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ALMIRALL, S.A.

Clinical Trial Protocol [M-14789-42]

Clinical Trial Protocol Title:	**Open phase IV study to assess the impact of tirbanibulin on the well-being of patients with actinic keratoses (TIRBASKIN)**
Investigational Medicinal Product(s):	**Tirbanibulin**
Indication:	**Actinic keratosis**
Development Phase:	**Phase 4**
Final Protocol Version Date:	**05-Aug-2022**
Amendment(s)	**Number:** None **Date:** N/A
EudraCT Number:	**2022-001251-16**
Sponsor:	**Almirall, S.A.** **Ronda General Mitre, 151** **08022 Barcelona, Spain**

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Protocol Amendment Summary of Changes

There have been no amendments to the trial protocol.

Amendment No.	Date	Summary of Changes	Rationale

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Protocol Approvers' Signatures

Clinical Trial Protocol Title: **Open phase IV study to assess the impact of tirbanibulin on the well-being of patients with actinic keratoses (TIRBASKIN)**

Trial Code: **M-14789-42**

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 ICH GCP guidelines, and to local regulatory requirements, wherever applicable.

Sponsor

Almirall, S.A.
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Functional Role	Name	Signature
PPD Spain	PPD MSc	PPD
PPD	PPD , PhD	PPD
PPD Spain	PPD PhD	PPD

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Functional Role	Name	Signature
PPD Italy	PPD MD	PPD
PPD Spain	PPD MD	PPD
PPD Italy	PPD , MD	PPD

Contract Research Organization

OPIS s.r.l
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Functional Role	Name	Signature
PPD	PPD MD MSc	PPD

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PPD	PPD MSc	

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Principal Investigator Signature

Clinical Trial Protocol Title:	**Open phase IV study to assess the impact of tirbanibulin on the wellbeing of patients with actinic keratoses (TIRBASKIN)**
Trial Code:	**M-14789-42**

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 ICH GCP guidelines, and to local regulatory requirements, wherever applicable.

Principal Investigator

Role	Name	Signature	Date

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1 Protocol Synopsis

Title:

Open phase IV study to assess the impact of tirbanibulin on the wellbeing of patients with actinic keratoses (TIRBASKIN)

Short Title:

Impact of tirbanibulin on the wellbeing of patients with actinic keratoses

Coordinating Investigators:

The Coordinating Investigators for this trial will be:

Dr. PPD

Servicio de Dermatología

Hospital Universitario Miguel Servet.

IIS Aragón

Zaragoza, Spain

Dr. PPD

Servicio de Dermatología

Instituto Valenciano de Oncología

Valencia, Spain

Trial Centre(s):

The trial is planned to be conducted at 35 centres in Spain and 7 centres in Italy.

Trial Duration:

The duration of the entire trial from first patient, first visit to last patient, last visit is anticipated to be approximately 9 months.

Phase of Development:

This is a Phase 4 trial.

Rationale:

Tirbanibulin is a new topical treatment for actinic keratosis (AK) of the face and scalp. The clinical development of tirbanibulin has been carried out entirely in the US and its efficacy and safety have been evaluated in 2 Phase III trials. Tirbanibulin is a novel, topical first-in-class microtubule inhibitor with a selective anti-proliferative mechanism of action that represents a significant step forward in the treatment of AK due to its short treatment protocol (one

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application daily for 5 days), proven efficacy and safety profile with very acceptable local tolerability.

There is currently no clinical experience with tirbanibulin in Spain and Italy, and patient-reported outcomes (PRO) such as wellbeing, treatment preference or satisfaction and quality of life (QoL) have not been assessed in patients treated with tirbanibulin. Furthermore, AK patients are usually elderly, and the actual meaning of wellbeing in this population may not be fully understood.

Based on this lack of clinical evidence, the present study aims to identify the treatment relevant effects of AK in terms of wellbeing in the AK population and how tirbanibulin may address them. This study will focus mainly on treatment satisfaction. This study will also help to understand the QoL in elderly AK patients, as enrollment of an elderly population is expected.

Objectives:

Primary

The primary objective is to assess treatment satisfaction on Day 57 in patients with AK of the face or scalp following treatment with tirbanibulin ointment 1% administered once daily for 5 consecutive days.

Secondary

The secondary objective is to evaluate patient-reported outcomes, physician-reported outcomes, efficacy, and safety following treatment with tirbanibulin ointment 1% administered once daily for 5 consecutive days.

Trial Design:

This is a multicentre single-cohort phase IV low-interventional clinical study conducted in 35 sites in Spain and 7 sites in Italy.

Sites will be hospitals where patients with AK are usually managed. The participating physicians will be dermatologists. To represent variations in current real-world patterns of care, where possible, sites will be selected on the basis of geographic region and institution size.

Following informed consent and verification of eligibility criteria, patients will begin treatment with tirbanibulin administered topically at a dose of 2.5 mg once daily for 5 consecutive days to a contiguous area. Tirbanibulin will be applied to evenly cover up to a 25 cm^2 treatment field on the face or scalp. Study visits will be held at screening and on Days 0 (baseline), Day 8, and Day 57. Only in 1 site (Hospital Clinic de Barcelona), study visits will be held at screening and on Day 0 (baseline), Day 8, Day 15, Day 29, and Day 57.

The total duration of the study will be approximately 9 months, including up to 6 months for recruitment, 1 month for screening and 2 months for treatment + follow-up.

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Number of Patients:

Approximately 420 patients will be enrolled, a minimum of 10 patients at each site.

Trial Population:

The study population will be made up of male and female adult patients with 4-8 non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp in a 25 cm^2 area not previously treated in the last 6 months on the same area. In the overall population, a minimum of 30% of patients previously treated in other small areas (up to 25cm^2) in the last >1 to <6 months to avoid patient recall bias from previous treatments will be enrolled.

Inclusion Criteria:

1. Written informed consent.
2. Males or females aged ≥18 years.
3. Diagnosis of clinically typical AK in one contiguous area on the face or scalp with a treatment area of 25 cm^2 containing 4–8 AK lesions.
4. Patients not previously treated for AK on the current treatment area of the face or scalp in the last 6 months. However, previous AK treatment in other small areas (up to 25cm^2) in the last >1 to <6 months is allowed.
5. Females must be postmenopausal (A female said to be postmenopausal should be >45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); or, if of child-bearing potential, must be using highly effective contraception for at least 30 days or 1 menstrual cycle, whichever is longer, prior to study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive implant, injection or patch, intrauterine device, or complete abstinence from sexual intercourse.
6. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.
7. All subjects must agree not to donate sperm or eggs from screening through 90 days following their last dose of study treatment.
8. Females of child-bearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 0 prior to dose administration.
9. Willing to avoid excessive sun or UV light exposure to the face or scalp.

Exclusion Criteria:

1. Clinically atypical and/or rapidly changing AK lesions.
2. Location of the treatment area is within 5 cm of an incompletely healed wound or a suspected basal cell carcinoma (BCC)/squamous cell carcinoma (SCC).
3. Skin disease (e.g., atopic dermatitis, psoriasis, eczema) or condition (e.g., open wounds, scarring) in the treatment area that might interfere with the study results or suppose an

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unacceptable risk.

4. History of sensitivity to any of the ingredients in the tirbanibulin formulation.
5. Participated in a clinical 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.
6. Patients with a history of tirbanibulin treatment for AK lesions and patients who are currently on tirbanibulin treatment for AK lesions.
7. Use of immunomodulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/ interferon inducers and systemic immunosuppressive agents (e.g., cyclosporine, prednisone, methotrexate, alefacept, infliximab) within 4 weeks prior to the Screening visit, except for organ transplant recipients under stable immunosuppressive therapy for 6 months.
8. Use of systemic retinoids (e.g., isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit.
9. Use of the following therapies and/or medications within 2 weeks prior to the Screening Visit:
    - Cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
    - Acid-containing therapeutic products (e.g., salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light chemical peels within the treatment area or within 2 cm of the selected treatment area
    - Topical salves (nonmedicated/nonirritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area
10. Females who are pregnant or nursing

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

Substance/name:	Tirbanibulin
Administration route:	Topical application
Unit dose/strength:	2.5 mg of tirbanibulin in 250 mg ointment (1%)
Dosage form:	10 mg/g ointment (1%)

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Methodology:

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

Duration of Treatment:

Each patient is treated once daily for 5 consecutive days.

Duration of Patients' Participation in the Trial:

The total duration of each patient's participation in the trial is estimated to be 3 months, including 1 month for screening and 2 months for treatment, and follow-up.

Statistical Methods

Sample Size Calculation

A sample size of 420 patients allows to estimate the mean of a specific component of TSQM-9 at Day 57 with a precision (half width) of the 95% confidence interval ranging from ±1.6 to ±2.1 if we assume a standard deviation between 15 and 20.

Endpoints

Primary Endpoint

The primary trial endpoint is Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) score at Day 57.

Secondary Endpoints

Patient-Reported Outcomes:

- Change from baseline in Skindex-16 at Day 57.
- Organoleptic properties of tirbanibulin assessed on a Likert Scale at Day 8.
- TSQM Version 1.4 (TSQM 1.4) at Day 57.
- Patient treatment preference assessed through question 1 (Q1) to question 9 (Q9) of the Expert Panel Questionnaire (EPQ) at Day 57.

Efficacy

- The percentage of patients with complete (100%) clearance of all lesions within the application area at Day 57.
- The percentage of patients with partial clearance, defined as a reduction of at least 75% in the number of lesions within the application area at Day 57.
- Number of old and new AK lesions at Day 57.

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- Olsen characterization at baseline (Day 0; pre-dose) and Day 57.
- Reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) of subclinical lesions (at only one selected site: Hospital Clinic de Barcelona) at baseline (Day 0; pre-dose), Day 8, Day 15, Day 29, and Day 57.

Physician Reported Outcomes

- Physician outcomes assessed through question 1 (Q1) to question 10 (Q10) of EPQ at Day 57.

Safety

- Incidence and severity of adverse events.
- Incidence and severity of local skin reactions (LSRs) (erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation and erosions or ulcerations at the application-site) on a grading scale ranging from 0=absent to 3=severe. Application-site reactions such as application-site pruritus and application-site pain (including pain, tenderness, stinging, and burning sensation) not classified as LSRs will be reported as adverse events (AE).

Adherence To the Therapy

- Medication adherence is recorded using a self-administered Patient Diary from Day 0 to Day 4. These questions will be related to usage pattern (dosage, frequency, and site) of study medication application, adverse reactions, and reasons for any missed or delayed doses.

At baseline (Day 0, pre-dose), Day 8 and Day 57, the Investigator or a qualified staff member must obtain a standardized photograph of each subject's treatment area. In the sites with Canfield® photography, the Investigator will utilize the Canfield® photography equipment to take photographs and will upload the photographs to a secure database on ongoing basis. For sites, without the Canfield® technology, their own cameras will be used to take photographs. 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. These photographs will be attached with the eCRF.

The photographs are to document the appearance of the subjects' treatment area and to assist with the identification and confirmation of the location of the treatment area throughout the study.

Statistical Analysis

All analyses will be performed by OPIS following internal standard operating procedures (SOPs).

