Patient and clinician Reported Outcomes for tirbanibulin effectiveness and safety in Actinic Keratosis (PROAK)

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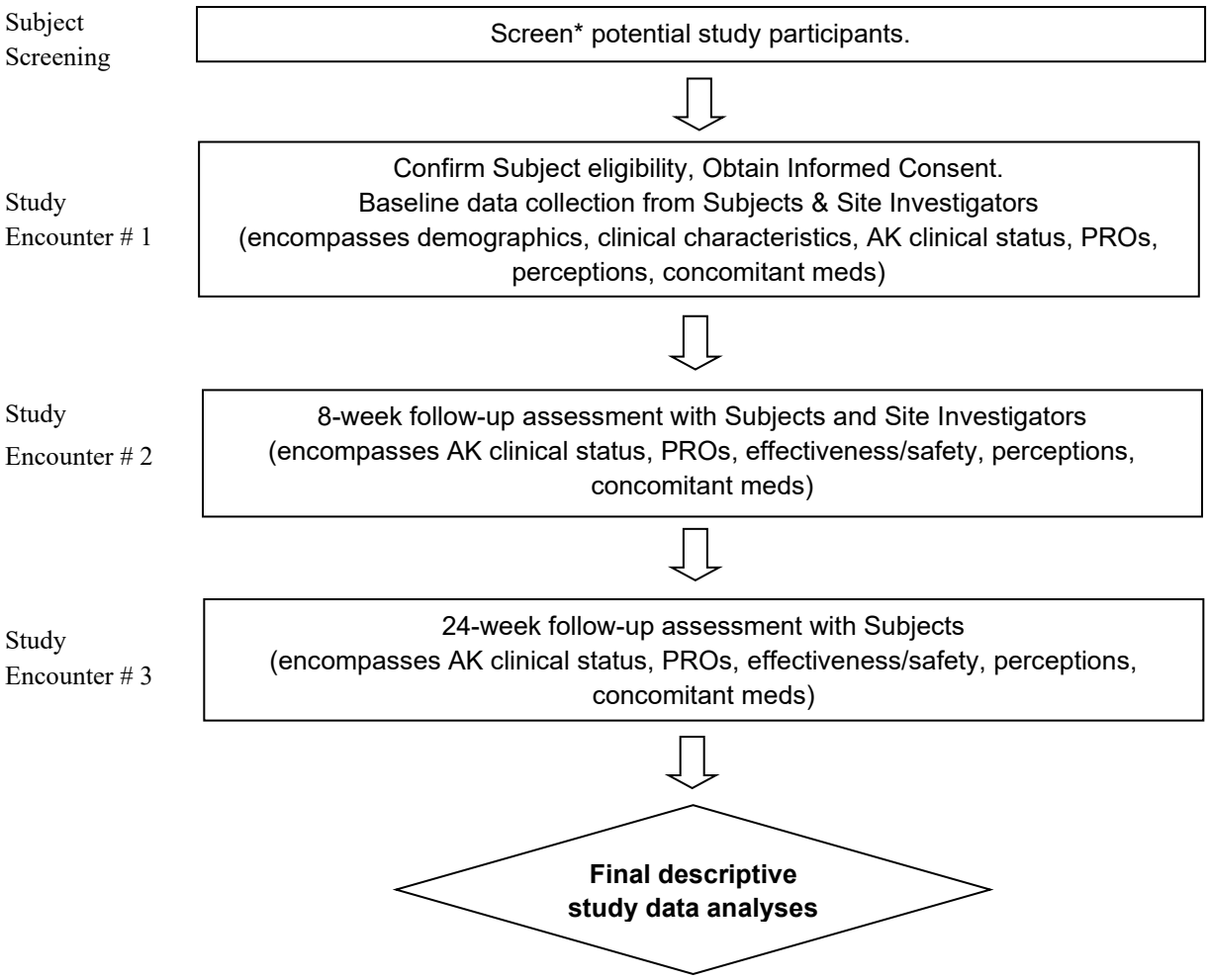
LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
App	Application / Mobile Application
Approx.	Approximately
AK	Actinic Keratosis
CFB	Change From Baseline
CRO	Clinical Research Organization
DCF	Data Collection Form
DMP	Data Management Plan
EC	Ethics Committee
EDC	Electronic Data Collection
eDCF	Electronic Data Collection Form
FAS	Full Analysis Set
FDA	The U.S Food and Drug Administration
HCP	Healthcare Provider
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
IGA	Investigator's Global Assessment
IRB	Institutional/Independent Review Board
LSR	Local Skin Reaction
N	Number (typically refers to participants)
PI	Principal Investigator
PRO	Patient Reported Outcome
PtGA	Patient Global Assessment
QoL	Quality of Life
Qr	Questionnaire
RCT	Randomized Controlled Trial
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard Deviation
TBD	To Be Decided
US	United States

PROTOCOL SUMMARY

Title:	Patient and clinician Reported Outcomes for tirbanibulin effectiveness and safety in Actinic Keratosis (PROAK).
Précis:	A prospective cohort study of patients with Actinic Keratosis (AK) in the face or scalp treated with tirbanibulin and followed for 24 weeks post treatment-initiation. Patient Reported Outcomes (PROs) and clinical profile of patients will be gathered for descriptive analyses of patient outcomes over the 24-week study observation period.
Objectives:	Evaluate PROs and clinician reported outcomes among patients with AK in the face or scalp who are prescribed tirbanibulin as part of usual care in clinical practice settings in the U.S. Primary: Evaluate PROs related to AK symptoms and impact. Secondary: Evaluate tirbanibulin treatment effectiveness, in terms of IGA of status of AK in the treated area on the face or scalp. Additional: Evaluate patient and clinician satisfaction with tirbanibulin treatment, future treatment preference, treatment adherence, and tirbanibulin safety/tolerability.
Population:	Approximately three hundred (300) patients of age ≥18 years at the time of initiation of treatment with tirbanibulin from clinical practices across the U.S.
Number of Sites:	Maximum of fifty sites will be recruited.
Duration of Treatment	5 days.
Study Drug & Mode of Administration	Klisyri® (1% tirbanibulin ointment); 1 single-dose packet (2.5 mg tirbanibulin in 250 mg) per administration; administered once a day for 5 consecutive days. Commercial supply of medication (5-day courses) may be supplied to clinical sites/Subjects.
Study Duration:	Approximately twenty-four months of study duration, including study set-up, 24 weeks of subject observation period and study close out, followed by study data analyses.

Schematic of Study Design



**Subject screening could be done via phone, prior to Subject's visit to the clinic; or it could be combined with Encounter # 1 (baseline data collection).*

*Clinicians shall prescribe tirbanibulin (*Klisyri®*) to eligible Subjects per own clinical judgement and manage them as they normally would, in clinical practice.*

1 KEY PERSONNEL AND CONTACT INFORMATION

Principal Investigator:

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Actinic Keratosis (AK) a common skin condition in which excessive and prolonged exposure to ultraviolet radiation. AK typically affects around 58 million people in the US and is more common in older adults, males, and those who are fair skinned. (Kempers et al, 2020). AK manifests as scaly, red lesions on face, trunk, scalp, and other sun exposed extremities; it could lead to epidermal lesions and eventually progress to squamous cell carcinomas (SCC) if left untreated (Khanna et al., 2017), with up to 65% of SCC arising from pre-existing AKs (Marks et al, 1988; Criscione et al, 2009). The rationale behind treating every AK lesion is based on the difficulty in predicting which single AK lesion will progress to SCC (Werner et al, 2015; Drake et al, 1995). The goal of treatment is to eliminate AK lesions, thereby minimizing their risk of progression to invasive SCC and reducing the associated morbidity and mortality, while obtaining the best cosmetic outcomes. While the clinical trials have compared the treatment outcomes of different therapies (Zane et al, 2016), patient reported outcomes (PROs), including patient preferences and what patients value the most for the AK treatment could improve total patient management in AK (Esmann et al, 2015, Siegel et al, 2017, Kopasker et al., 2019).

The AK lesions may cause cosmetic discomfort and due to the premalignant nature of the condition, patients may fear developing skin cancer. This fear may affect patients' overall well-being by leading to anxiety and stress (Tennvall et al, 2015). Patients may feel embarrassed and frustrated with AK lesions located on the face (Esmann et al, 2007). Studies have shown that AK has negative impact on the patient's daily living activities and their Quality of Life (QoL) (Grada et al, 2021), and presence of higher AK lesion counts on the face have been shown to be associated with worse skin-related quality of life among AK patients (Siegel et al, 2017; Emilio et al, 2016). AK treatments are associated with different levels of local skin reactions (LSRs) such as erythema, swelling, erosion, crusts, scaling, itching and burning sensation (Jansen et al, 2019), and such negative experiences with treatment may adversely impact the future willingness to retreat and treatment adherence among AK patients that can lead to poor outcomes in long term (Balcere et al, 2019; Del Rosso et al, 2014; Goldberg, 2017; Rosso et al., 2021). Therefore,

it is important to incorporate PROs that provides patient perspectives and provides important supplement to efficacy and safety data for the treatment(s), showcasing their complete value proposition.

