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

Statistical Analysis Plan

Version 0.9

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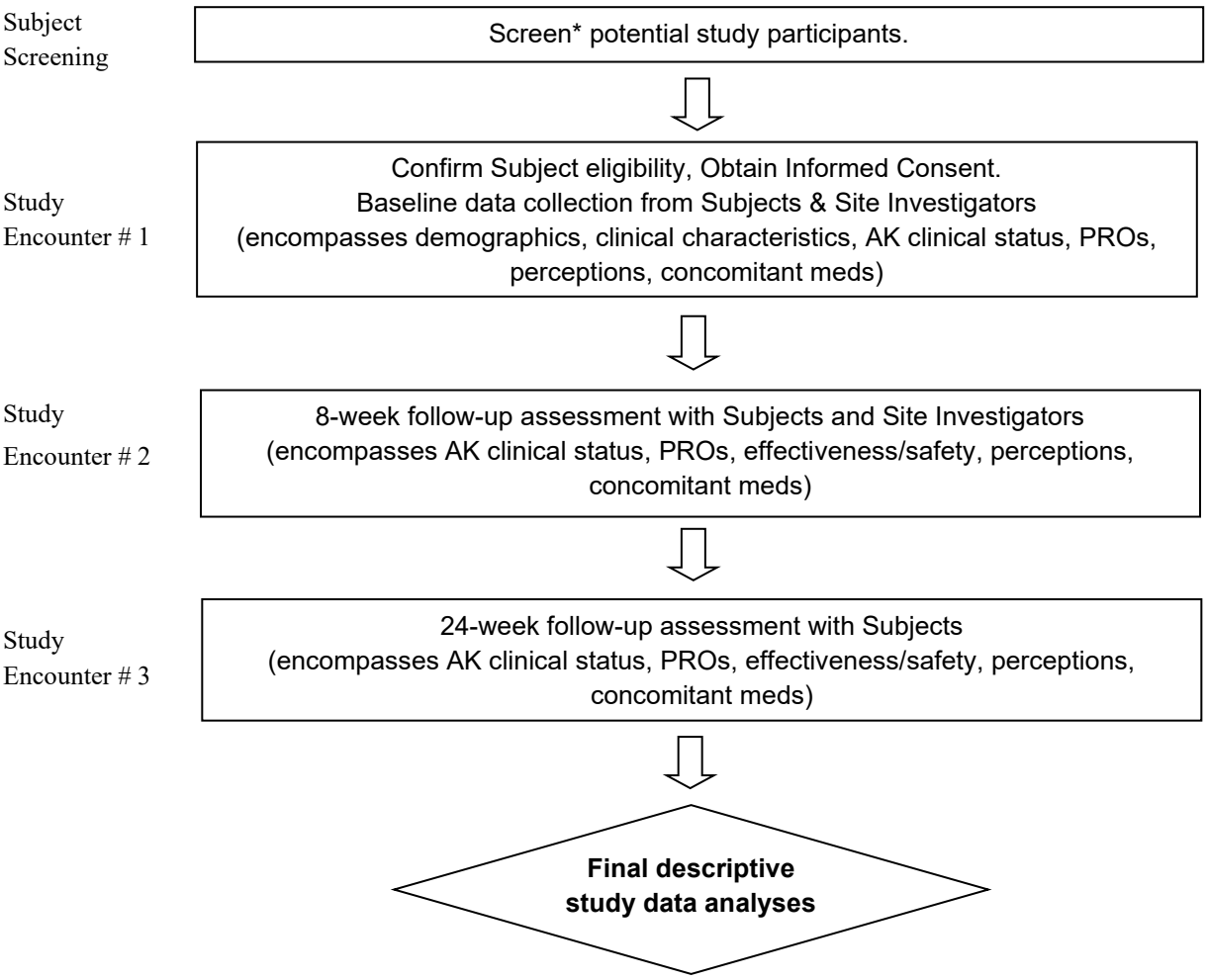
LIST OF ABBREVIATIONS

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

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 roupject'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 PROAK STUDY 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.

2 PROAK STUDY OBJECTIVES

2.1 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.

2.2 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/or '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/or '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.

3 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).

3.1 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.

3.2 Subject Exclusion Criteria

An individual who meets any of the following criteria were 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.

4 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.

5 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 with 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.

5.1 HRQoL Assessments

A combination of a validated questionnaire and an ad hoc questionnaire prepared via modified delphi panel consensus method involving dermatologists, were used for HRQoL assessments.

Skindex-16:

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 domain score is the average of all items within the domain and transformed to a linear scale of 100 varying from 0 (never bothered) to 100 (always bothered). 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.

5.2 Treatment Satisfaction Assessments

5.2.3 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.

5.2.1 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.

5.3 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.

5.3.1 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

5.3.2 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

5.3.3 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.

5.3.4 Study Subject Qualitative Narratives

All subjects from one (1) study site 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.

5.3.5 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.

5.4 Additional Subject Assessments

5.4.1 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.

5.4.2 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).

5.4.3 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.

5.4.4 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. If the patient was retreated with tirbanibulin after week-8, we also collect this data at Week-24 timepoint.

5.5 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.

5.6 Safety Assessments

5.6.1 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.

6 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.

6.1 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.

6.2 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.

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.

6.3 General Statistical Procedures

6.3.1 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.

6.3.2 Summary Statistics

The descriptive statistics for all the continuous variables will include the mean, median, 25th percentile, 75th percentile, standard deviation (SD), 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.

6.3.3 Subgroup Analysis

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

- Gender: male and female
- Age groups: ≤49 years, 50-64 years, and ≥ 65 years.
- Fitzpatrick skin type: I/II, and III/IV/V/VI.
- Skin photodamage at baseline: absent/mild, moderate/severe.
- History of skin cancer: yes and no.
- AK Treatment location: face only, scalp only, both face & scalp.
- Prior treatment experience, as applicable:
    - Cryosurgery vs. all others;
    - Other topical treatments vs. all others;
    - Treatment naïve vs. all others.

Subgroup analyses based on patient retreatment status between Week-8 and Week-24 visits (Klisyri vs. other topicals vs. non topicals vs. not retreated) may be considered for relevant outcome measures, based on data availability.

Subgroup analyses will either assess the difference in outcomes within a specific strata at a given time period (for measures collected only at Week-8 and/or Week-24), or assess CFB within a specific strata (for measures collected at baseline and at Week-8 and/or week-24).

6.4 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.

6.5 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 using the FAS dataset.

6.6 Additional Analysis

6.6.1 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 the FAS dataset.

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 the FAS dataset.

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.