This study is low-interventional in nature and statistical analyses will be descriptive for all endpoints. Data from all sites will be pooled and summarized.

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Continuous data will be summarized by mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %).

Bilateral 95% confidence interval (CI) will be presented as appropriate.

Further details will be provided in the Statistical Analysis Plan (SAP).

All statistical tables, listings and analyses will be produced using SAS® release 9.3 or later (SAS Institute, Inc, Cary, NC, USA).

Analysis Populations

The **Enrolled population** will consist of all patients who signed the informed consent form.

The **Full analysis set (FAS) population** will consist of all patients who signed the informed consent form and applied at least one dose of tirbanibulin.

The **Evaluable patient population** will consist of FAS patients who complete the 57 days of observation and have the TSQM-9 assessment.

The **Safety patient population** will consist of Full analysis set patients.

The primary and secondary analyses will be done on the Evaluable patient population.

Analyses of Endpoints

Primary Endpoint

The mean or the median for Convenience, Efficacy and Total satisfaction of TSQM-9 at Day 57 will be estimated with the corresponding 95% CI.

Secondary Endpoints

- Patient-reported outcomes
  - The mean or median change from baseline in total Skindex-16 and its components at Day 57 will be estimated with 95% CI.
  - The mean or median of the Likert Scale for organoleptic properties of tirbanibulin at Day 8 will be estimated with 95% CI.
  - The mean or median for Convenience, Efficacy, Side Effects and Total satisfaction of TSQM 1.4 at Day 57 will be estimated with 95% CI.
  - Treatment preference assessed through question 1 (Q1) to question 9 (Q9) of the EPQ at Day 57 will be summarized with frequency distribution and 95% CI for proportions.

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- Efficacy
  - The percentage of patients with complete (100%) clearance of all lesions within the application area at Day 57 will be estimated with the 95% CI for proportions.
  - The percentage of patients with partial clearance, defined as a reduction of at least 75% in the number of lesions within the application area, at Day 57 will be estimated with the 95% CI for proportions.
  - The mean or median number of old and new AK lesions at Day 57 will be estimated with corresponding 95% CI.
  - Olsen characterization at baseline (Day 0; pre-dose) and Day 57 will be summarized with frequency distribution and 95% CI for proportions.
  - RCM and OCT of subclinical lesions (at only one selected site: Hospital Clinic de Barcelona) at baseline (Day 0; pre-dose), Day 8, Day 15, Day 29, and Day 57 will be summarized.

- Physician Reported Outcomes
  - Physician outcomes assessed at Day 57 through question 1 (Q1) to question 10 (Q10) of EPQ will be summarized with frequency distribution and 95% CI for proportions.

- Safety Endpoints

All safety data collected from the study start through the last follow-up visit will be summarized.

- Adherence To Therapy

Medication adherence will be summarized with standard summary statistics.

Interim Analysis

An intermediate descriptive analysis is planned when 50% of patients have completed the study.

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Table 1 Schedule of Assessments

Period	**Screening** [a]	**Treatment**					**Follow-up**			
			-	-	-	-		**Additional Visits *** (Applicable for one site: Hospital Clinic de Barcelona)		**Final visit**
Visit	**1**	**Baseline 2**					**3**	**AV1**	**AV2**	**4**
Days	**-28 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**15**	**29**	**57**
Visit time window (days)	**± 3**	**± 3**	**-**				**± 3**	**± 3**	**± 3**	**± 3**
Informed consent	X									
Inclusion & exclusion criteria	X									
Socio-demographic characteristics	X									
AK therapy history [b]	X									
Identification of treatment area [c]	X	X [d]								
Medical history	X									
Prior and concomitant medications/therapies	X	X [d]	X	X	X	X	X	X	X	X
Physical Examination	X									X
Vital signs	X						X			X
Skindex-16		X [d]								X
Organoleptic properties (Likert scale)							X			
TSQM-9										X
TSQM 1.4										X
AK lesion count	X	X [d]								X
Standardized Photography		X [d]					X			X

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Period	**Screening** [a]	**Treatment**					**Follow-up**			
			-	-	-	-		**Additional Visits *** (Applicable for one site: Hospital Clinic de Barcelona)		**Final visit**
Visit	**1**	**Baseline 2**					**3**	**AV1**	**AV2**	**4**
Days	**-28 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**15**	**29**	**57**
Olsen grading		X [d]								X
RCM of subclinical lesions [f]		X [d]					X	X	X	X
OCT of subclinical lesions [f]		X [d]					X	X	X	X
EPQ [g]										X
AEs/SAEs [e]		X [d]	X	X	X	X	X	X	X	X
LSRs		X [d]	X	X	X	X	X	X	X	X
Serum Pregnancy test for WOCBP	X									
Urine Pregnancy test for WOCBP		X [d]								
Tirbanibulin (Study drug) application		X	X	X	X	X				
Patient Diary		X	X	X	X	X				
Return of Study drug sachets (used and unused) and patient diary							X			

Note: The duration of time window planned for this study is +/- 3 days

Abbreviations: TSQM=Treatment Satisfaction Questionnaire for Medication; RCM=Reflectance Confocal Microscopy; OCT=Optical Coherence Tomography; EPQ=Expert Panel Questionnaire; AK=Actinic Keratoses; AE=Adverse Event; SAE=Serious Adverse Event; LSRs=Local Skin Reactions; WOCBP=Women of Childbearing Potential;

* Additional visits 1 and 2 (AV1 and AV2) will be performed only in one clinical site: Hospital Clinic de Barcelona

a. The duration for screening is 1 month.
b. This includes history of treatments namely topical medications freezing, laser, scraping, etc.
c. The location and shape of the treatment area will be marked on an acetate transparency sheet for recording purposes and on the subject's skin for identification of the treatment area for daily self-administration of study ointment.

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d. These are baseline procedures/assessments and will be performed before application of study medication
e. AEs and LSRs will be reported separately. At each study visit, AEs will be recorded **before** assessment of LSRs in the treatment area. . From Day 0 to Day 4, AEs and LSRs will be recorded using patient diary. During rest of the study period, AEs and LSRs will recorded by the investigator at each visit or through telephonic follow-up in case of urgency.
f. RCM and OCT assessments are applicable only for one site: Hospital Clinic de Barcelona
g. EPQ comprises of 2 versions: patient version and clinician version. Patient version of the EPQ should be completed by the patient and clinician version by the clinicians.

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3 List of Abbreviations

AE	Adverse Event
AK	Actinic Keratoses
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time cure from zero to infinity
AUC_{0-t}	Area under the concentration-time curve from 1 to time t, where t is the time of the last concentration measured
BCC	Basal Cell Carcinoma
BID	Twice daily
BMI	Body Mass Index
BSA	Body Surface Area
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DM	Data Management
DMP	Data Management Plan
EC	European Community
EMA	European Medicines Agency
EPQ	Expert Panel Questionnaire
EQ-5D-5L	European Quality of Life survey
EU	European Union
FAS	Full Analysis Set
FDA	Food & Drug Administration (United States)
GCP	Good Clinical Practice

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GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQoL	Health-related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS/IVRS	Interactive Web/Voice Response System
LC-MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LLOQ	Lower Limit of Quantification
LSRs	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
nM	Nanomolar
OCT	Optical Coherence Tomography
PGA	Physician's Global Assessment
PIL	Patient Information Leaflet
PRO	Patient-Reported Outcomes
QD	Once daily
RCM	Reflectance Confocal Microscopy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SoE	Schedule Of Events
SOP	Standard Operating Procedure

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Src	non-receptor tyrosine kinase protein that in humans is encoded by the SRC gene
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSQM	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization
WOCBP	Women Of Child-Bearing Potential

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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)

The Coordinating Investigators for this trial are:

Dr. PPD

Servicio de Dermatología

Hospital Universitario Miguel Servet.

IIS Aragón

Zaragoza, Spain

Dr. PPD

Servicio de Dermatología

Instituto Valenciano de Oncología

Valencia, Spain

4.3 Administrative Structure

This study will be conducted by qualified Investigators under the sponsorship of Almirall S A. (the Sponsor) at approximately 35 investigational sites in Spain and 7 investigational sites in Italy.

The name, telephone number, and email address of the Medical Monitor and other contact personnel at the Sponsor are listed in the Investigator's Folder provided to each site.

The clinical trial-related operations including monitoring, data management, statistical analyses and pharmacovigilance will be organized and performed by OPIS, a contract research organization (CRO).

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5 Introduction

The novel microtubule inhibitor, tirbanibulin is indicated for the field treatment of non-hyperkeratotic, non-hypertrophic actinic keratoses (AK) of the face or scalp in adults.[1] Tirbanibulin was approved by the FDA in December 2020 and the European Commission in July 2021. The microtubule inhibitor was developed in collaboration with Athenex and Almirall (Sponsor).

A summary on the indication, mechanism of action, and completed non-clinical and clinical studies is provided below. A detailed description of the chemistry, pharmacology, efficacy, and safety of tirbanibulin is provided in the Summary of Product Characteristics (SmPC).

5.1 Background Information

5.1.1 Indication

Actinic keratoses interchangeably referred to as solar keratoses are common skin lesions primarily caused by non-ionizing radiation, in particular ultraviolet light associated with chronic sun exposure. The clinical manifestations are red, irregular, scaly plaques, or papules on the sun exposed areas, usually found on the face, balding scalp, cleavage, ears, lips. If left untreated, the lesions are associated with the risk of malignant transformation in non-melanoma skin cancer, including squamous cell carcinoma (SCC).[2] The risk of AK progression rate to invasive cutaneous SCC is estimated to be 0.25% to 1% each year. However, the causative factor of nearly 60% of SCC develops from AK.[3] The presence of AK lesions in photo-exposed areas, such as the face and scalp, is relatively frequent among the Spanish population and constitutes one of the main reasons for consulting a dermatologist.[2] In fact, AK prevalence is observed to increase with age for both sexes, reaching 60.4% of patients older than 80.[2]

The mainline of AK treatment modalities includes cryosurgery, skin field therapy (topical agents like 5-fluorouracil, imiquimod, diclofenac) and photodynamic therapy. Relatively, these therapies demanded a long treatment period of approximately 4-16 weeks and were associated with numerous local skin reactions (LSR) like irritations, pain, ulcerations, erosions, pigmentations and scarring of the skin. These unmet factors increased the chance of low treatment compliance and undermine treatment success.[4,5] The novel microtubule inhibitor tirbanibulin, its short treatment time (5 days) and minimal adverse reactions could address the unmet need of patients suffering from AK lesions, thereby increasing medication adherence and success.[6]

In this study, the impact of tirbanibulin on the wellbeing of patients will be evaluated in patients with a diagnosis of AK of the face or scalp following treatment with tirbanibulin ointment 1% administered once daily for 5 consecutive days. The study will mainly focus on treatment satisfaction.