Several PRO instruments have been utilized to measure patients' QoL and satisfaction with treatments for AK (Grada et al, 2021). Skindex-29 and Skindex-16 are frequently used validated PRO tools that measure skin-related QoL among dermatologic patients (Chren et al, 2001; Chren 2012); the 16-item shorter version is a newer instrument that measures the frequency at which skin condition's symptoms, personal emotions and functions impact patients' QoL, and could directly aid measurement of treatment effect in studies (Emilio et al, 2016; Augustin et al, 2015). Actinic Keratosis Quality of Life is a AK-specific validated instrument that assesses patient QoL; it is a 9-item questionnaire that has three domains covering function, emotions and control and one single global item (Esmann et al, 2013); potential overlap of these domains with Skindex-16 warrants consideration. Complementing QoL evaluations is the assessment of treatment satisfaction, which could add another dimension to the depiction of impact of treatments on patients. The Treatment Satisfaction Questionnaire for Medication (TSQM) is a frequently used validated instrument to measure patient satisfaction across different product attributes; TSQM-9, encompassing 9 items covering satisfaction with treatment effectiveness and convenience, and global satisfaction has been shown to correlate improvement in clinical outcomes to better satisfaction across the questionnaire domains (Bharmal et al, 2009; Augustin et al, 2015, Stockfleth et al, 2017). A combination of these PRO instruments may provide the foundation to assess patients' perspective and capture different aspects of health related QoL, impact of treatment on patient QoL, and patients' satisfaction with the AK medications and fill critical gaps in AK literature.

Several therapeutic options are currently available to manage AK, including, lesion-directed and field-directed therapies (Eisen et al, 2021). Field-directed therapies, such as topical treatments, are usually found effective, while causing LSRs at the treated area. The duration of topical treatments and severity of LSRs may affect patients' QoL, treatment adherence, satisfaction, and overall outcomes (Balcere et al, 2019; Del Rosso et al, 2014; Diepgen et al, 2019; Goldberg, 2017; Rosso et al., 2021). Some patients may even reject treatments altogether if they feel the

risks and burdens outweigh the benefits (Kopasker et al, 2019; Stockfleth et al, 2015). There remains an unmet need for a treatment which has more tolerable LSRs and more convenient dosing for patients while still being effective in clearing the lesions (Kempers et al, 2020). Congruently, assessment of patient perceptions of cosmetic outcomes and their future preference/willingness to retreat with a specific treatment could serve as key outcome measures in patient-centric studies, especially in the real-world settings, to inform optimal management of patients with AK in routine clinical practices.

Qualitative tele-depth interviews of AK patients were conducted to solicit their perspectives on impact of AK and topical treatments for AK on their QoL and daily activities. The interviews highlighted the importance of key QoL domains such as emotions and functioning, as well as the impact of treatment related LSRs on patient QoL, daily activities and overall treatment satisfaction. Using a qualitative modified delphi method, an expert panel was convened to determine the questions to solicit patient (and clinician) perspectives of clinical and cosmetic outcomes associated with AK, future treatment preferences and the perceptions of treatment related LSRs; the expert panel agreed on 11 specific items encompassing these topics. The overall appearance of the skin in the treated area, satisfaction with the treatment's ability to improve how skin looks, satisfaction with the treatment's ability to improve skin texture were suggested to address facets of cosmetic outcomes; likelihood to consider treatment again, and overall satisfaction with current (topical) treatment were suggested to support future preference assessment; relative rating of duration of LSRs and severity of LSRs associated with topical treatments, and relative impact of topical treatments on patient's daily activities were suggested to assess perceptions of LSR. The expert panel also suggested evaluating the relative 'convenience/ease of use' of topical treatments, considering its potential impact on treatment adherence. These collective recommendations are aligned with the consensus statement on core outcome set for AK (Reynolds et al, 2020). Lastly, the panel also suggested two novel clinical outcome measures to assess the clinical status of AK in the real-world settings, incl. an IGA on the level of AK lesion clearance, and an IGA of severity of skin photodamage in the treated area. These eleven questions constituted the Expert Panel Questionnaire (EPQ). As a consensus, the expert panel concluded that the EPQ, along with Skindex-16 and TSQM-9 are optimal tools to

use in community-based real world research involving AK patients to highlight treatment benefits. These tools are depicted in Appendix-B.

Tirbanibulin (Klisyri®) offers a safe and efficacious treatment option for AK patients. Tirbanibulin is a synthetic, first-in-class, potent anti-proliferative agent that inhibits tubulin polymerization and disrupts Src kinase signaling that are upregulated in AK and iSCC (Kempers et al, 2020). Two double-blind, vehicle-controlled, randomized Phase 3 studies, as well as supportive data from the Phase 2a study, demonstrated that treatment with tirbanibulin ointment 1% for 5 days was efficacious in the clearance of AK. When compared with vehicle, treatment with tirbanibulin ointment 1% resulted in statistically significantly higher rates of complete (100%) AK clearance, as well as clearance of each the face, and scalp subgroups, independently, for each Phase 3 study (Blauvelt et al, 2021). Concordant with the primary efficacy endpoint, partial (≥75%) clearance rates and reduction in AK lesion counts over time were also statistically higher in the tirbanibulin-treated group than the vehicle group in both Phase 3 studies. No discontinuations or SAEs related to tirbanibulin were reported in the two trials (Blauvelt et al, 2019). Due to the advantage of shorter treatment duration and less severe LSRs, tirbanibulin have potential to enhance treatment adherence and satisfaction, compared to other topical treatments (Marson et al, 2021; Rosso et al, 2021).

The clinical trial results of tirbanibulin highlight the clinical benefits derived by the AK patients. The demonstration of tirbanibulin-related benefits, including its impact on patient HRQoL, patient and clinician satisfaction with tirbanibulin treatment, and their preferences in real world community practice settings is warranted to highlight tirbanibulin value proposition to patients, clinicians and payers alike. The Skindex-16 questionnaire, AKQoL, and the complimentary novel EPQ, along with TSQM could be beneficial to use for research in community practice settings to assess treatment outcomes among patients using tirbanibulin.

2.2 Rationale

General understanding of AK impact on different aspects of patient QoL is still evolving. A real-world study leveraging validated instruments such as Skindex-16, AKQoL and the complimentary novel EPQ (developed using modified delphi method) could help portray a

broader picture of impact of AK and AK treatment on patients' QoL. Further, assessing the impact of tirbanibulin treatment on AK patient outcomes and preferences, including treatment satisfaction and future preference, in real-world community practice settings could highlight the humanistic and clinical benefits associated this tirbanibulin treatment.

3 OBJECTIVES

3.1 Study Objectives

The primary objective of the study is to evaluate PROs in terms of health-related quality of life (HRQoL) among Subjects with AK in the face or scalp who are administered tirbanibulin in real-world community practice settings in the U.S. The secondary objective is to evaluate effectiveness of tirbanibulin treatment, measured by Investigator Global Assessment (IGA) of the status of AK in the treated area on the face or scalp.

The additional study objectives include the following evaluations among study Subjects and Site Investigators:

- Subject and clinician satisfaction with tirbanibulin treatment and associated outcomes.
- Subject and clinician reported improvement in overall appearance of Subject's skin in the treated area.
- Subject and clinician reported effect/impact of LSRs.
- Subject and clinician reported future treatment preference.
- Safety and tolerability of tirbanibulin.

Note: Dermatologists are expected to predominantly constitute the Site Investigator category, while a few physician assistants and nurse practitioners may be included in the study, reflecting the routine care management of AK in community practice settings.

3.2 Key Study End Points

The primary endpoint of the study will be the PROs, in terms of self-perceived AK symptoms and impact of AK on emotional well-being and functioning as measured using Skindex-16, at Week 8.

The secondary endpoint will be the proportion of Subjects with IGA success, defined as an IGA score of completely cleared (0) or partially cleared (1) in AK status in the treated area at Week 8.

Additional endpoints of the study will include (not exclusively):

- At Week 8, Mean satisfaction scores on TSQM-9 (effectiveness, convenience and overall satisfaction) as well as ad hoc satisfaction questions.
- At Week 8, Mean satisfaction scores on ad hoc physician satisfaction questionnaire.
- At Week 8, proportion of Subjects and Investigators rating the overall appearance of the AK treated area as 'somewhat improved or much improved.'
- At Week 8, proportion of Subjects and Investigators reporting 'somewhat likely or very likely' to consider tirbanibulin in the future to retreat their AK.
- Frequency of documented adverse events (AEs), serious adverse events (SAEs) and LSRs during the first 8-weeks of the study observation period.
- Investigator rating of severity of skin photodamage at Weeks 8 and 24.
- Among Subjects with prior topical treatment experience at baseline:
    - At Week 8, proportion of Subjects and Investigators respectively rating 'convenience/ease of use' of tirbanibulin, and 'overall satisfaction' with tirbanibulin as 'somewhat better or much better' in comparison to previous topical treatments to treat their AK.
    - At Week 8, proportion of Subjects and Investigators respectively rating 'duration of skin reactions', 'severity of skin reactions' and 'impact on daily activities due to skin reactions' related to tirbanibulin, as 'somewhat better or much better' in comparison to previous topical treatments to treat their AK.

4 STUDY DESIGN

This will be a single-arm multi-center prospective cohort study which will enroll adult patients with AK of the face or scalp who are newly initiated with tirbanibulin (Klisyri®) treatment in real-world community practices in the U.S, as part of usual care. Study subjects will be followed for up to 24 weeks post-index date (with the 'index-date' defined as the date of initiation of

tirbanibulin). Study Site Investigators and subjects will complete electronic data collection forms (e-DCFs, or surveys) at baseline (at time of study enrollment), Week 8 and Week 24.

This study will entail provision of tirbanibulin treatment to study participants. Site Investigators will decide on who to prescribe tirbanibulin (Klisyri®) ointment (as per U.S label) as part of usual care, based on their best clinical judgment, prior to subject recruitment. The study is sponsored by Almirall, hereinafter referred to as the Sponsor. The study will be managed by Avant Health, hereinafter referred to as the Contract Research Organization (CRO).

