ALMIRALL, S.A.

Clinical Trial Protocol M-14867-33

Clinical Trial Protocol Title:	A Phase 3, Multicentre, Randomised, Double-blind, Vehicle-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field Larger Than 25 cm^2 and up to 100 cm^2 in Adult Patients With Actinic Keratosis			
Short Protocol Title	Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field 25 cm^2 to 100 cm^2 in Adult Patients With Actinic Keratosis			
Investigational Medicinal Product(s):	Tirbanibulin 10 mg/g ointment			
Indication:	Actinic keratosis (AK)			
Development Phase:	Phase 3			
Final Protocol Version Date:	3.0, 31 January 2024			
Amendment(s)	**Number:**	2	**Date:**	31 January 2024
		1		25 October 2023
EU Trial Number	2023-505487-11			
Sponsor:	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona, Spain			

Protocol Amendment Summary of Changes

Document	Date	Summary of Changes	Rationale
Clinical Trial Protocol final version 1.0	11 May 2023	Not applicable, original protocol	Not applicable
Clinical Trial Protocol final Version 2.0	25 Oct 2023	Section 5.2, a summary of safety from postmarketing is added.	To increase understanding of the safety data available for tirbanibulin 10 mg/g ointment.
		Section 7.2.1 was amended with a rationale for the 2:1 randomization allocation	To provide clarity on the study design
		Section 8.3, Exclusion Criteria 12 was amended to provide a more comprehensive definition of vulnerable subjects	For alignment with Regulation (EU) No 536/2014, ICH E6[R2], and the Declaration of Helsinki
		Section 9.4, study drug application instructions are expanded	For alignment with the Summary of Product Characteristics
		Section 9.4, study drug special warnings and precautions for use are added	For alignment with the Summary of Product Characteristics
		Section 14:2, "Investigator" replaced by "treating physician" for the first act of recruitment	For compliance with the Declaration of Helsinki
		Added Appendix 3 with cross-references included in Sections 8.8.3, 14.4, and 16	To identify protocol requirements specific to the Netherlands
Clinical Trial Protocol final version 3.0	31 January 2024	A 32-week Follow-Up Period is added to the overall study design allowing additional treatment with courses of tirbanibulin 10 mg/g ointment in patients who achieve complete clearance during the core study, as well as the capture of long-term safety data in patients who do not achieve complete clearance. Protocol updates include the study rationale, design, schedule of assessments, endpoints, treatment administration, concomitant medications, and statistical analyses.	The amended protocol will evaluate the long-term safety in patients treated with tirbanibulin 10 mg/g ointment up to Week 48. Patients who achieve complete clearance in the core study are eligible for retreatment of recurrent or new lesions during the Follow-Up Period. Patients who do not achieve complete clearance during the core study will not be retreated with study drug and will be allowed to receive treatment as per standard of care.
		CCI [redacted]	CCI [redacted]
		Section 6.2, discontinuation due to lack of efficacy is removed as a separate intercurrent event and will be analysed as all other treatment discontinuations. Related changes are made in Section 11.	Objective criteria defining lack of efficacy are not available.

Document	Date	Summary of Changes	Rationale
		Section 8.6 is updated with regard to the rescreening of patients	To provide clarification on the rescreening process.
		Minor editorial changes	Minor clarifications and correction of typographical errors and omissions.

Sponsor Signatures

Clinical Trial Protocol Title:	A Phase 3, Multicentre, Randomised, Double-blind, Vehicle-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field Larger Than 25 cm^2 and up to 100 cm^2 in Adult Patients With Actinic Keratosis
Trial Code:	M-14867-33

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

Sponsor

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

Functional Role	Name	Signature
PPD		

Coordinating Investigator Signature

Clinical Trial Protocol Title:	A Phase 3, Multicentre, Randomised, Double-blind, Vehicle-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field Larger Than 25 cm^2 and up to 100 cm^2 in Adult Patients With Actinic Keratosis
Trial Code:	M-14867-33

The individual signing this clinical trial protocol declares that he/she has read and understood the protocol and agrees to conduct this clinical trial at his Institution in adherence to the present document, to ICH GCP guideline, and to local regulatory requirements, wherever applicable.

Coordinating Investigator

Role	Name	Signature
Coordinating Investigator	PPD	

Principal Investigator Signature

Clinical Trial Protocol Title:	A Phase 3, Multicentre, Randomised, Double-blind, Vehicle-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field Larger Than 25 cm^2 and up to 100 cm^2 in Adult Patients With Actinic Keratosis
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Principal Investigator

Role	Name	Signature
Principal Investigator		

1 Protocol Synopsis

Title:

A Phase 3, Multicentre, Randomised, Double-blind, Vehicle-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Tirbanibulin 10 mg/g Ointment Applied to a Treatment Field Larger Than 25 cm^2 and up to 100 cm^2 in Adult Patients With Actinic Keratosis

Investigators:

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

Trial Centre(s):

The trial is planned to be conducted at approximately 35 centres in the European Union and the United Kingdom.

Trial Duration:

The study is comprised of a 4-week Screening Period, a 16-week double-blind Treatment and Response Assessment Period (core study), and a 32-week Follow-Up Period.

The duration of the entire study from first patient, first visit to last patient, last visit is anticipated to be approximately 25 months.

Phase of Development:

This is a Phase 3 trial.

Rationale:

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well controlled Phase 3 clinical trials, tirbanibulin 10 mg/g ointment was demonstrated to be an effective and safe treatment for actinic keratosis (AK) of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

Tirbanibulin 10 mg/g ointment has been approved in the United States (US) and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK is a precancerous condition that often affects larger areas of ultraviolet (UV) light-damaged skin; thus, there is a medical need to treat AK patients with affected fields larger than 25 cm^2. These larger fields may also show a greater disease burden, and, as such, additional treatment courses may be required in areas where complete clearance (CC) is not achieved after one 5-day course of tirbanibulin, since the rate of CC is inversely proportional to the number of lesions in the treatment field (TF).

The aim of the core study is to evaluate the efficacy, safety, and tolerability of tirbanibulin 10 mg/g ointment, compared to vehicle, after either one or two 5-day courses in adult patients with AK on the face or balding scalp over a field larger than 25 cm^2 and up to approximately 100 cm^2.

The aim of the Follow-Up Period is to evaluate the long-term safety of patients treated over an area larger than 25 cm^2 up to 100 cm^2. Because AK is a chronic disease requiring periodic monitoring and treatment, as needed, the Follow-up Period will allow retreatment with tirbanibulin 10 mg/g ointment in patients who achieve CC during the core study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after 1 course of treatment at Day 57 (Week 8) in adults with AK of the face or scalp	**Primary** • Percent change from baseline in lesion count at Day 57 **Key Secondary** • Proportion of patients with PC at Day 57, defined as ≥75% clearance in the TF at Day 57 • Proportion of patients with CC at Day 57, defined as 100% clearance in the TF at Day 57
Secondary	
To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after up to 2 courses of treatment at Day 113 (Week 16) in adults with AK of the face or scalp	**Key Secondary** • Proportion of patients with PC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, ≥75% clearance at Day 113 • Proportion of patients with CC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, 100% clearance at Day 113
CCI	CCI
To evaluate the safety and tolerability of tirbanibulin 10 mg/g ointment compared to vehicle up to Day 113 (Week 16) in adults with AK of the face or scalp	**Safety Endpoints** • Local tolerability score (0-3) by treatment course and visit for each individual sign • Maximum local tolerability score by treatment course for each individual sign

	• Time to the maximum local tolerability score is observed by treatment course for each individual sign • Local tolerability signs composite score (0-18) by treatment course and visit, defined as the sum of the scores graded from 0 to 3 on all six individual tolerability sign categories • Maximum local tolerability signs composite score by treatment course • Time to the maximum local tolerability signs composite score is observed by treatment course • Changes in pigmentation and scarring in the TF by treatment course and visit • AEs, SAEs, AESIs, abnormalities in clinical laboratory results and vital signs
CCI [redacted]	

Abbreviations: AE=adverse event; AESI=event of special interest; CC=complete clearance; PC=partial clearance; SAE=serious adverse event; TF=treatment field; CCI [redacted]

Trial Design:

This is a Phase 3, multicentre, randomised, double-blind, vehicle-controlled, parallel-group study to evaluate the efficacy and safety of tirbanibulin 10 mg/g ointment applied to a TF larger than 25 cm^2 and up to 100 cm^2 and containing 4 to 12 lesions, inclusive, in adult patients with AK.

The study is comprised of a 4-week Screening Period, a 16-week double-blind Treatment and Response Assessment Period (core study), and a 32-week Follow-Up Period. Study visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1 and Table 2).

At Day 1/Baseline, eligible patients will be randomised in a 2:1 ratio to either tirbanibulin 10 mg/g ointment or vehicle; the randomisation will be stratified by the number of lesions at baseline (≥4 to ≤8, >8 to ≤12), treatment location (face or balding scalp), and trial site. The Sponsor, Contract Research Organisation (CRO) and vendors involved in the conduct of the trial, the Investigators, trial site personnel, and patients will be blinded to the treatment assigned to each patient.

During the Treatment and Response Assessment Period, patients will apply study drug (tirbanibulin 10 mg/g ointment or placebo [vehicle]) once daily for 5 days beginning on Day 1. All patients will be evaluated for efficacy, safety, and tolerability at Days 8, 15, 29, and 57.

Those patients who do not achieve CC at Day 57 will receive a second 5-day course of the randomised treatment. Patients receiving a second treatment course will also be evaluated for efficacy, safety, and tolerability at Days 64, 71, and 85. All patients, regardless of whether they receive one or two treatment courses, will be evaluated at Day 113 (Week 16).

Patients who achieve CC (no lesions in the treatment field at either Day 57 or Day 113) will have the opportunity to receive treatment courses with tirbanibulin 10 mg/g ointment, as

needed, during the Follow-up Period. The first Follow-Up Period visit (FUP1) will coincide with the Day 113 core study visit. The Follow-up Period visits and assessments will be performed in accordance with the Schedule of Assessments (Table 2). Patients who have lesions in the treatment field at FUP1 will receive a course of tirbanibulin 10 mg/g ointment, if at least 16 weeks have elapsed since starting the most recent treatment course (ie, patients who received just 1 treatment course during the core study); otherwise, physical treatments should be administered. Follow-Up Period visit 2 (FUP2) will occur 16 weeks after FUP1. Patients with lesions in the treatment field at FUP2 will receive a course of tirbanibulin 10 mg/g ointment.

Patients who do not achieve CC at either Day 57 or Day 113 will not be treated with study drug during the Follow-Up Period and will only undergo safety assessments (AEs and concomitant medications). No site visits are required, and safety data collection will be done remotely (ie, by telephone or other means) (Table 2). During the Follow-Up Period, these patients may receive standard of care treatment, as per the discretion of their treating physician.

All patients will have a final visit or telephone contact at Week 48.

Number of Patients:

A sufficient number of patients will be screened to randomise approximately 270 patients.

Enrolment will be controlled so that approximately two-thirds of enrolled patients will be treated on the face and approximately one-third of enrolled patients will be treated on the scalp. Further, at least 25% of the patients will have an affected field of approximately 100 cm^2.

Trial Population:

Patients with AK, aged 18 years or older, and having ≥4 to ≤12 clinically typical, non-hypertrophic, non-hyperkeratotic, visible, and discrete AK lesions in a field larger than 25 cm^2 and up to approximately 100 cm^2 on the face or the balding scalp.

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

Medicinal product:	Tirbanibulin
Dosage:	10 mg/g
Pharmaceutical dosage form:	Ointment
Mode of administration:	Topical use
Frequency:	Once daily

- Time between treatment courses during the core study: 8 weeks after starting the first course.
- Time between treatment courses during the Follow-Up Period: 16 weeks after starting the most recent treatment course.

Reference Investigational Medicinal Product, Dosage, and Mode of Administration

Medicinal product:	Vehicle
Dosage:	0 mg/g
Pharmaceutical dosage form:	Ointment
Mode of administration:	Topical use
Frequency:	Once daily

- Time between treatment courses during the core study: 8 weeks after starting the first course.

Methodology:

Study visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1 for the Screening Period and Treatment and Response Assessment Period and Table 2 for the Follow-Up Period).

Duration of Treatment:

The duration of each treatment course is 5 days.

The maximum number of courses per patient during the core study is 2:

- 1 course for patients who achieve complete clearance at Day 57 and
- 2 courses for patients who do not achieve complete clearance at Day 57.

The maximum number of courses per patient during the Follow-Up Period is 2:

- 2 courses for patients who do not receive a second course at Day 57 of the core study and
- 1 course for patients who receive a second course at Day 57 of the core study.

Therefore, depending upon the response to treatment, patients could receive a maximum of 3 treatment courses (15 days' treatment) over the entire study.

