to the date of discontinuation. Samples retrieved up to the date of trial termination will be analyzed as per protocol.

If the trial is prematurely terminated or suspended, trial results will be reported according to the requirements outlined in this protocol, as far as applicable.

The Clinical Data Interchange Standards Consortium (CDISC) criteria should be followed while recording the patient trial discontinuation reasons.

9 Treatments

9.1 Identity of Trial Investigational Medicinal Products

Investigational medicinal product manufacturing, labelling, packaging, and release will be done following Good Manufacturing Practice (GMP).

Tirbanibulin is a white to off-white ointment containing tirbanibulin freebase active drug substance. For a full product description, refer to the KX2-391 Ointment 1% (tirbanibulin) Investigator's Brochure.

Test Investigational Medicinal Product

Substance Code/Name	Tirbanibulin
Route of Administration	Topical
Dosage Form	Ointment
Strength	1%

Reference Investigational Medicinal Product

This is single arm study; no reference IMP will be used.

9.2 Packaging and Labelling

Study drug will be packed and labeled in accordance with local regulations by the Sponsor according to GMP conditions, including but not limited to the Sponsor contact details, protocol number, drug identification, storage conditions, and content of study drug. A sample label will be filed in the Investigator file.

On Day 1, patients will be dispensed a study kit containing 5 zipper bags each with a single-dose packet containing 350 mg tirbanibulin ointment 1%.

Local regulatory requirements will be fulfilled for packaging and labelling (US 21 Code of Federal Regulations 312.6).

9.3 Shipment, Storage, and Accountability

Only participants enrolled in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All drug supplies must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Tirbanibulin ointment 1% must be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Do not refrigerate or freeze tirbanibulin ointment 1%. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and ensure that any discrepancies are reported and resolved before use of the study medication.

The Investigator, the trial staff, institution, or the head of the medical institution (where applicable) is responsible for clinical supplies accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study.

Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused investigational products are provided in the Study Reference or equivalent manual.

Empty packages and unused medication will be returned to Almirall or a designated depot, where the remaining medication will be destroyed according to regulatory requirements. Retention drug samples will be kept by the Sponsor or designee, during the trial and until it is legally required after trial completion.

The Investigator and trial staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional requirements.

9.4 Treatment Administration

Treatment will begin on Day 1, following confirmation of patient eligibility and collection of all pre-dose samples and assessments.

At Baseline (Day 1 pre-dose), the Investigator will confirm the TF on the face or balding scalp that was identified at Screening and the patients will receive instructions on how to apply the topical medication and how to care for the TF.

Patients will be provided with 5 single-dose packets containing tirbanibulin ointment 1%.

The first dose will be administered by the patient under the supervision of study personnel on Day 1 at the site. The patient will self-administer the remaining single-dose packets once daily at home for the next 4 consecutive days. The fifth dose should be applied by the patient at home before the Day 5 site visit.

Tirbanibulin ointment 1% will be applied to cover the treatment field of approximately 100 cm^2, corresponding to approximately 0.5% of the body surface area. Study medication should be applied each day at approximately the same time. The treatment field should not be wet, should be kept dry for approximately 8 hours after application, and should not be touched or covered with dressing. The ointment should not be applied near the eyes, mouth, or lips.

Patients will return the used medication packaging (all parts of each packet, including the torn opening part) and any unused study medication back to the clinical site at the next visit to check compliance and for drug reconciliation purposes. Further details will be given in the study manuals (see Section 9.5).

9.5 Treatment Compliance

Compliance with the study treatment will be assessed by site personnel on Day 5. Compliance will be assessed by counting the dispensed and returned used tirbanibulin ointment 1% single-use packets. Patients will be instructed to return both the used and unused study treatment back to the clinical site. This information will be recorded in the eCRF.

Deviations from the prescribed dosage regimen should be also recorded in the eCRF.

Patients will record dates and times of study treatment application, including dates for study treatment delays in the electronic diary of the study mobile application (Study App).

The amount of study drug applied will be determined based on weight. The site will record the weight, as a whole, of the 5 packets each one in their respective closed zipper storage bags before and after dosing to quantify the amount used by the patient. Patients will be required to bring back to the site the respective two torn parts of each packet in their respective closed

zipper storage bags. The weighing of the 5 packets will be performed on a balance with sufficient precision to calculate the weight by difference of tirbanibulin administered daily with high accuracy. To avoid losing any study drug by leakage issues, the total weight of 5 packets will be measured as a whole in their respective re-sealable zipper storage bags. Additional details for this process are provided in the study manuals.

The dosing logs for each patient will be kept during the study. The Clinical Research Associate (CRA) will review treatment compliance during monitoring site visits.

9.6 Methods for Assigning Patients to Treatment Groups

9.6.1 Patient Identification

In order to protect the patient identity and data confidentiality, each patient will be identified in the trial with one unique patient number. The unique patient number is a combination of his/her site number and a sequential number assigned by the Investigator.

The site number will be predetermined, but the sequential number is assigned by the Investigator upon signing the informed consent form (ICF). At each site, the first patient is assigned patient number 001, and subsequent patients are assigned the next consecutive number.

Once assigned to a patient, the patient number will not be reused. The patient number will be used to identify the patient throughout the trial.

9.6.2 Randomization

This is single-arm study in which all patients are treated with tirbanibulin ointment 1%; no randomization is performed.

9.7 Blinding

This is an open-label study with no active or placebo comparator; no study blind will be applied.

9.8 Unblinding by the Investigator

Not applicable.

9.9 Pre-trial, Concomitant, and Post-trial Medications/Therapy

9.9.1 Pre-trial Medications

Patients must not have received any other IMP within 30 days or 5 half-lives of the IMP, whichever is longer, before the first trial drug administration.

All medications, including over-the-counter (OTC) drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to screening will be recorded at Screening. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria to ensure proper washout is followed. Thereafter, a record of all medications

taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be captured in the patient's eCRF.

A complete study disease treatment history will be recorded in the eCRF.

Any medication taken for medical reasons (mainly diseases concomitant with studied disease) prior to trial entry, will be continued at the same dose and conditions during the entire experimental phase of the trial.

9.9.2 Concomitant Medications

No concomitant therapy will be allowed during the entire duration of the trial, other than the prior allowed medication or any other required for the treatment of AEs or local tolerability. In such cases, the drug will need to be prescribed by the Investigator and recorded in the Concomitant Medication eCRF. The following items should be specified: trade name, dose and frequency of dosing, route, indication, date and time of first dose, and date and time of last dose, when applicable.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used. The use of non-medicated therapies (eg, sunscreen and moisturizers) will also be recorded in the Concomitant Medication eCRF. The use of or change in the dose of any of the concomitant medications, either prescription or OTC, during the study will be recorded. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE.

Patients must be instructed to inform the Investigator of plans to take any new treatment during the participation in the trial, including OTC medicinal and herbal products.

9.9.3 Prohibited Concomitant Medications

The use of any non-study drug on the TF is prohibited during the study.