5 STUDY MEDICATION

The study protocol will require identification and selection of patients considered as candidates for a specific medication, namely, tirbanibulin (Klisyri®), as part of usual care. In this context, the study medication will be tirbanibulin (Klisyri®). Clinicians at individual sites (referred to as 'Site Investigators') shall provide the commercial supply of tirbanibulin (Klisyri®) to eligible study Subjects.

Tirbanibulin has an evolving market access in the U.S, with payers reimbursing for the commercial prescriptions on a restricted basis. Selection of only the patients who are able to fill the prescription for reimbursed tirbanibulin may not be representative of individuals who might be candidates for tirbanibulin in the U.S; this may impact the generalization of the study results. To avoid this potential selection bias and improve the prospect of generalization of study results, the commercial supply of tirbanibulin (Klisyri®) will be supplied to Site Investigators for the 5-day treatment episode for each of their Subjects.

Per FDA prescribing information, the recommended dosage of Klisyri® (tirbanibulin ointment 1%) is 1 single-dose packet (2.5 mg tirbanibulin in 250 mg) per application, for 5 consecutive days. The Site Investigators will prescribe tirbanibulin to patients per their clinical judgement. Correspondingly, tirbanibulin prescribed dose and frequency will be captured as part of study data collection.

The first dose of tirbanibulin may be administered by the subject at the clinic (under the supervision of study personnel, at baseline encounter), or at subject's home. Following the first application, Subjects will self-administer the remaining single-dose packets once daily at home for the next 4 consecutive days. Study medication should be applied each day at approximately the same time. It is preferable that study drug application is done early in the day. Subjects will be advised so that the treatment area is not touched or made wet for approximately 12 hours after application.

6 STUDY ENROLLMENT AND WITHDRAWAL

A total of three hundred (300) Subjects will be enrolled in the study, from a maximum of fifty (50) community practices (sites) from across the U.S. During the study enrollment window, study-eligible clinical sites will be sequentially screened, consented for study participation and completion of all study procedures, including enrollment of study eligible Subjects.

The study Subjects will be patients diagnosed with AK on the face or scalp, and aged 18 years or above at the time of initiation of treatment. The study cohort will be drawn from dermatology clinics from across the U.S.

6.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Diagnosed with AK of the face or scalp.
- Has clinically typical, visible, and discrete AK lesions.
- Considered as a potential candidate for tirbanibulin (Klisyri®) treatment to manage their AK.
- Male or female, aged 18 years and above at the time of initiation of treatment with tirbanibulin.
- Willing to avoid excessive sun or UV exposure, and/or use relevant sunscreen protection and protective clothing during the study duration.
- Able to read and write English.
- Provide consent to participate in the study.

- Willing to comply with all study procedures and be available for the duration of the study.

6.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Patients with any dermatological condition of the face or scalp that could interfere with the clinical evaluations.
- Hypertrophic AK lesions, open wounds or suspected skin cancers within close proximity of the treatment area.
- Anticipated need for in-patient hospitalization or in-patient surgery within the next 2 months.
- Patients unable to comply with the requirements of the study or patients who in the opinion of the study physician should not participate in the study.
- Patients for whom medical chart is inaccessible to physicians to complete baseline data collection.

6.3 Strategies for Screening, Recruitment and Retention

6.3.1 Site Investigators

Screening of potential study sites/investigators will take place by reaching out directly to sites and sharing study synopsis and soliciting their interest. If a site expresses interest in the study, they will be asked to consent for study participation. Subsequently, additional information will be shared for contracting and site initiation for subject screening.

All Site Investigators will undertake subject screening/recruitment and data collection using online electronic data collection forms (eDCFs) at baseline and at weeks 8 and 24 from baseline. Periodic follow-up with the study sites will take place throughout the study observation period to ensure engagement and retention.

6.3.2 Study Subjects

Upon successful recruitment of the study sites, the respective Site Investigators may identify a study coordinator at their clinics. Site Investigators and/or the study coordinator will approach, screen and consent up to a maximum of 25 study-eligible Subjects sequentially within the study enrollment window. The approach may take place during the routine patient visit or via email or phone; upon establishing contact with study Subjects, they will be provided with a description of study objectives and procedures.

In the case of in-person recruitment of study Subjects, Subjects will be screened for study eligibility using the study screener. The Subjects deemed eligible for the study will then be provided with a study informed consent form. The study coordinator or Site Investigator will ensure that Subjects can read the consent form and ask questions and be given adequate time to consider the benefits/risks associated with participation in the study. An informed consent will be obtained from each subject in accordance with applicable regulations prior to participating in any study procedures.

In the case of recruitment of study Subjects via email or phone, study coordinator or Site Investigator will pre-screen the Subjects for study eligibility and will then contact the subject to describe the study to each subject and give them adequate time to consider the risks associated with participation in the study. The eligible Subjects will be then provided with a weblink to an online screener and electronic consent (e-consent) form. If a Mobile App is used for the purpose of the study data collection from the Subjects, recruited study Subjects will be asked to download the Mobile App; as they log-in an e-consent form may be presented via the App. Subjects will be able to quickly read and provide informed consent prior to participating in any study procedures by checking a box next to the statement, “I have read the above statement and I consent to participate in this study” and signing their name(s) along with dating the online form (using their web browser or the study Mobile App).

Site Investigator or the study coordinator will assign subject IDs to Subjects sequentially, as they are recruited. Site coordinator will maintain a recruitment log that will identify the subject ID number to their name/contact info. Study site staff alone will have access to Subject contact

information to enable relevant study follow-ups with study Subjects; this information will never be shared with the study CRO or study sponsor, preserving the anonymity of study Subjects.

Only positively-screened and consenting subjects will be allowed to participate in the study and proceed with the study steps. Study subjects will be compensated (per fair market value) for survey completion at relevant study encounters. Study coordinators and/or their Site Investigators will serve as the main point of contact for participants/Subjects at their site for questions and ensure subject retention during the study observation period; reminders for eDCF completion may be sent to study Subjects via email, phone or via the Mobile App.

6.4 Subject Withdrawal

This is a real-world study, and the study participation is completely voluntary. Subjects may withdraw voluntarily from the study at any juncture during the study observation period following the enrollment, for any reason. Site Investigator may terminate a Subject's participation in the study at any juncture, in specific scenarios, as outlined below.

6.4.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

A Site Investigator may terminate a study Subject's participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the Subject. This may include pregnancy among female Subjects, per clinician judgment.
- The Subject meets a study exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The Site Investigator or the study coordinator is unable to reach the Subject and the Subject is considered as lost to follow-up.

6.4.2 Handling of Subject Withdrawals

If a Subject requests withdrawal from the study voluntarily for any reason, the Site Investigators or site coordinator will follow-up with the patient to solicit and document the reason for withdrawal, unless the Subject is considered as lost to follow-up. If the Site Investigator determines that the withdrawal is related to an adverse drug reaction (ADR) or serious adverse event (SAE) associated with tirbanibulin, he/she will gather necessary information concerning the ADR/SAE. The Site Investigator may follow-up with the subject subsequently to ensure resolution of ADR/SAE episode and close out the study documentation for the concerned Subject. There will be no replacement of Subjects who withdraw or discontinue early from the study.

7 STUDY SCHEDULE & PROCEDURES

Study eligible patients who are considered as candidates for tirbanibulin treatment as part of usual care AK management will be screened, consented, and recruited into the study, followed for up to 24 weeks post-index date, encompassing three distinct data collection encounters. With 'T' being the index date of tirbanibulin treatment initiation, the baseline data collection (from both Site Investigators and Subjects) may transpire anytime between T= -2 weeks post-index date and T= +7 days post-index date; the 8-week follow-up data collection (Study Encounter # 2; from both Site Investigators and Subjects) will happen at T=8 weeks post-index date $\pm$ 7 days; and 24-week follow-up data collection (Study Encounter #3; from both Site Investigators and Subjects) will happen at T=24 weeks post-index date $\pm$ 14 days. Index date is the planned date of first application/initiation of tirbanibulin treatment, after the subject was prescribed the tirbanibulin.

Different data elements will be collected from Site Investigators and from study Subjects at these data collection encounters, as outlined below.

The schedule of events is summarized in Appendix A.

7.1 First Study Encounter / Baseline

Baseline data collection will take place at the time of subject enrollment into the study or within a few days of recruitment. The subject encounters are expected to take place during in-person subject visits to the clinic. The recruited Site Investigators and study Subjects will be sent a weblink to the eDCFs and survey respectively for their completion. Subjects will be able to access the surveys on their mobile phone, using a study-specific Mobile App.

The following data elements will be collected at baseline, from patient medical charts and/or per Site Investigator's best clinical judgement based on their recent encounter with the study subject while prescribing tirbanibulin as part of usual care and based on subject's recent past medical history:

- Demographics (e.g., age, gender).
- General clinical characteristics, as documented in medical charts (incl. blood pressure, waist circumference, height/weight measurements, comorbidities).
- AK disease characteristics (incl. AK history, IGA of severity of current skin photodamage in the AK treated area on the face or scalp (using EPQ item)).
- Past AK treatment history (used ever, and those used within the past 6 months).
- Tirbanibulin treatment characteristics (dose, frequency, date of recommendation).
- Concomitant medications (for AK and comorbidities).