6.6.2 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 the FAS dataset.

6.6.3 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 using the FAS dataset.

6.6.4 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 the FAS dataset.

6.6.5 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 the FAS dataset.

- 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 the FAS dataset.

- 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 the FAS dataset.

- 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 the FAS dataset.

6.6.6 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.

6.6.7 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 the FAS dataset. Summaries will be presented using descriptive statistics for the Safety population.

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

6.6.8 Prior and Concomitant Medications

Medication usage is coded using the latest (2022) WHO Drug Dictionary. Medications are presented by WHO Drug Anatomical/Therapeutic/Chemical (ATC) category and WHO Drug preferred name. Summaries are presented for prior (prior to the first dose of study treatment, gathered as aggregate indicators as well as at individual item level) medication use and concomitant (after first dose of study treatment had been given, gathered at individual item level) medication use. Medications with an end date occurring before the first study treatment (tirbanibulin) date in the treatment period are identified as prior medications. Medications with a start date occurring on or after the first study treatment (tirbanibulin) date in the treatment period or medications with a start date prior to the first (tirbanibulin) dose that were ongoing or with end dates that were on or after 8 weeks post index date are identified as concomitant medications.

Concomitant AK and non-AK medications are captured at Baseline and at Week-8 to characterize the use of concomitant medications among the study cohort. Additional information is captured at Week-24 if the patient was re-treated with tirbanibulin, another topical treatment for AK, or a non-topical treatment for AK between the week-8 and week-24 timepoints.

All summaries present the number (%) of subjects for each medication. The denominators for calculating the percentages are based on the number of subjects in the FAS population.

6.6.9 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.

6.7 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.

6.8 Significant Protocol Deviations

A protocol deviation is defined as any intentional or unintentional failure to follow the requirements and procedures described in the study protocol. Deviations may have occurred at the subject level or at the site level, and could have been recorded by the site, or uncovered data review. Considering the real-world study design of PROAK, reflecting the routine clinical practices in the U.S and associated patient encounters and routine/standard of care data documentation, patients are expected to miss clinic visits or reschedule planned visits as life situations change. These will not be considered as protocol deviations.

Significant protocol deviations will be flagged, and these are defined as study-related issues that were likely to result in: significant impairment of the rights, welfare or safety of subjects; misconduct and/or fraud; and significant impairment of the integrity/validity of study results. Significant protocol deviations also include issues that were likely to impair monitoring and oversight of the study.

6.9 Sensitivity Analyses

Sensitivity analyses will explore the impact of missing data on the robustness of the results, if unusual number of missing data is observed in the study. 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.

7 DATA TABLES

All patients who received at least one dose of tirbanibulin during the study observation period and had at least some data pertaining to study primary endpoints (PROs) at Week 8 will be included in **Full Analysis Set (FAS)** to facilitate the planned descriptive analysis. Correspondingly, patients who completed the study survey at Week 8 will be included in FAS, since patients answering Week 8 survey will have completed all relevant PRO related questions.

Safety data analyses will be conducted among the **Safety Population**, that correspond to the entire study cohort that took at least one dose of tirbanibulin. Correspondingly, all patients completing the baseline survey and took at least one dose of tirbanibulin, amounting to N=300 will be included in this analysis.

Section 7.1 Patient Demographics, Perceptions & PROs (FAS Population)

Section 7.2 Tables from Clinician's DCF (FAS Population)

Section 7.3 Tables for Comparison of Patient and Clinician Data (FAS Population)

Section 7.4 Tables from Clinician DCF: Safety Population

Section 7.5 Sensitivity Analyses

7.1 Patient Demographics, Perceptions & PROs (FAS Population)

Patient data analysis including demographics, perceptions, and PRO data is analyzed using the FAS dataset. All results depicted in this section pertain to FAS Population.

Table 1.1 Population

S1: Population	
Total # of patients in FAS dataset	N (100%)

Note: Data from Patient DCF

Table 1.2 Patient Demographic Characteristics

Adult Demographic Data	Total (N=x)
S1: Age	**Mean (SD)** **Median** **Min, Max**
S3: Gender	
Male	n (%)
Female	n (%)
Other S3r3oe	n (%)
S4: Marital Status	
Not Married	n (%)
Not Marries, living with Partner	n (%)
Married or Civil Union	n (%)
Divorced or Separated	n (%)
Widow/Widower	n (%)
Prefer not to answer	n (%)
S5: Highest level of Education	
Less than high school diploma/degree	n (%)
High school degree or equivalent (e.g., GED)	n (%)
Some college but not degree	n (%)
Associated degree	n (%)
Bachelor's degree	n (%)
Graduate degree	n (%)
Prefer not to answer	n (%)
S6: Employment status	
Employed/Working full-time (paid)	n (%)
Employed/Working part-time (paid)	n (%)
Homemaker	n (%)
Student	n (%)
Retired	n (%)
Unemployed	n (%)
S7: Annual household income	
$20,000 or less	n (%)
$20,001-$50,000	n (%)
$50,001-100,000	n (%)
$100,001 or more	n (%)
Prefer not to answer	n (%)
S8: Regions/States	
Northeast	n (%)
Midwest	n (%)

West	n (%)
South	n (%)
S9: Number of household members	
0	n (%)
1	n (%)
2	n (%)
3	n (%)
4	n (%)
More than 4	n (%)
S14: Primary Health Insurance	
Private health insurance	n (%)
Medicaid	n (%)
Medicare	n (%)
Uninsured	n (%)
S10: Race/Ethnicity*	
S10r1: White	n (%)
S10r2: Black or African American	n (%)
S10r3: American Indian or Alaska Native	n (%)
S10r4: Asian	n (%)
S10r5: Native Hawaiian or other Pacific Islander	n (%)
S10r6: Other	n (%)
S10r7: Prefer not to answer	n (%)
S11: Hispanic, Latino, or of Spanish Origin	
Yes	n (%)
No	n (%)

*Not mutually exclusive. Note: Data from Patient DCF.