The use of moisturizers and sunscreens in the TF is prohibited during the study, but can be applied outside of the TF, as needed.

Patients will be reminded that AK lesions located outside the treatment field may be treated by physical lesion-directed treatment only (eg, cryotherapy) at the Investigator's discretion.

All medications requiring wash-out (see Exclusion Criteria, Section 8.3) are prohibited during the patient's participation in the study.

9.9.4 Post-trial Medications

Once study treatment and all visits and related study measurements are complete, patients should continue to take their usual medications allowed during the study and may resume other medications interrupted prior to study enrolment, as deemed appropriate by the Investigator. It is not planned to treat patients with tirbanibulin ointment 1% any further than scheduled in this study. No intervention or additional care is planned to follow the end of the study.

10 Trial Procedures and Assessments

10.1 General Conditions of the Trial

Informed consent will be obtained after the study has been fully explained to each patient and before the conduct of any screening procedures or assessments. Documentation will be required (documented in the patient's medical records) to confirm that the Investigator has ensured the informed consent process was done correctly, and that the patient understood what to expect, he/she had the opportunity to ask any questions and consider other treatment options and agreed to participate.

The ICF can be either in paper or electronic form. Patients will be able to download the signed ICF (in case of completing the electronic ICF) or will be given a hard copy (in case of completing the paper ICF).

Trial visits must be scheduled with respect to Baseline/Day 1. In order to adapt appointments to local holidays, patients´ availability or site internal organization needs, time windows are allowed as indicated in Table 1. The CRA or CRO Medical Monitor should be contacted for advice in case of exceptional situations.

As applicable, laboratory tests and other assessments will be performed using supplies or equipment provided by the Sponsor for this trial through a specialized provider who will perform centralized assessment and reporting.

Optimally, the evaluations for each patient (lesion counts, review of trial drug compliance, etc.) should be performed by the same Investigator (or other suitably qualified and experienced designee) throughout the trial to avoid inter-assessor bias.

Unless specified otherwise, the study assessments scheduled during the study visits must be performed before the study product administration, except on Day 5, when the study product application will be done by the patient at home prior to the site visit. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. Vital signs
2. ECG
3. Blood draw for laboratory tests

Table 1 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in the following sections.

10.2 Patient's General Conditions During the Trial

After the screening evaluation and while not at the research site, patients will maintain normal daily activities, following the instructions of the Investigator. Any event likely to interfere with the objectives of the trial will be communicated to the Investigator and reported without delay to the Sponsor.

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

All screening assessments will be performed after the patient provides informed consent. The Screening Visit (Visit 1) will occur between Day -28 and Day -1. Patient screening numbers will be assigned at Visit 1.

Prior to signature of the ICF, Investigators will evaluate eligibility of patients for entry in the trial by comparing past and current medical status, as documented in the patient's medical history, to the inclusion/exclusion criteria of the trial.

Eligible patients will receive a detailed description of all activities and requirements before signing the ICF to ensure their understanding and compliance with sample collection and clinical examinations.

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. 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.

The Screening visit and assessments will be performed in accordance with schedule detailed in Table 1.

Demographics and Baseline Characteristics

Data on demographic (sex, age, race, ethnicity) and baseline characteristics (body weight, height, smoking and alcohol habits) will be collected during Screening. Height will be measured at Screening only.

Skin type will be recorded according to the Fitzpatrick scale (Table 2).

Table 2 Fitzpatrick Skin Type

Skin Type	Description*
I	Always burns easily, never tans (sensitive)
II	Always burns easily, tans minimally (sensitive)
III	Burns moderately, tans gradually (light brown) (normal)
IV	Burns minimally, always tans well (moderate brown) (normal)
V	Rarely burns, tans very well (dark brown) (intensive)
VI	Never burns, deeply pigmented (intensive)

*Sunburn and tanning history based on first 30 to 45 minutes of sun exposure after winter season of non-sun exposure.

Medical and Actinic Keratosis History

Medical history at Screening will include:

- Significant medical and surgical history during the last 5 years (eg, a common cold would not be captured unless it was ongoing at Screening)

- The initial diagnosis date of AK on the face or balding scalp and on any other part of the body
- Any AK treatment history of the face or balding scalp including all commercial and investigational products and surgical modalities dating back to the initial diagnosis
- History of and location of cancers including skin cancers, eg, BCC, SCC, melanoma

Prior Medications

All medications, including OTC drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to screening will be recorded at the Screening visit (see Section 9.9.1).

Physical Examination

A complete Physical Examination includes 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 sun-exposed areas where photo-damage is likely. Height is measured at Screening only. Physician examinations will be conducted in accordance with schedule detailed in Table 1.

Treatment Field Identification

The size of the TF must be approximately 100 cm^2.

At Screening, the Investigator will select and measure the anatomical area (eg, approximately mid face or an area on the scalp) and will outline the TF with a marker pen over the skin. Each AK lesion within the TF will be also 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 the number and location of lesions inside it will be confirmed. A baseline photograph 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 photograph is needed at baseline, then the screening photograph will be considered the baseline assessment. The same field will be located during the study with the aid of imaging software before performing the study assessments. Study Manuals will be provided to describe the image procedures in detail. The number of AK lesions in the TF will be recorded in the eCRF and photographs will be taken according to the schedule in Table 1.

Pregnancy Testing

In females of childbearing potential, a highly sensitive urine pregnancy test will be performed at the Screening visit and according to the Schedule of Assessments (Table 1). Urine pregnancy test kits will be provided by the Sponsor.

Any pregnancy, whether occurring in a female patient or in the female partner of a male patient, for which the estimated date of conception was during the patient's study participation must be reported. In addition, pregnancies in female partners of male patients for which the estimated date of conception was within 90 days of the last study treatment must be reported.

10.3.2 Response Assessment Period

Response Assessment Period visits and assessments will be performed in accordance with the schedule detailed in Table 1. See Sections 10.4 and 10.5 for details on the lesion and safety assessments, respectively.

The trial visit at Day 5 cannot be repeated nor skipped. The trial visits at Day 8, Day 15, Day 29, and Day 57 may be rescheduled within the time windows allowed in this protocol, in case of:

- scheduling conflicts (weekends or holidays),
- technical problems with the equipment necessary for the visit (eg, ECG),
- any AEs that impede conduct of the visit,
- restrictions related to the coronavirus 2019 disease (COVID-19) pandemic.

10.3.3 Unscheduled and Repeated Tests

Unscheduled Tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the trial in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc. These additional tests outside of the initial schedule of the trial will be considered "unscheduled tests" and will not be associated with any trial visit.

Repeated Tests

Any safety test may be repeated at the Investigator's discretion under either of the following situations:

- When there is any kind of problem with the first test (ie, technical problem with the ECG machine, blood sample hemolyzed, presence of artifacts, etc.). The Investigator should repeat the individual test as soon as possible.
- At the screening visit any individual test(s) may be reasonably repeated during the screening window to confirm the eligibility criteria (eg, laboratory sample when there is any clinically significant abnormality, etc.).