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5.1.2 Mechanism of Action

Tirbanibulin is a highly selective and novel synthetic microtubule inhibitor exhibiting potent anti-proliferative and antitumor effects both in vitro and in vivo. Tirbanibulin mediates anti-proliferative effect by selectively inhibiting tubulin polymerization and Src signalling. Tirbanibulin is being developed as a topical treatment for AK and as an oral chemotherapeutic drug for oncology indications.[7]

The inhibitor promotes the disruption of microtubule network, causing arrest of cell division at interphase Gap 2/M and apoptosis of proliferating cells through stimulation of caspase-3 and PARP cleavage. In vitro, tirbanibulin has shown potential to inhibit the progression of primary human keratinocytes and numerous melanoma cell lines (50% growth inhibition [GI50 values] ≤50 nM). This clinically validated evidence warrants that tirbanibulin has the potential to inhibit proliferative expansion and promote apoptosis of abnormally proliferating cells in the epidermal and dermal layers upon topical application. Additionally, in pathologies supported by lymphocyte infiltration, inflammation, and/or angiogenesis, tirbanibulin has proven to exhibit potential benefits due to the inhibition of T cell migration and endothelial tubule formation in vitro.[7]

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5.1.4 Clinical Studies

Till date, 4 clinical studies (one phase 1, one phase 2, and 2 phase 3) have been conducted to evaluate the efficacy and safety of tirbanibulin ointment 1% in subjects with AK. Details of the 4 studies are available in the Tirbanibulin ointment SmPC.

KX01-AK-01-US Study, a Phase 1, safety, tolerability, and pharmacokinetic study, demonstrated that tirbanibulin ointment 1% had good tolerance and showed favorable clinical performance in 30 adults with AK manifesting on dorsal forearm when administered at 50 or 200 mg daily over 3 or 5 consecutive days in an area of 25 or 100 cm^2. Mild to moderate and transient LSRs were observed in the majority of the subjects. The LSRs observed in greater percentage were erythema and flaking/scaling that peaked around Day 5-10, before returning to or close to baseline. Symptoms of pruritus, stinging, and burning at the treatment area were generally mild and transient. There were no serious adverse events (SAEs) or deaths, and no subjects discontinued due to an AE.

KX01-AK-002 Study, a Phase 2a, open-label, sequential group study, evaluated the efficacy and safety of tirbanibulin ointment 1% when applied daily in a treatment area of 25 cm^2 for 3 consecutive days (n=84 subjects) or 5 consecutive days (n=84 subjects) in adults with AK on face or scalp.

Thirty-six of 84 subjects (43%) in the 5-day regimen and 27 of 84 subjects (32%) in the 3-day regimen had 100% clearance of AK lesions in the treatment area on Day 57.

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Preliminary data showed that most of the 168 subjects treated had mild to moderate LSRs (primarily erythema and flaking/scaling. Eleven (6.5%) subjects had 16 treatment-emergent adverse events (TEAEs) considered treatment-related by the Investigator. Eight of these subjects had mild application-site reactions including pruritus, tenderness, or stinging. The remaining AEs considered by the Investigator to be treatment-related were mild headache, mild to moderate dizziness, mild arthralgia, or mild darkening of hair color near the treatment area. All treatment-related TEAEs resolved prior to or stabilized by Day 57. Four subjects reported 5 treatment-emergent SAEs. All SAEs were considered unrelated to study drug. No subject discontinued treatment due to AEs.

Plasma concentrations of tirbanibulin were measured in Study KX01-AK-002 using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 0.1 ng/mL. Pharmacokinetic results showed that following 3 or 5 consecutive days of treatment with tirbanibulin ointment 1%, low systemic exposure (< 2 ng/mL) and limited drug accumulation were observed.

KX01-AK-003 and KX01-AK-004 Study The efficacy and safety of tirbanibulin applied on the face or scalp for 5 consecutive days was studied in 2 pivotal randomised, double-blinded, vehicle-controlled Phase III studies (KX01-AK-003 [Trial 1] and KX01-AK-004 [Trial 2]) including 702 adult patients (353 patients treated with tirbanibulin and 349 patients treated with vehicle). Efficacy, measured as complete (primary end point: 100% clearance) and partial clearance rate (secondary end point 75% clearance), was assessed at day 57.

In trial 1, complete clearance of all lesions at day 57 occurred in 44% of the patients in the tirbanibulin group and in 5% in the vehicle group with statistically significant results (P<0.001); partial clearance was achieved in 54% of the patients in the tirbanibulin group and in 13% in the vehicle group (P<0.001). At day 57, the mean percent reduction in the number of lesions was 76% in the tirbanibulin group and in 28% in the vehicle group. In trial 2, complete clearance of all lesions at day 57 occurred in 68% of the patients in the tirbanibulin group and in 16% in the vehicle group (P<0.001); partial clearance was achieved in 76% of the patients in the tirbanibulin group and in 20% in the vehicle group (P<0.001). The median percent reduction in the number of lesions, as compared with baseline, was 83% in the tirbanibulin group and 20% in the vehicle group in trial 1 and 100% and 25%, respectively, in trial 2.

After one year the pooled data indicated that the recurrence rate in patients treated with tirbanibulin was 73%. There was a higher recurrence rate for scalp lesions compared to facial lesions. Of the patients who developed recurrences, 86% had either 1 or 2 lesions. Furthermore, 48% of patients developing recurrences reported at least 1 lesion that was not identified at the time of the initial treatment (i.e., newly occurring lesions counted as recurrences). By Day 57, there were no reported cases of SCC in both trial 1 and 2

Across the 2 trials, the most common local reactions were erythema, flaking and scaling. The most common adverse reactions were application-site pruritus and application-site pain, which resolved without intervention.

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5.2 Summary of the Known Potential Risks and Benefits

Known Potential Risks

The primary safety concerns associated with tirbanibulin are local skin reactions (LSRs), namely erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation and erosion or ulceration in the treated area that occur after topical application of tirbanibulin. LSRs are assessed by the Investigators using a grading scale of 0 = absent, 1 = mild (slightly, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense). Events of application-site pruritus and application-site pain (including pain, tenderness, stinging, and burning sensation) are also associated with tirbanibulin, which are mild to moderate in severity, transient in nature (mostly occurring during the first 10 days since the start of treatment).

In non-clinical fertility and early embryonic development study in rats, tirbanibulin was related to testicular toxicity.

Known Potential Benefits

Topical microtubule inhibitor, tirbanibulin has been approved for treating AK of the face and scalp. This is due to the beneficial clinical performance demonstrated by tirbanibulin in the 4 clinical studies (one phase 1, one phase 2, and 2 phase 3)

Overall clinical trial results of KX01-AK-01-US and KX01-AK-002 studies validated the treatment protocol of tirbanibulin ointment 1% on field administration once daily for 5 consecutive days. The study demonstrated favorable clinical performance of tirbanibulin in the treatment of AK lesions on both the face and scalp regions, also including dorsal forearm. Data from KX01-AK-002 suggest that the 5-day regimen of KX2-391 Ointment 1% has greater activity (43%) than the 3-day regimen (32%).

Two identical phase 3 studies showed tirbanibulin 1% ointment applied once daily for 5 days achieved significantly better clinical outcomes compared with vehicle in clearing AK on the face and scalp. With high statistical significance, results of KX01-AK-003 and KX01-AK-004 concluded that complete (100%) clearance was achieved in 44% and 54% of patients receiving tirbanibulin versus with 5% and 13% of patients treated with vehicle, respectively.

In both the studies, partial (≥ 75%) clearance of lesions was achieved in higher frequency of the AK population treated with tirbanibulin versus vehicle. (68% of tirbanibulin vs 16% vehicle in KX01-AK-003, and 76% vs. 20% in KX01-AK-004.

Assessment of potential risks and benefits

Tirbanibulin has recently been approved for treating AK of the face and scalp. The study will evaluate the individual and clinical variables considered potentially determinant for the QoL and thus the benefit/risk profile of tirbanibulin is acceptable.

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5.3 Scientific Rationale for the Trial

Most AK treatments significantly reduce AK lesions, but they cause a series of LSRs that tend to negatively influence QoL.[8] In addition, some treatments have long treatment courses that can negatively influence adherence to treatment, which is associated with a bad response, and worse results in this disease. In consequence, both current guidelines and expert consensus advocate choosing the treatment schedule based not only on factors associated with AK, but also on the characteristics, expectations, opinions and preferences of the patients themselves.[9–11]

Tirbanibulin is a novel, topical first-in-class microtubule inhibitor with a selective anti-proliferative mechanism of action that represents a significant step forward in the treatment of AK due to its short treatment protocol of one application daily for 5 days, proven efficacy, and safety profile with very acceptable local tolerability. Tirbanibulin is a new topical treatment for AK of the face and scalp.[6] Tirbanibulin clinical development has been performed entirely in the US and its efficacy and safety have been evaluated in 2 Phase III trials.[12]

There is no clinical experience with tirbanibulin in Spain and Italy, also PROs, such as QoL, well-being, treatment preference or satisfaction, have not been assessed in patients treated with tirbanibulin. Furthermore, AK patients are usually elderly, and the actual meaning of QoL and wellbeing in this population may not be fully understood.

Based on this lack of evidence, we propose a study to find out which aspects are more relevant for AK patients in terms of wellbeing and QoL in this elderly population and how tirbanibulin may address these.

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6 Objectives and Endpoints

OBJECTIVES:

Primary Objective

- To assess treatment satisfaction on Day 57 in patients with AK of the face or scalp following treatment with tirbanibulin ointment 1% administered once daily for 5 consecutive days.

Secondary Objective

- To evaluate patient-reported outcomes, physician-reported outcomes, efficacy, and safety following treatment with tirbanibulin ointment 1% administered once daily for 5 consecutive days.

ENDPOINTS:

Primary Endpoint

- The primary trial endpoint is Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) score at Day 57.

Secondary Endpoints

Patient-reported outcomes:

- Change from baseline in Skindex-16 at Day 57.
- Organoleptic properties of tirbanibulin assessed on a Likert Scale at Day 8.
- TSQM Version 1.4 (TSQM 1.4) at Day 57.
- Patient treatment preference assessed through question 1 (Q1) to question 9 (Q9) of the Expert Panel Questionnaire (EPQ) at Day 57.

Efficacy

- The percentage of patients with complete (100%) clearance of all lesions within the application area at Day 57.
- The percentage of patients with partial clearance, defined as a reduction of at least 75% in the number of lesions within the application area at Day 57.
- Number of old and new AK lesions at Day 57.
- Olsen characterization at baseline (Day 0; pre-dose) and Day 57.

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- Reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) of subclinical lesions (at only one selected site: Hospital Clinic de Barcelona) at baseline (Day 0; pre-dose), Day 8, Day 15, Day 29, and Day 57.

Physician reported outcomes

- Physician outcomes assessed through question 1 (Q1) to question 10 (Q10) of the EPQ at Day 57.

Safety

- Incidence and severity of adverse events
- Incidence and severity of local skin reactions (LSRs) (erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation and erosions or ulcerations at the application-site) on a grading scale ranging from 0=absent to 3=severe. Application-site reactions such as application-site pruritus and application-site pain (including pain, tenderness, stinging, and burning sensation) not classified as LSRs will be reported as adverse events (AE).

Adherence to the therapy

- Medication adherence is recorded using a self-administered Patient Diary from Day 0 to Day 4. These questions will be related to usage pattern (dosage, frequency, and site) of study medication application, adverse reactions, and reasons for any missed or delayed doses.

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7 Trial Design and Rationale

7.1 Trial Design

This is an open phase IV multicentre, single-cohort, low-interventional clinical trial, which will be performed at 35 clinical centres in Spain and 7 clinical centres in Italy.