Table 1.3 Patient Self-Assessment: AK Treatment Motivators

Treatment Motivations*	Baseline (N=x)
S12: What motivated subject to see AK treatment most recently:	
[S12r1] Skin Cancer Screening	n (%)
[S12r2] Concerned about AK	n (%)
[S12r3] Concerned about scars	n (%)
[S12r4] Sent by partner	n (%)
[S12r5] Sent by family	n (%)
[S12r6] Recommended by Dermatologist	n (%)
[S12r7] Other: S12r7oe	n (%)

Note: *mutually exclusive. Data from Patient DCF; X patients had missing data; The denominator for the percentage is the number of patients with available data (N=XX)

Table 1.4 Patient Self-Assessment: Baseline Skin Texture

Skin Texture *	Baseline (N=x)
S13 If you run your hand across your face and/or scalp, how would you describe the texture:	
S13r1 Dry	n (%)
S13r2 Smooth	n (%)
S13r3 Rough	n (%)
S13r4 Bumpy	n (%)
S13r5 Scaly	n (%)
S13r6 Blistering	n (%)
S13r7 Peeling	n (%)

Note: *Mutually exclusive Data from Patient DCF; X patients had missing data; The denominator for the percentage is the number of patients with available data (N=XX)

Table 1.5 Patient Reported Medication Compliance

Character	Week 8 (N=X)
MC1: Did you take all five doses as prescribed?	
Yes	n (%)
No	n (%)
MC2: If no, how many doses did you miss (out of five total)?	
None^	n (%)
One	n (%)
Two	n (%)
Three	n (%)
Four	n (%)
Five	n (%)

Note: Data from Patient DCF. ^None corresponds to MC1=Yes; all other responses corresponds to MC1=No.

Table 1.6 SKINDEX-16: Patient Response Summary

Domain	Baseline (N=X)	Week 8 (N=X)
Symptoms		
SK1: Over the past week, how often have you been bothered by itching?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered (0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Symptoms		
SK2: Over the past week, how often have you been bothered by Burning or Stinging?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered (0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Symptoms		
SK3: Over the past week, how often have you been bothered by your skin condition hurting?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)

(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Symptoms		
SK4: Over the past week, how often have you been bothered by your skin condition being irritated?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK5: Over the past week, how often have you been bothered by persistence/recurrence of skin condition?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK6: Over the past week, how often have you worried about your skin condition spreading, worsening, scarring (etc.)?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)

(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK7: Over the past week, how often have you been bothered by the appearance of your skin condition?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK8: Over the past week, how often have you been frustrated by your skin?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK9: Over the past week, how often have you been embarrassed by your skin?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)

Always Bothered (6)	n (%)	n (%)
Emotions		
SK10: Over the past week, how often have you been annoyed about your skin?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Emotions		
SK11: Over the past week, how often have you been feeling depressed about your skin condition?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Functioning		
SK12: Over the past week, how often has your interactions with others been affected by your skin condition?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)

Always Bothered (6)	n (%)	n (%)
Functioning		
SK13: Over the past week, how often has your desire to be with people been affected by your skin condition?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Functioning		
SK14: Over the past week, how often has skin condition made it hard to show affection?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)
Functioning		
SK15: Over the past week, how often has your skin effected your daily activities?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)

Functioning		
SK16: Over the past week, how often has skin condition made it hard to work or do what you enjoy?	n Mean (SD), Median,Min,Max	n Mean (SD), Median,Min,Max
Never Bothered(0)	n (%)	n (%)
(1)	n (%)	n (%)
(2)	n (%)	n (%)
(3)	n (%)	n (%)
(4)	n (%)	n (%)
(5)	n (%)	n (%)
Always Bothered (6)	n (%)	n (%)

Note: Data from Patient DCF; X patients had missing data; The denominator for the percentage is the number of patients with available data (N=XX)

Table 1.7 SKINDEX-16: CFB at Week-8 for Individual Items

Domain	Baseline (N=X)	Week 8 (N=X)	CFB in Proportion at Week 8	p-value
Symptoms **SK1:** Over the past week, how often have you been bothered by itching?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Symptoms **SK2:** Over the past week, how often have you been bothered by Burning or Stinging?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Symptoms **SK3:** Over the past week, how often have you been bothered by your skin condition hurting?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Symptoms				

SK4: Over the past week, how often have you been bothered by your skin condition being irritated?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Emotions				
SK5: Over the past week, how often have you been bothered by persistence/recurrence of skin condition?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Emotions				
SK6: Over the past week, how often have you worried about your skin condition spreading, worsening, scarring (etc.)?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Emotions				
SK7: Over the past week, how often have you been bothered by the appearance of your skin condition?				

0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Emotions				
SK8: Over the past week, how often have you been frustrated by your skin?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Emotions				
SK9: Over the past week, how often have you been embarrassed by your skin?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Emotions				
SK10: Over the past week, how often have you been annoyed about your skin?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Emotions				
SK11: Over the past week, how often have you been feeling				

depressed about your skin condition?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Functioning				
SK12: Over the past week, how often has your interactions with others been affected by your skin condition?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value
Functioning				
SK13: Over the past week, how often has your desire to be with people been affected by your skin condition?				
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	*p-value*
Functioning				
SK14: Over the past week, how often has skin condition made it hard to show affection?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value

Functioning				
SK15: Over the past week, how often has your skin effected your daily activities?	n (%)	n (%)	%	*p-value*
	n (%)	n (%)	%	
0 / 1	n (%)	n (%)	%	*p-value*
2 / 3 / 4				
5 / 6				
Functioning				
SK16: Over the past week, how often has skin condition made it hard to work or do what you enjoy?				
0 / 1	n (%)	n (%)	%	p-value
2 / 3 / 4	n (%)	n (%)	%	
5 / 6	n (%)	n (%)	%	p-value

Note:
Data from Patient DCF; X patients had missing data; The denominator for the percentage is the number of patients with available data (N=XX). For all Skindex items, the response options ranged from 0 (never bothered) to 6 (always bothered).

Table 1.8 SKINDEX-16: Domain Scores

Domain	Scores at Baseline (N=x)	Scores at Week 8 (N=x)	CFB in Scores at Week 8 (N=x)	*p*-value
Symptoms				
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max	Mean, SE (SD) Median	*p*
Emotions				
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max	Mean, SE (SD) Median	*p*
Functioning				
	Mean, SE (SD) Median Min, Max	Mean, SE (SD) Median Min, Max	Mean, SE (SD) Median	*p*

Note: Data from Patient DCF.

Table 1.9 Subgroup Analysis of SKINDEX-16 Domain Scores

Subgroups	Symptoms			Emotions			Functioning		
	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P
Gender									
Male									
Female									
Age Group									
≤ 49 years									
50 – 64 Years									
≥ 65 years									
AK Treatment Location									
Face									
Scalp									
Both									
BL Fitzpatrick Skin Type									
I / II									
III / IV / V / VI									
BL Skin Photodamage									
Absent/mild									
Moderate/Severe									
BL History of Skin Cancer									
Yes									
No									
Prior Treatment Experience: Use of Cryosurgery									
Yes									
No									
Prior Treatment Experience: Use of Other Topical Treatments									
Yes									
No									
Prior Treatment Experience: Treatment Naïve at Baseline									
Yes									
No									

P-values correspond to CFB at week-8, within respective strata.