10.4 Lesion Assessments

To the extent possible, the Investigator who conducts the lesion count at Baseline/Day 1 and through the study visits according to the Schedule of Assessments (see Table 1) **must** be the same for an individual patient. All other intermediate assessment visits **should** be conducted by the same Investigator, to the extent possible.

A dermatologist (Investigator or Subinvestigator) will count all lesions in the TF for all subjects, according to the Schedule of Assessments (see Table 1). Details on whether the lesion present in the TF is new or an existing lesion at baseline will be recorded at each visit in the eCRF.

Lesions identified at baseline will be followed during the study using appropriate tools such as imaging software, where baseline lesions will be identified and new lesions appearing along the study recognized.

10.5 Safety and Tolerability Assessments

Safety will be assessed periodically during the study by recording AEs, including SAEs, local tolerability, pigmentation and scarring, and AESIs. Safety assessments also include PEs and vital signs measures, ECGs, clinical laboratory evaluations and pregnancy testing for WOCBP (see Table 1).

10.5.1 Adverse Events

10.5.1.1 Adverse Events

At each study visit, patients will be asked a general question "How have you been since the last visit?" before assessment of local tolerability, pigmentation, and scarring in the TF.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, vital sign measurements), including those that worsen from baseline which are determined to be clinically significant in the medical and scientific judgment of the Investigator, are to be recorded as AEs or SAEs.

Local tolerability signs will be reported separately from AEs (see Section 10.5.2). The Investigator, or designee, may report an AE based on his or her judgement. See Section 10.5.1.2 for definitions and reporting of AESIs.

All patients who have unresolved treatment-related AEs at Day 57/Early Termination (ET) 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.

Adverse event and SAE definitions and reporting requirements are detailed in Section 10.7.

10.5.1.2 Adverse Events of Special Interest

The following have been identified as AESIs based on their relevance for the current intended use:

Skin Cancers

Skin cancers (including BCC, SCC, and melanoma) appearing within or outside the TF during the study will be reported as AESIs. Details of the skin cancer and any other associated AE will be recorded in the AE form in the eCRF and by using the Skin Cancer Report Form. The location and treatment will be recorded. In the case of an SCC arising within the TF, it will be recorded if an AK had been present at the same location at baseline. See Section 10.7.4 for reporting requirements for AESIs.

If the skin cancer meets seriousness criteria, an SAE Report Form must also be completed and sent along with Skin Cancer Report Form, as specified in Section 10.7.4.

10.5.2 Focused Dermatological Examination of the Treatment Field

The focused dermatological examination will include evaluations for local tolerability signs, pigmentation, and scarring in the TF.

10.5.2.1 Local Tolerability

Local tolerability assessments in the TF will be recorded per the schedule in Table 1. The assessment for local tolerability is to be done after the assessment for AEs. The evaluation of local tolerability is done by the Investigator (or an appropriate trained designee). The local tolerability signs to be assessed and the corresponding grading scale for each sign are provided in Table 3.

Table 3 Local Tolerability Signs and Grading Scale

Local Tolerability Signs	Local Tolerability Score
Erythema Flaking/scaling Crusting Swelling Vesiculation/pustulation Erosion/ulceration	0=absent 1=mild (slightly, barely perceptible) 2=moderate (distinct presence) 3=severe (marked, intense)

Application site symptoms such as itching, burning, stinging, tenderness, pain etc., are not classified as local tolerability signs and will be reported as AEs.

All patients who have unresolved local tolerability signs in the TF at Day 57/ET 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 Investigator.

Any sign of local tolerability leading to temporary or permanent discontinuation of the study drug application or requiring the use of concomitant medications should be reported as an AE. If a sign of local tolerability leads to an AE meeting the criteria of seriousness (ie, an SAE), the SAE form will be completed with all the available information and reported within the same timeframe and following the same routing as for an SAE (see Section 10.7.4).

In case of occurrence of possible contact dermatitis in the TF, an evaluation (patch test) will be made to confirm or rule out the diagnosis (see Appendix 2).

10.5.2.2 Pigmentation Changes and Scarring

Hypo- and hyperpigmentation and scarring in the TF will be assessed as being present or absent in accordance with the Schedule of Assessments (Table 1). The assessment of pigmentation and scarring is to be done after the assessment for AEs.

All patients who have unresolved hypo- or hyperpigmentation or scarring in the TF at Day 57/ET 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 Investigator.

10.5.3 Physical Examinations and Vital Signs

Physical Examinations

A complete PE includes 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 sun-exposed areas where photo-damage is likely. Height is measured at Screening only.

Vital Signs

Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and body temperature. Measurements of systolic and diastolic blood pressure will be conducted after at least 5 minutes resting in the supine position and preferably on the same arm. If there is any suspicion of unreliable measurement, blood pressure will be measured again. The value obtained this time will be considered as definitive and should be recorded in the eCRF.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded in the AE form in the eCRF.

10.5.4 Electrocardiograms

Electrocardiogram training, equipment, and a procedural manual will be provided to the sites by a central ECG vendor. Refer to the procedural manual for details.

Electrocardiograms will be performed according to the schedule in Table 1. Patients must be in a supine position for 5 minutes prior to ECG and ECG is to be done prior to any blood sampling.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded on the AE form in the eCRF.

10.5.5 Laboratory Testing

Routine laboratory assessments will be performed at a designated central laboratory (refer to the laboratory manual). Tests to be performed at the central laboratory are detailed in Table 4.

Table 4 Laboratory Testing Parameters

Assessment	Specific Tests
Hematology	Red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood chemistry	Electrolytes: Chloride, potassium, sodium, bicarbonate (HCO3) Liver Function Tests: alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, direct bilirubin Renal Function Tests: Blood urea/blood urea nitrogen, creatinine Other: Total protein, albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, triglycerides, uric acid
Urinalysis	Hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood.

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes according to the Schedule of Assessments (Table 1). Blood samples are to be collected before administration of concomitant medications (if any), and after vital signs measures and ECGs are performed. Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must also be recorded on the AE form in the eCRF.

Urine pregnancy testing for WOCBP will be performed at the study site in accordance with the Schedule of Assessments (Table 1).

10.6 Other

Standardized Photography

Standardized photography of each patient's TF will be performed prior to dosing while on treatment (see Table 1) for illustrative purposes and to support the TF and AK lesion identification within the TF. Each AK lesion within the TF will be identified at the screening/baseline visit with a label placed over the skin, a photo will be captured as a reference to support AK lesion follow up during the study. Refer to the study manuals for detailed instructions.

Care must be taken to ensure that the same lighting, background, subject positioning relative to the camera, and camera settings are used for each photograph. Equipment, supplies, and detailed instructions for obtaining and managing the photographs will be provided to the clinical study site prior to the initiation of patient enrollment.

10.7 Adverse Events

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the patient.

10.7.1 Definitions

Adverse Event

An AE is defined as any untoward medical occurrence in a clinical trial participant, regardless of the administration of the IMP and its causal relationship to it.