Sites will be hospitals where patients with AK are usually managed. The participating physicians will be dermatologists. To represent variations in current real-world patterns of care, where possible, sites will be selected based on the geographical region and institution size.

Patients will be approached for informed consent to participate in the study. Approximately 420 patients will be enrolled, a minimum of 10 patients at each site. The study population consists of adult patients with non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp who have not been previously treated in the same area in the last 6 months. A minimum of 30% of patients previously treated in other small areas (up to 25cm^2) in the last >1 to <6 months to avoid patient recall bias from previous treatments will be enrolled. Tirbanibulin will be applied at a dose of 2.5 mg once daily for 5 consecutive days to a contiguous 25 cm² area of the face or scalp. Study visits will be held at screening and on Days 0 (baseline), Day 8, and 57. Only in 1 site (Hospital Clinic de Barcelona), study visits will be held at screening and on Day 0 (baseline), Day 8, Day 15, Day 29, and Day 57.

The total duration of the study will be approximately 9 months, including up to 6 months for recruitment, 1 month for screening and 2 months for treatment + follow-up.

An intermediate analysis is planned when 50% of patients have completed the study.

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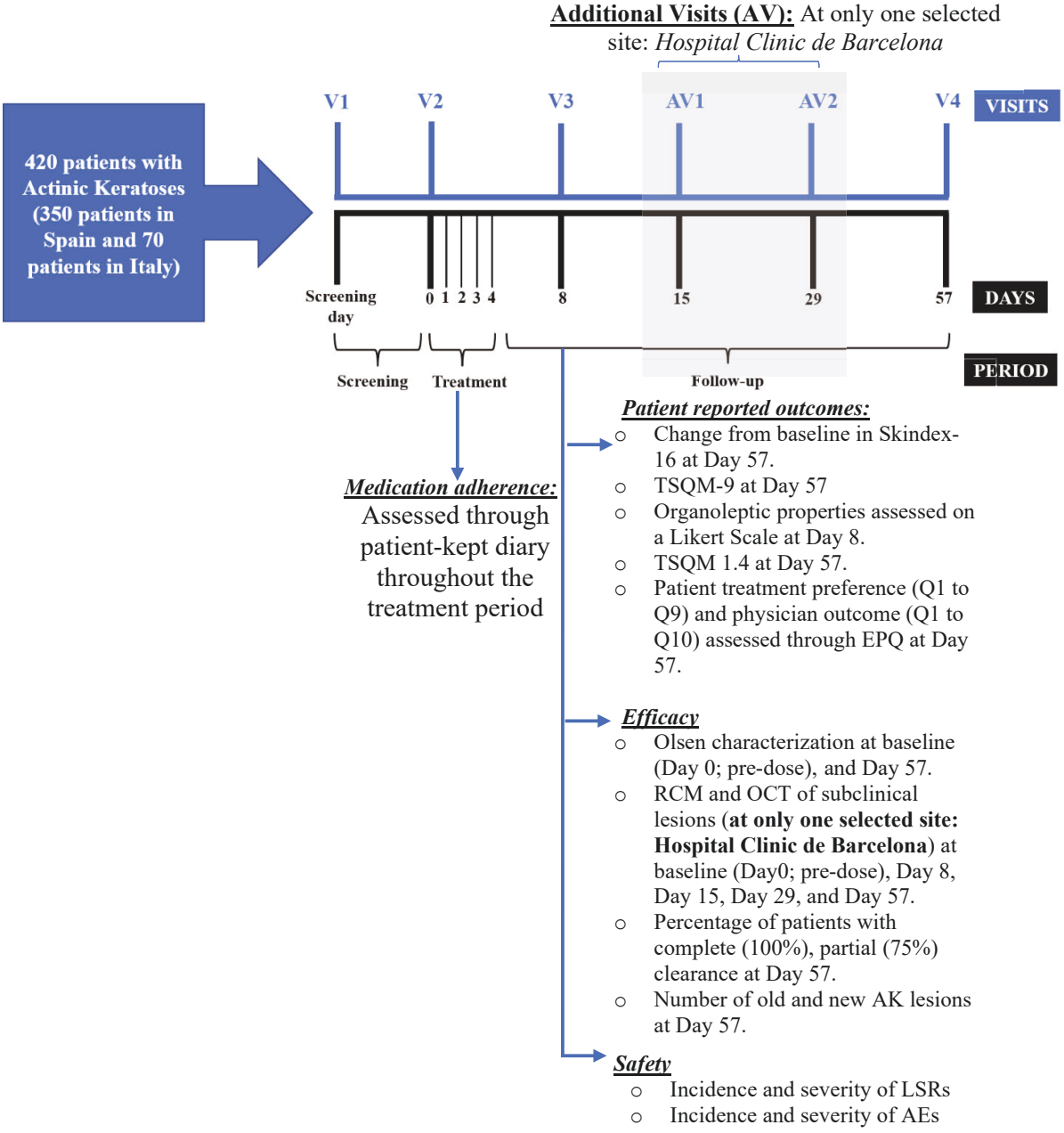
The trial design is represented schematically in Figure 1.

Figure 1 Schematic Trial Design



**Abbreviations: TSQM- Treatment Satisfaction Questionnaire for Medication; EPQ-Expert Panel Questionnaire; RCM- Reflectance Confocal Microscopy; OCT- Optical Coherence Tomography; LSR-Local Skin Reactions; AE-Adverse Event; AV1: Additional Visit 1; AV1: Additional Visit 2; Q: Question; Note: The duration of time window planned for each visit is +/- 3 days.*

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7.2 Trial Rationale

7.2.1 Rationale for trial design

The limited clinical experience with tirbanibulin in Spain and Italy, and lack of data regarding the assessment of wellbeing and QoL in elderly patients requires the evaluation of these parameters in AK patients in Spain and Italy. Furthermore, AK patients are usually elderly, and the actual meaning of wellbeing and QoL in this population may not be fully understood. This study will also help to understand the well-being in elderly AK patients, as enrollment of an elderly population is expected.

7.2.2 Rationale for trial Population

Tirbanibulin is approved for the field treatment of non-hyperkeratotic, non-hypertrophic AK (Olsen grade 1) of the face or scalp in adults. The trial population will consist of male and female adult patients with 4-8 non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp in a 25 cm^2 area who have not been previously treated in the same area in the last 6 months. A minimum of 30% of patients previously treated in other small areas (up to 25cm^2) in the last >1 to <6 months to avoid patient recall bias from previous treatments will be enrolled.

7.2.3 Rationale for trial Dose and Regimen

Tirbanibulin dose and regimen will be designed as per the SmPC. i.e., once daily for one treatment cycle of 5 consecutive days. A thin layer of ointment should be applied to cover the treatment field of up to 25cm^2.

7.2.4 Rationale for trial Assessments

Health-related QoL assessments: The TSQM-9, a psychometrically robust and validated instrument comprising 3 domains: efficacy (questions 1-3), convenience (questions 4-6), and global satisfaction (questions 7-9) has been chosen for evaluating the impact of tirbanibulin of AK patients in terms of treatment satisfaction following drug application at Day 57.

Physician and Patient Reported Outcome assessments: Likert Scale at Day 8, Skindex-16 at Day 0 (predose) and Day 57, Clinician and Patient versions of the EPQ at Day 57 and TSQM 1.4 at Day 57, have been chosen to understand patient treatment preference and tirbanibulin treatment outcomes.

Efficacy assessments: AK lesion count at Day 57, Olsen characterization at Day 0 (predose) and Day 57, RCM, and OCT assessments of subclinical lesions at Day 8, Day 15, Day 29, and Day 57 have been chosen to accurately assess the clinical efficacy of tirbanibulin in AK patients.

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Safety assessments: Pregnancy test for women of child-bearing potential (WOCBP), will be determined at screening (serum pregnancy test) and baseline (urine pregnancy test) visit to confirm eligibility criteria before the IMP administration. Adverse events assessment, LSR assessments during the treatment period will be collected through patient diary and also at each visit or through telephonic follow-up will be done as final safety evaluation.

Adherence to treatment medication assessment: Medication adherence assessed using the patient-kept diaries during the treatment period has been chosen to monitor treatment compliance among the study population.

8 Selection of Trial Population and Withdrawal of Patients

8.1 Number of Patients

The study will enroll approximately 420 patients with AK of the face and scalp. Approximately, 350 patients in Spain (35 sites) and 70 patients in Italy (7 sites) are expected to be enrolled.

8.2 Trial Population

The study population will be made up of male and female adult patients with 4-8 non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp in a 25 cm^2 area not previously treated in the last 6 months on the same area. A minimum of 30% of patients previously treated in other small areas (up to 25cm^2) in the last >1 to <6 months to avoid patient recall bias from previous treatments will be enrolled.

8.3 Inclusion Criteria

1. Written informed consent.
2. Males or females aged ≥18 years.
3. Diagnosis of clinically typical AK in one contiguous area on the face or scalp with a treatment area of 25 cm^2 containing 4–8 AK lesions.
4. Patients not previously treated for AK on the current treatment area of the face or scalp in the last 6 months. However, previous AK treatment in other small areas (up to 25cm^2) in the last >1 to <6 months is allowed.
5. Females must be postmenopausal (A female said to be postmenopausal should be >45 years of age with at least 12 months of amenorrhea), surgically sterile (by hysterectomy, bilateral oophorectomy, or tubal ligation); or, if of child-bearing potential, must be using highly effective contraception for at least 30 days or 1 menstrual cycle, whichever is longer, prior to study treatment and must agree to continue to use highly effective contraception for at least 30 days following their last dose of study treatment. Highly effective contraception includes oral hormonal contraceptives, hormonal contraceptive

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implant, injection or patch, intrauterine device, or complete abstinence from sexual intercourse.

6. Sexually active males who have not had a vasectomy, and whose partner is reproductively capable, must agree to use barrier contraception from Screening through 90 days after their last dose of study treatment.
7. All subjects must agree not to donate sperm or eggs from screening through 90 days following their last dose of study treatment.
8. Females of child-bearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 0 prior to dose administration.
9. Willing to avoid excessive sun or UV light exposure to the face or scalp.