Table 1.10 Patient Evaluation of Overall Appearance in the Original Treated Area

Questions	PER1 Week 8 (N=x)	PER24_1 Week 24 (N=x)
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?	Mean (SD), Median, Min, Max	Mean (SD), Median, Min, Max
1. Much Worse	n (%)	n (%)
2. Somewhat Worse	n (%)	n (%)
3. No Change	n (%)	n (%)
4. Somewhat Improved	n (%)	n (%)
5. Much Improved	n (%)	n (%)
(1 / 2) Much / Somewhat Worse	n (%)	n (%)
(3) No Change	n (%)	n (%)
(4 / 5) Somewhat / Much Improved	n (%)	n (%)

Table 1.11 Subgroup Analysis of Patient Evaluation of Overall Appearance in the Original Treated Area

% Somewhat/Much Improved Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.12 Treatment Satisfaction Questionnaire for Medication (TSQM-9): Patient Scores in the Original Treated Area

Domain	Week 8 (N=x)	Week 24 (N=x)
Effectiveness		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max
Convenience		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max
Global Satisfaction		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max

Note: Data from Patient DCF

Instructions for TSQM Scoring:

Variables TS1 - TS9

TSQM			
Scoring Steps	**Global Satisfaction Score**	**Effectiveness Score**	**Convenience Score**
1	Sum TS7 TS8 TS9	Sum TS1 TS2 TS3	Sum TS4 TS5 TS6
2	Subtract 3	Subtract 3	Subtract 3
3	Divide 14	Divide 18	Divide 18
4	Multiple 100	Multiple 100	Multiple 100
	Output: Average Score per patient		

Table 1.13 Subgroup Analysis of TSQM-9 Patient Domain Scores

Subgroups	Effectiveness			Convenience			Global Satisfaction		
	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P
Gender									
Male									
Female									
Age Group									
≤ 49 years									
50 – 64 Years									
≥ 65 years									
AK Treatment Location									
Face									
Scalp									
Both									
BL Fitzpatrick Skin Type									
I / II									
III / IV / V / VI									
BL Skin Photodamage									
Absent/mild									
Moderate/Severe									
BL History of Skin Cancer									
Yes									
No									
Prior Treatment Experience: Use of Cryosurgery									
Yes									
No									
Prior Treatment Experience: Use of Other Topical Treatments									
Yes									
No									
Prior Treatment Experience: Treatment Naïve at Baseline									
Yes									
No									

P-values correspond to CFB at week-8, within respective strata.

Table 1.14 Patient Satisfaction with Tirbanibulin in the Original Treated Area (looks/texture)

Domain	Week 8 (N=x)	Week 24 (N=x)
PT1: How satisfied are you with this treatment's ability to improve how your skin looks (example: reduced redness, discoloration, crusting, scaling) in the original AK treated area?	**Mean (SD), Median,Min,Max**	**Mean (SD), Median,Min,Max**
1. Extremely Dissatisfied	n (%)	n (%)
2. Very Dissatisfied	n (%)	n (%)
3. Dissatisfied	n (%)	n (%)
4. Somewhat Satisfied	n (%)	n (%)
5. Satisfied	n (%)	n (%)
6. Very Satisfied	n (%)	n (%)
7. Extremely Satisfied	n (%)	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)	n (%)
PT2: 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 AK treated area?	**Mean (SD), Median,Min,Max**	**Mean (SD), Median,Min,Max**
1. Extremely Dissatisfied	n (%)	n (%)
2. Very Dissatisfied	n (%)	n (%)
3. Dissatisfied	n (%)	n (%)
4. Somewhat Satisfied	n (%)	n (%)
5. Satisfied	n (%)	n (%)
6. Very Satisfied	n (%)	n (%)
7. Extremely Satisfied	n (%)	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)	n (%)

Table 1.15 Subgroup Analysis of Patient Satisfaction with Treatment Ability to Improve How Skin Looks in the Original Treated Area

% Extremely/Very Satisfied Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline*		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.16 Subgroup Analysis of Patient Satisfaction with Treatment Ability to Improve Skin Texture in the Original Treated Area

% Extremely/Very Satisfied Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
< 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.17 Patient Relative Satisfaction of Tirbanibulin in Comparison with Other Topical Medications for AK in the Original Treated Area

Domain	Week 8 (N=x)
TT1: 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?	**Mean (SD), Median,Min,Max**
1. Duration of skin reactions was much shorter with tirbanibulin	n (%)
2. Duration of skin reactions was somewhat shorter with tirbanibulin	n (%)
3. Duration of skin reactions was the same with tirbanibulin	n (%)
4. Duration of skin reactions was somewhat longer with tirbanibulin	n (%)
5. Duration of skin reactions was much longer with tirbanibulin	n (%)
(1 / 2) Duration of skin reactions was much / somewhat shorter with tirbanibulin	n (%)
(3) Duration of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Duration of skin reactions was somewhat / much longer with tirbanibulin	n (%)
TT2: 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?	**Mean (SD), Median,Min,Max**
1. Severity of skin reactions was much better with tirbanibulin	n (%)
2. Severity of skin reactions was somewhat better with tirbanibulin	n (%)
3. Severity of skin reactions was the same with tirbanibulin	n (%)
4. Severity of skin reactions was somewhat worse with tirbanibulin	n (%)
5. Severity of skin reactions was much worse with tirbanibulin	n (%)
(1 / 2) Severity of skin reactions was much / somewhat better with tirbanibulin	n (%)
(3) Severity of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Severity of skin reactions was much / somewhat worse with tirbanibulin	n (%)

TT3: 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?	**Mean (SD), Median,Min,Max**
1. Much better with tirbanibulin	n (%)
2. Somewhat better with tirbanibulin	n (%)
3. Same with tirbanibulin	n (%)
4. Somewhat worse with tirbanibulin	n (%)
5. Much worse with tirbanibulin	n (%)
(1 / 2) Much / somewhat better with tirbanibulin	n (%)
(3) Same with tirbanibulin	n (%)
(4 / 5) Somewhat / much worse with tirbanibulin	n (%)
TT4: 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?	**Mean (SD), Median,Min,Max**
1. Ease of use & convenience was much better with tirbanibulin	n (%)
2. Ease of use & convenience was somewhat better with tirbanibulin	n (%)
3. Ease of use & convenience was the same with tirbanibulin	n (%)
4. Ease of use & convenience was somewhat worse with tirbanibulin	n (%)
5. Ease of use & convenience was much worse with tirbanibulin	n (%)
(1 / 2) Ease of use & convenience was much / somewhat better with tirbanibulin	n (%)
(3) Ease of use & convenience was the same with tirbanibulin	n (%)
(4 / 5) Ease of use & convenience was somewhat / much worse with tirbanibulin	n (%)
TT5: 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?	**Mean (SD), Median,Min,Max**
1. My satisfaction is much better with tirbanibulin	n (%)
2. My satisfaction is somewhat better with tirbanibulin	n (%)
3. My satisfaction is same with tirbanibulin	n (%)
4. My satisfaction is somewhat worse with tirbanibulin	n (%)