An AE can therefore be any unfavorable and unintended medical occurrence during the patient's participation in the trial, including deterioration of a pre-existing medical condition, an abnormal value in a laboratory assessment, ECG abnormality, or an abnormal finding in the physical examination.

Adverse events must be temporally associated with the patient's participation in the trial, ie, occur after signing the ICF. At the time of the occurrence of an AE, the administration of the IMP does not need to have already been initiated. If initiated, it does not necessarily need to have a positive causal relationship to the event.

Serious Adverse Event

An SAE is an adverse event, which falls into one or more of the following categories:

- results in death

- is life-threatening (ie, an event which, in the view of the Investigator, places the patient at immediate risk of death from the event as it occurred.) It does not mean that the event might hypothetically have caused death if it was more severe or lasted longer
- requires in-patient hospitalization or prolongs existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is any other medically important event that may jeopardize the patient or may require intervention to prevent one of the other above outcomes.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. These are considered "other important medical events."

Hospitalization is defined as an overnight stay at the hospital or emergency room.

Prolongation of hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician.

10.7.2 Reporting of Adverse Events

Adverse events either reported by the patient or observed by the Investigator must be recorded in the AE page of the eCRF and should be described in the following manner:

- The nature of the AE will be described in precise, standard medical terminology (ie, not necessarily the exact words used by the patient). If known, a specific diagnosis should be recorded instead of listing signs and symptoms (eg, allergic contact dermatitis)
- The duration of the AE will be described by the start date and end date
- The location for cutaneous adverse events will be described as at or just around the TF (≤2 cm from the TF) or distant (>2 cm from the TF)
- The intensity of the AE will be described in terms of mild, moderate, or severe according to the Investigator's clinical judgment, using the following definitions:
  - **Mild**: Awareness of event, symptoms, or signs, but easily tolerated (acceptable)
  - **Moderate**: Sufficient discomfort and interferes with usual activity (disturbing)
  - **Severe**: Incapacitating with inability to do normal daily living activities or significantly affects clinical status and warrants intervention (unacceptable)
- The causal relationship of the event to use of the IMP will be described in terms of:
  - **Not related**: Event or laboratory test abnormality, definitely not related to trial drug, as related to other drug, chemicals, or underlying disease
  - **Unlikely related**: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable; disease or other drugs, chemicals or underlying disease provide plausible explanations

- **Possibly related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake; could also be explained by underlying disease or other drugs or chemicals; information on drug withdrawal may be lacking or unclear
- **Related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake, unlikely to be attributed to underlying disease or other drugs or chemicals; response to withdrawal clinically reasonable (positive dechallenge)

'Possibly related' and 'related' will be considered as 'related' terms for reporting purposes. If the events are assessed as 'unlikely related' or 'not related' to the suspect IMP, the event does not qualify for reporting purposes. In the absence of information on causality from the reporting Investigator, the CRO will immediately contact the reporting Investigator to request a causality assessment. The case will be updated with the follow-up information and reported accordingly. If no causality is provided by the Investigator, the Sponsor assessment will be considered for submission purposes.

- The outcome of the event will be described in terms of:
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal
  - Unknown
- The action taken on the IMP will be captured as:
  - Drug withdrawn
  - Dose not changed
  - Not applicable

An AE will be collected only once with its maximum severity, except when the AE started before first IMP administration and persisted after it and worsened in severity any time after first IMP application. In this latter case, the AE will be collected with each respective severity. The AE term recorded must be exactly the same at the different time points where this AE is reported again in the eCRF.

10.7.3 Recording of Adverse Events

Adverse events will be collected from signature of the ICF up to Day 57/ET. Any AE reported by the patient up to 30 days after the last study contact (Day 57/ET) should also be captured in the eCRF.

Medical disorders present at the time of signing the informed consent that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Abnormalities detected before IMP administration in the PE, laboratory tests, ECGs, or other safety assessments will not be considered AEs if already known as part of the medical history or in relation to prior medical conditions and will be recorded in the eCRF/CRF Medical History/physical examination form/page. However, abnormalities detected in screening/baseline tests, thought to be due to a trial procedure, will be considered AEs.

Abnormalities (newly occurring or worsening of previously known abnormalities) detected after IMP administration in physical exam, laboratory tests, ECGs, or other safety assessments, which are considered clinically relevant by the Investigator, or which require an intervention or a diagnosis test, or may result in the IMP discontinuation, should be reported as AEs.

Reported terms should accurately characterize the adverse event. When a patient experiences an unspecified injury, signs or symptoms, active investigation should be conducted to reach a final diagnosis. If reached, then the disease diagnosis is the preferred reported term.

Adverse events will be elicited by asking the patients non-leading questions (eg, "How do/did you feel?") and by collecting AEs spontaneously reported by the patient to the Investigator or a designee.

All AEs elicited by the Investigator during the defined AE collection period must be recorded in the eCRF. In addition, when an AE meets the criteria of seriousness (ie, an SAE), it must also be recorded on the SAE form and reported following the defined timelines in Section 10.7.4.

10.7.4 Reporting of Serious Adverse Events and Adverse Events of Special Interest

Serious adverse events and AESIs will be collected from signature of the ICF up to Day 57/ET. Any SAE or AESI reported by the patient up to 30 days after the last study contact (Day 57/ET) should be collected in the eCRF.

The Investigator must report any SAE or AESI within 24 hours from the moment she/he first learns of it to the CRO pharmacovigilance unit on a SAE report form. This reporting will take place regardless of whether the Investigator considers the event to be causally related to the IMP(s), to any other medicinal product(s), to the clinical trial procedure or to any intervention undergone by the patient.

Original reports are to be kept by the Investigator in the Investigator's File.

Contact details and specific instructions on the flow of SAE and AESI reports will be provided to all sites by the CRO.

The minimum information that must be included in the initial report is:

- An event meeting the criteria of SAE or AESI.
- A qualifiable reporter, defined as an Investigator of this trial or his/her delegate.
- A qualified patient, defined as a patient who has consented to this trial.
- A suspect medicinal product.
- The Investigator's causality assessment.

Unless the SAE or AESI has been sufficiently documented in the initial report, the Investigator will provide all available additional information in follow-up reports by using a new form and adhering to the same routing and time frames as defined for the initial report. This will be continued until the event has been fully documented and reported.

An event reported to the CRO pharmacovigilance unit which does not meet the SAE or AESI criteria shall be nullified by the Investigator by forwarding a follow up report.

Depending on the local requirements, a regulatory report of the SAE or AESI (if serious) will be produced by the CRO pharmacovigilance unit and submitted to relevant Competent Authorities and Investigators, when applicable according to local regulations.

Serious adverse events NOT considered to require reporting to the CRO pharmacovigilance unit will be:

- Hospitalization for a treatment/surgical procedure which was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the trial.

10.7.5 Follow-up of Adverse Events / Serious Adverse Events

Those AEs and SAEs, including AESIs, recorded for Screening failure patients will be followed-up until resolution or until otherwise agreed between the Sponsor and the Investigator.