Duration of Patients' Participation in the Trial:

The total duration of each patient's participation in the study is approximately 12 months, including the 4-week Screening Period, a 16-week double-blind Treatment and Response Assessment Period, and a 32-week Follow-Up Period.

Statistical Methods

CCI

Statistical Analysis

The following analysis populations are defined:

- Intent-To-Treat (ITT) Population: defined as all randomised patients

- Safety Population: defined as all randomised patients who received at least one dose of study treatment during the core study
- CCI [redacted]
- CCI [redacted]

Efficacy

The efficacy analyses will be performed based on the ITT population.

The primary endpoint, the percent change from baseline in lesion count at Day 57 (Week 8), will be analysed by means of an analysis of covariance (ANCOVA) model using treatment group, treatment location, and country as factors, and baseline number of lesions as covariate. CCI [redacted]

The key secondary efficacy endpoints will be analysed by treatment group using a Cochran-Mantel-Haenszel (CMH) method controlling for treatment location, baseline number of lesions (≤8 or >8), and country.

CCI [redacted]

Safety and Tolerability

All safety endpoints will be analysed descriptively by treatment group and by the number of courses received, using the safety populations for the core study and Follow-Up Period.

Interim Analysis

No interim analysis is planned for this trial.

Table 1: Schedule of Assessments – Screening Period and Treatment and Response Assessment Period

Period	Screening Period*	Treatment & Response Assessment Period										
		1st treatment course for all patients		Response Assessment			Response Assessment 2nd treatment course for non-CC patients		Response Assessment			
Visit(s)	**1**	**2**	**At home**	**3**	**4**	**5**	**6 EoT (CC patients)**	**At home**	**7[b]**	**8[b]**	**9[b]**	**10 ET / EoS**
Day(s)	**-28 to -1**	**1 (Baseline)**	**2-5**	**8**	**15**	**29**	**57 (Week 8)**	**58-61**	**64**	**71**	**85**	**113 (Week 16)**
Visit Time Window (days)	**None**	**None**		**±2**	**±2**	**±2**	**±2**		**±2**	**±2**	**±2**	**±3**
Informed consent	X											
Inclusion & exclusion criteria	X	X[a]										
Demographics	X											
Medical/surgical history	X											
AK history/AK treatment history	X											
Prior and concomitant medications/therapies	X	X[a]		X	X	X	X[g]		X	X	X	X
Fitzpatrick skin type	X											
Treatment field identification[l]	X	X[a]										
Vital signs[m]	X	X[a]					X[g]					X
Physical examination[f]	X											X
Clinical chemistry and haematology	X											X

Period	Screening Period*	Treatment & Response Assessment Period										
		1st treatment course for all patients		Response Assessment			Response Assessment 2nd treatment course for non-CC patients		Response Assessment			
Visit(s)	**1**	**2**	**At home**	**3**	**4**	**5**	**6 EoT (CC patients)**	**At home**	**7[b]**	**8[b]**	**9[b]**	**10 ET / EoS**
Day(s)	**-28 to -1**	**1 (Baseline)**	**2-5**	**8**	**15**	**29**	**57 (Week 8)**	**58-61**	**64**	**71**	**85**	**113 (Week 16)**
Visit Time Window (days)	**None**	**None**		**±2**	**±2**	**±2**	**±2**		**±2**	**±2**	**±2**	**±3**
Pregnancy test for WOCBP[d]	X	X[a]					X[g]					X
Randomisation		X										
Study App installation and instructions or diary dispensed[n]		X[a]										
Study drug application		X	X				X[e]	X[e]				
Instructions for self-administration and study drug dispensing		X					X[e]					
Study drug return				X					X[e]			
Patient diary review by Investigator[n]				X					X			
Treatment field location		X[a]	X	X	X	X	X	X[e]	X	X	X	X
AK lesion count in the treatment field	X	X[a,h]		X[o]	X[o]	X[o]	X[g,o]		X[o]	X[o]	X[o]	X[o]
Standardized photography	X	X[a,i]		X	X	X	X[g]		X	X	X	X
AEs[j]	X	X[a]		X	X	X	X[g,k]		X	X	X	X[k]

Period	Screening Period*	Treatment & Response Assessment Period										
		1st treatment course for all patients		Response Assessment			Response Assessment 2nd treatment course for non-CC patients		Response Assessment			
Visit(s)	1	2	At home	3	4	5	6 EoT (CC patients)	At home	7[b]	8[b]	9[b]	10 ET / EoS
Day(s)	-28 to -1	1 (Baseline)	2-5	8	15	29	57 (Week 8)	58-61	64	71	85	113 (Week 16)
Visit Time Window (days)	None	None		±2	±2	±2	±2		±2	±2	±2	±3
Focused dermatological exam of treatment field												
Local tolerability		X[a]		X	X	X	X[g,k]		X	X	X	X[k]
Hypo- and hyperpigmentation and scarring		X[a]		X	X	X	X[g,k]		X	X	X	X[k]
CCI [redacted]												

Abbreviations: AE=adverse event; AK= Actinic Keratosis, ET=Early Termination; EoT=End of Treatment; EoS=End of Core Study, ICF=informed consent form; TF=treatment field; CCI [redacted] WOCBP=women of child-bearing potential

* Patients who require a washout period from prohibited medication (detailed in Section 9.9.3) longer than 4 weeks, the participant would be considered a screen failure and documented as such in the eCRF. The participant may be rescreened once.

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

[b] Visits 7, 8, and 9 and associated assessments are applicable only for patients who receive a second treatment course with study drug.

CCI [redacted]

[d] Highly sensitive urinary pregnancy test performed at the clinical trial site. At Day 57, only for non-CC patients who are to be treated with a second course.

[e] Study drug application, instructions, and dispensing at Day 57, and study drug return at Day 64, are only for patients who receive a second treatment course with study drug.

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

[g] Assessments prior to dose administration.

[h] Olsen grade (1 or 2) of lesions in the TF will be assessed Day 1/Baseline, Day 57, and, for patients who receive a second course of treatment, Day 113.

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

[j] At each study visit, patients will be asked a general question "How have you been since the last visit?" AEs will be recorded before assessments of local tolerability, pigmentation, and scarring in the TF. AEs will be reported separately from local tolerability signs.

[k] All patients who have unresolved local tolerability signs, hypo- or hyperpigmentation, scarring in the TF, or treatment-related AEs at End of Treatment (Day 57 for CC pts and Day 113) will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

[l] Treatment Field location (face/scalp) and measurement of the size at screening or baseline in case of non-valid measurement at screening.

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

[n] Patients will complete a diary daily to record dates and times of study treatment application. The diary will be checked by the Investigator at the next visit scheduled after the study treatment course(s).

[o] AK lesion count will include the total number of lesions in the TF as well as separately the number of new lesions (ie, not present at baseline).

[p] Only applicable to patients who receive a second course of treatment.

CCI [redacted]

Table 2: Schedule of Assessments – Follow-Up Period

Period	**Long Term Follow-up Period**				
Visit(s)	**FUP1**	**At home**	**FUP2**	**At home**	**FUP3 ET/EoS**
Day(s)	**113 (Week 16)**	**+4 days**	**225 (Week 32)**	**+4 days**	**337 (Week 48)**
Visit Time Window (days)	±7		±7		±7
Procedures and Assessments for Patients Who Achieved CC at Day 57 or 113 of the Core Study					
Informed consent signed[a]	X				
Concomitant medications/therapies			X		X
Vital signs[b]					X
Physical examination[c]					X
Clinical chemistry and haematology					X
Pregnancy test for WOCBP[d,g]			X		X
Study drug application[e]	X	X	X	X	
Instructions for self-administration and study drug dispensing[e]	X		X		
Study drug return[e]			X		X
Patient diary review by Investigator [j]			X		X
Treatment field location[g]		X	X	X	X
AK lesion count in the treatment field [g,f]			X[k]		X[k]
Standardized photography[g]			X		X
AEs[g,h]			X		X[i]

Period	**Long Term Follow-up Period**				
Visit(s)	**FUP1**	**At home**	**FUP2**	**At home**	**FUP3 ET/EoS**
Day(s)	**113 (Week 16)**	**+4 days**	**225 (Week 32)**	**+4 days**	**337 (Week 48)**
Visit Time Window (days)	±7		±7		±7
Procedures and Assessments for Patients Who Did Note Achieve CC at Day 57 or 113 of the Core Study[l]					
Informed consent signed[a]	X				
Concomitant medications/therapies			X		X
AEs[h]			X		X[i]
Site to contact patient by telephone or other means			X[h]		X[h]

Abbreviations: AE=adverse event; AK= Actinic Keratosis, CC=complete clearance; ET=Early Termination; EoS=End of Study, FUP=Follow-Up Period, ICF=informed consent form; TF=treatment field; WOCBP=women of child-bearing potential

[a] All patients to sign a consent for enrolment in the Follow-Up Period.

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

[c] Physical examination to include weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems.

[d] Highly sensitive urinary pregnancy test performed at the clinical trial site only for non-CC patients who are to be treated with a tirbanibulin course.

[e] Study drug application, instructions, and dispensing only for non-complete clearance patients who receive a tirbanibulin course.

[f] Olsen grade (1 or 2) of lesions in the TF will be assessed every visit.

[g] Assessments prior to dose administration.

[h] At each study visit (or telephone contact), patients will be asked a general question "How have you been since the last visit?"

[i] All patients who have unresolved treatment-related AEs will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

[j] Patients will complete a diary daily to record dates and times of study treatment application. The diary will be checked by the Investigator at the next visit scheduled after the study treatment course(s).

[k] AK lesion count will include the total number of lesions in the TF as well as separately the number of new lesions (ie, not present at baseline).

[l] No site visits are required per protocol and all data will be collected remotely.

2 Table of Contents

Table of Tables

Table of Figures

3 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AK	Actinic keratosis
ALCOA+	Attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available
ANCOVA	Analysis of covariance
BCC	Basal cell carcinoma
CCI	CCI
CC	Complete clearance
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
DPO	Data Protection Officer
DMP	Data Management Plan
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of Study
EoT	End of Treatment
ET	Early termination
eTMF	Electronic Trial Master File
EU	European Union
FUP	Follow-Up Period (visit)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
LS	Least-squares
CCI	CCI
OTC	Over-the-counter
PC	Partial clearance
PDF	Portable document format
PE	Physical examination

PIS	Patient Information Sheet
PK	Pharmacokinetic
RD	Risk difference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma
SOP	Standard Operating Procedure
TF	Treatment field
TMF	Trial Master File
CCI	CCI
US	United States
UV	Ultraviolet
WOCBP	Women of child-bearing potential

4 Sponsor, Investigator(s) and Trial Administrative Structure

4.1 Sponsor

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

4.2 Investigator(s)

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

4.3 Administrative Structure

Medical Expert appointed by the Sponsor for this trial:

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

Telephone: PPD
Email: PPD

The roles and responsibilities of other staff involved in the conduct of this study from the Sponsor, Contract Research Organisation (CRO), and other vendors, will be defined in a separate document and updated, as appropriate, throughout the course of the study.

5 Introduction

A summary on the indication, mechanism of action, and completed nonclinical and clinical studies is provided below. A detailed description of the chemistry, pharmacology, efficacy, and safety of tirbanibulin 10 mg/g ointment is provided in the Athenex KX2-391 Ointment 1% (tirbanibulin 10 mg/g) Investigator's Brochure.

5.1 Background Information

5.1.1 Indication

Actinic keratosis (AK) is an ultra-violet (UV) light-induced pre-cancerous lesion of the skin that represents the initial clinical manifestation of intra-epidermal abnormal keratinocyte proliferation (Röwert-Huber, 2007; Fernandez Figueras, 2017). Given the demonstrated potential for progression to invasive squamous cell carcinoma (SCC), dermatologists encourage and actively pursue treatment, as recommended in current national and international

guidelines (Hofbauer, 2014; Werner, 2015; de Berker, 2017; Leitlinienprogramm Onkologie, 2019).

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

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

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

5.1.2 Unmet Medical Need

Tirbanibulin 10 mg/g ointment is approved in the US and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK often affects greater areas of UV light-damaged skin; thus, there is a need for a product to treat AK patients over fields larger than 25 cm^2.

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

5.1.3 Mechanism of Action

Tirbanibulin has potent anti-proliferative and anti-tumour activities *in vitro* and *in vivo* by virtue of its ability to induce cell cycle arrest and apoptotic cell death by disrupting the cellular microtubule network via direct binding to tubulins. Furthermore, it is associated with disruption of Src tyrosine kinase signalling.

5.1.4 Nonclinical Studies

5.1.5 Clinical Studies

The clinical development program for topical tirbanibulin includes 9 completed clinical trials that enrolled a total of 1310 subjects, 961 subjects who received tirbanibulin 10 mg/g ointment and 349 subjects who received vehicle ointment. Of the 961 subjects treated with tirbanibulin 10 mg/g ointment, 569 were patients with AK and 392 were healthy adults.