The following data elements will be collected at baseline, from study Subjects, via online survey portal or a mobile app:

- Demographics (e.g., gender, race/ethnicity, education, employment/school status, living status).
- Perceptions of AK-related symptoms and impact of AK on Subject QoL, incl. emotional well-being and functioning, using Skindex-16.

7.2 Shipment of Study medication

Following the Site Investigator's decision to prescribe tirbanibulin (Klisyri®) to study eligible patients, a commercial supply of the appropriate dose and quantity of study medication will be shipped to the attention of Site Investigator at their clinic/site. The Site Investigators will be asked to record the planned first day of administration of tirbanibulin, and this date will constitute the study 'index date', upon which the follow-up encounter timepoints (at weeks 8 & 24) will be determined.

7.3 Second Study Encounter

At the completion of 8 weeks (± 7 days) post-index date, the Site Investigators and Subjects will be asked to complete the data collection corresponding to the study primary endpoints. The subject encounters (post-baseline) are expected to take place during in-person subject visits to the clinic, but remote/virtual visits may be allowed where COVID-related protocols prevent in-person visits.

The Site Investigators will complete the following, based on the information documented in the corresponding patient medical charts, and per Subject interaction and per clinical judgment guided by observing study Subject via in-person or remote/virtual visit:

- IGA of AK status (in relation to baseline), and current severity of skin photodamage in the AK treated area on the face or scalp (using EPQ item).
- Investigator rating of overall appearance of the AK treated area (using EPQ item).
- Modifications to tirbanibulin treatment characteristics following the initial prescription, if applicable.
- Perceptions and satisfaction with different attributes of tirbanibulin, and future preference to re-treat with tirbanibulin (using ad hoc and EPQ items).
- Any unplanned patient encounters in the past 8 weeks.
- Newly documented changes to patient clinical characteristics (incl. comorbidities and concomitant medications), as documented in medical charts in past 8 weeks since the baseline encounter.

- AEs, ADRs and LSRs observed in the past 8 weeks, as documented in the medical charts.
- Information on withdrawal from study (if occurred within the past 8 weeks).

The study Subjects will provide the following information via online survey portal or a mobile app:

- Perceptions of AK-related symptoms and impact of AK on Subject QoL, incl. emotional well-being and functioning, using Skindex-16.
- Self-rating of overall appearance of the AK treated area (using EPQ item).
- Perceptions and satisfaction with different attributes of tirbanibulin (using TSQM-9 and EPQ items, where applicable), and future preference to re-treat with tirbanibulin.

7.4 Third Study Encounter

At the completion of 24 weeks (± 14 days) post-index date, the Site Investigators and Subjects will be asked to complete the final study data collection

The Site Investigators will complete the following, based on the information documented in the corresponding patient medical charts, and per Subject interaction and per clinical judgment guided by observing study Subject via in-person or remote/virtual visit:

- IGA of AK status (in relation to baseline), and current severity of skin photodamage in the AK treated area on the face or scalp (using EPQ item).
- Investigator rating of overall appearance of the skin in the original AK treated area.
- Perceptions and satisfaction with different attributes of tirbanibulin, and future preference to re-treat with tirbanibulin (using ad hoc and EPQ items).
- Newly documented changes to patient's AK concomitant medications, as documented in medical charts in past 16 weeks since the Week-8 encounter.
    - Information of topical regimen used for re-treatment (since Week 8) and associated outcomes, if applicable.
    - In case of re-treatment with tirbanibulin:
        - AEs, ADRs and LSRs observed since the re-treatment, as documented in the medical charts.

- Information on withdrawal from study (if occurred within the past 16 weeks).

Subjects will be asked to complete a brief survey, via online survey portal or a mobile app, encompassing the following:

- Self-rating of overall appearance of the skin in the original AK treated area (using EPQ item).
- Self-rating of overall appearance of the skin in the new AK re-treated area (using EPQ item), if re-treated within past 16 weeks.
- Perceptions and satisfaction with different attributes of tirbanibulin (using TSQM-9 and EPQ items, where applicable), and future preference to re-treat with tirbanibulin.

Both the Site Investigators and Subjects will be thanked for their participation in the study. No specific study close-out tasks are expected of the study Subjects. Site Investigators will be asked to submit any outstanding data queries to the research team and then close out the study records at their respective sites.

7.5 AK Photography & Subject Insights

In a small subset of sites (up to 2), Site Investigators will utilize Canfield® photography equipment to take photographs of Subject's AK treated area in the face or scalp to visually capture the clinical status of AK at baseline (study entry) and at Weeks 1, 2, 4 and 8, and will document their assessment/grading of LSR. In addition to the baseline and Week-8 encounters, Subjects at these sites will hence be consented to undertake additional in-person visits at Weeks 1, 2 & 4. At Week 8, the Subjects from these sites will also be asked to record a 1-3 minute audio narrating their perceptions of treatment benefits associated with the tirbanibulin.

7.6 Early Termination Encounter (Study Encounter # x)

Site Investigators will attempt to follow the progress of every subject admitted to the study through to study completion. If a subject fails to complete requested study procedures (i.e, completion of online surveys, or complete study visits), a reasonable effort will be made to contact the subject and ascertain the reason(s) for non-compliance with study procedures.

If a subject does not complete the study for any reason (including Site Investigator discretion), the reason and circumstances for the subject's early termination will be documented; if possible, the assessments specified for the forthcoming (next) study encounter will be performed.

8 STUDY ASSESSMENTS

PROs, encompassing HRQoL, treatment satisfaction and elements from EPQ, will be assessed with study Subjects. Tirbanibulin treatment effectiveness and treatment satisfaction will be assessed by treating Site Investigators. Future treatment preferences will be assessed with both Subjects and Site Investigators. Safety will be evaluated in terms of AEs and ADRs during the treatment period. For pertinent measures, the study respondents will be given an option to indicate "don't know / not applicable", especially related to absence of information tied to a missing visit or Subject discontinuation from the study.

8.1 HRQoL Assessments

The Skindex 16 consists of 16 items that are classified into three domains: symptoms (four items), emotions, (seven items) and functioning (five items) (Chren 2012; Chren et al, 2001). The following questions (items) correspond to each subscale:

Scale	Items
Symptoms	1-4
Emotions	5-11
Functioning	12-16

All items are scored on a seven-point adjectival response scale, with a potential score of 0 to 6. A total score is the average of all 16 items and transformed to a liner scale of 100 varying from 0 (never bothered) to 100 (always bothered). A domain score is determined by the average of scores in each scale within the domain. The higher the score, the more severe is the impairment. The questionnaire will be administered in entirety, at baseline and at Week 8 post-index date.

8.2 Treatment Satisfaction Assessments

8.2.1 Study Subject Treatment Satisfaction Assessments

Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be used to assess the treatment satisfaction of Subjects at Weeks 8 & 24 for all patients, in relation to the tirbanibulin treatment they received at the beginning of the study. TSQM-9 will measure patient satisfaction with treatment on three key domains, namely, effectiveness, convenience, and global satisfaction. The following questions (items) correspond to each subscale:

Scale	Items
Effectiveness	1-3
Convenience	4-6
Global satisfaction	7-9

Most items are scored on a 7-point Likert scale of: 1: very dissatisfied; 2: moderately dissatisfied; 3: slightly dissatisfied; 4: neutral; 5: slightly satisfied; 6: moderately satisfied; 7: very satisfied. Items 7 and 8 of TSQM-9 are scored on a 5-point scale of: 1: not at all confident/certain; 2: a little confident/certain; 3: somewhat confident/certain; 4: very confident/certain; 5: extremely confident/certain. TSQM subscale scores will be computed per tool owner specifications and transformed to scores ranging from 0 to 100, with higher scores representing higher satisfaction on respective domains. The TSQM-9 questionnaire will be administered in entirety, at Weeks 8, and 24 post-index date.

The TSQM-9 questionnaire will also be administered at Week 24 among Subjects who are retreated with tirbanibulin in the past 16 weeks (since Week 8 visit), to solicit their satisfaction with the most recent course of tirbanibulin treatment.

Subject's rating (at Weeks 8 & 24) of their satisfaction with the ability of tirbanibulin treatment to 'improve how their skin looks' and 'improve their skin texture' respectively, in the original treated area will be assessed. The responses will be solicited on the following 7-point Likert scale: 1: very dissatisfied; 2: moderately dissatisfied; 3: slightly dissatisfied; 4: neutral; 5:

slightly satisfied; 6: moderately satisfied; 7: very satisfied. These two EPQ items will also be administered at Week 24 again among Subjects who are retreated with tirbanibulin between Week-8 and Week-24 visits, to solicit their satisfaction with the respective attributes associated with the most recent course of tirbanibulin treatment.

Subject's rating of their 'overall satisfaction' with tirbanibulin treatment, in comparison to other topical treatment(s) will be assessed using a 5-point Likert scale of: 1: much worse; 2: somewhat worse; 3: same; 4: somewhat better; 5: much better. This 'overall satisfaction' assessment will be conducted among two Subject subgroups:

- Among Subjects who have experienced other topical treatments before start of tirbanibulin at baseline: At Week 8, compare rating of tirbanibulin treatment vs. previous topical treatment(s).
- Among Subjects who have been retreated with other topical treatments (other than tirbanibulin) between Week-8 and Week-24 visits: At Week 24, compare rating of original tirbanibulin treatment (at beginning of the study) vs. most recent topical treatment(s).

To complement the overall satisfaction question, factors associated with Subject's satisfaction rating will be assessed.