All AEs and SAEs, including AESIs, that are still present after the last study visit (including AEs that have led to premature discontinuation), will be followed-up at least 2 weeks for AEs and 4 weeks for SAEs after the last trial drug administration, by means of a follow-up contact or visit (whichever is considered more appropriate by the Investigator). In case the AE/SAE is still ongoing after that time point, this will be followed-up until its resolution or until otherwise agreed between the Sponsor and the Investigator. The same timeframes will apply for AEs from screening failures which are ongoing at the time the patient is withdrawn from the trial.

Additional safety data collected at a contact/visit to follow-up the ongoing AE will not be included into the clinical database, if this was already locked; therefore, the clinical database lock will not be delayed due to this situation. Any SAE will be followed up if needed after clinical database lock and the information will be only stored in the safety database.

10.8 Pregnancies

There is no information about effects that tirbanibulin could have on the development of the fetus in humans. However, consistent with its mode of action, tirbanibulin was embryo- and fetotoxic in preclinical studies.

Any pregnancy, whether occurring in a female patient or in the female partner of a male patient, for which the estimated date of conception was during the patient's study participation must be reported. In addition, pregnancies in female partners of male patients for which the estimated date of conception was within 90 days of the last study treatment must be reported.

In case of pregnancy during the participation in the trial, the patient will be immediately discontinued.

The Sponsor will be informed according to the safety reporting procedure: the Investigator must complete a study specific pregnancy form upon confirmation of a pregnancy and send it to the CRO Safety Contact within 24 hours of confirmation of the pregnancy. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate.

The Investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, the follow-up period will be deemed to have ended when the health status of the child has been determined on its birth or after an appropriate period post-delivery considered necessary to monitor the development of the new-born is completed.

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriage, developmental delay, fetal death, SAE in a neonate, and congenital abnormalities will be reported as SAEs. The Investigator will inform the CRO Safety Contact of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

10.9 Unblinding for Safety Reasons

Not applicable.

11 Statistics

The statistical analyses described below will be supplemented by a comprehensive Statistical Analysis Plan (SAP) that will be finalized before the database is locked. Any changes to the statistical plans will be described and justified in the final report. All statistical processing will be performed using the SAS® system.

11.1 Sample Size Calculation

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.

11.2 Structure and Methodology of the Statistical Analysis

Statistical analyses of demographic, baseline characteristics, safety, tolerability, and lesion count data will be performed by the CRO Biostatistics department.

The SAP will be prepared by the CRO statistician under Almirall Standard Operating Procedures (SOPs) prior to database lock. SAS will be the statistical software used to analyze the data sets. A complete set of raw data listings will be appended to the Statistical Report. All tables, figures, and listings will be presented in portable document format (PDF) documents without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

Tables, figures, and listings will be compiled in the statistical report and appended to the CSR.

11.3 Analysis Populations

There will be one analysis population in this trial:

- Safety population, defined as all patients who have received at least one dose of study treatment.

11.4 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. When applicable, these summaries will be provided by visit and time-point of assessment.

11.5 Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics.

11.6 Study and Treatment Compliance

Descriptive statistics will be used to summarize study and treatment compliance.

11.7 Prior and Concomitant Medications

The number and percentage of the patients with concomitant medications during the study will be summarized by anatomical therapeutic chemical class, standardized drug name.

11.8 Statistical Methods

The statistical approach for the analysis of safety and other endpoints is described below. A more detailed description of the statistical methods to be used will be provided in the SAP.

11.8.1 Analysis of Safety Endpoints

Descriptive statistics will be provided for all safety endpoints.

Local tolerability signs composite score, and specific local tolerability scores will be analyzed by means of descriptive statistics and provided by visit. The maximum local tolerability score and maximum local tolerability composite score will be presented. The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by visit as well as the number and percentage of patients with change from baseline in hypo- or hyperpigmentation and scarring in the TF.

An AE will be considered to be a TEAE, if it was not present prior to the first dose of trial drug or was present prior to the first dose of trial drug but increased in severity after the date of the first dose of study treatment. An AE that occurs more than 57 days after the last IMP application will not be counted as a TEAE.

TEAEs and TESAEs recorded during the study will be presented, including the total number of events and the number and percentage of patients with events. Summaries of the number

and percentage of patients with TEAEs (and number and percentage of events), study drug-related TEAEs, TEAEs by severity, TESAEs, TESAEs with an outcome of death, and TEAEs leading to temporary or definite discontinuation of the study treatment will be provided. Specific tables describing AESIs will be also provided. The number and percentage of patients who experience one or more AESI will be tabulated by AESI.

For PEs, ECGs, vital signs, and clinical laboratory parameters, the number and percentage of patients with normal or abnormal results will be presented at scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. Shift tables will be provided when appropriate.

11.8.2 Analysis of Exploratory Endpoints

Descriptive statistics will be provided for exploratory endpoints overall and by subgroup (see Section 11.11). An Observed Cases approach will be used for handling missing data, as the main analysis (see Section 11.9). Any other sensitivity analyses will be defined in the SAP.

11.9 Handling of Missing Data

No imputation will be made for missing data.

11.10 Multiplicity Strategy

Not applicable.

11.11 Subgroup Analyses

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

11.12 Interim Analysis

No interim analysis is planned for this trial.

12 Data Handling, Processing, and Record Keeping

The Investigator will conduct the trial in accordance with the protocol and ICH E6 GCP guidelines. In addition to the routine monitoring procedures, training records should be in place to ensure investigators and CROs understand the data processing in any of the computerized systems to be used to ensure the confidence in the reliability, quality, and integrity of the patient data.

Sponsors, CROs, data safety monitoring boards, and other authorized personnel can view the trial data elements in the eCRF before and after the clinical Investigator(s) has electronically signed the completed eCRF. Reviewing trial data dynamically will allow early detection of trial-related problems (eg, safety concerns, protocol deviations) and problems with conducting the trial (eg, missing data, data discrepancies).

According to the eCRF entry guidelines, eCRFs must be completed for each patient by qualified and authorized personnel. Any data entry and corrections made in the eCRF must have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the trial should be collected.

A list of all authorized data originators (ie, persons, systems, devices, and instruments) should be developed and maintained by the CRO and made available at each clinical site.

The eCRF is an auditable electronic record of information reported to the Sponsor on each trial patient, according to this clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.

12.1 Data Collection

12.1.1 Identification of the Trial Data Sources

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.

When a device or instrument is the data originator (eg, blood pressure monitoring device or glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is the source.

Access to source data is critical to the review and inspections of clinical investigations. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.

The trial data sources are outlined below:

- Signed informed consent forms
- Patient medical history records will include trial diagnosis and inclusion/exclusion criteria age, sex, demographics, physical examination, medical history, vital signs, previous medication, original or certified copy of a laboratory reports, instrument printout, trial progress notes of the physician
- Laboratory test results reports (hematology, clinical chemistry, urinalysis, etc)
- Digital photographs
- ePatient diary (Study App)
- eCRF

12.1.2 Electronic Case Report Forms

To comply with the requirement to maintain accurate case histories Investigators should review and electronically sign the completed eCRF for each patient before the data are archived or submitted. Use of electronic signatures must comply with US Title 21 Code of Federal Regulations part 11.