8.4 Exclusion Criteria

1. Clinically atypical and/or rapidly changing AK lesions.
2. Location of the treatment area is within 5 cm of an incompletely healed wound or a suspected basal cell carcinoma (BCC)/squamous cell carcinoma (SCC).
3. Skin disease (e.g., atopic dermatitis, psoriasis, eczema) or condition (e.g., open wounds, scarring) in the treatment area that might interfere with the study results or suppose an unacceptable risk.
4. History of sensitivity to any of the ingredients in the tirbanibulin formulation.
5. Participated in a clinical 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.
6. Patients with a history of tirbanibulin treatment for AK lesions and patients who are currently on tirbanibulin treatment for AK lesions.
7. Use of immunomodulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, methotrexate) or interferons/ interferon inducers and systemic immunosuppressive agents (e.g., cyclosporine, prednisone, methotrexate, alefacept, infliximab) within 4 weeks prior to the Screening visit, except for organ transplant recipients under stable immunosuppressive therapy for 6 months.
8. Use of systemic retinoids (e.g., isotretinoin, acitretin, bexarotene) within 6 months prior to the Screening visit.
9. Use of the following therapies and/or medications within 2 weeks prior to the Screening Visit:
    - Cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within the treatment area or within 2 cm of the selected treatment area
    - Acid-containing therapeutic products (e.g., salicylic acid or fruit acids, such as alpha- and beta-hydroxyl acids and glycolic acids), topical retinoids, or light

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chemical peels within the treatment area or within 2 cm of the selected treatment area

- Topical salves (nonmedicated/nonirritant lotion and cream are acceptable) or topical steroids within the treatment area or within 2 cm of the selected treatment area; artificial tanners within the treatment area or within 5 cm of the selected treatment area

10. Females who are pregnant or nursing.

8.5 Treatment Discontinuation and 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 discontinuation or withdrawal from the study must be documented in the eCRF.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy of the female participant.
- Significant study intervention non-compliance.
- If any AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Screening failure: Non-fulfilment of inclusion/exclusion criteria (only possible per screening period).
- 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 3 documented attempts) should be made to contact the patient and documented in the medical records. If patient cannot be reached after that, he or she will be considered lost to follow-up.
- Trial terminated by Sponsor
- Physician Decision
- Technical problems

  The date and cause of discontinuation not only for patient's not completing the treatment phase but also for screening failures will be collected in the eCRF.

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8.6 Screening Failures

Screen failures are defined as participants who consent to participate in the clinical trial but who do not meet the specific requirements of the trial intervention. 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.

8.7 Termination of the Trial

8.7.1 End of Trial Definition

The "end of trial" is defined as the date when all patients complete the Day 57 visit or prematurely discontinue from the study.

8.7.2 Completed Patient Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit and the last scheduled procedure shown in the SoE. Only patients who perform the last scheduled follow-up contact will be considered trial completers.

8.7.3 Premature Trial Termination

Almirall reserves the right to prematurely terminate (i.e., 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.
- Data not known before becoming available and raise concern about the safety of the trial drug so that continuation would pose potential risks to the patient.
- The Sponsor decides to discontinue the trial due to specific other reasons.

If the trial is terminated or suspended, the Sponsor will promptly inform the Investigators and the Competent Authorities. The IRB/IEC should be promptly informed and provided the reason(s) for the termination or suspension by the Investigator/ Sponsor, 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.

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9 Treatments

9.1 Identity of Trial Investigational Medicinal Product(s)

Treatments administered will be topical tirbanibulin ointment 1%.

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

Test Investigational Medicinal Product

Substance Code/Name	Tirbanibulin
Route of Administration	Topical (TOP)
Dosage Form	10 mg/g ointment (1%)
Unit Dose/Strength	2.5 mg of tirbanibulin in 250 mg ointment (1%)
Frequency	Once daily for 5 consecutive days
Duration	5 consecutive days
Packaging Description	Each sachet contains 2.5 mg of tirbanibulin in 250 mg ointment. The sachet has an inner layer of linear low-density polyethylene

9.2 Packaging and Labelling

IMP manufacturing, labelling, packaging, and release will be conducted following GMP (Annex 14). Tirbanibulin ointment 1% will be supplied in single use sachets, each of which contains 250 mg of the ointment. Each sachet is for use as a single-dose application. Complete formulation contents for Tirbanibulin ointment 1% are provided in the SmPC.

Each eligible subject will be assigned a study kit containing 5 sachets filled with tirbanibulin ointment 1%. Each sachet and study kit will be labelled in accordance with national regulations. Detailed information regarding the study drugs, including labelling information, will be in the Pharmacy Manual provided to the site.

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9.3 Shipment, Storage, and Accountability

Study drug will be stored in accordance with labelled storage conditions. The product can be stored at 20°C-25°C. The product should not be refrigerated or frozen. Patients should not discard the used and unused sachets and return all these sachets to the site at Day 8.

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 labelled storage conditions with access limited to the Investigator and authorized site staff.

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 (i.e., receipt, reconciliation, and final disposition records), following Sponsor's instructions. The Investigator and trial staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional requirements. Under no circumstances will the Investigator allow the trial drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the trial.

Empty sachets and boxes as well as unused medication will be returned to Almirall, where the remaining medication will be destroyed according to SOPs. Retention drug samples will be kept by the Sponsor during the trial and until it is legally required after trial completion.

Further guidance and information for the final disposition of unused trial interventions are provided in the Pharmacy Manual.

9.4 Treatment Administration.

At baseline (Day 0) prior to dosage, subjects will be administered both verbal and written instructions that describe the method of dosage application and treatment care through patient leaflet in the study kit.

Tirbanibulin will be administered topically at a dose of 2.5 mg (ointment 1%) once daily for 5 consecutive days (Day 0 to Day 4) to a contiguous area of 25 cm^2 of the face or scalp. Area of treatment administration will be manifested and located with indelible marker at baseline (Day 0 pre-dose) at the investigational site. The location and shape of the treatment area will be marked on an acetate transparency sheet for recording purposes on the subject's skin and photographed for identification of the treatment area for daily self-administration of study ointment. The trial participants will be given a study kit. The study kit consists of 5 single-dose individual sachets with an inner layer of linear low-density polyethylene. Each sachet contains 250 mg of tirbanibulin ointment.

At the site, under the supervision of the study personnel the subjects will apply the first dose on Day 0. Following which, the subjects will self-administer the remaining individual sachets once daily at home. Preferably, the trial medication should be administered in the evening

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(potentially before bed) and at the same time. For approximately 12 hours after the administration, it is imperative that the application-site remain untouched and dry. Subjects will be educated to wash their hands with soap and water after ointment application.

Patient leaflet can be referred for subject instructions and precautions to be followed while administering trial medication during the treatment period

9.5 Drug Accountability and Treatment Compliance

9.5.1 Drug Supplies and Accountability

Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the drug labels.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (e.g., shipment, dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to GCP guidelines, as well as local or regional requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies and dispensing of study drug to the subject must be maintained.

All forms will be provided by the Sponsor (or its designee). Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. A copy of the drug accountability record must be provided to the Sponsor (or its designee).

The clinical research associate (CRA) will review drug accountability during monitoring site visits.

The Investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply. Post-Day 57, and as appropriate during the study, the Investigator (or a designated pharmacist) will return all used and unused drug sachets, study kits, drug labels, and a copy of the completed drug disposition form.

9.5.2 Treatment Compliance

Compliance will be assessed using patient-kept diaries that record the drug accountability, dosage and frequency and mode of drug administration during the treatment period. The prescribed dosage, timing, and mode of administration of the study drugs described in this protocol should not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

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Subjects will return the used ointment sachets (or unused ointment, if not administered) back to the clinical site on Day 8 (Visit 3) post dose, to check compliance.

The dosing logs in the patient diary for each patient will be kept during the trial. The CRA will review treatment compliance during monitoring site visits. Additional visits will be done at the sites in case of emergency or non-compliance

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

Medications to be reported on the eCRF are concomitant prescription medications, over-the-counter medications, and supplements.

9.6.1 Pre-trial Medications

Patients must not have received any IMP within the preceding 30 days from the first trial drug administration or any medication that could not be eliminated from the body (5 elimination half-lives of the IMP).

Any treatment (prescription and non-prescription including vitamins and dietary supplements) and procedure taken during the 28 days before Day 0 are considered as prior therapy and must be recorded into a specific eCRF section (previous and concomitant medication).

A complete AK treatment history of face and scalp will be recorded on the eCRF.

9.6.2 Concomitant Medications

Concomitant medications/therapies are any new or existing therapy received by the subject after signing the ICF through the final subject contact in the study. Concomitant medications/therapies will be recorded in the eCRF.

Sunblock usage from Day 8 onward or any topical products for treatment of LSRs in the treatment area allowed by the Investigator will be recorded in the concomitant medication eCRF up to Day 57.

During the Follow-up Period, only concomitant medications/therapies for the treatment of AEs in the treatment area and those that may affect the assessment of AK lesion recurrence in the treatment area will be entered in the eCRF.

9.6.3 Prohibited Medications/Therapy

Use of any treatment for AK lesions other than study drug on the treatment area will be prohibited during the study. Subjects will be reminded that AK lesions located outside the treatment area may be treated by lesion-directed treatment only, e.g., cryotherapy or biopsy.

Prohibited medications are as follows:

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Prohibited drug products and treatments that might influence or mask the effects of treatment until Day 57 include: immunomodulators or immunosuppressive therapies (except for organ transplant recipients under stable immunosuppressive therapy), cytotoxic drugs, interferon/interferon inducers, topical or systemic steroids, 5-FU, imiquimod, diclofenac, topical or systemic retinoids, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, acid-containing therapeutic products, benzoyl peroxide, chemo destruction, medicated/therapeutic topical salves, photodynamic therapy, psoralen plus UVA or UVB therapy, artificial tanner, excessive or prolonged exposure to UV light source.[13]

Subjects will be prohibited from applying any topical products, including but not limited to, lotions, creams, and ointments, moisturizers, sunscreen, artificial tanners, or make-up to the treatment area up until the end of Day 57 (Visit 4), except when those medications are prescribed by the Investigator for the management of LSRs. Subjects should avoid direct sun or UV exposure to the treatment area throughout the study. However, from Day 8 onward, if a subject is unable to avoid direct sun or UV exposure to the treatment area, the Investigator may allow the use of sunblock only.

During the Follow-up Period, use of treatments that may interfere with the assessment of AK recurrence in the treatment area will be prohibited. This includes use of AK treatment and medicated topical products in the treatment area and use of systemic therapies (e.g., immunosuppressive agents and systemic AK treatment) that may interfere with the assessment of AK recurrence.

Any subjects who start systemic or topical therapies for the treatment of AK will be withdrawn from the study.

The decision to administer a prohibited medication/treatment is made with the safety of the study subject as the primary consideration.

9.6.4 Post-trial Medications

Once the last IMP dose is applied and related trial measurements are completed [last visit of the study on Day 57 (Visit 4)], patients should continue to take their usual medications, also allowed during the trial, and may resume other medications interrupted prior to trial enrolment as deemed appropriate by the Investigator.

It is not planned to treat patients with tirbanibulin any further than scheduled in this trial.

10 Trial Procedures and Assessments

10.1 General Conditions of the Trial

Informed consent must be obtained before performing any procedure related to the trial. This can be done at any time before or during the screening visit. Informed consent must be signed after the patient has received sufficient information about the trial and after he/she has had the opportunity to ask any questions and consider other treatment options. The participation in the

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trial must be documented in the patient´s medical records and a copy of the informed consent will be given to the patient. The participation in the trial must be documented in the patient's medical records.

Following informed consent and verification of eligibility criteria, patients will begin treatment with tirbanibulin administered topically at a dose of 2.5 mg once daily for 5 consecutive days to a contiguous area. Tirbanibulin will be applied to evenly cover up to a 25 cm^2 treatment field on the face or scalp. Except at Hospital Clinic de Barcelona, study visits will be held at screening and on Days 0 (baseline), 8, and 57. At only one selected site (Hospital Clinic de Barcelona), study visits will be held at screening and on Days 0 (baseline), 8,15, 29 and 57

Trial visits will be scheduled in the morning. At the scheduled visit (Day 0) during the Treatment Period, IMP dosing must occur while being witnessed by the research personnel at the clinic in order to ensure the proper IMP application, as well as the correct timing of activities to occur before and after dosing.