8.2.1 Site Investigator Treatment Satisfaction Assessments

An ad hoc satisfaction questionnaire very similar to TSQM-9 will be used to assess Site Investigators' satisfaction with tirbanibulin treatment at Weeks 8 & 24, in relation to the tirbanibulin treatment they administered to Subjects at the beginning of the study. The individual item and subscale scorings will be done similar to the original TSQM-9 questionnaire.

The same ad hoc questionnaire will also be administered at Week 24 among Site Investigators managing Subjects who are retreated with tirbanibulin in the past 16 weeks (since Week 8 visit), to solicit their satisfaction with the most recent course of tirbanibulin treatment.

Site Investigator's rating (at Weeks 8 & 24) of their satisfaction with the ability of tirbanibulin treatment to 'improve how their patient's skin looks' and 'improve their patient's skin texture' respectively, in the original treated area will be assessed. The responses will be solicited on the following 7-point Likert scale: 1: very dissatisfied; 2: moderately dissatisfied; 3: slightly dissatisfied; 4: neutral; 5: slightly satisfied; 6: moderately satisfied; 7: very satisfied. These two EPQ items will also be administered at Week 24 again among Subjects who are retreated with tirbanibulin between Week-8 and Week-24 visits, to solicit their satisfaction with the respective attributes associated with the most recent course of tirbanibulin treatment.

Site Investigator's rating of their 'overall satisfaction' with tirbanibulin treatment, in comparison to other topical treatment(s) will be assessed using a 5-point Likert scale of: 1: much worse; 2: somewhat worse; 3: same; 4: somewhat better; 5: much better. This 'overall satisfaction' assessment will be conducted among two Subject subgroups:

- Among Subjects who have experienced other topical treatments before start of tirbanibulin at baseline: At Week 8, compare rating of tirbanibulin treatment vs. previous topical treatment(s).

- Among Subjects who have been retreated with other topical treatments (other than tirbanibulin) between Week-8 and Week-24 visits: At Week 24, compare rating of original tirbanibulin treatment (at beginning of the study) vs. most recent topical treatment(s).

To complement the overall satisfaction question, factors associated with Site Investigator's satisfaction rating will be assessed.

8.3 Treatment Effectiveness Assessments

The effectiveness of tirbanibulin treatment will be assessed from the perspective of Site Investigators as well as the Subjects. It is expected that the Site Investigator assessments will be conducted via in-person visits/encounters at baseline, Week 8 and Week 24, and when in-person assessments are not feasible (owing to COVID-related travel restrictions), the assessments

maybe done via virtual/remote visits. The same evaluator at study site shall perform all evaluations for a subject during the study, as feasible.

8.3.1 Investigator Global Assessment (IGA):

Site Investigators to assess the status of subject's AK in the treated area on the face or scalp using the following IGA scale, at Weeks 8 and 24. The IGA should be representative of the investigator's overall general assessment of the subject's AK and take into account the quality, as well as the quantity, of AK lesions.

Outcome Measure	Score
Completely cleared - Approximately 100% clearance of AK lesions in the treated area	0
Partially cleared - Approximately ≥75% clearance of AK lesions in the treated area	1
Moderately cleared - Approximately 50-74% clearance of AK lesions in the treated area	2
Minimally Cleared - Approximately <50% clearance of AK lesions in the treated area	3
Not Cleared - Approximately 0% clearance, i.e., all AK lesions remained in the treated area	4

8.3.2 Severity of Skin Photodamage

Site Investigators will be asked to rate the severity of skin photodamage in the AK treated area (at baseline, Weeks 8 and 24), on the following 4-point Likert scale:

Outcome Measure	Score
Absent - Smooth evenly pigmented skin	0
Mild - Freckling and/or other dyspigmentation	1

Moderate - Above plus mildly rough "dry" skin, fine wrinkling and/or telangiectasias or blotchy erythema	2
Severe - Above plus pronounced "dryness" and/or dyspigmentation and/or telangiectasia or erythema, and/or wrinkling, with or without areas of actinic purpura	3

8.3.3 Cosmetic Appearance of Skin

Subjects and Site Investigators will be asked to rate current 'overall appearance of the skin' in the AK treated area (at Weeks 8 and 24, in comparison to baseline), on the following 5-point Likert scale: 1: much worse; 2: somewhat worse; 3: no change; 4: somewhat improved; 5: much improved.

Subjects will be asked to state how often has he/she been bothered by the appearance of the skin, at Baseline and Week 8, using item # 7 in Skindex-16 questionnaire. This item however will not be analyzed individually but assessed as part of emotions subscale of Skindex-16.

8.3.4 Study Subject Qualitative Narratives

Subjects from a small subset of study sites (up to 2) will be asked to record a 1-3 minute audio (using the Mobile App) narrating their perceptions of treatment benefits associated with the tirbanibulin, at Week 8. This qualitative data will be used to ascertain attributes that study Subjects associate with tirbanibulin treatment in an un-prompted manner.

8.3.5 Study Subject Photographic Assessments

Site Investigators from a subset of study sites (up to 2) will take photographs of AK lesions in Subject's treatment area on the face or scalp at baseline encounter and at Weeks 1, 2, 4 and 8, during the in-person visits. This photographic data will be used to document and depict the changes in AK lesions and LSRs that may be associated with tirbanibulin treatment in the study.

8.4 Additional Study Assessments

8.4.1 Future Treatment Preference

Subjects and Site Investigators will be asked to state their likelihood to consider tirbanibulin to retreat AK, on a 5-point Likert scale of: 1=very unlikely, 2=somewhat unlikely, 3=neutral, 4=somewhat likely, 5=very likely). This will be assessed at Weeks 8 and 24.

8.4.1 Convenience/Ease of Use

Subjects and Site Investigators will be asked to rate the convenience/ease of use associated with tirbanibulin treatment, in comparison to other topical treatment(s), using a 5-point Likert scale of: 1: much worse; 2: somewhat worse; 3: same; 4: somewhat better; 5: much better. This assessment will be conducted among two Subject subgroups:

- Among Subjects who have experienced other topical treatments before start of tirbanibulin at baseline: At Week 8, compare rating of tirbanibulin treatment vs. previous topical treatment(s).

- Among Subjects who have been retreated with other topical treatments (other than tirbanibulin) between Week-8 and Week-24 visits: At Week 24, compare rating of original tirbanibulin treatment (at beginning of the study) vs. most recent topical treatment(s).

8.4.2 Perceptions of LSRs

The following three assessments will be conducted at Week-8 for Subjects who have experienced other topical treatments before start of tirbanibulin at baseline, and at Week-24 for Subjects who have been treated with other topical treatments (other than tirbanibulin) between Week-8 and Week-24 visits:

- Subjects and Site Investigators will be asked to rate the ‘duration of skin reactions’ associated with tirbanibulin, in comparison to other topical treatments (previous or most recent retreatment). The relative assessment will be based on a 5-point Likert scale of: 1: much longer; 2: somewhat longer; 3: the same; 4: somewhat shorter; 5: much shorter.

- Subjects and Site Investigators will be asked to rate the 'severity of skin reactions' associated with tirbanibulin, in comparison to other topical treatments (previous or most recent retreatment). The relative assessment will be based on a 5-point Likert scale of: 1: much worse; 2: somewhat worse; 3: the same; 4: somewhat better; 5: much better.
- Subjects will be asked to rate the 'impact on their daily activities due to skin reactions' associated with tirbanibulin use, in comparison to other topical treatments (previous or most recent retreatment). The relative assessment will be based on a 5-point Likert scale of: 1: much worse; 2: somewhat worse; 3: the same; 4: somewhat better; 5: much better.

8.4.3 Unscheduled Patient Encounters

Number of unscheduled clinician encounters (via in-person clinic visits, telehealth visits and phone calls) that AK patient had in the past 8 weeks will be assessed, based on the information documented in the patient medical charts at Week 8 encounter.

8.4.4 Adherence to Treatment

Subjects will report (at Week 8) their adherence to tirbanibulin treatment by indicating the number of missed single-dose applications within the expected 5-day application period/regimen.

8.5 Safety Assessments

8.5.1 Definition of Adverse Events & Adverse Drug Reactions

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

The Site Investigator will use the following terms to assess the severity of each AE:

- Mild: Awareness of symptoms or signs, but easily tolerated (acceptable)
- Moderate: Enough discomfort to interfere with usual activity (disturbing)
- Severe: Interferes significantly with ability to do work or usual activity (unacceptable)

A Serious Adverse Event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any event which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization* or prolongation of hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
    - social reasons and respite care in the absence of any deterioration in the subject's general condition.
- results in persistent of significant disability / incapacity, or
- is a congenital anomaly / birth defect,
- is a significant or important medical event that, based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

* Hospitalization is defined as an overnight (in-patient) stay at the hospital or emergency room.

For all AEs (either related or not related to study medication), information about the outcome (i.e., recovered, recovering, not recovered, recovered with sequelae, fatal, unknown) and the action taken with the study treatment (i.e., drug withdrawn, dose reduced, dose increased, dose not changed, not applicable) will be documented.

Each AE, either serious or non-serious for which a causal relationship to tirbanibulin cannot be excluded, will be considered as an ADR. An ADR is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a medicinal product or

result from the combination of two or more medicinal products. LSRs (such as: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration), skin scarring and pigmentation (such as: hypo- and hyper-pigmentation) as a result of application of tirbanibulin in AK treatment area will not be considered as ADRs, but will be documented separately.

The determination of whether an AE is related to study treatment (tirbanibulin) will be based on information regarding the degree to which the study treatment had caused or contributed to the event and will be categorized per the following criteria:

- Related: There were good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the study medication in the sense that it is plausible, conceivable or likely.