5. My satisfaction is much worse with tirbanibulin	n (%)
(1 / 2) My satisfaction is much / somewhat better with tirbanibulin	n (%)
(3) My satisfaction is same with tirbanibulin	n (%)
(4 / 5) My satisfaction is somewhat / much worse with tirbanibulin	n (%)

Table 1.18 Subgroup Analysis of Patient Relative Satisfaction of Tirbanibulin, Regarding Duration of Skin Reactions

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.19 Subgroup Analysis of Patient Relative Satisfaction of Tirbanibulin, Regarding Severity of Skin Reactions

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.20 Subgroup Analysis of Patient Relative Satisfaction of Tirbanibulin, Regarding its Impact on Daily Activities

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.21 Subgroup Analysis of Patient Relative Satisfaction of Tirbanibulin, Regarding its Convenience / Ease of Use

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.22 Subgroup Analysis of Patient's Overall Satisfaction with Tirbanibulin Relative to Previous Topical Treatments

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.23 Factors Influencing Overall Patient Satisfaction with Tirbanibulin in the Original Treated Area

TT6_2 What factors influenced your response to the previous question (TT5) about your overall satisfaction with tirbanibulin (Klisyri®)? **Selected**

Domain	Week 8 N=x	Week 24 N=x
[TT6_2r1]. Product convenience: Length of treatment, frequency, and easiness to take, etc.	n (%)	n (%)
[TT6_2r2] Product effectiveness: Impact on skin appearance.	n (%)	n (%)
[TT6_2r3] Product effectiveness: Impact on AK lesion clearance.	n (%)	n (%)
[TT6_2r4] Product effectiveness: Amount of time it takes to start working.	n (%)	n (%)
[TT6_2r5] Product side-effects: Amount of time it takes for local skin reactions to resolve.	n (%)	n (%)
[TT6_2r6] Product side-effects: Number and type of local skin reactions.	n (%)	n (%)
[TT6_2r7] Product side-effects: Severity of the local skin reactions.	n (%)	n (%)
[TT6_2r8] Product tolerability: Ability to adhere to treatment dose, or intensity.	n (%)	n (%)
[TT6_2r9] Other: **TT6_2r9oe**	n (%)	n (%)

Note: Data from patient DCF.

Table 1.24 Top-3 Factors Influencing Overall Patient Satisfaction with Tirbanibulin in the Original Treated Area Ranking at Week 8

TT6_2A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[TT6A_2r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r9] **Other: (N=x)** TT6A_2r9oe	n (%)	n (%)	n (%)	

Note: Data from patient DCF. Percentages are based on number of patients choosing a particular attribute to previous question (TT6_2).

Table 1.25 Top-3 Factors Influencing Overall Patient Satisfaction with Tirbanibulin in the Original Treated Area Ranking at Week 24

TT6_2A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[TT6A_2r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r9] **Other: (N=x)** TT6A_2r9oe	n (%)	n (%)	n (%)	

Note: Data from patient DCF. Percentages are based on number of patients choosing a particular attribute to previous question (TT6_2).

Table 1.26 Patient Likelihood of Retreatment with Tirbanibulin

Domain	Week 8 (N=x)	Week 24 (N=x)
PT3: In case you need to be retreated for AK, how likely are you to consider tirbanibulin (Klisyri®) again?	**Mean (SD), Median,Min,Max**	**Mean (SD), Median,Min,Max**
Very Unlikely	n (%)	n (%)
Somewhat Unlikely	n (%)	n (%)
Neutral	n (%)	n (%)
Somewhat Likely	n (%)	n (%)
Very Likely	n (%)	n (%)
Very / Somewhat Unlikely	n (%)	n (%)
Neutral	n (%)	n (%)
Somewhat / Very Likely	n (%)	n (%)

Note: Data from patient DCF.

Table 1.27 Subgroup Analysis of Patient Likelihood of Retreatment with Tirbanibulin

% Somewhat / Very Likely Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 1.28 Patient Treatment Details, If Retreated After Week 8: Patient Reported

Domain	Week 24 (N=x)
TH24: Did you start a new AK treatment within the past 16 weeks, following the Week-8 visit?	
TH24 = 0 No	n (%)
TH24_1Ar1: Tirbanibulin (Klisyri®)*	n (%)
TH24_1Ar2: Another topical treatment*	n (%)
TH24_1Ar3: Another treatment (which is not topical) *	n (%)

Note: *Not mutually Exclusive. Data from patient DCF, from week-24.

Table 1.29 Treatment Satisfaction Questionnaire for Medication (TSQM-9): Patient Scores, If Retreated with Tirbanibulin after Week 8

Domain	Week 24 N=xx
Effectiveness	
	Mean (SD) Median Min, Max
Convenience	
	Mean (SD) Median Min, Max
Global Satisfaction	
	Mean (SD) Median Min, Max

Note: Data from Patient DCF, from week-24.

Instructions for TSQM Scoring:

Variables TS1 - TS9

TSQM			
Scoring Steps	Global Satisfaction Score	Effectiveness Score	Convenience Score
1	Sum TS7 TS8 TS9	Sum TS1 TS2 TS3	Sum TS4 TS5 TS6
2	Subtract 3	Subtract 3	Subtract 3
3	Divide 14	Divide 18	Divide 18
4	Multiple 100	Multiple 100	Multiple 100
	Output: Average Score per patient		

Table 1.30 Patient Satisfaction with Tirbanibulin, If Retreated with Tirbanibulin after Week-8 (looks/texture)

Domain	Week-24 (N=x)
PT1: How satisfied are you with this treatment's ability to improve how your skin looks (example: reduced redness, discoloration, crusting, scaling) in the most recent AK treated area?	**Mean (SD), Median,Min,Max**
1. Extremely Dissatisfied	n (%)
2. Very Dissatisfied	n (%)
3. Dissatisfied	n (%)
4. Somewhat Satisfied	n (%)
5. Satisfied	n (%)
6. Very Satisfied	n (%)
7. Extremely Satisfied	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)
PT2: 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 most recent AK treated area?	**Mean (SD), Median,Min,Max**
1. Extremely Dissatisfied	n (%)
2. Very Dissatisfied	n (%)
3. Dissatisfied	n (%)
4. Somewhat Satisfied	n (%)
5. Satisfied	n (%)
6. Very Satisfied	n (%)
7. Extremely Satisfied	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)

Note: Data from patient DCF, from week-24.