For trial data elements transcribed from paper or electronic to the eCRF, the electronic or paper documents from which the data elements are transcribed are the source.

These data must be maintained by the Investigators and available to the monitor or inspector if requested (eg, an original or certified copy of a laboratory report, instrument printout, progress notes of the physician, the trial patient's hospital chart(s), nurses' notes).

Direct Entry of Data Into the eCRF

The direct entry of data can eliminate errors by not using a paper transcription step before entry in the eCRF. For the following data elements, the eCRF may be the source:

- Date of ICF signature (in the case of a paper ICF; in the case of an electronic ICF the eConsent will be the source)
- Inclusion and exclusion criteria confirmation (checking)
- Patient demographics and physical examination, including. age, gender, race, ethnicity height, weight, and Fitzpatrick skin type
- Relevant previous and concomitant therapies
- Up-to-date relevant medical history, including trial diagnosis
- TF measurements and location (face or scalp)
- Number of lesions in the TF and identification of whether each lesion is new or existed at baseline
- Vital signs (blood pressure, pulse, body temperature, and respiratory rate)
- Pregnancy test results
- Trial/visit dates
- Visit assessment (checking compliance, trial diary data, drug application, blood sample collection, tolerability score, end of treatment)
- Drug accountability (medication given and returned and product weight before and after application)
- Adverse events

For the above trial data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for monitoring or inspection.

Direct data entry should meet ALCOA+ principles for data integrity in life sciences. In case trial data cannot be entered at the time of the patient visit, eg, laboratory tests results, then Investigators are requested to make their entries at the time when the report with the results is received.

All non-CRF entered external data (ie, images) will not be loaded into the eCRF, but it will be integrated in SAS datasets and reconciled frequently with the eCRF data by CRO Data Management.

The information directly collected in the eCRF must match the source documents. The source data verification will be performed by the CRO Clinical Research Associate (monitor) according to the requirements specified in the Monitoring Plan.

At the trial end, the CRO will generate a PDF copy of the completed CRFs which will be sent to the Investigator(s) for all patients enrolled at his or her location.

12.1.3 Patient Diary

During the study, patients will use a mobile application. Clinical personnel will be instructed on the use of the Study App in order that they further instruct the patients at the Day1/Baseline visit, and as many times as deemed necessary. Patients will also receive written instructions on the Study App use. The Study App will be installed onto the patient's own mobile phone, and there will also be the possibility to provide patients with a mobile phone, if necessary. The Study App will be installed onto the mobile phone during the baseline visit. Clinical personnel will check and confirm the correct installation of the Study App during the visit.

On the Study App, patients will:

- Receive notifications, communications, and reminders through the patient retention tool
- Complete the eDiary: Patients, and assisted by caregivers, as needed, will complete a diary to record daily the study treatment application dates and times of application. The eDiary will be completed by the patient and will be checked by the Investigator (or designee) in accordance with the Schedule of Assessments (Table 1).

At the study end, the Investigator will receive a CD/DVD with the mobile application data (in PDF) from the patients enrolled at his/her location. The Investigator will keep this CD/DVD with the rest of the original data for as long as required by local regulations. The mobile application files are relevant documentation for registration.

The mobile application data is the sole property of the Sponsor and should not be available in any form to third parties without the written permission of the Sponsor, except to authorized representatives of appropriate Competent Authorities.

12.2 Data Management and Quality Control

Data Management of the trial will be performed by the CRO Data Management department according to the CRO SOPs and supervised by Data Management at Almirall, according to Almirall SOPs.

In order to facilitate the collection of accurate and complete data, the CRO will target the risks associated with critical trial data and these will be documented into the Data Management Plan (DMP) and the Monitoring Plan.

Investigators will respond to any query generated by the Data Management group or any data risk indicator reported.

Main Data Management activities and procedures will be accurately described in the DMP, created by the CRO and approved by Almirall.

Database checks will be programmed by the CRO, based on the Data Validation Plan. The listings will be documented in the DMP. The checks and listings programming will be appropriately validated by the CRO.

Reconciliation of trial data and SAEs between Clinical and Drug Safety databases will be performed by the CRO on an ongoing basis and before database lock. Procedures to be followed will be detailed in the DMP.

Encoding of specific data will be conducted by the CRO. For this trial, medical history, AEs, and concomitant medications (including rescue medications) will be coded; Medical Dictionary for Regulatory Activities (MedDRA) and WHO-DRUG Enhanced dictionaries will be used, version number of each dictionary will be documented in the DMP.

A Quality Control check to ensure the accuracy of the data will be done by the CRO, when data are cleaned on an ongoing basis and just before the database lock. Specifications of the Quality Control check will be found in the DMP.

An audit trail will be maintained in order to protect the authenticity and integrity of the clinical data.

12.3 Investigator and Trial Master Files

The Investigator's file and Sponsor Trial Master File (TMF) will contain all trial documents indicated in the ICH GCP guidelines and local regulations.

At the trial end the Investigator will receive one CD/DVD/USB key with the electronic data capture (EDC) data, as well as one CD/DVD with the tablet PC and electronic Patient Diary data from the patients enrolled at his/her location. The Investigator will keep these in the Investigator’s file.

The CRO will provide Almirall with an electronic TMF (eTMF). Almirall will have on-line access to the eTMF during the study and study documents will be reviewed, approved, and managed within the system. At the end of the study the eTMF and complete audit trail will be transferred to the TMF-dedicated Sponsor server for long-term storage. Information about eTMF contents, index, structure, nomenclature, metadata, and oversight metrics will be detailed in other documents (ie, eTMF Management Plan, CROOP, etc.).

All records must be stored in a secure facility protected from fire, flood, and unauthorized access where they may be readily accessed in the event of an audit or inspection.

12.4 Documents and Record Keeping

The Investigator should retain control of the records (ie, completed and signed eCRF or certified copy of the eCRF). The Investigator maybe requested by inspectors with access to the records that serve as the electronic source data.

When data elements are transcribed from paper sources into an eCRF, the Investigator must also retain the paper sources, or certified copies, for later review. Other records (electronic and paper) required to corroborate data in the eCRF may also be requested during an inspection.

All trial data (including electronic data), all hard copies including protocol, consent forms, CRFs, queries and printouts, and all essential documents relating to the conduct of the clinical trial will be stored at the research site for a period of 25 years after completion of the trial, unless otherwise communicated in writing by the Sponsor.

CROs/vendors will store the databases, including audit trails and related documentation, for a period of 25 years after completion of the trial, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13 Quality Control and Quality Assurance

13.1 Training of Staff

During the set-up phase of the trial, appropriate kick-off meetings will be performed between Almirall and the CRO and/ or vendors (eg, eCRF, laboratories, central ECG), in order to train CRO staff on trial procedures.

An Investigators' meeting will be performed, including training on GCP procedures, trial protocol, efficacy and safety assessments, laboratory procedures, eCRF completion, usage of any specific device and any other applicable process/procedure/method, as applicable.