- Not Related: There were good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the study medication.

8.5.2 Documentation of AEs and Reporting of SAEs and Serious ADRs

The Site Investigator is responsible for assessing and documenting (in subject medical charts, as part of usual care) all AEs that occur at any time during the study. The Site Investigator will determine the relatedness, seriousness, and severity for each AE, which is then recorded in the Adverse Events page of the eDCF, per study schedule of events (Appendix A). Following the Subject encounter at Weeks 8 and 24 (be it, via in-person or remote encounters), the Site Investigator will evaluate the documentation (in subject medical charts; corresponding to the time since the last visit) to report AEs and indicate whether those events resulted in stoppage or changes to dose of tirbanibulin, as applicable.

Each AE that meets the definition of SAE or Serious ADR will be recorded in the eDCF and comprehensively documented on the "Safety Report Form" and reported within 1 working day (24 hours) of learning of the event to Almirall via email. If any additional information is needed

to adequately document the SAEs or Serious ADRs, the study CRO will follow-up with the Site Investigators to ensure data completeness and will report the updated information back to the study sponsor. If an SAE or Serious ADR results in modification of study medication dose or discontinuation of study medication and/or withdrawal of subject from the study, such information will be documented as part of eDCF and in the Safety Report form.

As part of usual care, Site Investigator will follow Subjects concerning all SAEs and Serious ADRs until adequate resolution or stabilization. If the SAE/Serious ADR has not resolved or stabilized by the time the subject completed the final study encounter or at the time of Subject's termination from the study, the Site Investigator may subsequently follow-up with the Subject to check the status of Subject's SAE/Serious ADR, prior to completing the eDCF for Subject's last encounter, if feasible.

If a study subject (in case of female) becomes pregnant during the study period, the Site Investigator may withdraw the patient from the study (i.e., early termination) for safety reasons. In this scenario, the Site Investigator will document the reasons for withdrawal in the eDCF and may conduct necessary follow-ups with the patient to ensure safety, as part of usual care. Occurrence of this (pregnancy) event will be reported to the study sponsor within 1 working day (24 hours) of learning of the event.

The full description of safety reporting logistics will be outlined in the study Safety Reporting Plan.

9 STUDY OVERSIGHT

The overall study principal investigators (PIs) along with the principal investigator (Program Lead) at CRO will be responsible for this real-world study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The Program Lead within the CRO will review the data for safety concerns and data trends at regular intervals, and will promptly report to the study PIs, the central IRB (and any local IRBs, if applicable) and to the study Sponsor any ADRs, protocol deviation, or any other significant event that arises during the conduct of the study.

10 SITE MONITORING, QUALITY CONTROL AND ASSURANCE

Study site monitoring is conducted to ensure that the rights of human Subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Site monitoring for this minimal-risk, real-world study will be performed by the CRO. The CRO will routinely evaluate study processes and documentation based on the protocol and other applicable requirements, if any.

All site monitoring activities will be performed remotely for this study, with occasional visits to select sites to check on study procedures. Site Investigators or the assigned study coordinators will be contacted routinely by phone and email to ensure that study procedures are followed per protocol and study subject follow-ups happen as planned. Study data review will be undertaken by the CRO staff following the baseline and follow-up encounters for data collection from Site Investigators and study Subjects. Data inquiries will be shared with the Site Investigators for clarification and/or fill missing data elements, or gather additional information, as it may pertain to reported AEs/SAEs.

11 DATA MANAGEMENT

The study data portal will comprise of two distinct, linked data sources, one being the traditional EDC containing eDCF to gather data from Site Investigators; another being the mobile App that gathers data directly from study Subjects. The back-end EDC platform will be programmed with edit checks and will be reflected on the Data Validation Plan and the programmer-version of eDCFs with edit checks will be made part of the DMP. The EDC will be appropriately validated by the CRO and pre-tested with a few clinicians and patients prior to start of the study. The study data procedures will ensure that the incoming data from Site Investigators and Subjects are automatically checked for data quality and safety events.

A centralized data review strategy will ensure consistency, integrity and logical completeness of the AE data. Queries will be generated for study sites to solicit additional required information, as needed. Site Investigators will respond to any data query generated by the CRO in a prompt

manner. Incoming AE data will be routinely checked to flag SAEs and serious ADRs and Pregnancy reports, ensuring site's completion of relevant Safety Report or Pregnancy Report forms, and sharing them with the study sponsor in an expedited manner. As a result of data queries, if any data corrections are required in the EDC portal, those edits will be made at the back-end by the central research staff and ratified by the CRO Program Lead for appropriateness and correctness.

Any additional quality assessment(s) will be carried out at the time of pre-specified study analytic timeframes, per the data management plan. Following completion of all data review activities for all patients, records within the master dataset will be locked, followed by completion of medical coding for concomitant medications and adverse events and preparation of dataset for statistical analyses. The medical history, AEs, and concomitant medications (including rescue medications) will be coded; Medical Dictionary for Regulatory Activities and WHO-DRUG Enhanced dictionaries will be used, version number of each dictionary will be documented in the DMP. A Quality Control check to ensure the accuracy of the data will be done by the CRO when data is cleaned prior to the database lock and analyses. Specifications of the Quality Control check will be found in the DMP. An audit trail of data modifications will be maintained in order to protect the authenticity and integrity of the study data.

12 STATISTICAL CONSIDERATIONS

Detailed plans for the statistical methods will be provided in a Statistical Analysis Plan (SAP) which will be finalized prior to database lock.

12.1 Sample Size Considerations

No formal sample size and power calculations were undertaken. Considering the descriptive nature of the study and the feasibility of recruiting the study population, approximately 300 study Subjects from across a maximum of 50 clinical sites for the entire study has been identified as a sample to guide the planned analysis addressing the study objectives.

12.2 Analysis Populations and Datasets

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

- Safety Population: All patients who received at least one dose of tirbanibulin during the study observation period of 8-weeks related to primary endpoint, as part of usual care.
- Full Analysis Set (FAS): All patients within the Safety Population that had at least some data pertaining to the key variables studied at relevant timepoints, post-baseline.

There is a likelihood that the Safety population and FAS may be the same in certain scenarios, including when no patient discontinues tirbanibulin following study enrollment and prior to 8-week follow-up data collection. In such scenarios, FAS will be the main dataset for all analyses. In the event that the safety population and FAS differ, all safety evaluations (part of additional objectives) will be conducted among the safety population, while FAS will be used to conduct analyses addressing rest of the study objectives, including the primary objective.

12.3 General Statistical Procedures

12.3.1 Overview

Data from Site Investigators and study Subjects will be combined into one dataset. No site-specific analyses will be conducted. Validated instruments will be scored according to developer guidelines, reporting domain scores and overall summary scores, as appropriate. EPQ and other ad hoc questions will be analyzed and reported individually, based on the respective response scales. For all outcome measures, the analyses will focus on baseline, Week-8 and Week-24, as applicable.

All statistical analyses will be based on all available data assuming that all missing data are uninformative and will be conducted using appropriate statistical software, such as SAS. An interim analysis will be conducted after the completion of 8 weeks of data collection for all study

Subjects. The final study analyses will be conducted after the completion of 24 weeks of data collection for all study Subjects.

12.3.2 Summary Statistics

The descriptive statistics for all the continuous variables will include the mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of mean (SEM), minimum, maximum, and number of Subjects. Descriptive summaries will be provided for raw, CFB, and %CFB values for relevant endpoints, where applicable. Frequency distributions for all the categorical variables will be presented as counts and percentages. Summaries will be provided by encounters, as appropriate. Results from the descriptive analyses will be presented as summary tables and figures.

12.3.3 Subgroup Analysis

Primary, secondary, and additional (non-safety) endpoints may be summarized and repeated for the following subgroups, if sample size permits, using FAS:

- AK Treatment location: face, scalp.
- Age groups: <49 years, 50-64 years, and ≥ 65 years.
- Fitzpatrick I/II, and III/IV/V/VI.
- Prior treatment experience, as applicable:
    - Cryosurgery vs. all others;
    - Other topical treatments vs. all others;
    - Treatment naïve vs. all others.
- Patients re-treated between Week-8 and Week-24 visits, vs. all others, as applicable.

Descriptive analyses of Safety data will be carried out using safety population dataset.

12.3.4 Multivariate Analyses

Key study outcome measures at Week 8 post-index date (incl. CFB at Week 8, where applicable), and at Week 24 (where applicable) post-index date will be assessed using relevant multivariate analyses, adjusting for subject baseline characteristics and other variables (such as medication adherence) to discern the factors influencing these outcomes, as feasible. Pearson correlation coefficients may be used to assess the correlation between key outcome measures; this may also inform the consideration of covariates in the selected multivariate analyses (to reduce multicollinearity).

12.4 Primary Endpoint Analysis

The primary endpoint of PROs measured using Skindex-16 at Week 8 will be assessed descriptively using the FAS dataset.

The individual item and domain/subscale scores of Skindex-16 will be created per instrument developer instructions, analyzed descriptively (ie, using mean, SD, median, minimum and maximum), for the baseline and Week 8 encounters, treating the responses as categorical variables and/or continuous variable, as appropriate. CFB in Skindex-16 score will be explored and reported using descriptive statistics. For the overall questionnaire data evaluation, no missing data imputation will be applied to compute domain/subscale scores.

12.5 Secondary Endpoint Analysis

The secondary endpoint of the study is the proportion of Subjects with an IGA success, defined as achieving a rating of 'completely cleared' (0) or 'partially cleared' (1) in IGA of AK status at Week 8. This analyses of IGA will be conducted for the overall cohort (using FAS).