Pharmacokinetics

Pharmacokinetic studies showed that tirbanibulin 10 mg/g ointment was minimally absorbed in patients with AK after topical application to 25 cm^2 on the face or balding scalp once daily for 5 consecutive days. Exposure (C_{max}, AUC_{0-24}) was somewhat higher (<1.5-fold) when tirbanibulin 10 mg/g ointment was applied to the face versus the scalp. In a Phase 1 trial (M-14867-01, N=28), treatment with tirbanibulin ointment 10 mg/g over an area measuring 100 cm^2 on the face or balding scalp under maximal use conditions resulted in a proportional increase (~4-fold) in systemic exposure (C_{max}, AUC_{0-24}) compared to treatment over an area of 25 cm^2. The elimination half-life of tirbanibulin was approximately 18 hours when applied to 100 cm^2 on the face and 28 hours when applied to the scalp.

Efficacy and Safety

The pivotal efficacy and safety studies included two Phase 3 double-blind, vehicle-controlled, randomised trials, KX01-AK-003 (N=351) and KX01-AK-004 (N=351), that were conducted in the US to evaluate the efficacy and safety of tirbanibulin 10 mg/g ointment compared to vehicle ointment when applied to a contiguous area of 25 cm^2 on the face or balding scalp containing 4 to 8 clinically typical AK lesions. Tirbanibulin 10 mg/g ointment once daily for 5 days was effective in the treatment of AK on either the face or balding scalp, with statistically significantly higher rates of complete clearance (CC) and partial clearance (PC) at Day 57 in the treated field as compared to control vehicle (49% vs 9% respectively). Treatment-related adverse events (AEs) were few (16% vs 10%, respectively) and consisted of mostly transient mild to moderate application site pruritus and pain that required no treatment; there were no treatment-related SAEs. Signs assessing local tolerability were mostly mild to moderate erythema and flaking/scaling. Mean composite scores for local tolerability signs peaked at Day 8 and were mostly resolved by Day 29. These studies formed the basis for approval of tirbanibulin 10 mg/g ointment (Klisyri) in Europe and the US.

In the Phase 1 study M-14867-01, the safety profile of tirbanibulin 10 mg/g ointment when applied to 100 cm^2 was consistent with that observed in the pivotal trials. The most frequently reported treatment-related AEs were application site pruritus and application site pain. All AEs were mild or moderate in intensity; no severe AEs were reported. The most frequently reported local tolerability signs were erythema and flaking/scaling. Most local tolerability signs were mild or moderate, with severe erythema and flaking/scaling reported in 14.3% of patients each. Local tolerability sign composite scores peaked around Day 7 to 8 and were mostly resolved by Day 29.

5.2 Summary of the Known Potential Risks and Benefits

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

Data from the two pivotal Phase 3 studies demonstrate that treatment with tirbanibulin 10 mg/g ointment once daily for 5 days is effective in the treatment of AK of the face or balding scalp when applied to an area measuring 25 cm^2. Tirbanibulin 10 mg/g ointment showed a low rate of treatment-emergent AEs and no unexpected or unanticipated safety findings. The overall incidence of treatment-emergent AEs was similar between the tirbanibulin 10 mg/g ointment and vehicle groups, and there were no treatment-related serious treatment-emergent AEs or discontinuations due to a treatment-emergent AEs. There were also no long-term safety concerns related to tirbanibulin 10 mg/g ointment in patients followed up to 1 year after Day 57. Treatment-related AEs were mostly transient, mild to moderate application-site pruritus or pain, and most did not require treatment. The most frequently reported local tolerability signs were transient, mild to moderate erythema and flaking/scaling. Mean composite scores for local tolerability signs peaked at Day 8 and were mostly resolved by Day 29.

In the Phase 1 study M-14867-01, treatment with tirbanibulin 10 mg/g ointment over an area measuring 100 cm^2 under maximal use conditions showed an increase in systemic exposure that was proportional to the increase in surface area treated compared to prior studies. However,

this increase in systemic exposure did not impact the safety profile of tirbanibulin 10 mg/g ointment and no new safety signals were identified. The elimination half-life of tirbanibulin was 18 to 28 hours in the Phase 1 study, and pivotal 3-month studies in rat and minipig showed no accumulation of tirbanibulin after 4 treatment cycles 23 days apart. Given these observations, no accumulation is anticipated in patients who are given a second course of tirbanibulin 10 mg/g ointment 8 weeks after the first treatment course; therefore, a second course of treatment is not expected to impact the safety profile of tirbanibulin 10 mg/g ointment.

Based on the available efficacy and safety data from the completed clinical and nonclinical studies, the benefit-risk assessment is considered positive and supports the evaluation of tirbanibulin 10 mg/g ointment applied to an area measuring up to 100 cm^2 in this Phase 3 study of patients with AK of the face or scalp.

Post-marketing safety data is available for tirbanibulin 10mg/g ointment applied to an area measuring up to 25cm^2. With more than 400,000 patients exposed to tirbanibulin since the authorisation of the product in December 2020, no safety concerns have been detected.

5.3 Scientific Rationale for the Trial

Tirbanibulin is an antiproliferative agent that causes cell cycle arrest and apoptosis. In two well controlled Phase 3 clinical trials, tirbanibulin 10 mg/g ointment was demonstrated to be an effective and safe treatment for actinic keratosis (AK) of the face or balding scalp, when applied topically once daily for 5 consecutive days to a field of 25 cm^2 containing 4 to 8 clinically typical, visible, and discrete AK lesions.

Tirbanibulin 10 mg/g ointment has been approved in the United States (US) and Europe for the topical treatment of AK on the face or scalp, over a field up to 25 cm^2. However, AK is a precancerous condition that often affects larger areas of ultraviolet (UV) light-damaged skin; thus, there is a medical need to treat AK patients with affected fields larger than 25 cm^2. These larger fields may also show a greater disease burden, and, as such, additional treatment courses may be required in areas where CC is not achieved after one 5-day course of tirbanibulin, since the rate of CC is inversely proportional to the number of lesions in the treatment field (TF).

The aim of the core study is to evaluate the efficacy, safety, and tolerability of tirbanibulin 10 mg/g ointment, compared to vehicle, after either one or two 5-day courses in adult patients with AK on the face or balding scalp over a field larger than 25 cm^2 and up to approximately 100 cm^2.

The aim of the Follow-Up Period is to evaluate the long-term safety of patients treated over an area larger than 25 cm^2 up to 100 cm^2. Because AK is a chronic disease requiring periodic monitoring and treatment, as needed, the Follow-up Period will allow retreatment with tirbanibulin 10 mg/g ointment in patients who achieve CC during the core study.

6 Objectives and Endpoints

6.1 Objectives and Endpoints

The study objectives and endpoints are summarised in Table 3.

Table 3: Objectives and Endpoints

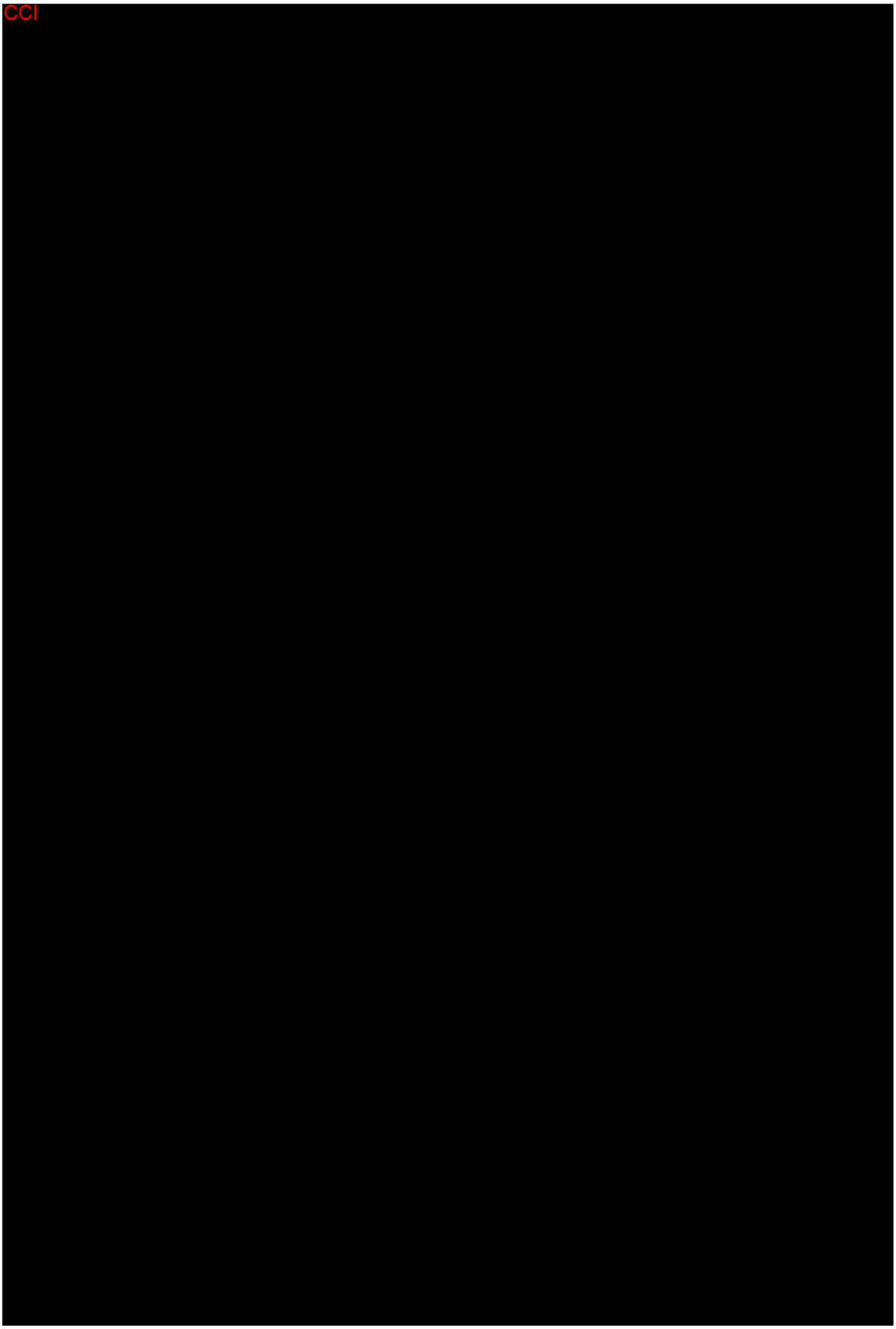
Objectives	Endpoints
Primary	
To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after 1 course of treatment at Day 57 (Week 8) in adults with AK of the face or scalp	**Primary** • Percent change from baseline in lesion count at Day 57 **Key Secondary** • Proportion of patients with PC at Day 57, defined as ≥75% clearance in the TF at Day 57 • Proportion of patients with CC at Day 57, defined as 100% clearance in the TF at Day 57
Secondary	
To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after up to 2 courses of treatment at Day 113 (Week 16) in adults with AK of the face or scalp	**Key Secondary** • Proportion of patients with PC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, ≥75% clearance at Day 113 • Proportion of patients with CC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, 100% clearance at Day 113 CCI
CCI	
To evaluate the safety and tolerability of tirbanibulin 10 mg/g ointment compared to vehicle up to Day 113 (Week 16) in adults with AK of the face or scalp	**Safety Endpoints** • Local tolerability score (0-3) by treatment course and visit for each individual sign • Maximum local tolerability score by treatment course for each individual sign • Time to the maximum local tolerability score is observed by treatment course for each individual sign • Local tolerability signs composite score (0-18) by treatment course and visit, defined as the sum of the scores graded from 0 to 3 on all six individual tolerability sign categories

	• Maximum local tolerability signs composite score by treatment course • Time to the maximum local tolerability signs composite score is observed by treatment course • Changes in pigmentation and scarring in the TF by treatment course and visit • AEs, SAEs, AESIs, abnormalities in clinical laboratory results and vital signs
CCI	

Abbreviations: AE=adverse event; AESI=event of special interest; CC=complete clearance; PC=partial clearance; SAE=serious adverse event; TF=treatment field; CCI

CCI

CCI



CCI

[redacted]