An initiation visit will be performed at each site by the trial CRA designated by the CRO to assess if all the material and supplies (eg, eCRF, IMP) arrived in good conditions and to train the site staff for protocol compliance.

Appropriate study manuals will be provided to the research sites as written help to support all trainings on all trial procedures (eg, laboratory samples, eCRF).

13.2 Monitoring

The trial will be monitored by CRO CRA/Monitors according to the details specified in the Monitoring Plan.

The trial CRA/Monitor will conduct monitoring visits according to a pre-agreed schedule and with enough frequency to perform source data verification, check the accuracy of entries in the CRFs, the adherence to the protocol and to GCP, the progress of enrollment and to ensure that trial medication is being stored, dispensed, and accounted for, according to specifications and report any deviation as soon as possible to the Clinical Trial Manager.

Standard monitoring reports will be produced by the trial CRA/Monitor after each visit and filed in the TMF. Key trial personnel must be available to assist the field CRA/Monitor during these visits.

The Investigator must also keep the original informed consent form signed by the patient and maintain source documents for each patient in the trial, case and visit notes medical records, all information in eCRFs must be traceable to these source documents in the patient´s file.

A close out visit to solve pending issues and to agree on the shipment of remaining trial materials to the Sponsor (eCRF and other data source, medication) will be performed by the trial CRA/Monitor once all patients have completed the trial.

13.3 Inspections and Audits

The trial site, trial processes, CRO, providers and/or trial documents may be subject to Quality Assurance audits by Almirall (or authorized partner companies) as well as to inspection by competent authorities, as applicable, during the trial or after trial completion. Audits and inspections may include, but are not limited to, drug supply, presence of required documents, informed consent process, medical records, general protocol compliance and comparison of data recorded in the eCRF and queries against source documents. Investigator will ensure direct access to source medical records for inspection and audit purposes.

14 Ethics

This trial will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly of Helsinki (1964), as amended in Fortaleza, Brazil (2013) (World Medical Association, 2013), as well as in compliance with ICH GCP guidelines, and local laws of the Countries in which the trial centers are located.

14.1 Responsibilities

The Investigator is responsible for conducting the trial in accordance with the procedures described in this protocol. All the personnel involved in the clinical trial will be fully informed about the drug and the nature of the trial and will be patient to protocol procedures concerning their duties in the trial.

The Investigator, the CRO/vendors and the Sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted according to the highest standards of Good Clinical Practice (ICH GCP guidelines) and local regulations.

The Investigator, the CRO and the Sponsor will work according to the ICH guidelines, EU Clinical Trials Directive 2001/20/EC and/or Clinical Trials Regulation No 536/2014, and Title 21 of the US Code of Federal Regulations (US Food and Drug Administration [FDA]).

The Investigator shall administer the trial medication to patients under his or her personal supervision or under the supervision of any co-Investigator reporting to him/her who are identified in the delegation of responsibilities and signatures log. The Investigator and designees will be responsible for the patient's compliance throughout the trial.

Refer to Section 9.9.4, for details on post-trial medications.

14.2 Patient Information and Informed Consent

Patients will be informed by the Investigator in detail of the characteristics of the drug to be administered, the nature of the clinical investigation, the risks and the discomfort that can reasonably be expected as a result of their participation and the uses of the data, as described in the Patient Information Sheet (PIS).

The patients will be informed that they are free to withdraw their consent and suspend their participation in the trial at any time with no penalty or loss of benefits to which the patient is otherwise entitled. Administration of the drug may be interrupted, and a patient withdrawn from the trial at the discretion of the Investigator. The Investigator should justify his decision in the patient's eCRF.

Any patient considered by the Investigator to be suitable for inclusion must document his or her willingness to participate in the trial by giving his or her informed consent in writing before starting any trial procedure by signing the ICF, which must be signed and dated by the patient and the Investigator. Explicit consent to participate in the standardized photography procedure will also have to be given by patient.

At such time the patient must be given adequate time to understand the information provided and ask questions, if required. Any new relevant information that becomes available during the trial will be provided to the patient.

The PIS and ICF will include all elements required according to the applicable legislation. These documents or any modification will have been authorized by Almirall, S.A. and approved by the relevant IRB/IEC before use.

Patients will have access to the written PIS and ICF in paper or electronic format, preferably but not exclusively through a web system (eConsent). When using the eConsent process, the system will allow for on-line meetings between the patient and Investigator to facilitate answering patient questions and recording the responses. Patients will give their consent by signing electronically the ICF (eConsent). Patients will be requested to download the signed ICF, and/or ask the Investigator for a printed version. While they are in the study, patients will always have access to the PIS and ICF through eConsent. When eConsent cannot be used, the patient will sign a paper ICF.

14.3 Institutional Review Board/Independent Ethics Committee

This protocol, PIS and the ICF should be submitted to an IRB/IEC for review and approval. Notification in writing of approval must be obtained from the IRB/IEC by the Investigator before initiation of patient enrolment.

The Investigator must promptly report to the IRB/IEC all changes in the implementation of the research (protocol amendments) and will not make such changes without IRB/IEC approval except where necessary to eliminate apparent immediate hazards to the trial patients or administrative changes.

Serious adverse events reasonably related to the trial drug will be communicated by the Investigator/CRO to the IRB/IEC.

The Investigator is required to maintain accurate and complete records of all written correspondence sent to and received from the IRB/IEC and must agree to share these documents and any reports with the Sponsor.

14.4 Patient Data Protection

The trial patients shall be informed by the Investigator that complete confidentiality will be maintained concerning their identity. On eCRFs/EDC and all trial data records (eg, electronic patient diary) patients will be identified only by the assigned patient identification number.

A signed written ICF signifies the explicit acceptance by the individual that data from the trial will be available to the Investigator and his/her staff, the authorized representatives of the Sponsor and, if required, by the IRB/IEC and Competent Authorities. However, all data contained in the patient's medical history will be considered as confidential. Almirall will treat data according to personal data regulations (Health Insurance Portability and Accountability Act [HIPAA]), and any other applicable national and international regulation.

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

15 Financing and Insurance

Almirall will set up a contract with the CRO with the economic aspects for trial funding.

All patients recruited will have an insurance policy provided by Almirall to cover any possible risk resulting from their participation in the clinical trial.

Except in the proven case of clinical malpractice, the insurance company will indemnify against any claim or claims made by patients or their dependents which may result from administration of the IMP.

16 Publication Policy

Almirall will disclose clinical trials in a manner consistent with applicable national laws and rules governing personal data privacy and protection of intellectual property rights. Clinical trials will be registered, and results disclosed by means of recognized public databases, such as clinicaltrials.gov in the US and EudraCT in the European Union.

The Investigator understands and accepts that his/her name and trial center may be disclosed in the context of this national or international legislation.

All the information related to this clinical trial is considered strictly confidential and is the property of Almirall. This information will not be given to a third party without the written consent of Almirall.