12.6 Additional Analysis

12.6.1 Treatment Satisfaction Analyses

Subject's satisfaction with tirbanibulin treatment at Weeks 8 and 24 measured using TSQM-9 will be analyzed for relevant groups of Subjects, using descriptive statistics (ie, mean, SD, median, minimum and maximum), for each of the three TSQM subscales, using FAS. Site

Investigator's satisfaction with tirbanibulin treatment at Weeks 8 and 24 measured using ad hoc questions that are similar to TSQM-9 will be analyzed for relevant groups of Subjects, similar to TSQM-9 employing descriptive statistics, using FAS.

Subject and Site Investigator's satisfaction with the ability of AK treatment to 'improve how skin looks' and 'improve skin texture' will be respectively analyzed descriptively using data from Weeks 8 and 24, for relevant groups of Subjects, and frequency of responses will be assessed. Proportion of respondents who indicated 'moderately satisfied or very satisfied' on the response scales will be reported for these respective questions, using FAS.

Among Subjects who have experienced other topical treatments before start of tirbanibulin at baseline, Subject and Site Investigator's rating of their 'overall satisfaction' with tirbainbulin treatment at Week 8 and Week 24, in comparison to previous topical treatments to treat Subject's AK will be respectively analyzed descriptively using data from Weeks 8 and 24, and frequency of responses will be tallied for all Subjects. Proportion of respondents who indicated 'somewhat better or much better' on the response scale will be reported, using FAS. Similar analysis of 'overall satisfaction' with tirbanibulin in comparison to most recent topical treatment reported by Subjects and Site Investigators will be performed for the subgroup of Subjects who are re-treated with another topical treatment (other than tirbanibulin) between Week-8 and Week-24, and descriptive results reported using FAS, along with the proportion of respondents who indicated 'somewhat better or much better' on the response scales.

12.6.2 Cosmetic Appearance of Skin

Subject and Site Investigator's rating of overall appearance of the skin in the AK treated area at Weeks 8 and 24 will be respectively analyzed descriptively, and frequency of responses will be tallied for all Subjects. Proportion of respondents who indicated 'somewhat improved or much improved' on the response scale will be reported, using FAS.

12.6.3 Photodamage Severity Analyses

The proportion of Subjects with a severity of score of 0 (absent) and proportion of subjects with a severity score of 0 (absent) or 1 (mild) in clinician assessment of AK-related photodamage at baseline, and at Weeks 8 and 24 will be assessed respectively. CFB in photodamage severity

score at Weeks 8 and 24 will be explored and reported using descriptive statistics. This analysis will be conducted for the overall cohort (using FAS).

12.6.4 Future Treatment Preference

Subject and Site Investigator's statements (at Week 8 and 24) of their likelihood to consider tirbanibulin to retreat AK in the future will be respectively analyzed descriptively, and frequency of responses will be tallied for all Subjects. Proportion of respondents who indicated 'somewhat likely or very likely' on the response scale will be reported, using FAS.

12.6.5 Other Outcome Measures

Among Subjects who have experienced other topical treatments before start of tirbanibulin at baseline, the following outcome measures will be analyzed descriptively, and frequency of responses tallied for all Subjects:

- Subject and Site Investigator's rating (at Week 8 and 24, for relevant groups of Subjects) of 'convenience/ease of use' associated with tirbanibulin treatment, in comparison to previous (or most recent) topical treatment(s) to treat their AK; proportion of respondents who indicated 'somewhat better or much better' on the response scale will be reported using FAS.

- Subject and Site Investigator's rating (at Week 8 and 24, for relevant groups of Subjects) of 'duration of skin reactions' associated with tirbanibulin treatment, in comparison to previous (or most recent) topical treatment(s) to treat their AK; proportion of respondents who indicated 'somewhat shorter or much shorter' on the response scale will be reported using FAS.

- Subject and Site Investigator's rating (at Weeks 8 and 24, for relevant groups of Subjects) of 'severity of skin reactions' associated with tirbanibulin treatment, in comparison to previous (or most recent) topical treatment(s) to treat their AK; proportion of respondents who indicated 'somewhat better or much better' on the response scale will be reported using FAS.

- Subject and Site Investigator's rating of how tirbanibulin (at Weeks 8 and 24, for relevant groups of Subjects) treatment impacted their daily activities due to skin reactions, in comparison to previous (or most recent) topical treatment(s) to treat their AK; proportion of respondents who indicated 'somewhat better or much better' on the response scale will be reported using FAS.

12.6.6 Unscheduled Patient Encounters

Number of unscheduled clinician encounters (via in-person clinic visits, telehealth visits and phone calls) that AK patient had in the past 8 weeks will be analyzed at Week 8 using descriptive statistics (i.e., mean, SD, median, minimum and maximum) and reported.

12.6.7 Treatment Adherence

Treatment adherence will be assessed (at Week 8) as the number of missed single-dose applications within the expected 5-day application period/regimen divided by five, the expected number of single-dose applications of tirbanibulin during the study observation period within first 8 weeks. Treatment adherence will be calculated for each subject, using FAS. Summaries will be presented using descriptive statistics for the Safety population.

Percentage Adherence = [1 - [# of missed single-dose applications out of 5] / 5]*100

12.6.8 Safety Assessments

The safety data will be analyzed descriptively using Safety Population dataset (if it is different from FAS), to report the frequency of occurrences of AEs, SAEs, ADRs, and LSRs. These will be reported at individual item level as well in aggregate at relevant category level for Week 8 post-index date. The number of patients discontinuing treatment within the 8-week post-index date because of AEs, ADRs and for any other reasons will be reported, as documented in patient medical charts.

12.7 Missing Data Handling

The missing data pertinent to the validated instruments Skindex-16, and TSQM-9 will be handled per instrument owner instructions / scoring manual. For all study variables and endpoints, no missing data imputation is planned.

12.8 Sensitivity Analyses

Sensitivity analyses will explore the impact of missing data on the robustness of the results. Reasons for missing data and time to drop-out will be explored in a descriptive manner. The key study outcomes will be explored for Subjects that completed the study versus those that discontinued the study, using descriptive statistics. If some Subject visits are conducted via remote visits instead of in-person visits, the nature of visit (remote vs. in-person) may be used to stratify the analysis of secondary endpoint involving IGA, if sample size permits. Details of the sensitivity analyses will be further described in SAP prior to database lock.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study for the integrity of research and protection of confidentiality of Subjects. Study staff will permit authorized representatives of the IRB and study CRO to examine research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

The eDCFs represent a record of the subject's experience in the study, therefore, the eDCF data will be supported by original (or source) medical records, where feasible. Prior to enrolling a subject in the study, the s Site Investigator or site staff will document his/her review of subject eligibility criteria in the source records for the subject. Current or changes in clinical characteristics of the AK patients, including current or changes to disease severity and medications will be documented in patient medical charts as part of routine clinical practice, and these may constitute source records for the Subjects. Data recorded directly into the eDCF (via online portal) is also considered source data when there are no other written or electronic records

preceding the eDCF entry; data from online surveys completed by study Subjects will be considered as source data, with no back-up records (or data copies) in patient medical charts.

No study monitoring visits will be conducted by the CRO as part of the study, as the sites and Subjects will be managed remotely, and all data will be collected using eDCFs.

The electronically collected data will be periodically reviewed to evaluate the progress of the study; to verify the accuracy and completeness of eDCFs; to ensure that all protocol requirements, and Investigator's obligations are being fulfilled; and to resolve any inquiries related to the study data.

The Site Investigators agrees that the Study CRO or the IRB will have reasonable access to study source documentation (albeit, in de-identified manner) for purposes of audit both during and after completion of the study.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigators will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6, or per central IRB guidelines.

14.2 Institutional Review Board

The protocol, informed consent form(s), and all participant materials will be submitted to a central IRB for review and approval. Approval of both the protocol and the consent forms must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. A progress report will be submitted by the Study CRO Program Lead to the IRB at intervals specified by the IRB, but not less than annually.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

The participating Site Investigator will ensure that written informed consent is obtained from each adult Subject in accordance with applicable regulations. Study Subjects may provide consent using online data collection portal. Each subject will provide informed consent prior to participating in any study procedures, as outlined in Section 6.3.2 of this protocol. As an addendum to the main consent form, the Subjects from a small subset of sites will be consented to allow photographs of their face/scalp taken at baseline, and Weeks 1, 2, 4 and 8 by their clinician at the privacy of the clinician's office, and will be consented to provide a 1-3 minute testimonial of Subject's experience with tirbanibulin at Week 8.

14.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The final research data will constitute only **de-identified** data, for research analyses and reporting. Participants will be identified by a unique study ID number assigned by the site coordinator and/or study CRO, which will be listed on the paper-based consent forms or online e-consent forms and on each of the online e-DCFs. The site coordinator and the CRO project team may review the e-DCFs for any missing data periodically. Access to the online e-DCFs will be restricted to the patient/caregiver, the site coordinator/Investigator, and the relevant representatives from the CRO.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. Site Investigator and study subject contact information will be collected strictly for administrative purposes, such as processing of incentives and to share study follow-up reminders. This personally identifiable information will remain separate from research data.

Photographs to document AK clinical status at baseline and Weeks 1, 2, 4 and 8 will be obtained from a small subset of study Subjects. Audio testimonials depicting Subject's experience with tirbanibulin may be obtained from the same subset of study Subjects at Week 8. All of these data

will be stored electronically and anonymized (using appropriate digital technology) before using this data for further analyses and/or publications.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor or the study CRO. The study CRO or other authorized representatives of the sponsor may inspect all study documents and records, but at no juncture will study subject identifiable information will be collected or disclosed.