Table 1

Table 2

CCI

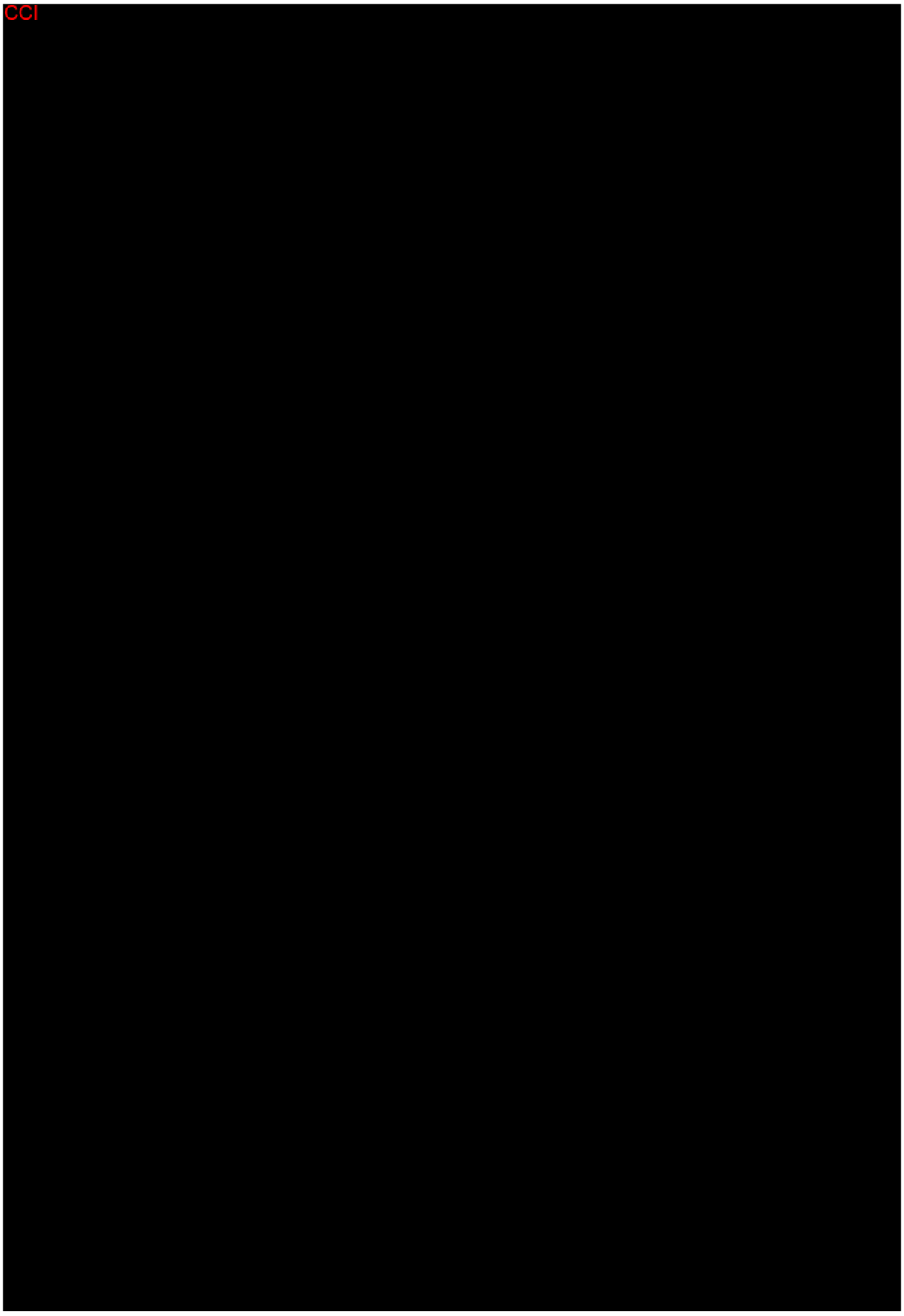
efficacy, safety, and tolerability at Days 64, 71, and 85. All patients, regardless of whether they receive one or two treatment courses, will be evaluated at Day 113 (Week 16).

Patients who achieve CC (no lesions in the treatment field at either Day 57 or Day 113) will have the opportunity to receive treatment courses with tirbanibulin 10 mg/g ointment, as needed, during the Follow-up Period CCI . The first Follow-Up Period visit (FUP1) will coincide with the Day 113 core study visit. The Follow-up Period visits and assessments will be performed in accordance with the Schedule of Assessments (Table 2). Patients who have lesions in the treatment field at FUP1 will receive a course of tirbanibulin 10 mg/g ointment CCI , if at least 16 weeks have elapsed since starting the most recent treatment course (ie, patients who received just 1 treatment course during the core study); otherwise, physical treatments should be administered. Follow-Up Period visit 2 (FUP2) will occur 16 weeks after FUP1. Patients with lesions in the treatment field at FUP2 will receive a course of tirbanibulin 10 mg/g ointment.

Patients who do not achieve CC at either Day 57 or Day 113 will not be treated with study drug during the Follow-Up Period and will only undergo safety assessments (AEs and concomitant medications) CCI . No site visits are required, and safety data collection will be done remotely (ie, by telephone or other means) (Table 2). During the Follow-Up Period, these patients may receive standard of care treatment, as per the discretion of their treating physician.

All patients will have a final visit or telephone contact at Week 48.

CCI



7.2 Trial Rationale

7.2.1 Rationale for Trial Design

This study will enrol adult patients having ≥4 to ≤12 clinically typical, visible, and discrete AK lesions over a field larger than 25 cm^2 and up to approximately 100 cm^2 on the face or the balding scalp. Tirbanibulin 10 mg/g ointment is an approved product for the treatment of AK of the face or scalp over an area up to 25 cm^2. The core study will evaluate the efficacy, safety, and tolerability of tirbanibulin 10 mg/g ointment when applied to a larger TF, as well as examining the effects of up to 2 treatment courses. The Follow-Up Period will examine long-term safety and the need for retreatment. Patients who achieved CC in the core study and have recurrence or new lesions in the treatment field may receive treatment with up to 2 courses of tirbanibulin 10 mg/g ointment during the Follow-Up Period, while patients who did not achieve CC will be evaluated remotely only for safety.

The duration of the core study considers both efficacy and safety. From the local tolerability perspective, most of the local signs are expected to be resolved by Day 29. Efficacy is assessed at Day 57 (ie, 8 weeks after starting treatment), consistent with the timing in the pivotal studies. However, in order to assess the efficacy and safety of up to 2 treatment courses, the core study duration is extended up to Day 113 (ie, 8 weeks after starting the second course) for all patients. The Follow-Up Period will examine the longer-term efficacy and safety of tirbanibulin 10 mg/g ointment over an additional 32 weeks.

In the pivotal trials, patients had 4 to 8 lesions within and area measuring 25 cm^2, and the primary endpoint was the CC rate in the TF. The CC rate is dependent on the number of baseline AK lesions within the treated area, where CC rates fall with increasing baseline lesion counts (Szeimies 2016; Dirschka 2016). Therefore, in this trial with a higher baseline lesion count, the percent change in lesion count from baseline at Day 57 will be used as the primary endpoint, rather than CC. Since the percent change in lesion count is virtually unaffected by the number of baseline lesions (Skov 2018), use of this endpoint will allow for comparisons between observed treatment outcomes over small fields (≤25 cm^2) and over larger fields (>25 cm^2 up to 100 cm^2).

The choice of the 2:1 allocation ratio with more patients assigned to the intervention will allow the reduction of the number of patients in the vehicle group, more patients will be able to benefit from treatment with tirbanibulin, and more safety data will be available for tirbanibulin 10 mg/g ointment applied to larger treatment areas.

7.2.2 Rationale for Trial Population

Tirbanibulin 10 mg/g ointment has been demonstrated to be effective in the field treatment of AK lesions up to 25 cm^2. However, the clinical presentation of the disease frequently takes place in sun-damaged skin areas exceeding the 25 cm^2 on the face or the balding scalp (Dirschka, 2017). Therefore, this study will evaluate the efficacy, safety, and tolerability of tirbanibulin 10 mg/g ointment in patients having at baseline 4 to 12 AK lesions, inclusive, within a field larger than 25 cm^2 and up to approximately 100 cm^2. In a survey of dermatologists in France >40% of patients (N=202) had an area larger than 25 cm^2 and up to 100 cm^2 on the face or the balding scalp that was targeted for treatment (Savary 2019); thus the treatment of fields up to 100 cm^2 is clinically relevant.

7.2.3 Rationale for Trial Dose and Regimen

Tirbanibulin 10 mg/g ointment is authorised for the field treatment of non-hyperkeratotic, non-hypertrophic AK of the face or scalp in adults over an area measuring up to 25 cm^2. In this study patients will be treated with tirbanibulin 10 mg/g ointment or vehicle daily for 5 consecutive days beginning on Day 1. Treatment will be applied to a field measuring larger than 25 cm^2 and up to approximately 100 cm^2 on the face or balding scalp. There are no changes in treatment course duration. However, prior studies have shown that the rate of CC is inversely proportional to the number of lesions in the TF; thus, when treating a larger field, some patients may require a second treatment course to optimise their clinical outcome. Even when only a few visible lesions may remain in the TF following the first course of treatment, retreatment with tirbanibulin 10 mg/g ointment is considered clinically appropriate because both clinical and subclinical lesions coexist across the field of cancerization and require treatment. Therefore, patients who do not achieve CC following a single course of treatment will be given a second course beginning at Day 57.

Human pharmacology studies have shown minimal systemic absorption of tirbanibulin. The elimination half-life of tirbanibulin was 18 to 28 hours in the Phase 1 study M-14867-01, and the pivotal 3-month studies in rat and minipig showed no accumulation of tirbanibulin after 4 treatment cycles 23 days apart. Given these observations, no accumulation is anticipated in patients who are given a second course of tirbanibulin 10 mg/g ointment 8 weeks after the first treatment course; therefore, a second course of treatment is not expected to impact the safety profile of tirbanibulin 10 mg/g ointment.

During the Follow-Up Period, the time between consecutive tirbanibulin treatments for recurrence or new lesions in the treatment field after CC will be at least 16 weeks. Approximately 30% of patients who achieved CC in the pivotal studies showed recurrence or new lesions in the treatment field within 5 months after starting treatment; therefore, in this chronic condition some patients treated with tirbanibulin may be expected to require an additional course as early as 4 months following the initial treatment course.

7.2.4 Rationale for Trial Assessments

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

Standard safety assessments will be performed throughout the study including the capture of AEs, SAEs, adverse events of special interest (AESIs), concomitant medications, laboratory testing for haematology, blood chemistry, and vital signs measures.

Lesion counts will be performed to evaluate the treatment effect of tirbanibulin 10 mg/g ointment, when applied to an area measuring larger than 25 cm^2 and up to approximately 100 cm^2 on the face or balding scalp. CCI

8 Selection of Trial Population and Withdrawal of Patients

8.1 Number of Patients

A sufficient number of patients will be screened to randomise approximately 270 patients.

Enrolment will be controlled so that approximately two-thirds of enrolled patients will be treated on the face and approximately one-third of enrolled patients will be treated on the scalp. Further, at least 25% of the patients will have an affected field of approximately 100 cm^2.

CCI [redacted]

8.2 Inclusion Criteria

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

1. Patients with AK who are ≥18 years old.
2. Having a TF on the face or balding scalp (excluding lips, eyelids, and inside nostrils and ears) that
   - contains ≥4 to ≤12 clinically typical, visible, and discrete (non-confluent) AK lesions and
   - measures more than 25 cm^2 (eg, one cheek) and up to approximately 100 cm^2 (eg, mid face).
3. Willing to avoid excessive sunlight or UV light exposure, including the use of tanning beds, to the face or scalp during the study.
4. Women of childbearing potential (WOCBP), ie, fertile, defined as a female in the life period from menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (with hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months prior to Screening) must:
   - have a negative urine pregnancy test using a highly sensitive method at screening and on Day 1 prior to treatment administration,
   - be using highly effective methods of birth control (defined in Appendix 1) for at least 30 days or 1 menstrual cycle, whichever is longer, and until at least 30 days or 1 menstrual period, whichever is longer, after the last dose of investigational product,
   - agree to have pregnancy tests while in the study and at the end of the study (according to the Schedule of Assessments in Table 1 and Table 2), and
   - agree not to be egg (oocyte) donors while on study and until at least 30 days or 1 menstrual period, whichever is longer, after the last dose of investigational product.
5. Sexually active males with female partners who are WOCBP must agree to use two forms of contraception, one of which must be barrier contraception, from Screening through 90 days after their last dose of study treatment. All non-sterile male patients must agree not to donate sperm or attempt conception from Screening through 90 days following their last dose of study treatment.

6. Ability to understand the purpose and risks of the trial, willingness and ability to comply with the protocol, and provided written informed consent in accordance with institutional and regulatory guidelines.