Also, at the scheduled visits in the follow-up period, patient reported outcome assessments, physician reported outcome assessments, efficacy and safety assessments will be recorded by the research personnel.

An overview of the trial is provided via the schematic Trial flow chart, which summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below.

10.2 Patients General Conditions During the Trial

There are no restrictions during the study on smoking/tobacco use, diet, alcohol/caffeine, water or other beverages, or physical activity.

After self-application, subjects will avoid touching or wetting the treatment area for approximately 12 hours. When washing the treatment area, the patient will be instructed to wash it gently with a mild, nonabrasive, non-medicated soap or shampoo.

The treatment area should not be occluded with bandages, and band aids. The treatment area should not be exposed to excessive sunlight or UV light. Refer to SmPC for all prohibited activity.

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

This period will start with the signature of the ICF and continue until Day 0 (pre-dose).

After the 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 records, to the inclusion/exclusion criteria of the trial.

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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.

The screening visit and assessments will be performed in accordance with the schedule detailed in Table 1. Screening (Visit 1) will occur between Day -28 and Day -1.

The eCRF must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

10.3.2 Treatment Period

Treatment period visit (Day 0; Visit 2) 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 efficacy and safety assessments, respectively.

The trial visit cannot be repeated or skipped but may be postponed (if not started yet) within the time window of ± 3 days allowed in this protocol.

10.3.3 Follow-up Period

Follow-up visits and assessments will be performed in accordance with the schedule detailed in **Table 1**.

10.4 Study Assessments

The specific timing of procedures/evaluations to be done at each study visit are listed in **Table 1**, SoE.

10.4.1 Patient Reported Outcome and Physician Reported Outcome (PRO) Assessments

TSQM: Two versions of TSQM namely TSQM 1.4 and TSQM-9 have been used in the TIRBASKIN study.

- ***TSQM 1.4:*** TSQM 1.4 is a 14-item robust instrument that psychometrically evaluates the treatment satisfaction of the administered medication. The instrument is designed with 4 scales consisting of 14 questions. These 14 questions were derived from an original set of 55 questions extracted from exhaustive literature review and treatment groups through multistep iterative process. The 4 scales focussed on efficacy (questions 1 to 3), side effects (questions 4 to 8), convenience (questions 9 to 11) and global satisfaction (questions 12 to 14). The global total score ranges from 0 – 100, where lower scores imply less satisfaction whilst higher scores imply higher satisfaction.[14]

- ***TSQM-9:*** TSQM-9 is a 9-item clinically validated psychometric instrument developed from the TSQM 1.4. In this self-administered questionnaire the 5 items associated with

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side effects related to the medication were excluded. The TSQM-9 global total scores vary from 0 to 100 with higher score indicating higher treatment satisfaction.[14]

On comparing the 2 versions of TSQM, Q1 to Q3 in TSQM 1.4 is equivalent to Q1 to Q3 in TSQM-9, and Q9 to Q14 in TSQM 1.4 is equivalent to Q4 to Q9 in TSQM-9. To reduce patients' burden in answering similar questions, only the most extensive version of TSQM i.e., TSQM-1.4 will be administered to the patients in PRO Booklet.

Skindex-16: Skindex-16 may be used for patients to rate skin conditions that have occurred within the previous week. It is a short 16-item patient-completed assessment that are classified into three domains: symptoms [four items, 1-4], emotions, [seven items, 5-11] and functioning [five items, 12-16]. All items are scored on a seven-point numerical analogue scales (0=never bothered to 6=always bothered). The potential global score is the average of all 16 items ranging from 0 (best HRQoL) to 96 (worst HRQoL). Each item is then transformed to a linear scale from 0 (never bothered) to 100 (always bothered). The higher the score, the more severe is the impairment. [15]

Likert Scale: Likert scale is an instrument used to measure the individual's degree of agreement and disagreement with a variety of statements about some attitude, options, or their feelings. In this study, the product's organoleptic properties are evaluated with Likert scale. The questionnaire is built with questions related to the product's characteristics namely appearance, color, convenience, texture, smell, and the feelings experienced during drug application. The Likert scale offers 7 possible answers, from "totally agree" to "totally in disagreement."[16]

EPQ: In this study, an expert panel on consensus developed a questionnaire consisting of 10 simple items. Using a qualitative modified delphi method, the scale was developed to accommodate adequate validity as a real-world evidence tool to solicit patient's treatment preference and physician treatment outcomes. The expert panel agreed on 10 specific items encompassing related to the following :

- Overall appearance of the skin in the treated area
- Treatment satisfaction related to skin appearance post-treatment
- Treatment satisfaction on ability to improve skin texture were suggested to address facets of cosmetic outcomes
- Likelihood to consider treatment again, and overall satisfaction with current (topical) treatment were suggested to support future preference assessment
- Relative assessment of duration and severity of LSRs associated with topical treatments
- Relative impact of topical treatments on patient's QoL were suggested to assess perceptions of LSR

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- Relative 'convenience/ease of use' of topical treatments, considering its potential impact on treatment adherence.

- IGA of severity of skin photodamage in the treated area

These collective recommendations for the EPQ items are aligned with the consensus statement on core outcome set for AK.[17] This question has been designed in a manner to identify both patient and physical treatment preference. EPQ comprises of 2 versions, namely clinician and patient version. Clinician version comprises 10 questions and patient version comprises 9 questions. The questions used in both the versions are similar, but they have been reworded to address both clinician and patients. Clinician version of the EPQ will be administered to the clinician through physician reported outcome booklet. Patient version of the EPQ will be administered to the patients through patient reported outcome booklet.

10.4.2 Efficacy Assessments

Actinic Keratosis Lesion Count: A dermatologist (Investigator or Sub Investigator) will perform a count of clinically visible AK lesions (lesion count) for all subjects at baseline (Day 0; pre-dose). The same Investigator or Sub Investigator will conduct the lesion count at Day 57 (Visit 4) for an individual subject. For this assessment, an AK lesion should be counted only if it is completely inside the treatment area.

Olsen characterization: The lesions in the identified treatment area will be classified based on Olsen characterization. Classification of AK lesions according to Olsen grade of baseline lesions are the following:[18]

- *Olsen Grade I*: Early AK appear as single or few, differently sized (from 0.1-0.3-5.0 cm in size, rough, blurred, less visible than palpable (palpable on the roughness of the surface), red, rough spots or very flat, non-edged plaques which reach into the reddish color and are easier to feel than to see (Olsen Grade I).
- *Olsen grade II* describes advanced AK as clearly visible and palpable, flat, and irregularly raised, with sharp or blurred boundaries, red, rough keratinized surface. If the surface is more strongly keratinized, the AK can also be white, yellow, or light brown. After scratching effects (frequently), a black or blue-black shade may appear (older bleeding).
- *Olsen grade III* denotes "late" AK that have existed for a longer period of time and are firmly anchored on the lower surface, with an irregular, humpy surface, also wart-like and of different colors (white, brown, black). When the horn deposits are removed, an erosive subsurface is formed.

RCM: RCM is a non-invasive, optical imaging technique that allows *in vivo* visualization of the epidermis until the superficial dermis at mere histologic resolution. It affords the clinicians

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the benefit of a "virtual skin biopsy" and aids in diagnostic attributes with mitigation of skin biopsies. RCM in combination with dermoscopy has been widely used to delineate between AK and SCC. When visualized with RCM, the microscopical characteristic of AK include hyperkeratosis, parakeratosis, architectural disarray of epidermis, atypical keratinocytes, mononuclear inflammatory cells infiltration, dense collagen in the dermis,distorted and dilated vessels. [19]

OCT: OCT is a high-resolution imaging tool that provides real-time non-invasive diagnosis and monitoring of epidermis and superficial dermis. Comparatively, higher diagnostic accuracy of AK was achieved using OCT than conventional techniques. Many studies have indicated that OCT facilitates *in vivo* diagnosis of AK.[20]

10.4.3 Medication Adherence Assessments

Patient-kept diaries: This is a self-assessment tool that facilitates in coherently documenting the pattern in which the patient follows the recommended posology. Patient diaries improve psychological outcomes by mitigating gaps in memory and help in contextualizing the pattern of drug usage.[21] The questions will be related to usage pattern (dosage, timing, frequency and site) of study medication application, possibilities of missed dose and delayed dose. The patients will be asked to record the AEs and LSRs experienced during the treatment period and other required information (e.g., symptoms and concomitant medications/therapies, etc.).

10.4.4 Standardized Photography

The Investigator or a qualified staff member must obtain standardized photography of each subject's treatment area before application of study medication. The photographs are to document the appearance of the subjects' treatment area and to assist with the identification and confirmation of the location of the treatment area throughout the study.

For sites with Canfield® photography, the Investigator will utilize the Canfield® photography equipment to take photographs and will upload the photographs to a secure database on ongoing basis. Further detail for trial photography will be provided in Canfield User Manual. Research personnel will have on-line access to the photographs during the trial.

For sites, without the Canfield® technology, their own cameras will be used to take photographs. For these sites, the following recommendations must be observed by the research personnel to ensure that the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph.

- Background should be solid (blue, black, or white).
- Ensure that the lighting allows the lesions to be well lighted with no shadows showing.
- Capture the full area of interest in the centre of the frame.
- Remove all jewelry (if applicable).

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- Use of same mobile, with same lens, settings and illumination and subject patient positions at each visit. (Study coordinator should use his/her own camera to collect photographs for study database).
- Camera position/distance from the lesion has to be no greater than 1.5 meters.
- Photos may be taken with or without flash, as needed.
- Preferably, the same photographer should take the pictures.
- Avoid taking identifiable photographs: photographs with any identifiable characteristic such as tattoos, scars, or piercings.

These standardized photographs will be attached with the eCRF. The photographs are 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.

10.5 Safety and Other Assessments

10.5.1 Adverse Events

See Section 10.6 for adverse event definitions and reporting requirements

10.5.2 Medical History, Physical Examinations, and Vital Signs

Demographic characteristics

The following demographic characteristics will be obtained by the Investigator or qualified designee at the Screening visit and recorded in the eCRF

- Age, Weight, Gender, Height, and Race
- Inclusion/Exclusion Criteria
- Fitzpatrick skin type (I, II, III, IV, V, VI)
  The Fitzpatrick skin type scale classifies skin into six separate categories based on color and response to sunlight. Type I is the lightest in color and most sensitive to sun exposure; type VI is the darkest and most sun-resistant.
- AK treatments received
- Number of AK lesions at baseline
- Identification of the location of treatment area (face or scalp)
  At baseline (Day 0; predose), the Investigator will confirm the 25 cm^2 treatment area affected with 4 to 8 AK lesions on the face or scalp that was identified at Screening. The treatment area identified should contain 4-8 non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp in a 25 cm^2 area not previously treated in the last 6 months on the same area. However, previous treatment in other areas of the body is allowed. Treatment area will be photographed at baseline (Day 0; predose) using standardized photographic conditions or Canfield® Technology for identification. Also,

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the location and shape of the treatment area and the specific AK lesions will be recorded on an acetate transparency sheet gridded with 1 cm^2 squares. The study personnel will record on an acetate transparency sheet by:

1. Placing the transparency sheet over the treatment area
2. With a fine-tip indelible marker:
    - Mark at least 3 anatomical landmarks in the vicinity of the treatment area on the transparency sheet. Examples of landmarks could be bony prominences, scars, moles, seborrheic keratosis, and veins.
    - Mark the outline of the treatment area on the transparency sheet.
    - Mark the location of each of the AK lesions inside the treatment area on the transparency sheet.
3. On the subject's skin, outline the treatment area with dots and dashes with the indelible marker. The transparency sheet will be kept at the site and will be used to locate the treatment area and AK lesions during the follow-up visits.