15 OTHER INFORMATION

15.1 Publication and Disclosure Policy

Publication and disclosure policy is addressed in a separate agreement.

15.2 Termination of the Study

If the study is terminated prematurely or suspended, the appropriate IRB will be promptly informed of the termination or suspension and will be provided the reason(s) for the termination or suspension. All obligations and responsibilities of the Sponsor and the Investigator will remain in force if the study is terminated prematurely.

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APPENDICES

Appendix A: Study Schedule of Events

Appendix B: Select Study Questionnaires

Appendix C: Signature Page

APPENDIX A: STUDY SCHEDULE OF EVENTS

Study Encounter (physical or virtual)	**Baseline E1**	**E2**	**End of Study E3**	**Early Termination Visit**
Week†		Wk 8 (± 7 d)	Wk 24 (± 14 d)	-
Informed consent	X			
Selection criteria	X			
Demographics & baseline clinical characteristics[1]	X			
Physical examination[2]	X	X		
AK medical history and relevant comorbidites[3]	X	X		X*
Tirbanibulin dose[4]	X			
Prior AK medication (since diagnosis & past 6 months)	X			
Concomitant general medication	X	X		X*
Concomitant anti-AK medication	X	X	X	X*
Site Investigator assessments[5]	X	X	X	X*
Study subject questionnaires[6]	X	X	X	X*
AEs/SAEs[7]	X	X	X	X*
Reasons for premature study withdrawal				X

*Collected, if relevant.

† Expected in-person or virtual encounter schedule, in relation to the index date (date of first administration of tirbanibulin).

[1] Clinical characteristics data assessed retrospectively based on what is documented in patient medical charts.

[2] Routine physical examination conducted as part of usual care alone and as documented in patient medical charts; such data may include - blood pressure, waist circumference, height/weight measurements.

[3] May include AK date of diagnosis, baseline severity, relevant comorbidities, per clinician judgment and/or as documented in patient medical charts immediately before the index date; new emerging comorbidities during the study period will be recorded, based on the documentation in patient medical charts.

[4] Expected usage is once daily, every day during the duration of the trial.

[5] Site Investigator assessments may be conducted during subject visit to clinician offices, or via remote/virtual (telehealth) visits owing to Covid-related travel restrictions; this will include data related to LSRs.

[6] Subject self-assessments may include assessment of AK, HRQoL, treatment satisfaction, and future preferences; Subjects will enter data into online portal or study mobile App.

[7] All AE information will be reported in the eDCF. If the SAE/Serious ADR has not resolved or stabilized by the time the subject completed the final study encounter or at the time of Subject's termination from the study, the Site Investigator may subsequently follow-up with the Subject to check the status of Subject's SAE/Serious ADR, prior to completing the eDCF for Subject's last encounter, if feasible.

Note: AE, adverse event; eDCF, electronic Data Collection Form; V, visit; W, week.

APPENDIX B: SELECT STUDY QUESTIONNAIRES

Expert Panel Questionnaire (EPQ)

1. Compared to {8 or 24} weeks ago (at the beginning of the study), how has the **overall appearance of the skin** in the original AK treated area changed?

   - ☐ Much worse
   - ☐ Somewhat worse
   - ☐ No change
   - ☐ Somewhat improved
   - ☐ Much improved

2. How satisfied are you with this treatment's **ability to improve how your skin looks** (example: reduced redness, discoloration, crusting, scaling) in the original {or most recent} AK treated area?

   - ☐ Extremely Dissatisfied
   - ☐ Very Dissatisfied
   - ☐ Dissatisfied
   - ☐ Somewhat Satisfied
   - ☐ Satisfied
   - ☐ Very Satisfied
   - ☐ Extremely Satisfied

3. How satisfied are you with this treatment's **ability to improve your skin texture** (i.e., how your skin feels in terms of roughness, bumpiness, scaliness) as a result of the treatment, in the original {or most recent} AK treated area?

   - ☐ Extremely Dissatisfied
   - ☐ Very Dissatisfied
   - ☐ Dissatisfied
   - ☐ Somewhat Satisfied
   - ☐ Satisfied
   - ☐ Very Satisfied
   - ☐ Extremely Satisfied

4. Compared to your previous experience with topical treatment X for AK, how would you rate the **duration of skin reactions** (i.e., how long the skin reactions lasted) associated with tirbanibulin (Klisyri®) in the original AK treated area?

- ☐ Duration of skin reactions was much shorter with tirbanibulin
- ☐ Duration of skin reactions was somewhat shorter with tirbanibulin
- ☐ Duration of skin reactions was the same with tirbanibulin
- ☐ Duration of skin reactions was somewhat longer with tirbanibulin
- ☐ Duration of skin reactions was much longer with tirbanibulin

5. Compared to your previous experience with topical treatment X for AK, how would you rate the **severity of skin reactions** (i.e., how bad the skin reactions were) associated with tirbanibulin (Klisyri®) in the original AK treated area?
   - ☐ Severity of skin reactions was much better with tirbanibulin
   - ☐ Severity of skin reactions was somewhat better with tirbanibulin
   - ☐ Severity of skin reactions was about the same with tirbanibulin
   - ☐ Severity of skin reactions was somewhat worse with tirbanibulin
   - ☐ Severity of skin reactions was much worse with tirbanibulin

6. Compared to your previous experience with treatment X, how would you rate the **impact on your daily activities** (such as shopping, bathing, social engagements, scheduling vacations, outdoor activities, activities at work, attendance at work, etc.) due to skin reactions associated with tirbanibulin (Klisyri®) use in the original AK treated area?
   - ☐ Much better with tirbanibulin
   - ☐ Somewhat better with tirbanibulin
   - ☐ Same with tirbanibulin
   - ☐ Somewhat worse with tirbanibulin
   - ☐ Much worse with tirbanibulin

7. Compared to your previous experience with topical treatment X for AK, how would you rate the **convenience / ease of use** (such as frequency of use, easy to follow instructions, comfortable at apply, etc.) associated with tirbanibulin (Klisyri®) treatment?
   - ☐ Ease of use & convenience was much better with tirbanibulin
   - ☐ Ease of use & convenience was somewhat better with tirbanibulin
   - ☐ Ease of use & convenience was the same with tirbanibulin
   - ☐ Ease of use & convenience was somewhat worse with tirbanibulin
   - ☐ Ease of use & convenience was much worse with tirbanibulin

8. Compared to your previous experience with topical treatment X for AK, how would you rate your **overall satisfaction** (considering the factors such as convenience/ ease of use, duration and severity of skin reactions, impact on daily life, etc.) with tirbanibulin (Klisyri®) treatment?

- ☐ My satisfaction is much better with tirbanibulin
- ☐ My satisfaction is somewhat better with tirbanibulin
- ☐ My satisfaction is same with tirbanibulin
- ☐ My satisfaction is somewhat worse with tirbanibulin
- ☐ My satisfaction is much worse with tirbanibulin

9. In case you need to be retreated for AK, how likely are you to consider tirbanibulin (Klisyri®) again?

- ☐ Very unlikely
- ☐ Somewhat unlikely
- ☐ Neutral
- ☐ Somewhat likely
- ☐ Very likely

10. Overall, how is your patient's AK in the original treated area right now?

- ☐ **Completely cleared -** Approximately 100% clearance of AK lesions in the treated area
- ☐ **Partially cleared -** Approximately ≥75% clearance of AK lesions in the treated area
- ☐ **Moderately cleared -** Approximately 50-74% clearance of AK lesions in the treated area
- ☐ **Minimally Cleared -** Approximately <50% clearance of AK lesions in the treated area
- ☐ **Not Cleared -** Approximately 0% clearance, i.e., all AK lesions remained in the treated area

11. How do you rate the current **severity of skin photodamage** in the original AK treated area?

Note: Photodamage can be described as alterations in the structure, function, and appearance of the skin as a result of prolonged or repeated exposure to ultraviolet (UV) radiation from the sun or other UV sources.

- ☐ **Absent -** Smooth evenly pigmented skin
- ☐ **Mild -** Freckling and/or other dyspigmentation
- ☐ **Moderate -** Above plus mildly rough "dry" skin, fine wrinkling and/or telangiectasias or blotchy erythema
- ☐ **Severe -** Above plus pronounced "dryness" and/or dyspigmentation and/or telangiectasia or erythema, and/or wrinkling, with or without areas of actinic purpura

Note:

- For Subjects re-treated with another topical treatment (other than tirbanibulin) at Week-24, questions 3-8 are reworded to enable the assessment of relative satisfaction associated with tirbanibulin in comparison to the 'most recent topical treatment for AK'.
- The clinician version of the questions 3-8 will refer to clinician experience / observation of tirbanibulin effects among their patients.
- Questions 10 & 11 are answered only by clinicians.

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication (tirbanibulin/Klisyri®) you {'took at the beginning of', or 'most recently took in'} this clinical study. We are interested in your evaluation of the effectiveness and convenience of the medication *since you last used it*. For each question, please select the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Note:

- Study clinician will be asked to answer ad hoc version of these satisfaction questions, referring to their experience / observation of tirbanibulin effects among their patients.

Skindex-16

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

APPENDIX-C: SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

[redacted]

Almirall Approvals:

[redacted] MD

[redacted] Signature

PPD Date

Global Medical Affairs

[redacted] Signature

[redacted] Date

Global Development – R&D