8.3 Exclusion Criteria

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

1. Presence in the TF of:
   a) Clinically atypical and/or rapidly changing AK lesions in the TF
   b) Hyperkeratotic or hypertrophic lesions, recalcitrant disease (defined as failure to respond to cryosurgery on 2 previous occasions) and/or cutaneous horn
   c) History of invasive SCC, Bowen's disease, basal cell carcinoma (BCC), or other malignant tumours in the TF
   d) Any other dermatological disease that causes difficulty with examination
2. Location of the TF is:
   - On any location other than the face or balding scalp
   - Within 5 cm of an incompletely healed wound
   - Within 5 cm of a suspected BCC or other neoplasms
   - Periorbital, lips, or nostrils
3. Having a previous treatment with tirbanibulin 10 mg/g ointment
4. Females who are pregnant or nursing or seeking to become pregnant
5. Intention to use any concomitant medication that is not permitted by this protocol or failure to undergo the required washout period for a particular prohibited medication or therapy (see Section 9.9.3)
6. Anticipated need for inpatient hospitalization or inpatient surgery from Day 1 to Day 113
7. A history of sensitivity and/or allergy to any of the ingredients in the study medication
8. Patients with significant abnormalities on the medical history, physical examination (PE) findings, vital signs, clinical chemistry, or haematology results that in the judgment of the Investigator may interfere with the interpretation of the results.
9. A skin disease (eg, atopic dermatitis, psoriasis, eczema) or condition (eg, scarring, open wounds) that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the patient to unacceptable risk by study participation
10. Significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the patient to unacceptable risk by study participation
11. Participated in an investigational drug trial during which an investigational study medication was administered within 30 days or 5 half-lives of the investigational product, whichever is longer, before dosing in the current study
12. Subject is vulnerable as defined in the ICH E6[R2] Guideline for GCP, as a subject whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory

response from senior members of a hierarchy in case of refusal to participate. For example, a patient who is employee or a relative to an employee at the research site or the Sponsor.

8.4 Treatment Discontinuation Criteria

Any patient may discontinue from study treatment at any time during the trial at the discretion of the Investigator or at the request of the patient. Study drug must be permanently discontinued for patients who experience the following:

- Patient decision to stop treatment
- Severe non-compliance with study protocol, including use of a prohibited concomitant medication as outlined in Section 9.9.3
- AEs, laboratory abnormality, or intercurrent illness for which continued treatment, that, in the opinion of the Investigator, would affect assessments of clinical status or patient safety to a significant degree
- Pregnancy

For patients who discontinue treatment, efforts should be made to encourage the patient to remain in the trial and complete the trial-related assessments as planned in Table 1 and Table 2.

8.5 Trial Withdrawal Criteria

The Investigator will make reasonable efforts to keep each patient in the study. However, patients may withdraw or be withdrawn from the study for the following reasons:

- Voluntary withdrawal of consent to participate in the study participation, at any time
- In the opinion of the Investigator, continued participation in the study is not in the best interest of the patient
- Serious protocol deviation or procedure prohibited by the protocol
- Lost to follow-up

Patients who withdraw from the core study or the Follow-up Period will undergo an early termination visit as detailed in Table 1 and Table 2. All information, including the reason for being withdrawn will be recorded in the patient's study records and in the electronic case report form (eCRF).

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Two attempts (eg, telephone contact, emails) to contact the patient must be documented in a patient's study records for all patients who are believed to be lost to follow-up. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death.

8.6 Screening Failures

Screening failures are defined as patients who consent to participate in the clinical trial but are not subsequently treated in the study. A minimal set of screen failure information is required to be entered into the database to ensure transparent reporting of screen failure patients to meet

the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from Competent Authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAE. In case of a Screening laboratory value abnormality, the test can be repeated once within the original Screening time window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if retested.

Patients who do not meet the criteria for participation in this trial (eg, screen failures) may be rescreened once. At the time of rescreening, the patient must sign a new ICF and repeat all Screening procedures.

If the study Screening window exceeds 4 weeks because of the exceptional circumstances, the patient would be considered a screen failure and documented as such in the eCRF. The participant may be rescreened once. If rescreening is required more than once, it must first be approved by the Sponsor.

The Screening procedures per the Schedule of Assessments (Table 1 and Table 2) should be followed to ensure participant eligibility for the study. Before rescreening, the participant must sign a new ICF and receive a new identification number.

8.7 Patient Replacement Criteria

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

8.8 Termination of the Trial

8.8.1 End of Trial Definition

The "end of trial" is defined as the date of the last visit of the last patient, either at Day 113 or earlier, if the last patient discontinues prematurely. The end of trial will be communicated to the Competent Authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) according to local regulations.

8.8.2 Completed Patient Definition

Patients who receive all planned treatment applications and undergo Day 113 assessments will be considered completed patients.

8.8.3 Premature Trial Termination

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

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

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

If the trial is terminated or suspended, the Sponsor/CRO will promptly inform the Investigators. The IRBs/IECs should be promptly informed and provided the reason(s) for the termination or suspension by the Investigator, as specified by the applicable regulatory requirement(s) (for the Netherlands, see Appendix 3).

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 analysed as per protocol.

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

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

9 Treatments

9.1 Identity of Trial Investigational Medicinal Products

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

The test IMP, tirbanibulin 10 mg/g ointment, is a white to off-white ointment containing tirbanibulin freebase active drug substance. For a full product description, refer to the Athenex KX2-391 Ointment 1% (tirbanibulin 10 mg/g) Investigator's Brochure.

Test Investigational Medicinal Product

Substance Code/Name	Tirbanibulin
Route of Administration	Topical
Dosage Form	Ointment
Strength	10 mg/g
Frequency	Once daily

- Time between treatment courses during the core study: 8 weeks after starting the first course.
- Time between treatment courses during the Follow-Up Period: 16 weeks after starting the most recent treatment course.

Reference Investigational Medicinal Product

Substance Code/Name	Vehicle
Route of Administration	Topical
Dosage Form	Ointment
Strength	0 mg/g

Frequency	Once daily

- Time between treatment courses during the core study: 8 weeks after starting the first course.

9.2 Packaging and Labelling

Study drug will be packed and labelled in accordance with local regulations, including Annex VI of the European Union (EU) Clinical Trials Regulation 536/2014, by the Sponsor according to GMP conditions, including but not limited to the Sponsor contact details, protocol number, drug identification, storage conditions, and content of study drug. A sample label will be filed in the Investigator file.

On Day 1, patients will be dispensed a study kit containing 5 single-dose sachets containing either 350 mg tirbanibulin 10 mg/g ointment or vehicle. Patients who do not achieve CC at Day 57 will be dispensed a second study kit containing 5 single-dose sachets containing either 350 mg tirbanibulin 10 mg/g ointment or vehicle, according to the original randomisation.

Patients who are eligible for treatment with tirbanibulin 10 mg/g ointment at FUP1 or FUP2 will be dispensed a study kit containing 5 single-dose sachets containing 350 mg tirbanibulin 10 mg/g ointment.

9.3 Shipment, Storage, and Accountability

Only patients 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.

Study drug must be stored at 15°C to 30°C. Do not refrigerate or freeze tirbanibulin 10 mg/g ointment. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication upon receipt of the product(s) and ensure that any discrepancies are reported and resolved before use of the study medication.

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

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

Patients will be instructed to return the used and unused medication to the study site at the next study visit. Used and unused medication will be stored for final accountability. Empty packages and unused medication will be returned to the Sponsor or a designated depot, where the remaining medication will be destroyed according to Standard Operating Procedures (SOPs).

Retention drug samples will be kept by the Sponsor or designee, during the trial and until it is legally required after trial completion.

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

9.4 Treatment Administration

Tirbanibulin ointment is for application on the face or scalp. Before applying tirbanibulin, patients should wash the treatment field with mild soap and water and dry it. Some ointment from 1 single-use sachet should be squeezed onto a fingertip and a thin layer applied evenly over the entire selected treatment field larger than 25 cm^2 up to a maximal treatment area of 100 cm^2. The ointment should be applied at approximately the same time each day. The treated area should not be bandaged or otherwise occluded. Washing and touching of the treated area should be avoided for approximately 8 hours after application of tirbanibulin. After this period, the treated area may be washed with mild soap and water. Hands should be washed with soap and water before and immediately after application of the ointment.

Contact with the eyes should be avoided. Tirbanibulin ointment may cause eye irritation. In the event of accidental contact with the eyes, the eyes should be rinsed immediately with large amounts of water, and the patient should seek medical care as soon as possible. Tirbanibulin ointment must not be ingested. If accidental ingestion occurs, the patient should drink plenty of water and seek medical care.

Tirbanibulin ointment should not be used on the inside of the nostrils, on the inside of the ears, or on the lips. Application of tirbanibulin ointment is not recommended until the skin is healed from treatment with any previous medicinal product, procedure or surgical treatment and should not be applied to open wounds or broken skin where the skin barrier is compromised.

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

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

Patients will be provided with a kit containing 5 single-dose sachets of either tirbanibulin 10 mg/g ointment or vehicle. The first dose will be administered by the patient under the supervision of study personnel on Day 1 at the site. The patient will self-administer the remaining single-dose sachets once daily at home for the next 4 consecutive days.

Patients who do not achieve CC at Day 57, will be provided a second kit containing 5 single-dose sachets of either tirbanibulin 10 mg/g ointment or vehicle, according to the original randomisation. Treatment will be applied beginning at Day 57 in the same manner as the first kit.

During the Follow-Up Period, patients with lesions in the treatment field at FUP1 (only those with complete clearance at Day 57) or at FUP2 will be provided another kit of 5 single-dose sachets of tirbanibulin 10 mg/g ointment. Treatment will start the same day and will be applied in the same manner as previous courses.

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

9.5 Treatment Compliance

Compliance with the study treatment will be assessed according to the schedule in Table 1 and Table 2. Compliance will be assessed by counting the dispensed and returned used single-use sachets. Patients will be instructed to return both the used and unused study treatment back to the clinical site. This information will be recorded in the eCRF.

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

Patients will record dates and times of study treatment application, including dates for study treatment delays in the patient diary. Refer to Section 12.1.3 for details.

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

9.6 Methods for Assigning Patients to Treatment Groups

9.6.1 Patient Identification

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

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

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

9.6.2 Randomisation

At Day 1/Baseline, eligible patients will be randomised in a 2:1 ratio to either tirbanibulin 10 mg/g ointment or vehicle; the randomisation will be stratified by the number of lesions at baseline (≥4 to ≤8, >8 to ≤12), treatment location (face or balding scalp), and trial site. A total of approximately 270 patients will be randomised with an allocation ratio of 2:1 (180 tirbanibulin 10 mg/g ointment and 90 vehicle).

Enrolment will be controlled so that approximately two-thirds of patients enrolled will be treated on the face and approximately one-third of patients enrolled will be treated on the scalp. Further, at least 25% of patients will have a TF measuring approximately 100 cm^2.

Interactive response technology (IRT) will be used to administer the randomisation schedule. The IRT will assign a randomisation number to the patient, which will be used to link the

patient to a treatment arm and will specify unique medication pack number(s) for the packages of trial treatment.

Patients who receive a second course of study drug on Day 57 will be given the same blinded treatment as assigned on Day 1.

9.7 Blinding

The Sponsor, CRO/vendors involved in the clinical conduct of the trial, the Investigators, trial site personnel, and patients will be blinded to the treatment that is assigned to each patient during the core study. The integrity of this clinical trial must be maintained by observing the treatment blind during this period.

After database lock for the core study analysis (first data delivery, see Section 11.14), the Sponsor and CRO staff/vendors will be unblinded to the treatment assignment during the core study in accordance with the Blinding Plan. Open-label tirbanibulin 10 mg/g ointment will be administered during the Follow-Up Period; however, the Investigator, site personnel, and patients will remain blinded to the core study treatment assignment.

9.8 Unblinding by the Investigator

Whenever the maintenance of the safety and well-being of the patient – as assessed by the Investigator – requires knowledge of the information on the actual administered study drug, the Investigator shall break the blind. Also, in the case of unintended pregnancy of the patient, or the female partner of a male patient participating in the trial, the Investigator can break the blind.

In case of any doubt, the Investigator should contact the Sponsor/Medical Monitor from the CRO to evaluate whether the blind should be broken.

The treatment assignment will be unblinded through the IRT. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented. The Sponsor/CRO Pharmacovigilance unit must be immediately informed of any unblinding.

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

9.9.1 Pre-Trial Medications

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

All medications, including over-the-counter (OTC) drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to Day 1 will be recorded at Screening. Thereafter, a record of all medications taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be captured in the patient's eCRF.

A complete study disease treatment history will be recorded in the eCRF for the 2 years prior to baseline, including response to the most recent topical treatment.

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

9.9.2 Concomitant Medications

Any medication taken for medical reasons (mainly diseases concomitant with studied disease) before trial entry, will be continued at the same dose and under the same conditions, at the discretion of the Investigator. All chronic medications will be recorded.

9.9.2.1 Core Study

At the Baseline Visit all patients will be asked to provide information about concomitant medications taken in the 4 weeks prior to the Baseline visit. Patients should be instructed to consult with the Investigator prior to initiating any new medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) while participating in the study.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the Investigator should base decisions on the patient and clinical factors. Any additional medication (including the limited use of therapeutic agents which, if used under treatment regimens other than for treatment an AE or for appropriate medical management, might be considered therapies), whether prescription or non-prescription, used at baseline and/or during the course of the study, must be documented, including the dose and regimen, start and stop dates, and indication.