By signing this trial protocol, the Investigator affirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her in relation to or resulting from this trial. The Investigator will only divulge such information as may be necessary to the IRB/IEC, the members of the staff and the patients who are involved in this trial.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and CRO.

In all cases, the trial results shall be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations of the trial. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication.

Publication and/or presentation whether complete or partial, of any part of the data or results of this trial will not be allowed until global publication and trial results disclosure by the Sponsor as per US FDA regulatory compliance obligations, and only after mutual agreement between the Investigator and Almirall.

17 Other Practical Considerations

17.1 Investigator's Brochure

The Investigator's Brochure contains a summary of the pre-clinical and clinical data. The same confidentiality procedures apply for the Investigator's Brochure as for the protocol.

The Investigator's Brochure will be included in the Investigator file. The Investigator will sign a receipt form.

17.2 Final Clinical Trial Report

The CSR will be written by the CRO following the ICH guidelines requirements. It will be approved and signed by the Coordinating Investigator and Almirall representatives according to internal SOPs.

The CSR will be audited by the CRO and/or Almirall before issuing the final version.

The final version of the electronic CSR will be e-published (hyperlink, bookmarks, etc.) including all appendices according to ICH Guidelines.

The summary of the CSR will be sent to all the Investigators participating in the clinical trial.

17.3 Protocol Amendments

Modifications of the original protocol are referred to as "amendments" to the trial protocol. Modifications of the original protocol may only be made with Almirall approval. Two types of amendment maybe produced:

- Substantial Amendments (related to the safety or physical or mental integrity of the patients, scientific value of the trial, conduct or management of the trial or the quality or safety of any IMP used) must be notified to the IRB and/or Competent Authorities and approved by them before implementation.
- Non-substantial Amendments do not require notification but should be recorded and be available on request for inspection at the trial site and/or Sponsor premises as appropriate.

17.4 Protocol Deviations

Any protocol deviations during the conduct of the trial will be recorded by the CRA/Monitors as detected or derived from data collected in the clinical database.

Relevant deviations will be promptly reported to Almirall after detection. Major protocol deviations will be included in the corresponding listing of the CSR.

Additionally, protocol deviations will be reported to the IRBs/IECs and/or Competent Authorities according to the local regulation in each country.

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19 Appendices

1. Highly Effective Methods of Birth Control
2. Patch test for the Assessment of Contact Dermatitis

Appendix 1, Highly Effective Methods of Birth Control

Highly effective methods or birth control (ref. CTFG 2014 guidance document):

- Intrauterine device, intrauterine hormone-releasing system or bilateral tubal occlusion or ligation (1)
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable (1))
- Vasectomized partner (2). Female patient must agree to implement one of the other highly effective methods of birth control if her lifestyle/partner changes
- Sexual abstinence (3)

Notes

(1) Low user dependency methods from at least 3 months before trial screening

(2) Only provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

(3) Only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments (from Day1 to at least 30 days after the last dose of the investigations product).

Appendix 2, Patch Test for the Assessment of Contact Dermatitis

In the event the patient experiences a skin reaction of such nature or severity that an allergic contact dermatitis is suspected, the patient can be treated with topical treatment with corticosteroids (eg, betamethasone) and oral antihistamines and should temporally discontinue the study medication. The event should be documented as an adverse event and the medication given recorded. The patient should be re-challenged using the assigned study medication (patch test in the back) to confirm or rule out contact dermatitis. If the diagnosis of allergic contact dermatitis is confirmed the patient may have an additional patch test with both the tirbanibulin-containing ointment and the vehicle base.

The patch test will be performed at least 2 weeks after last treatment or discontinuation of the study medication. Patches will be applied to untreated areas on the back for 48 hours. Readings will be performed approximately 15 to 30 minutes and 48 hours following the removal of the patches. At the investigator's discretion, a facultative additional reading might be performed at 96 or 120 hours after removal of the patches if an equivocal reaction is observed at the previous reading. If allergic contact dermatitis is confirmed the patient will discontinue permanently the study medication, on the contrary the patient can be treated with the study medication if necessary.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical Approval	24-Mar-2022 09:33 GMT+0
PPD	Clinical Approval	24-Mar-2022 09:36 GMT+0
PPD	Clinical Statistics Approval	24-Mar-2022 09:48 GMT+0

eDMS R&D Object_ID: CCI [redacted]

almirall

PPD MD, PhD
PPD R&D, ALMIRALL

Barcelona, 8th of August 2022

Dear Investigator,

You are currently screening patients for M-14867-32 study.
By the present letter Study Sponsor would like to provide you further clarification on some questions received around contraception methods and guidance concerning contraceptive measures acceptable for enrollment in this study.

Current Inclusion Criterion in the Protocol Section 8.3 mentions:

- highly effective methods of birth control (defined in Appendix 1) for at least 30 days or 1 menstrual cycle, whichever is longer, prior to the study treatment.

Appendix 1 Footnote 1 mentions: Low user dependency methods from at least 3 months before trial screening.
This letter aims to clarify that the three months period mentioned in Appendix 1 Footnote 1only applies to the following low user dependency methods:

- Bilateral tubal occlusion or ligation
- Vasectomized partner

In order to avoid any ambiguity and guarantee patients´ safety as priority, we recommend the following. If tubal occlusion /ligation or vasectomy were performed in the period of 30 days to 3 months before this study, please reach out to sponsor.

We believe that these particular cases must be reviewed by Innovaderm and Almirall medical team in case by case manner.

PPD

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona, Spain

Letter of Protocol Clarification - *Administrative Change 1*

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
Protocol Number:	M-14867-32
Date:	03-JAN-2023

Dear Investigator(s),

After the issuance of M-14867-32 Protocol Version 2.0 dated 21 March 2022, and for the correct development of the trial, clarifications were determined to be needed in relation to the completion of patient's eDiary.

At section "12.1.3 Patient Diary", the protocol details the usage of an electronic diary (Study App) to record daily the study treatment application dates and times of application for the above-mentioned study, to be completed by subjects. However, in case of need, a paper diary was also developed as an alternative when needed.

This contingency plan was not included in the protocol by mistake, and therefore it is not listed in the section "12.1.1 Identification of the Trial Data Source" as a valid source document.

The mentioned paper diary was developed, submitted, and approved by the Ethics Committee prior to implementation at sites. However, since this contingency plan was not included in the Protocol, there was the need to issue this clarification letter to specify that both the Study App and the paper diary, when applicable, are considered trial data sources for study treatment application dates and times.

Since this is a minor correction, an amendment to the Protocol is not expected.

DocuSigned by:
PPD
Nombre del firmante: PPD
Motivo de la firma: He revisado este documento
Hora de firma: 10-ene.-2023 | 13:21:32 CET
PPD

PPD
International Clinical Trial Manager

DocuSigned by:
PPD
Nombre del firmante: PPD
Motivo de la firma: Apruebo este documento
Hora de firma: 10-ene.-2023 | 14:13:10 CET
PPD

PPD
Global Clinical Lead

cc: Trial Master File