Table 1.31 Patient Relative Satisfaction of Tirbanibulin in Comparison with Other Topical Medications for AK, If Retreated with Another Topical Treatment after Week 8

Domain	Week 24 (N=x)
RS1: Compared to your experience with your most recent topical treatment for AK (other than tirbanibulin (Klisyri®), how would you rate the duration of skin reactions (i.e., how long the skin reactions lasted) associated with tirbanibulin (Klisyri®)?	**Mean (SD), Median,Min,Max**
1. Duration of skin reactions was much shorter with tirbanibulin	n (%)
2. Duration of skin reactions was somewhat shorter with tirbanibulin	n (%)
3. Duration of skin reactions was the same with tirbanibulin	n (%)
4. Duration of skin reactions was somewhat longer with tirbanibulin	n (%)
5. Duration of skin reactions was much longer with tirbanibulin	n (%)
(1 / 2) Duration of skin reactions was much / somewhat shorter with tirbanibulin	n (%)
(3) Duration of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Duration of skin reactions was somewhat / much longer with tirbanibulin	n (%)
RS2: Compared to your experience with your most recent topical treatment for AK (other than tirbanibulin (Klisyri®),, how would you rate the severity of skin reactions (i.e., how bad the skin reactions were) associated with tirbanibulin (Klisyri®)?	**Mean (SD), Median,Min,Max**
1. Severity of skin reactions was much better with tirbanibulin	n (%)
2. Severity of skin reactions was somewhat better with tirbanibulin	n (%)
3. Severity of skin reactions was the same with tirbanibulin	n (%)
4. Severity of skin reactions was somewhat worse with tirbanibulin	n (%)
5. Severity of skin reactions was much worse with tirbanibulin	n (%)
(1 / 2) Severity of skin reactions was much / somewhat better with tirbanibulin	n (%)
(3) Severity of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Severity of skin reactions was much / somewhat worse with tirbanibulin	n (%)
RS3: Compared to your experience with your most recent topical treatment for AK (other than tirbanibulin (Klisyri®), how would you rate the impact on your daily activities (such as shopping, bathing,	**Mean (SD),**

social engagements, scheduling vacations, outdoor activities, activities at work, attendance at work, etc.) due to skin reactions associated with tirbanibulin (Klisyri®) use?	**Median,Min,Max**
1. Much better with tirbanibulin	n (%)
2. Somewhat better with tirbanibulin	n (%)
3. Same with tirbanibulin	n (%)
4. Somewhat worse with tirbanibulin	n (%)
5. Much worse with tirbanibulin	n (%)
(1 / 2) Much / somewhat better with tirbanibulin	n (%)
(3) Same with tirbanibulin	n (%)
(4 / 5) Somewhat / much worse with tirbanibulin	n (%)
RS4: Compared to your experience with your most recent topical treatment for AK (other than tirbanibulin (Klisyri®), 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®)?	**Mean (SD), Median,Min,Max**
1. Ease of use & convenience was much better with tirbanibulin	n (%)
2. Ease of use & convenience was somewhat better with tirbanibulin	n (%)
3. Ease of use & convenience was the same with tirbanibulin	n (%)
4. Ease of use & convenience was somewhat worse with tirbanibulin	n (%)
5. Ease of use & convenience was much worse with tirbanibulin	n (%)
(1 / 2) Ease of use & convenience was much / somewhat better with tirbanibulin	n (%)
(3) Ease of use & convenience was the same with tirbanibulin	n (%)
(4 / 5) Ease of use & convenience was somewhat / much worse with tirbanibulin	n (%)
RS5: Compared to your experience with your most recent topical treatment for AK (other than tirbanibulin (Klisyri®), 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?	**Mean (SD), Median,Min,Max**
1. My satisfaction is much better with tirbanibulin	n (%)
2. My satisfaction is somewhat better with tirbanibulin	n (%)
3. My satisfaction is same with tirbanibulin	n (%)
4. My satisfaction is somewhat worse with tirbanibulin	n (%)
5. My satisfaction is much worse with tirbanibulin	n (%)

(1 / 2) My satisfaction is much / somewhat better with tirbanibulin	n (%)
(3) My satisfaction is same with tirbanibulin	n (%)
(4 / 5) My satisfaction is somewhat / much worse with tirbanibulin	n (%)

Note: Data from patient DCF, from week-24.

Table 1.32 Factors Influencing Overall Patient Satisfaction with Tirbanibulin, If Retreated with Tirbanibulin after Week 8

TT6_2 What factors influenced your response to the previous question (RS5) about your overall satisfaction with tirbanibulin (Klisyri®)? **Selected**

Domain	Week 24 If retreated with Klisyri® (N=x)	Week 24 If retreated with another topical treatment (N=x)
[TT6_2r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc.	n (%)	n (%)
[TT6_2r2] **Product effectiveness**: Impact on skin appearance.	n (%)	n (%)
[TT6_2r3] **Product effectiveness:** Impact on AK lesion clearance.	n (%)	n (%)
[TT6_2r4] **Product effectiveness:** Amount of time it takes to start working.	n (%)	n (%)
[TT6_2r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve.	n (%)	n (%)
[TT6_2r6] **Product side-effects:** Number and type of local skin reactions.	n (%)	n (%)
[TT6_2r7] **Product side-effects:** Severity of the local skin reactions.	n (%)	n (%)
[TT6_2r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity.	n (%)	n (%)
[TT6_2r9] **Other:** TT6_2r9oe	n (%)	n (%)

Note: Data from patient DCF, from week-24.

Table 1.33 Top-3 Factors Influencing Overall Patient Satisfaction with Tirbanibulin Ranking, If Retreated with Tirbanibulin after Week 8

TT6_2A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[TT6A_2r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r9] **Other: (N=x)** TT6A_2r9oe	n (%)	n (%)	n (%)	

Note: Data from patient DCF, from week-24. Note: Data from patient DCF. Percentages are based on number of patients choosing a particular attribute to previous question (TT6_2).

Table 1.34 Top-3 Factors Influencing Overall Patient Satisfaction with Tirbanibulin Ranking, If Retreated with Another Topical Treatment after Week 8

TT6_2A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[TT6A_2r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[TT6A_2r9] **Other: (N=x)** TT6A_2r9oe	n (%)	n (%)	n (%)	

Note: Data from patient DCF, from week-24. Percentages are based on number of patients choosing a particular attribute to previous question (TT6_2).