The use of physical treatments for AK (eg, cryotherapy) is permitted only for lesions >2 cm outside of the TF.

The use of any non-study drug on the TF is prohibited during the study. If for safety reasons the Investigator considers it necessary to apply topical treatment (eg, corticosteroid) to the TF during the study, then the patient should be encouraged to continue in the study in order to allow further assessments.

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

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

9.9.2.2 Follow-Up Period

For patients who achieve complete clearance at Day 57 or Day 113 and are eligible to receive treatment with tirbanibulin 10 mg/g ointment during the Follow-Up Period, the same

restrictions on concomitant medications apply as described in Section 9.9.2.1 and Section 9.9.3.

Patients who do not achieve complete clearance at Day 57 or Day 113 of the core study will be evaluated only for safety in the Follow-Up Period and will not receive further treatment as part of the study. As such, these patients should be treated according to standard of care, at the discretion of their treating physician and/or the Investigator.

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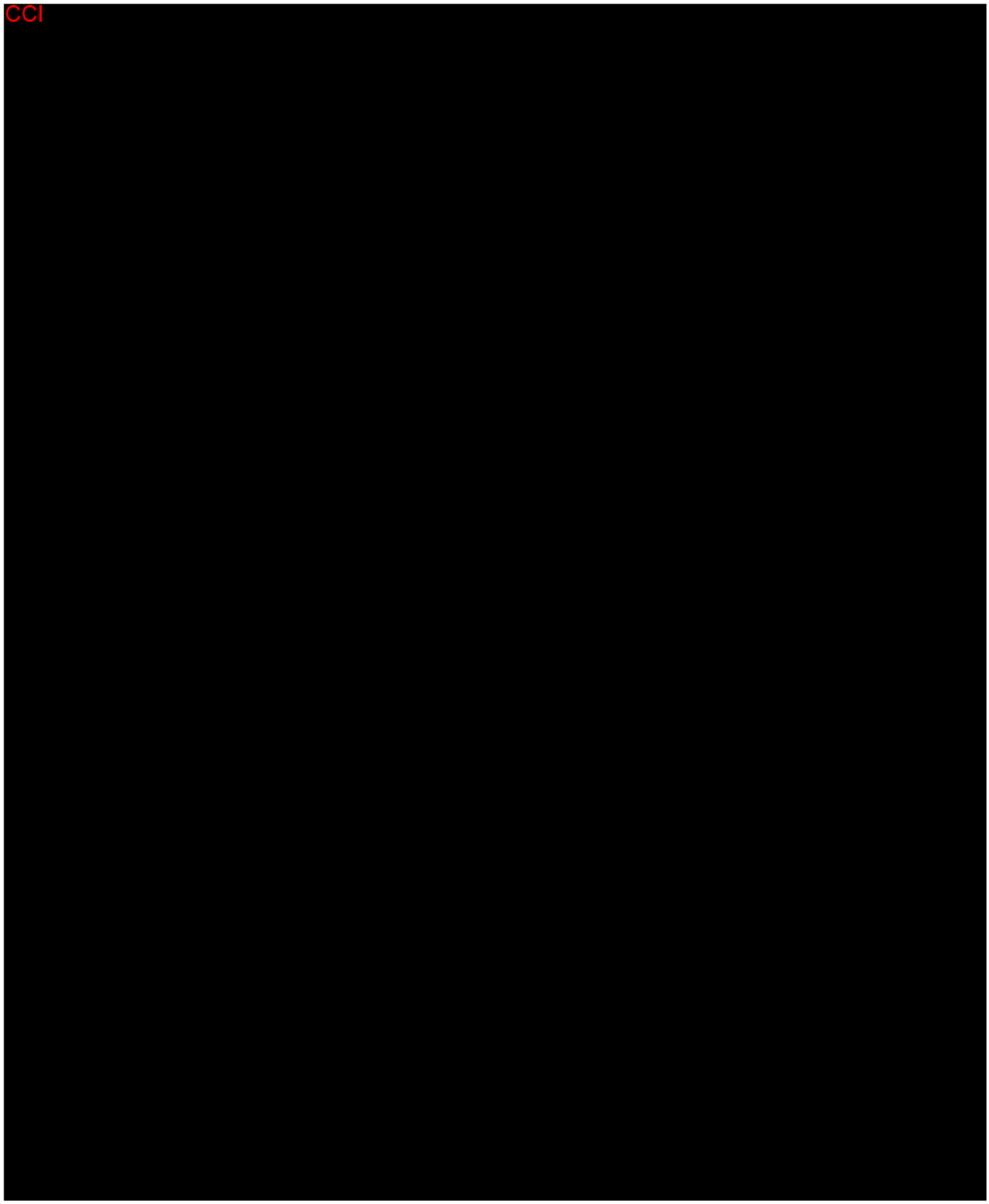

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9.9.4 Post-Trial Medications

Once study treatment and all visits and related study measurements are complete, patients should continue to take their usual medications allowed during the study and may resume other medications interrupted prior to study enrolment, as deemed appropriate by the Investigator. It is not planned to treat patients with tirbanibulin 10 mg/g ointment any further than scheduled in this study. No intervention or additional care is planned following the end of the study.

10 Trial Procedures and Assessments

10.1 General Conditions of the Trial

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

Trial visits must be scheduled with respect to Baseline/Day 1. In order to adapt appointments to local holidays, patients´ availability or site internal organization needs, time windows are allowed as indicated in Table 1 and Table 2. The CRA or CRO Medical Monitor should be contacted for advice in case of exceptional situations.

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

Optimally, the evaluations for each patient (lesion counts, review of trial drug compliance, etc.) should be performed by the same Investigator throughout the trial to avoid inter-assessor bias (see Section 10.4).

Unless specified otherwise, the study assessments scheduled during the study visits must be performed before the study product administration. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. Vital signs
2. Blood draw for laboratory tests

Table 1 and Table 2 summarise the trial procedures to be performed at each visit. Individual trial procedures are described in the following sections.

10.2 Patient's General Conditions During the Trial

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

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

The ICF must be signed before any trial-related procedures are performed (see Section 14.2).

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

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

For patients who require washout from a prohibited concomitant treatment (see Table 5), they should be seen and sign the ICF prior to the Screening visit, to ensure completion of the necessary washout period. No trial assessments will be performed on that date and the Screening visit will be scheduled according to the washout length required for the specific medication stopped.

The Screening Visit (Visit 1) will occur between Day -28 and Day -1. Patient screening numbers will be assigned at Visit 1. The Screening visit and assessments will be performed in accordance with schedule detailed in Table 1 and Table 2.

Demographics and Baseline Characteristics

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

Skin type will be recorded according to the Fitzpatrick scale (Table 6).

Table 6 Fitzpatrick Skin Type

Skin Type	Description*
I	Always burns easily, never tans (sensitive)
II	Always burns easily, tans minimally (sensitive)
III	Burns moderately, tans gradually (light brown) (normal)
IV	Burns minimally, always tans well (moderate brown) (normal)

Skin Type	Description*
V	Rarely burns, tans very well (dark brown) (intensive)
VI	Never burns, deeply pigmented (intensive)

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

Medical and Actinic Keratosis History

Medical history at Screening will include:

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

Prior Medications

All medications, including OTC drugs, food supplements, herbal remedies, and vitamins, taken within 30 days prior to Day 1 will be recorded at Screening. A history of topical AK treatments will be captured for the 2 years prior to baseline, including response to the most recent treatment (see Section 9.9.1).

Physical Examination

A complete PE includes height, weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, neurological systems, and an expanded dermatological examination to cover sun-exposed areas where photo-damage is likely. Height is measured at Screening only. Physical examinations will be conducted in accordance with schedule detailed in Table 1 and Table 2.

Treatment Field Identification

The size of the TF must be larger than 25 cm^2 (eg, approximately one cheek) and up to approximately 100 cm^2 (eg, approximately mid face).

At Screening, the Investigator will select and measure the anatomical area and will outline the TF with a marker pen over the skin. Each AK lesion within the TF will be also identified with a label. A photograph will be captured using imaging devices to be used to support the location of the same TF identified at Screening during the follow up study visits assessments.

At Baseline (Day 1), the area of the TF and the number and location of lesions inside it will be confirmed. A baseline photograph is only required in case of any significant change from Screening is detected in the TF as per the investigator judgement or if the quality of the image captured at screening is not appropriate. If no photograph is needed at baseline, then the screening photograph will be considered the baseline assessment. The same field will be located during the study with the aid of imaging software before performing the study assessments. Study Manuals will be provided to describe the image procedures in detail. The

number of AK lesions in the TF will be recorded in the eCRF and photographs will be taken according to the schedule in Table 1 and Table 2.

Pregnancy Testing

In females of childbearing potential, a highly sensitive urine pregnancy test will be performed at the Screening visit and according to the Schedule of Assessments (Table 1 and Table 2). Urine pregnancy test kits will be provided by the Sponsor.

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

10.3.2 Core Study

Treatment and Response Assessment Period visits and assessments will be performed in accordance with the schedule detailed in Table 1.

The trial visits may be rescheduled within the time windows allowed in this protocol (see Table 1), in case of:

- scheduling conflicts (weekends or holidays),
- technical problems with any equipment necessary for the visit, or
- any AEs that impede conduct of the visit.

See Sections 10.4 and 10.5 for details on the efficacy and safety assessments, respectively.

10.3.3 Follow-Up Period

Follow-Up Period visits and assessments will be performed in accordance with the schedule detailed in Table 2.

The trial visits may be rescheduled within the time windows allowed in this protocol (see Table 2), in case of:

- scheduling conflicts (weekends or holidays),
- technical problems with any equipment necessary for the visit, or
- any AEs that impede conduct of the visit.

See Sections 10.4 and 10.5 for details on the efficacy and safety assessments, respectively.

10.3.4 Unscheduled and Repeated Tests

Unscheduled Tests

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

Repeated Tests

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

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

10.4 Efficacy Assessments

Lesion Assessments

At assessment visits, a dermatologist will identify baseline lesions and new lesions in the TF and will perform a count of clinically visible AK lesions inside the TF according to the Schedule of Assessments (Table 1 and Table 2). The total number of lesions and whether a lesion is new or was an existing lesion at Baseline will be recorded in the eCRF.

The Investigator who conducts the lesion count at Baseline/Day 1 and at Days 57 and 113 **must** be the same for an individual patient, to the extent possible. All other core study and Follow-Up Period assessment visits **should** be conducted by the same Investigator, to the extent possible.

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

At Baseline/Day 1, the dermatologist will classify each visible, discrete, non-hypertrophic, non-hyperkeratotic AK lesion as Olsen 1 or 2, as per Table 7. Patients with Olsen Grade 3 lesions in the TF are excluded from the study, as these are considered hyperkeratotic/hypertrophic for the purposes of this study (see Section 8.3). For each baseline lesion, the lack of response to most recent topical therapy, if any, will be captured.

Table 7 Olsen Grade of Actinic Keratoses

Score	Severity	Definition
1	Mild	Slight palpability, with actinic keratoses felt better than seen
2	Moderate	Moderately thick actinic keratoses that are easily seen and felt
3	Severe	Very thick and/or obvious actinic keratoses

Source: Olsen, 1991.

10.5 Safety and Tolerability Assessments

Safety will be assessed periodically during the study by recording AEs, including SAEs, local tolerability, pigmentation, and scarring, and AESIs. Safety assessments also include PEs and vital signs measures, clinical laboratory evaluations and pregnancy testing for WOCBP (see Table 1 and Table 2).

10.5.1 Adverse Events

10.5.1.1 Adverse Events

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

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

Local tolerability signs will be reported separately from AEs (see Section 10.5.2). See Section 10.5.1.2 for definitions and reporting of AESIs.

All patients who have unresolved treatment-related AEs at Day 113/ET (patients who do not enrol in the Follow-Up Period) or Week 48/ET (patients who enrol in the Follow-Up period) will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

Adverse event and SAE definitions and reporting requirements are detailed in Section 10.8.

10.5.1.2 Adverse Events of Special Interest

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

Skin Cancers

Skin cancers (including BCC, SCC, and melanoma) appearing within or outside the TF during the study will be reported as AESIs. Details of the skin cancer and any other associated AE will be recorded in the AE form in the eCRF and by using the Skin Cancer Report Form. The location and treatment will be recorded. In the case of an SCC arising within the TF, it will be recorded if an AK had been present at the same location at baseline. See Section 10.8.4 for reporting requirements for AESIs. If the skin cancer is associated with an SAE, an SAE Report Form should also be completed and sent along with Skin Cancer Report Form.

10.5.2 Focused Dermatological Examination of the Treatment Field

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

10.5.2.1 Local Tolerability

Local tolerability assessments in the TF will be recorded per the schedule in Table 1 and Table 2. The assessment for local tolerability is to be done after the assessment for AEs. The evaluation of local tolerability is done by the Investigator (or an appropriate trained designee).