Medical History

A detailed medical history and current medical conditions including the AK clinical history will be obtained by the Investigator or qualified designee at the screening visit and recorded in the eCRF.

Patient history should include information on clinically significant personal history including identification of current and past smoking history, current alcohol use, past history of infections, AK clinical history, history of non-melanoma skin cancer (NMSC) malignancies, and major cardiovascular conditions.

Physical Examinations

A complete physical examination will be performed at screening and should include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded to allow calculation of body mass index (BMI). For this, patients should be in light indoor clothes without shoes.

If it is required, symptom-directed examination may be performed at post-baseline visits, if clinically indicated.

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 carried out after at least 5 minutes resting in the supine position and always 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 informed consent form and that meet the definition of an AE must also be recorded in the eCRF.

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10.5.3 Laboratory Testing

Routine laboratory assessments will be performed at a local laboratory. Tests to be performed are detailed in **Table 2**.

Table 2 Laboratory Testing Parameters

Assessment	Specific Tests
Pregnancy Testing	serum pregnancy test or urine pregnancy test, as per **Table 1**

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes according to the Schedule of Assessments (**Table 1**).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

10.5.4 LSR Assessments

After the assessment of AEs at the scheduled visits as mentioned in **Table 1**, the Investigator or Sub investigator will assess for LSRs in the treatment area.

LSR signs on the treatment area at the application-site include the following:

- erythema/redness
- flaking/scaling
- crusting/scabs
- swelling
- vesiculation/pustulation
- erosion/ulceration

These signs will be assessed using a 4-point grading scale; 0=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense).

Application-site reactions such as application-site pruritus and application-site pain (including pain, tenderness, stinging, and burning sensation) not classified as LSRs will be reported as adverse events (AE). LSRs will be reported separately from AEs. The same Investigator or Sub investigator will conduct the LSR assessment at all visits for an individual subject.

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All application site reactions and LSRs will be followed to resolution, or if resolution is unlikely, to stabilization. Treatment for any LSR and other application site reactions will be recorded on the Concomitant Medications eCRF. Interruption/discontinuation of study treatment for an LSR will be recorded on the eCRF.

10.6 Adverse Events

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

10.6.1 Definitions

Adverse Event

As defined by ICH GCP, an adverse event is as any untoward medical occurrence associated with the use of an intervention in humans after providing written informed consent for participation in the study until the end of study visit, whether considered intervention-related or not.

Serious Adverse Event

An AE or suspected adverse event is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.6.2 Reporting of Adverse Events

The reported or observed AEs must be recorded on 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 (i.e., not necessarily the exact words used by the patient). If known, a specific diagnosis should be recorded instead of listing signs and symptoms (e.g., 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 application area (≤2 cm from the application area) or distant (>2 cm from the application area).
- The intensity of the AE will be described in terms of mild, moderate, or severe according to the Investigator's clinical judgment. And assign to 1 of the following categories:
  - Mild – means awareness of symptoms or signs, but easily tolerated (acceptable).

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- Moderate – means enough discomfort to interfere with usual activity (disturbing).
- Severe – interferes significantly with ability to do work or usual activity (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' 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's 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 reduced
  - Dose increased
  - Dose not changed
  - Not applicable

AEs will be collected only once with its maximum severity, except when the AE started before first IMP administration, persisted after it and worsened in severity any time after first IMP. In

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this latter case, the AE will be collected with each respective severity. AE term recorded must be exactly the same in the different time-points where AE is reported in the eCRF.

10.6.3 Recording of Adverse Events

Adverse events will be collected from signature of the informed consent up to 30 days following the last contact or Day 57, whichever is shorter. Any AE reported by the patient from the last trial contact (follow-up phone contact or visit) until Day 30 following the last contact or Day 57, should be collected in the eCRF.

Adverse events reported from Day 0 to Day 7 will be recorded in the patient diary. Adverse events from Day 8 to Day 57 informed by the patient will be recorded by the Investigator during the study visits or through telephonic follow-up in the AE page of 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 physical exam, pregnancy tests 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 on 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, 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 unspecified injury, signs and symptoms, active investigation should be conducted to reach final diagnosis. Disease diagnosis would be the preferred reported term.

AEs will be elicited by asking the patients non-leading questions (e.g., "How do/did you feel?) and by collecting AEs spontaneously reported by the patient to the Investigator or a designee. Patients should be instructed to record AEs in the Patient Diary on a daily basis between visits. Any AE recorded on the Patient Diary will be transcribed in standard medical terms as AE on the eCRF AE page by the Investigator.

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

10.6.4 Reporting of Serious Adverse Events

Serious adverse events will be collected from signature of informed consent up to 30 days following the last contact or Day 57, whichever is shorter. All SAEs will be reported regardless of causality.

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The Investigator must report any SAE within 24 hours from the moment she/he first learns of it to the Sponsor/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.

Information about all SAEs will be recorded using the e-safety tool of the eCRF. The Investigator must complete all applicable sections, assess, and record the relationship of each SAE to each specific study treatment and submit the completed form within 24 hours from awareness. In case of technical difficulties, SAE notification can be carried out using a paper SAE form and by contacting OPIS, a CRO, via email at all_phv@opis.it or by fax using the following number: +39 0362 633622.

All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic. Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. Other supporting documentation of the event may be requested by the study Sponsor and should be provided as soon as possible. The study Sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information.

Contact details and specific instructions on the flow of the SAE 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.
- 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 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 Sponsor/CRO pharmacovigilance unit which does not meet the SAE criteria shall be nullified by the Investigator by forwarding a follow-up report.

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A regulatory report of the SAE (depending on the local requirements) will be produced by the Sponsor/CRO pharmacovigilance unit and submitted to the Competent Authorities, IEC and/or Investigators, when applicable according to local regulations.

Serious adverse events NOT considered to be reported to the Sponsor 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.

10.6.5 Follow-up of Adverse events / Serious Adverse Events

Those AEs/SAEs recorded for the screening Failure patients will be followed-up until resolution or until otherwise agreed between the Sponsor and the Investigator.

All AEs/SAEs that are still present after the last trial drug administration (including AEs that have led to premature discontinuation), will be followed-up at least 7 days for non-serious AEs and 30 days for SAEs, unless otherwise specified in the protocol 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 timepoint, 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 after the follow-up 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.

10.6.6 Adverse Events of Special Interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the study drug. An AESI may be serious or non-serious. All AESIs must be reported in an expedited manner similar to SAEs.

Information about all AESIs will be recorded using the e-safety tool of the eCRF and sent through the system within 24 hours from awareness. In case of technical difficulties, AESI notification can be carried out using a paper SAE form and by contacting OPIS, a CRO, via email to: (all_phv@opis.it) or by fax using the following number: +39 0362 633622.

Event of special interest during the Treatment and Follow-up Periods (Days 0 to 57) is as follows:

- Skin cancers (including BCC, SCC, and melanoma);

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10.6.6.1 Skin Cancer

During the Treatment and Follow-up Periods (Days 0 to 57), all skin cancers (including BCC, SCC, and melanoma) within the treatment area will be reported as events of special interest. The location and treatment will be reported. The treatment of the skin cancer will be reported. The Skin Cancer Report Form must be used for reporting. The skin cancer must be reported by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event. The contact information for the reporting of skin cancers is provided in the Investigator File.

The skin cancer must be captured on the Adverse Event eCRF. Any other AEs associated with the skin cancer must be captured on the Skin Cancer Report Form and the Adverse Event eCRF. If the skin cancer is associated with an SAE, an SAE report form should be completed and sent along with Skin Cancer Report Form.

10.6.7 Pregnancies

Pregnant women will not be permitted to participate in this study. A negative serum and urine pregnancy test will be required to enter the study. The Investigator shall report all pregnancy exposures occurring in a female patient within 24 hours to the Sponsor using a paper pregnancy form and by contacting the CRO via email at all_phv@opis.it or by fax using the following number: +39 0362 633622. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus potentially induced by participation in the study. Monitoring of the subject should continue until conclusion of the pregnancy.

The pregnancy should be followed-up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A female subject who becomes pregnant during the Treatment Period must be withdrawn from study treatment but may continue all study assessments and be followed for study outcome. Male subjects whose female partners become pregnant during the Treatment Period may continue with study treatment and all assessments.

A pregnant female subject should be requested to provide outcome information on any pregnancy occurring during the Treatment Period or the Follow-up Period whether or not the subject elects to continue with study assessments. Male subjects whose female partners become pregnant within 90 days of the last study treatment should be requested to provide outcome information on the pregnancy.

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10.7 Pharmacokinetic Assessment

Not applicable

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11 Statistics

11.1 Sample size Calculation

A total of 420 patients will be enrolled in the trial. A sample size of 420 patients allows to estimate the mean of a specific component of TSQM-9 at Day 57 with a precision of the 95% confidence interval (CI) ranging from ±1.6 to ±2.1 and assuming a standard deviation between 15 and 20.[22] Screening failures will not be replaced. Drop-outs will not be replaced

11.2 Statistical Analysis

Analysis Populations

The **Enrolled population** will consist of all patients who signed the informed consent form.

The **Full analysis set (FAS) population** will consist of all patients who signed the informed consent form and applied at least one dose of tirbanibulin.

The **Evaluable patient population** will consist of FAS patients who complete the 57 days of observation and have the TSQM-9 assessment.

The **Safety patient population** will consist of FAS patients.

The primary and secondary analyses will be done on the Evaluable patient population.

All safety outcomes and other variables (i.e., concomitant medication, number of withdrawals) will be analyzed considering the Safety Population.

11.2.1 General methodology

The data collected in this study will be listed and summarized as appropriate as described below. The data from all centres will be pooled.

Continuous data will be summarized by mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %). Bilateral 95% confidence limits will be presented as appropriate.

All statistical tables, listings and analyses will be produced using SAS® release 9.4 or later (SAS Institute, Inc, Cary, NC, USA).

Further details will be provided in the Statistical Analysis Plan (SAP).

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11.2.2 Demographic and Baseline Characteristics

Demographic and background information will be summarized using frequency distributions for categorical variables and descriptive statistics as mean, standard deviation, median, minimum, and maximum for continuous variables.

Medical History will be coded using MedDRA and will be presented by System Organ Class (SOC), Preferred Term (PT).

Concomitant treatment, other than tirbanibulin, will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term.

11.3 Analysis of the Primary Endpoint

The mean or the median for Convenience, Efficacy and Total satisfaction of TSQM-9 at Day 57 will be estimated with the corresponding 95% CI.