7.2 Tables from Clinician's DCF (FAS Population)

Clinician data is analyzed using the FAS dataset. In relevant instances (such as IGA and physician satisfaction evaluations), only FAS dataset with corresponding week clinician data is used. All data tables in this section correspond to FAS population.

Table 2.1 Site Characteristics

Domain	(N=x)
SC1: Current workplace	
Private, office-based practice	n (%)
Hospital-based practice	n (%)
SC2: Total number of board-certified dermatologists in the practice (including yourself, if applicable)	N, Mean (SD), Median, Min, Max
SC3: At present, how many patients with AKs do you personally manage in a given month?	N, Mean (SD), Median, Min, Max
SC4: How long have you been practicing dermatology, post-residency?	N, Mean (SD), Median, Min, Max

Note: Data from Clinician DCF. The denominator for the percentage is N which refers to total number of unique sites in PROSES study.

Table 2.2 Study Subject Selection Criteria

Domain (N=X)	Yes	No
SS1r1 Diagnosed with actinic keratosis of the face and/or scalp?	n (%)	n (%)
SS1r2 Has clinically typical, visible, and discrete AK lesions?	n (%)	n (%)
SS1r3 Considered a candidate for tirbanibulin (Klisyri®) AND you plan to administer tirbanibulin (Klisyri®) treatment?	n (%)	n (%)
SS1r4 At least 18 years of age at the time of initiation of tirbanibulin (Klisyri®) treatment?	n (%)	n (%)
SS1r5 Willing to avoid excessive sun or UV exposure, and/or use relevant sunscreen protection and protective clothing during the study duration.	n (%)	n (%)
SS1r6 Able to read and write English.	n (%)	n (%)
SS1r7 Able to provide consent to participate AND is willing to comply with study procedure?	n (%)	n (%)
SS2r1 Have another dermatological condition of the face that could interfere with the actinic keratosis clinical evaluations?	n (%)	n (%)
SS2r2 Hypertrophic AK lesions, open wounds or suspected skin cancers within close proximity of the treatment area	n (%)	n (%)
SS2r3 Anticipated need for in-patient hospitalization or in-patient surgery within the next 2 months.	n (%)	n (%)
SS2r4 Have a medical chart accessible to complete baseline data collection?	n (%)	n (%)

Note: Data from Clinician DCF. The denominator for the percentage is the number of patients with available data (N=X). There are no missing data.

Table 2.3 Patient Clinical Characteristics from Medical Chart

Character	Statistics	Baseline (N=XX)
PC1 Gender		
Male	n (%)	
Female	n (%)	
Other	n (%)	
PC2 Primary Health Insurance		
Private health insurance	n (%)	
Medicaid	n (%)	
Medicare	n (%)	
Uninsured	n (%)	
Other: Self Pay	n (%)	
Not available	n (%)	
PC3 Height (in inches)	N, Mean (SD), Median, Min, Max	
PC4 Weight (in lbs/pound)	N, Mean (SD), Median, Min, Max	
PC5 Waist circumference (in inches)	N, Mean (SD), Median, Min, Max	
Body Mass Index (BMI - calculated)	N, Mean (SD), Median, Min, Max	
PC6 Blood pressure (in mm HG)		
Systolic	N, Mean (SD), Median, Min, Max	
Diastolic	N, Mean (SD), Median, Min, Max	
PC7 Concomitant (comorbid) conditions		
None	n (%)	
Anxiety	n (%)	
Anemia or other blood disease	n (%)	
Asthma	n (%)	
Atopic dermatitis	n (%)	
Cancer (of any type)	n (%)	
Crohn's disease / IBD	n (%)	
Diabetes	n (%)	
Depression	n (%)	
Dyslipidemia/Hyperlipidemia	n (%)	
Gastroesophageal reflux disease	n (%)	
Heart disease	n (%)	
Hypertension	n (%)	
Kidney disease	n (%)	

Liver damage or disease	n (%)
Lung disease	n (%)
Osteoarthritis, degenerative arthritis	n (%)
Other gastrointestinal disease	n (%)
Other	n (%)
X Y Z	n (%)
PC8 History of Skin Cancer	
Yes	n (%)
No	n (%)
AK2 Fitzpatrick Skin-type classification?	
Type I	n (%)
Type II	n (%)
Type III	n (%)
Type IV	n (%)
Type V	n (%)
Type VI	n (%)

Note: Data from Clinician DCF; X patients had missing data; The denominator for the percentage is the number of patients with available data (N=X)

Table 2.4 Tirbanibulin Treatment Characteristics for the Original Treated Area

Character	Baseline (N=x)
TH1B:Prescription dose	
1. 1% tirbanibulin, single-dose packets	n (%)
2. Other, please specify [TH1Br2oe]	
a. X	n (%)
TH1C:Prescription frequency	
1. Once daily for 5 consecutive days	n (%)
2. Other, please specify: [TH1Cr2oe]	
a. X	n (%)

Table 2.5 Area of Tirbanibulin Treatment for the Original Treated Area

Character	Baseline (N=x)
AK3A1: What is the AK treatment area you have identified for the patient, to apply tirbanibulin (Klisyri®)?	
Left	
Face	n (%)
Scalp	n (%)
Right	
Face	n (%)
Scalp	n (%)
Center	
Face	n (%)
Scalp	n (%)
Unknown	
Face	n (%)
Scalp	n (%)
Overall	
Face (any area)	n (%)
Scalp (any area)	n (%)

Table 2.6 Tirbanibulin Treatment Completion Rate for the Original Treated Area

Character	Week 8 (N=X)
P2: Did the patient complete 5-day treatment course of tirbanibulin (Klisyri®) at the beginning of the study? (N=X)	
Yes	n (%)
No	n (%)

Note: Data from clinician CRF.