The local tolerability signs to be assessed and the corresponding grading scale for each sign are provided in Table 8.

Table 8: Local Tolerability Signs and Grading Scale

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

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

All patients who have unresolved local tolerability signs at Day 57, Day 113/ET, or Week 48/ET will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

Any sign of local tolerability leading to temporary or permanent discontinuation of the study drug application or requiring the use of concomitant medications should be reported as an AE. If a sign of local tolerability leads to an AE meeting the criteria of seriousness (ie, an SAE), the SAE form will be completed with all the available information and reported within the same timeframe and following the same routing as for an SAE (see Section 10.8.4).

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

10.5.2.2 Pigmentation Changes and Scarring

Hypo- and hyperpigmentation and scarring in the TF will be assessed as being present or absent in accordance with the Schedule of Assessments (Table 1 and Table 2). The assessment for changes in pigmentation and scarring is to be done after the assessment for AEs.

All patients who have unresolved hypo- or hyperpigmentation and scarring in the TF at Day 57, Day 113/ET, or Week 48/ET, will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigator.

10.5.3 Physical Examinations and Vital Signs

Physical Examinations

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

Vital Signs

Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and tympanic temperature. Measurements of systolic and diastolic blood pressure will be conducted 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 ICF and that meet the definition of an AE must also be recorded in the AE form in the eCRF.

10.5.4 Laboratory Testing

Routine laboratory assessments will be performed at a designated central laboratory (refer to the laboratory manual). Tests to be performed at the central laboratory are detailed in Table 9.

Table 9: Laboratory Testing Parameters

Assessment	Specific Tests
Haematology	Red blood cells (RBC), haemoglobin, haematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood chemistry	Electrolytes: Chloride, potassium, sodium, bicarbonate (HCO_3) Liver Function Tests: alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, direct bilirubin Renal Function Tests: Blood urea/blood urea nitrogen, creatinine Other: Total protein, albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, triglycerides, uric acid

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes according to the Schedule of Assessments (Table 1 and Table 2). Blood samples are to be collected before administration of concomitant medications (if any), and after vital sign measures are performed.

Urine pregnancy testing for WOCBP will be performed at the study site in accordance with the Schedule of Assessments (Table 1 and Table 2).

All abnormal laboratory test results will be evaluated by the Investigator and those that are clinically significant, per the Investigator's judgement, will be recorded as AEs (see Section 10.8.3). The Investigator's evaluation of clinically significant abnormalities will be specifically documented.

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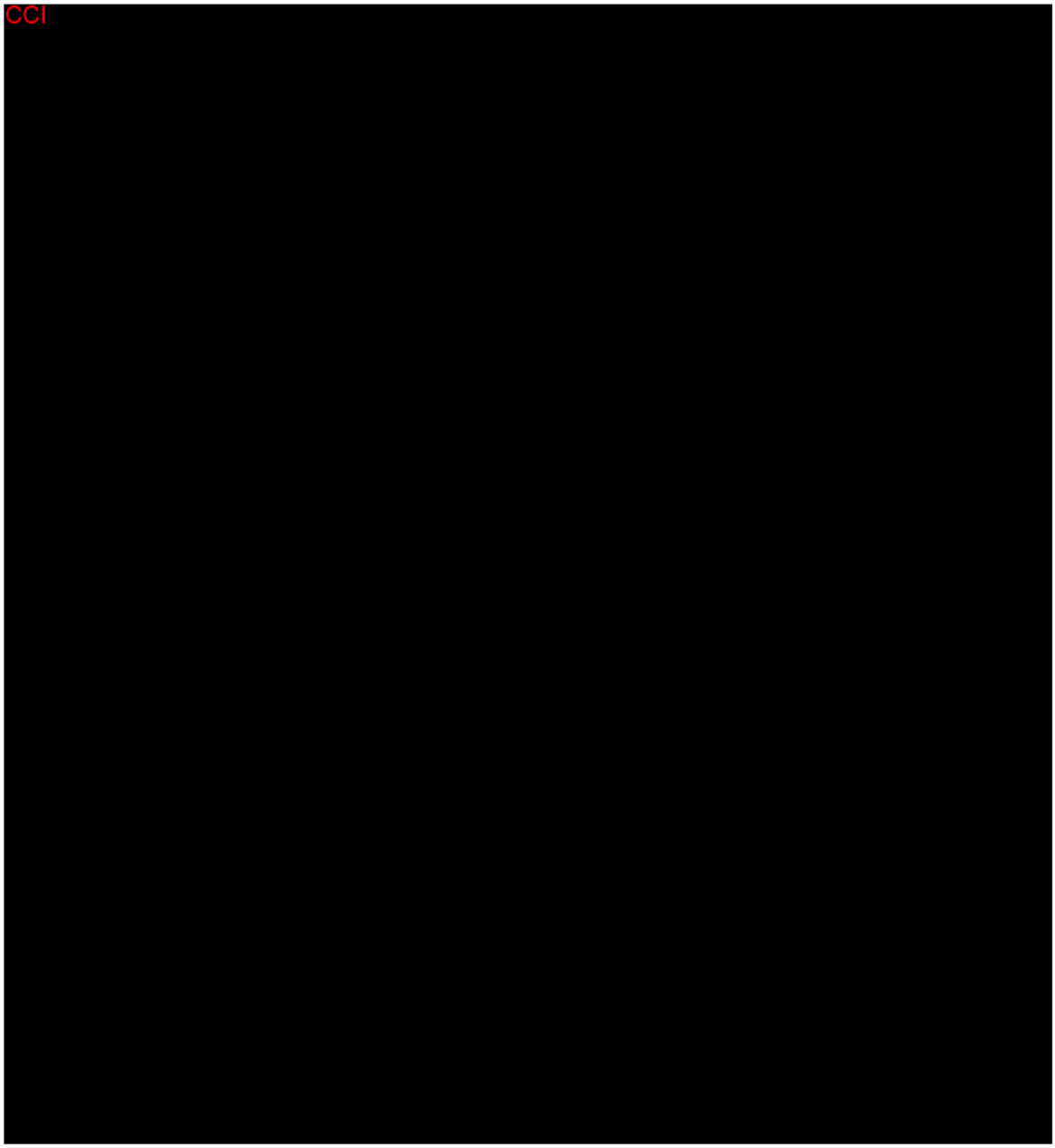

10.7 Other

Standardized Photography

Standardized photography of each patient's TF will be performed prior to dosing while on treatment (see Table 1 and Table 2) for illustrative purposes and to support the TF identification. Refer to the study manuals for detailed instructions.

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

10.8 Adverse Events

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

10.8.1 Definitions

Adverse Event

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

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

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

Adverse Event of Special Interest

See Section 10.5.1.2 for details.

Serious Adverse Event

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

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

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

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

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

10.8.2 Reporting of Adverse Events

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

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

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

- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

- The action taken on the IMP will be captured as:
  - Drug withdrawn
  - Dose not changed
  - Not applicable

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

10.8.3 Recording of Adverse Events

Adverse events will be collected from signature of the ICF up to Day 113/ET (patients who do not enrol in the Follow-Up Period) or Week 48/ET (patients who enrol in the Follow-Up Period). Any AE reported by the patient up to 30 days after the last study contact (Day 113/ET or Week 48/ET) should also be captured in the eCRF.

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

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

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

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligations to report as AEs.

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

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

All AEs elicited by the Investigator during the defined AE collection period must be recorded in the eCRF. In addition, when an AE meets the criteria of seriousness (ie, an SAE), it must also be recorded on the SAE form and reported following the defined timelines in Section 10.8.4.

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

Serious adverse events and AESIs will be collected from signature of the ICF up to Day 113/ET (patients who do not enrol in the Follow-Up Period) or Week 48/ET (patients who enrol in the Follow-Up Period). Any SAE or AESI reported by the patient up to 30 days after the last study contact (Day 113/ET or Week 48/ET) should be collected in the eCRF.

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

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

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

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

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

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

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

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

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

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

- Events that result in hospital stays for observation of <24 hours and that do not require a therapeutic intervention/treatment (eg, an emergency room visit for haematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

10.8.5 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether an event is causally related to study treatment. The Sponsor (or designee) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC (where required) within 7 days after the Sponsor (or designee) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IECs within 15 calendar days after the Sponsor (or designee) first has knowledge of them.

The Sponsor (or designee) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities (including reporting to the Eudravigilance database) and for informing Investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IECs of reportable events within the applicable timeframes.

10.8.6 Follow-up of Adverse Events / Serious Adverse Events

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

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

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

10.9 Pregnancies

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

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

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

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

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

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

10.10 Overdose

An overdose is defined as any dose higher than the maximum dose described in the study protocol. For this study, any single dose greater than 350 mg (1 sachet) or applying drug over an area larger than defined within the protocol will be considered an overdose. There is no specific treatment for tirbanibulin 10 mg/g ointment overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

If an overdose leads to an AE, the AE will be recorded in the eCRF. In addition, if the overdose leads to an AE meeting the criteria of seriousness (ie, an SAE), the SAE form will be completed with all the available information and reported within the same timeframe and following the same routing as for a SAE (see Section 10.8.4). The patient must be followed-up and the Investigator will make every effort to obtain information on how the overdose was managed, any treatment administered and the final outcome. This follow-up information will be reported, following the same procedure and timeframes as for the initial report.

10.11 Unblinding for Safety Reasons

For any unblinding done by Investigator, please refer to Section 9.8.

According to pharmacovigilance legislation the Sponsor's Corporate Drug Safety Department can break the blind of specific patient for regulatory reporting purposes (ie, suspected unexpected serious adverse reaction, also known as a SUSAR case). Unblinding will be done according to the applicable SOP.

10.11.1 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention. The Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Patients will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

Time Period for Detecting Product Complaints:

- Product complaints that result in an AE will be detected, documented, and reported to the Sponsor during all periods of the study in which the drug is used.
- If the Investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the Investigator will promptly notify the Sponsor.

Prompt Reporting of Product Complaints to Sponsor:

- Product complaints will be reported to the Sponsor within 24 hours after the Investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the Sponsor.

Follow-up of Product Complaints:

- Follow-up applies to all participants, including those who discontinue study intervention.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator and submitted to the Sponsor.

11 Statistics

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

11.2 Structure and Methodology of the Statistical Analysis

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

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

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

11.3 Analysis Populations

There will be two different analysis populations in this trial:

- **Intent-To-Treat (ITT) Population**: defined as all randomised patients
- **Safety Population**: defined as all randomised patients who received at least one dose of study treatment during the core study

- CCI [redacted]
- CCI [redacted]

All efficacy analyses will be performed on the ITT Population and safety analyses will be performed on the Safety Population.

CCI [redacted]

11.4 Descriptive Statistics

Categorical variables will be summarised with counts (n) and percentages (%) and will be tabulated by treatment and/or overall, where appropriate. For continuous variables, the number of non-missing observations (n), mean, standard deviation (SD), standard error (SE) of the mean, 95% confidence interval (CI) of the mean, median, first (Q1) and third (Q3) quartiles, minimum (min) and maximum (max) will be tabulated by treatment and/or overall. When applicable, these summaries will be provided by visit and time-point of assessment.

11.5 Patient Disposition

The number of screened patients will be summarised, the number and percentage of screening failures and the associated reasons for failure will be tabulated.

The number of included patients entering the trial and number and percentage of patients included in each trial population (ITT and Safety) will be summarised. The number and percentage of patients who prematurely discontinued the trial will be tabulated by reasons for discontinuation and the number and percentage of patients available at each visit will be presented.

The above summaries will be presented overall and by each combination of the stratification factors.

The disposition of the patients will be presented in listings.

11.6 Demographics and Baseline Characteristics

The trial population will be described using demographic and baseline characteristics recorded during the Screening period. If not specified, the baseline value of each assessment will be defined as the latest non-missing value assessed before the first dose of study treatment.

Analyses of demographic and baseline characteristics will be based on the ITT population.

All demographic and baseline characteristics will also be provided for screening failures.

11.7 Study and Treatment Compliance

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

11.8 Treatment Exposure

The total amount of product applied (number of sachets) over the course of the study will be described.

11.9 Prior and Concomitant Medications

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

11.10 Statistical Methods

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

11.10.1 Analysis of Efficacy Endpoints

All efficacy analyses will be performed on the ITT population.

Primary Endpoint

The primary endpoint, the percent change from baseline in lesion count at Day 57 (Week 8), will be analysed by means of an analysis of covariance (ANCOVA) model using treatment group, treatment location, and country as factors, and baseline number of lesions as covariate. Least-squares (LS) mean percent change from baseline and 95% CI will be presented by treatment group. Between-treatment group LS mean difference and 95% CI will be presented overall. Forest plots with the 95% CI for the between-group difference in mean percentage change by stratification subgroup will be presented.