11.4 Analysis of Secondary Endpoints

Patient-reported outcomes

- The mean or median change from baseline in total Skindex-16 and its components at Day 57 will be estimated with 95% CI.
- The mean or median of the Likert Scale for organoleptic properties of tirbanibulin at Day 8 will be estimated with 95% CI.
- The mean or median for Convenience, Efficacy, Side Effects and Total satisfaction of TSQM 1.4 at Day 57 will be estimated with 95% CI.
- Treatment preference assessed through question 1 (Q1) to question 9 (Q9) of the EPQ at Day 57 will be summarized with frequency distribution and 95% CI for proportions.

Efficacy

- The percentage of patients with complete (100%) clearance of all lesions within the application area at Day 57 will be estimated with the 95% CI for proportions.
- The percentage of patients with partial clearance, defined as a reduction of at least 75% in the number of lesions within the application area, at Day 57 will be estimated with the 95% CI for proportions.
- The mean or median number of old and new AK lesions at Day 57 will be estimated with corresponding 95% CI.

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- Olsen characterization at baseline (Day 0; pre-dose) and Day 57 will be summarized with frequency distribution and 95% CI for proportions.
- RCM and OCT of subclinical lesions (at only one selected site: Hospital Clinic de Barcelona) at baseline (Day 0; pre-dose), Day 8, Day 15, Day 29, and Day 57 will be summarized.

Physician reported outcomes

- Physician outcomes assessed at Day 57 through question 1 (Q1) to question 10 (Q10) of EPQ will be summarized with frequency distribution and 95% CI for proportions.

11.4.1 Analysis of Safety and Tolerability Endpoints

The analyses of safety and tolerability outcomes will be performed on the Safety Population. Safety outcomes include adverse events, blood pressure and heart rate (vital signs).

LSRs

LSRs assessment results obtained through Day 57 will be summarized by visit reporting for each of the six signs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration at the application-site) the number and percentage of patients corresponding to each of the score ranging from 0=absent to 3=severe. In addition, a composite score will be calculated as the sum of the scores for all six signs (range 0 to 18, with higher scores indicating more severe reactions) at each visit for each patient and summarized with standard summary statistics for continuous variables.

Application-site reactions such as application-site pruritus or application-site pain (including pain, tenderness, stinging, and burning sensation) not classified as LSRs will be reported as adverse events (AE)..

Adverse Events

The incidence of AEs, SAEs and AESI recorded throughout the study will be summarized by MedDRA SOC and PT. A summary of AEs by SOC, PT and severity will be also provided. All related AEs, SAEs, AEs with an outcome of death, AEs leading to treatment discontinuation will be summarized by MedDRA SOC and PT. Deaths will be listed together with all relevant information.

The frequency of comorbidities will be analyzed descriptively.

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Vital Signs

Vital signs (blood pressure and heart rate) will be summarized at each time point and as change from screening value with descriptive statistics.

Medication Adherence

Medication adherence assessed with patient-kept diary will be summarized with frequency distribution from Day 0 to Day 4

11.4.2 Analysis of Pharmacokinetic Parameters

Not applicable

11.4.3 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable

11.5 Handling of Missing Data

In case of missing values, no imputation will be done. Further details on the handling of missing data will be provided in the SAP.

11.6 Multiplicity Strategy

No statistical test will be conducted, so there is no need to consider multiplicity issue.

11.7 Interim Analysis

An intermediate descriptive analysis is planned when 50% of patients have completed the study. Further details will be provided in the SAP.

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12 Data Handling, Processing, and Record Keeping

The Investigator will conduct the trial in accordance with the protocol and ICH E6 (R2) 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 (e.g., safety concerns, protocol deviations) and problems with conducting the trial (e.g., 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 on 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 (i.e., 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.

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 records will include trial diagnosis and inclusion/exclusion criteria age, gender, physical examination, previous medication, original or certified copy of laboratory reports, instrument printout, trial progress notes of the physician

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- Patient diary
- Laboratory test results reports (pregnancy)
- Images (e.g., photographs)
- Patient Reporting Outcomes Questionnaires
- 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 part 11 (21 CFR 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 (e.g., 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).

12.1.3 Patient Diary

The patient diary provided at baseline (Day 0) will be used to record usage pattern of the tirbanibulin ointment applications during the Treatment Period (Day 0 to Day 4). The questions will be related to the posology recommendations i.e., dosage, timing, frequency, and site of tirbanibulin ointment applications. The questions will also be related to AEs and LSRs experienced and any other required information (e.g., symptoms and concomitant medications, etc.). The diary will also aid us to document the reasons of missed dose and delayed dose. The information recorded by the patient will be transcribed in the corresponding eCRF page by the Investigator or other authorized trial personnel. The original patient diary will be kept at the centre. The patient diary should be returned by the patient on Day 8 (Visit 3).

The Patient Diary 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 authorize representatives of appropriate Competent Authorities.

12.1.4 Patient Reported Outcome Booklets

The patient reported outcome booklet is a document in paper format that consists of all 4 questionnaires namely Skindex-16, Likert Scale, TSQM-1.4 and patient version of the EPQ. PRO booklet will be stored at the site and will be dispensed to the patients at each visit for completing the respective questionnaires as per the SoE. The PROs in the booklet should be completed by the patients only during the designated study visits under the supervision of authorized trial personnel.

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12.1.5 Physician Reported Outcome Booklets

The physician reported outcome booklet is a document in paper format that consists of only 1 questionnaire, namely clinician version of the EPQ. Booklets will be stored at the site and should be completed by the clinicians only during the designated study visits as mentioned in **Table 1**.

12.2 Data Management and Quality Control

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

Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the electronic data capture system until they are trained.

Web-based software will be used, and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring user ID and password and may read, modify, and update only the information entered at his or her site and according to their profile. Each page reports site code and patient code.

On-line validation programs will check for data discrepancies and generate automatic warning messages, allowing the Investigator to confirm or correct the data entered. The Investigator will certify that the data entered in the eCRF are complete and accurate.

After database lock, the Investigator will receive a CD-ROM of patient data for archiving at the investigational site.

Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The data manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. The occurrence of any protocol deviations will also be evaluated.

If clarifications are needed, the data manager will raise queries through the web application. Designated Investigator site staff will be required to respond to queries and to make the relevant corrections, if needed.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

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Concomitant and prior medications entered in the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

The database will be locked after all the aforementioned actions have been completed and the database has been declared complete and accurate

12.3 Investigator's and Trial Master Files

The Investigator's file and Sponsor Trial Master File 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 with the electronic data capture (EDC) data, as well as one CD/DVD with the paper PRO Booklet and paper Patient Diary data from the patients enrolled at his/her location. The Investigator will keep these in the Investigator's file.

Patient medical records, Patient Diary and PRO Booklet will be kept at the research site with the rest of the original data.

The Sponsor's Trial Master File will contain at a minimum all documents indicated in the ICH GCP guidelines. The documents needed in the Sponsor's file (originals and copies) generated or obtained by the CRO will be sent to Almirall following adequate time-points and in the format defined by Almirall.

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 (i.e., completed, and signed eCRF or certified copy of the eCRF). The Investigator may be 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

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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 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 (e.g., CRF, IMP) arrived in good conditions and to train the site staff for protocol compliance.

Appropriate Trial Manuals will be provided to the research sites as written help to support all trainings on all trial procedures (e.g., laboratory samples, eCRF).

13.2 Monitoring

The trial will be monitored by clinical CRO 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 on 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 Trial Master File. Key trial personnel must be available to assist the field CRA 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 on CRFs 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/CRFs and other data source, medication) will be performed by the trial CRA/Monitor once all patients have completed the trial.

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13.3 Inspections and Audits

The trial site, trial processes, CRO, providers and/or trial documents may be patient to Quality Assurance audits by Almirall (or authorized partner companies) as well as inspection by the appropriate Competent Authorities 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 on 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), as well as in compliance with ICH GCP E6 (R2) guidelines, and local laws of the Countries in which the trial centres 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 and the Sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of GCP and local regulations.

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.

At the completion of treatment (or premature discontinuation) patients will be instructed to resume the medication they were taking before starting the clinical trial, or any other as deemed appropriate by the Investigator. Medical care after discharge from the trial should be provided by the patient's family practitioner or specialist that usually treats his/her condition

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.

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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 CRF.

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 dated by the patient and the Investigator. At such time the patient must be given adequate time to understand the information provided and ask questions. A copy of the signed ICF will be given to the patient. The original shall be kept on file by the Investigator and the CRO. Any new relevant information that becomes available during the trial will be provided to the patient.

The Patient Information Sheet 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 IEC/IRB before use.

After the completion of the trial, lay summaries summarizing main results from the trial will be make available for patients.

14.3 Independent Ethics Committee or Institutional Review Board Review

This protocol, patient information, and the informed consent form should be submitted to an IRB or IEC for review and approval. Notification in writing of approval must be obtained from the EC by the Investigator before initiation of patient enrollment.

The Investigator/Sponsor or CRO (per regulations: i.e., Investigator in Italy and Spain or Sponsor in the European Union) must promptly report to the IEC/IRB all changes in research (protocol amendments) and will not make such changes without IEC/IRB 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 IEC/IRB.

Within 1 year after completion of the trial, the responsible person according to local regulations, CRO will send to the IEC/IRB and to the Competent Authority a brief summary explaining the results obtained in the trial.

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

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14.4 Patient Data Protection

The trial patients shall be informed by the Investigator that complete confidentiality will be maintained concerning their identity. On CRFs/EDC and all trial data records (e.g., electronic Patient Diary) patients will be identified only by the assigned patient identification number and year of birth.

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 IEC/IRB 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 Regulation (EU) 679/2016 of 27 April 2016, the Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD), 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, S.A. will set up a contract with the CRO with the economic aspects for trial funding.

Almirall, S.A. has an insurance policy that complies with current Spanish (Royal Decree 1090/2015) and Italian legislation. 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 Spanish Clinical Trials Register (https://reec.aemps.es/) and the EU Clinical Trials Register. e.g.www.clinicaltrials.gov and https://www.clinicaltrialsregister.eu/

The Investigator understands and accepts that his/her name and trial centre 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.

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By signing this trial protocol, the Investigator affirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her or resulting from this trial. The Investigator will only divulge such information as may be necessary to the IEC/IRB, 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 European Medicines Agency (EMA)/ US Food & Drug Administration (FDA) regulatory compliance obligations, and only after mutual agreement between the Investigator and Almirall.

17 Other Practical Considerations

17.1 Final Clinical Trial Report

The clinical Trial Report (CSR) will be written by the CRO following the ICH guidelines requirements. It will be approved and signed by the Principal/Coordinating Investigators and Almirall representatives according to internal SOPs.

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

Final version of 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 as well as to the IECs and/or Competent Authorities according to the local regulation.

17.2 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 IEC and/or Competent Authorities and approved by them before implementation.
- Non-substantial Amendments do not require approval but should be recorded and be available on request for inspection at the trial site and/or Sponsor premises as appropriate.

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The amendments should be notified to the IEC and/or Competent Authorities before implementation

17.3 Protocol Deviations

Any protocol deviations during the conduct of the trial will be recorded by 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 IECs and/or Competent Authorities according to the local regulation in each country.

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