CCI [redacted]

Key Secondary Endpoints

The four key secondary efficacy endpoints, PC rate at Day 57 (Week 8), CC rate at Day 57 (Week 8), PC rate at Day 113 (Week 16), and CC rate at Day 113 (Week 16) will be analysed by treatment group using the Cochran-Mantel-Haenszel (CMH) method controlling for treatment location (face or scalp), baseline number of lesions (≤8 or >8), and country.

Patients with missing data on AK lesion numbers at Week 8 for patients with 1 treatment course or at Week 16 for patients with 2 treatment courses will be considered failures for the binary endpoints at Weeks 8 and 16, respectively. Also, patients who permanently discontinued treatment will be considered as failures.

For the binary endpoints (PC and CC), CCI [redacted] and risk difference with 95% CIs will be presented together with the p-value of the CMH test. For ease of interpretation, the 95% CI for the difference in proportions of patients with success will also be presented using the Miettinen and Nurminen approach (Farrington 1990).

The percentage of patients with PC and the 95% CI and the percentage of patients with CC and the 95% CI will be provided for each treatment group overall and for each treatment group by treatment location, by baseline number of lesions (≤8 or >8), and country using Wilson´s score method. The 95% CI for the difference in proportions of patients with success will also be presented for each treatment location, for each baseline number of lesions (≤8 or >8), and for each country using Newcombe confidence limits.

CCI [redacted]

11.10.3 Analysis of Safety Endpoints

Descriptive statistics will be provided for all safety endpoints. Safety analyses will be performed by treatment group and by the number of treatment courses applied (1 or 2) during

the core study. Safety analyses will be reported separately for the Follow-Up Period safety populations, CCI [redacted]

Local tolerability signs composite score, and specific local tolerability scores will be analysed by means of descriptive statistics and provided by treatment group for Weeks 1 to 8 and, for those patients who received 2 courses, by treatment group for Weeks 1 to 16. The maximum local tolerability score and maximum local tolerability composite score will be presented by treatment group for Weeks 1 to 8 and, for those patients who received 2 courses, by treatment group for Weeks 8 to 16. Time when the maximum local tolerability score is observed for each individual sign and time when the maximum local tolerability composite score will be described by treatment group for weeks 1 to 8 and by number of courses received and treatment group for Weeks 1 to 16. The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by treatment group for Weeks 1 to 8 and by number of courses received and treatment group for Weeks 1 to 16.

Treatment-emergent AEs and SAEs recorded during the study will be presented and will include the total number of events with number and percentage of patients with AEs. Summaries of the number and percentage of patients (and number and percentage of events) for study drug-related AEs, severe AEs, serious AEs, AEs with an outcome of death, AEs leading to temporary or definite discontinuation of the study treatment, and AEs leading to study discontinuation will be provided. The number and percentage of patients who experience one or more AESI will also be tabulated. Data will be analysed for the core and the follow-up studies.

For clinical laboratory parameters, the number and percentage of patients with normal or abnormal results will be presented at scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. Shift tables will be provided when appropriate. These data will be analysed for the core study and for the Safety Population – CCI [redacted]
CCI [redacted]

CCI [redacted]

CCI

11.14 Interim Analysis

No interim analysis is planned for this trial.

Nevertheless, it is important to note that the overall study has 2 periods during which treatment may be administered, the Treatment and Response Assessment Period and the Follow-Up Period, and consequently there will be 2 different result deliveries according to 2 different database locks. The first results delivery will be at the end of the core study, including efficacy and safety up to Day 113/ET (Week 16). The second results delivery will be after finalizing the Follow-Up Period at Week 48/ET and will include the overall safety results.

12 Data Handling, Processing, and Record Keeping

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

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

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

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

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

12.1 Data Collection

12.1.1 Identification of the Trial Data Sources

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

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

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

The trial data sources are outlined below:

- Signed informed consent forms
- Patient medical history records will include trial diagnosis and inclusion/exclusion criteria age, sex, physical examination, previous medication, original or certified copy of a laboratory reports, instrument printout, trial progress notes of the physician, reason for withdrawal, dose, contraception methods, change in child-bearing potential
- Laboratory test results reports (haematology, clinical chemistry, etc)
- Digital photographs
- Patient diary
- eCRF
- PRO/ePRO

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 (US Title 21 Code of Federal Regulations part 11).

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

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

Direct Entry of Data Into the eCRF

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

- Inclusion and exclusion criteria confirmation
- Patient demography and physical examination, including. age, race, ethnicity height, weight, and skin type
- Relevant previous and concomitant therapies
- Up-to-date relevant medical history, including trial diagnosis
- TF measurements and location (face or scalp)
- Number of lesions in the TF, identification of whether each lesion is new or existed at Baseline, and Olsen grade (at Baseline only)
- Vital signs (blood pressure, pulse, temperature and respiratory)
- Pregnancy test results
- Trial/visit dates
- Visit assessment (checking compliance, dispense and collect trial diary, drug application, blood sample collection, score for skin reaction, end of treatment)
- CCI [redacted]
- Drug accountability (medication given and returned)
- AEs

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

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

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

The information directly collected in the eCRF must match the source documents. The source data verification will be performed by the CRA according to the requirements specified in the Monitoring Plan.

At the trial end, the CRO will generate one certified "true copy" of the completed CRFs at site and will send to the Investigator(s) that copy certification together with the completed eCRFs (in PDF) from all patients enrolled at his or her location.

12.1.3 Patient Diary

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

there will also be the possibility to provide patients with a mobile phone, if necessary. The Study App will be installed onto the mobile phone during the baseline visit. Clinical personnel will check and confirm the correct installation of the Study App during the visit.

On the Study App, patients will:

- Receive notifications, communications, and reminders through the patient retention tool.
- Complete the eDiary: Patients, and assisted by caregivers, as needed, will complete a diary to record daily the study treatment application dates, time of application, The eDiary will be completed by the patient continuously from the Day 1/Baseline visit to the last study visit and will be checked by the Investigator in accordance with the Schedule of Assessments (Table 1 and Table 2).

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In cases where patients are unable to complete an eDiary, an alternative paper-based diary may be used. Only in these specific cases, patients will be able to complete a paper diary to collect the information related to the medication, and site personnel will be responsible for transcribing the paper entries to the electronic system.

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

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

12.2 Data Management and Quality Control

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

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

Investigators will respond within 48 hours to any query generated by the Data Management group, or any data risk indicator reported.

Main Data Management activities and procedures will be accurately described in the DMP, which is created by the CRO and approved by The Sponsor.

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

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

Encoding of specific data will be conducted by the CRO. For this trial, medical history, AEs, and concomitant medications will be coded; Medical Dictionary for Regulatory Activities and WHODrug Global Enhanced dictionaries will be used, version number of each dictionary will be documented in the DMP.

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

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

12.3 Investigator and Trial Master Files

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

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

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

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

12.4 Documents and Record Keeping

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

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

All trial data (including electronic data), all hard copies including protocol, consent forms, CRFs, queries and printouts, and all essential documents relating to the conduct of the clinical trial will be stored at the research site for a period of 25 years after completion of the trial, unless otherwise communicated in writing by the Sponsor. After this period of time the documentation may be anonymised or destroyed with the previous approval from the Sponsor.

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

13 Quality Control and Quality Assurance

13.1 Training of Staff

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

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

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

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

13.2 Monitoring

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

The trial CRA will conduct monitoring visits according to a pre-agreed schedule and with enough frequency to perform source data verification, check the accuracy of entries in the CRFs, the adherence to the protocol and to GCP, the progress of enrolment 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. The schedule can be adapted to the monitoring workload and/or prevailing circumstances at the site.

Standard monitoring reports will be produced by the trial CRA after each visit and filed in the TMF. 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 in eCRFs must be traceable to these source documents in the patient´s file.

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

13.3 Inspections and Audits

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

14 Ethics

This trial will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly of Helsinki (1964), as amended in Fortaleza, Brazil (2013) (World Medical Association, 2013), as well as in compliance with ICH GCP guidelines, and local laws of the Countries in which the trial 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/vendors and the Sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance to the highest standards of Good Clinical Practice (ICH GCP guidelines) and local regulations.

The Investigator, the CRO and the Sponsor will work according to the ICH guidelines and Clinical Trials Regulation No 536/2014.

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

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

14.2 Patient Information and Informed Consent

As the first act of recruitment into the study, patients will be informed by the treating physician in detail of the characteristics of the drug to be administered, the nature of the clinical investigation, the risks and the discomfort that can reasonably be expected as a result of their participation and the uses of the data, as described in the Patient Information Sheet (PIS).

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

in the patient's eCRF. Any retained samples from patients who withdraw consent will be destroyed.

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

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

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

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

14.3 Institutional Review Board/Independent Ethics Committee

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

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

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

Within 1 year after completion of the trial, the responsible party according to local regulations, the Investigator will send to the IRB/IEC a brief summary explaining the results obtained in the trial.

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

14.4 Patient Data Protection

The trial patients shall be informed by the Investigator that complete confidentiality will be maintained concerning their identity. On eCRFs/EDC and all trial data records (eg, eDiary) 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 IRB/IEC and Competent Authorities. However, all data

contained in the patient's medical history will be considered as confidential. The Sponsor will treat data according to personal data regulations (EU General Data Protection Regulation 2016/679), and any other applicable national and international regulation (for the Netherlands, see Appendix 3).

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.

The Sponsor has in place a program for personal data protection and prevention and management of Personal Data breaches: Policy PCG-24 (Personal Data Protection Policy); SOP-24/01 (Personal Data Management SOP), and a Protocol for Information Security Incident Management defining a procedure to properly manage and handle information security incidents, with or without impact on personal data, and the corresponding responsibilities, minimizing the potential damage and making sure all impacts are managed appropriately.

In case of data breach, the Sponsor shall be notified without undue delay, gathering as much information as possible to permit an assessment by its Data Protection Officer (DPO) in relation to whether the breach is likely to result in a high risk to the rights and freedoms of natural persons and to arrange any necessary measures to secure the data and to minimize any possible adverse consequences for subjects' data, as applicable. Any data breach will pass through five phases of incident handling (Detection, Analysis, Response, Recovery, and Post-incident Management), involving different stakeholders. Depending on the nature of the breach an Incident Response Team will form, where the DPO shall participate to minimize the adverse impacts to subjects' data. Depending on the nature and impact of the data breach, the DPO will notify supervisory authorities of the personal data breach without undue delay and, where feasible, no later than 72 hours, where applicable.

15 Financing and Insurance

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

All patients recruited will have an insurance policy provided by the Sponsor 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

The Sponsor will disclose clinical trials in a manner consistent with applicable national laws and rules governing personal data privacy and protection of intellectual property rights (for the Netherlands, see Appendix 3). Clinical trials will be registered, and results disclosed by means of recognized public databases, such as clinicaltrials.gov in the US and the Clinical Trial Information System (CTIS, euclinicaltrials.eu) in the 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 the Sponsor. This information will not be given to a third party without the written consent of the Sponsor.

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

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

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

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

17 Other Practical Considerations

17.1 Investigator's Brochure

The Athenex KX2-391 Ointment 1% (tirbanibulin 10 mg/g) Investigator's Brochure contains a summary of the pre-clinical and clinical data. The same confidentiality procedures apply for the Investigator's Brochure as for the protocol.

The Athenex KX2-391 Ointment 1% (tirbanibulin 10 mg/g) Investigator's Brochure will be included in the Investigator file. The Investigator will sign a receipt form.

17.2 Final Clinical Trial Report

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

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

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

The summary of the CSR will be sent to all the Investigators participating in the clinical trial as well as to the IRB and/or Competent Authorities according to the local regulation.

17.3 Protocol Modifications

Modifications of the original protocol are referred to as "amendments" to the trial protocol. Modifications of the original protocol may only be made with the Sponsor's 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/IRB and/or Competent Authorities and approved by them before implementation.
- Non-substantial Amendments do not require notification but should be recorded and be available on request for inspection at the trial site and/or Sponsor premises as appropriate.

17.4 Protocol Deviations

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

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

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

18 References

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19 Appendices

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

Appendix 1, Highly Effective Methods of Birth Control

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

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

Notes

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

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

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

Appendix 2, Patch Test for the Assessment of Contact Dermatitis

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

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

Appendix 3, Specific Requirements for the Netherlands

Section 8.8.3 – Premature Trial Termination:

For the Netherlands with regard to terms of premature termination, the standard clauses of the Dutch model clinical trial agreement apply.

Section 14.4 – Patient Data Protection:

As specified within the protocol in Section 14.4, data from the trial will be available to the Investigator and his/her staff, the authorized representatives of the Sponsor and, if required, by the IRB/IEC and Competent Authorities.

Although the Medical Research Ethics Committee in the Netherlands has no regular access to the (coded) research data or other personal data of trial patients, access will be given upon request.

Section 16 – Publication Policy:

For the Netherlands with regard to terms of publication and authorship, the standard clauses of the Dutch model clinical trial agreement apply.