Table 2.7 Clinician Evaluation of Current Severity of Photodamage in the Original Treated Area

Character	Baseline (N=X)	Week 8 (N=x)	Week 24 (N=X)
How do you rate the <u>current</u> severity of skin photodamage in the AK affected area?			
Responses will need to be recoded	AK4	AK8_3	AK8_3
0. Absent	n (%)	n (%)	n (%)
1. Mild	n (%)	n (%)	n (%)
2. Moderate	n (%)	n (%)	n (%)
3. Severe	n (%)	n (%)	n (%)
Absent/ Mild (0/1)	n (%)	n (%)	n (%)
Moderate/Severe (2/3)	n (%)	n (%)	n (%)
Who did the evaluation of patient's AK severity?			
	AK5	AK8_4	AK8_4
1. Dermatologist	n (%)	n (%)	n (%)
2. Nurse practitioner	n (%)	n (%)	n (%)
3. Physician's assistant	n (%)	n (%)	n (%)
How was the evaluation of AK severity done?			
	AK6	AK8_5	AK8_5
1. During in-person patient visit (face-to-face)	n (%)	n (%)	n (%)
2. Via tele-health visit (video)	n (%)	n (%)	n (%)

Table 2.8 CFB for Current Severity of Photodamage in the Original Treated Area

Domain	CFB in Proportion at Week 8 N=X (%)	*p*-value	CFB in Proportion at Week 24 N=X (%)	*p*-value
How do you rate the current severity of skin photodamage in the AK affected area?				
Absent (0)	%	*p*	%	*p*
Mild / Moderate / Severe (1 / 2 / 3)	%		%	
Absent / Mild (0 / 1)	%	*p*	%	*p*
Moderate / Severe (2 / 3)	%		%	

Table 2.9 Subgroup Analysis of Current Severity of Photodamage in the Original Treated Area

% Absent / Mild (0 / 1)	Baseline	Week 8		Week 24	
Subgroups	**n (%)**	**n (%)**	P	**n (%)**	P
Gender					
Male					
Female					
Age Group					
≤ 49 years					
50 – 64 Years					
≥ 65 years					
AK Treatment Location					
Face					
Scalp					
Both					
Fitzpatrick Skin Type					
I / II					
III / IV / V / VI					
Skin Photodamage					
Absent/mild					
Moderate/Severe					
History of Skin Cancer					
Yes					
No					
Prior Treatment Experience: Use of Cryosurgery					
Yes					
No					
Prior Treatment Experience: Use of Other Topical Treatments					
Yes					
No					
Prior Treatment Experience: Treatment Naïve at Baseline					
Yes					
No					

P-values correspond to CFB at respective time periods, within the corresponding strata.

Table 2.10 Clinician Evaluation of IGA in the Original Treated Area

Character	Week 8 (N=x)	Week 24 (N=X)
Overall, how is your patient's AK in the original treated area right now?		
Responses will need to be recoded	AK8_1	AK8_1
0. Completely Cleared	n (%)	n (%)
1. Partially Cleared	n (%)	n (%)
2. Moderately Cleared	n (%)	n (%)
3. Minimally Cleared	n (%)	n (%)
4. Not Cleared	n (%)	n (%)
(0 / 1) Completely/Partially Cleared	n (%)	n (%)
2 Moderately Cleared	n (%)	n (%)
3 /4 Minimally/ Not Cleared	n (%)	n (%)

Table 2.11 IGA Success at Week 8 in the Original Treated Area

Character	Week 8
IGA Success	**N=x**
No	n (%)
Yes	n (%)

Note: IGA success at Week 8, defined as an IGA score of completely cleared (0) or partially cleared (1) in AK status in the original treated area at Week 8. The denominator for the percentages is the number of patients with available data (N=XX). X patients had missing data at Week 8.

Table 2.12 Subgroup Analysis of IGA Success

% IGA Success (Completely/Partially Cleared) Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		
p-value		

Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.13 Clinician Evaluation of Overall Appearance in the Original Treated Area

Character	Week 8 (N=x)	Week 24 (N=X)
Compared to 8 / 24 weeks ago, how has the patient's overall appearance of the skin in the original AK treated area changed?		
	AK8_2	AK8_2
1. Much Worse	n (%)	n (%)
2. Somewhat Worse	n (%)	n (%)
3. No Change	n (%)	n (%)
4. Somewhat improved	n (%)	n (%)
5. Much Improved	n (%)	n (%)
(1/2) Much/Somewhat Worse	n (%)	n (%)
(3) No Change	n (%)	n (%)
(4/5) Somewhat/Much Improved	n (%)	n (%)

Table 2.14 Subgroup Analysis of Clinician Evaluation of Overall Appearance in the Original Treated Area

% Somewhat / Much Improved Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.15 Treatment Satisfaction Questionnaire for Medication: Clinician Scores in the Original Treated Area

Domain	Week 8 N=xx	Week 24 N=xx
Effectiveness		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max
Convenience		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max
Global Satisfaction		
	Mean (SD) Median Min, Max	Mean (SD) Median Min, Max

Note: Data from Clinician DCF. Questions and scoring were based on TSQM-9

Instructions for TSQM Scoring:

Variables TS1 - TS9

TSQM			
Scoring Steps	Global Satisfaction Score	Effectiveness Score	Convenience Score
1	Sum TS7 TS8 TS9	Sum TS1 TS2 TS3	Sum TS4 TS5 TS6
2	Subtract 3	Subtract 3	Subtract 3
3	Divide 14	Divide 18	Divide 18
4	Multiple 100	Multiple 100	Multiple 100
	Output: Average Score per patient		

Table 2.16 Subgroup Analysis of Clinician Treatment Satisfaction Questionnaire for Medication Domain Scores in the Original Treated Area

Subgroups	Effectiveness			Convenience			Global Satisfaction		
	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P	Baseline n, Mean	Wk-8 n, Mean	P
Gender									
Male									
Female									
Age Group									
≤ 49 years									
50 – 64 Years									
≥ 65 years									
AK Treatment Location									
Face									
Scalp									
Both									
BL Fitzpatrick Skin Type									
I / II									
III / IV / V / VI									
BL Skin Photodamage									
Absent/mild									
Moderate/Severe									
BL History of Skin Cancer									
Yes									
No									
Prior Treatment Experience: Use of Cryosurgery									
Yes									
No									
Prior Treatment Experience: Use of Other Topical Treatments									
Yes									
No									
Prior Treatment Experience: Treatment Naïve at Baseline									
Yes									
No									

*If sample size permits. P-values correspond to CFB at week-8, within respective strata.

Table 2.17 Clinician Satisfaction with Tirbanibulin in the Original Treated Area (looks/texture)

Domain	Week 8 (N=x)	Week 24 (N=x)
EPQ1: How satisfied are you with this treatment's ability to improve how your patient's skin looks (example: reduced redness, discoloration, crusting, scaling), in the original AK treated area?	**Mean (SD), Median, Min,Max**	**Mean (SD), Median, Min,Max**
1. Extremely Dissatisfied	n (%)	n (%)
2. Very Dissatisfied	n (%)	n (%)
3. Dissatisfied	n (%)	n (%)
4. Somewhat Satisfied	n (%)	n (%)
5. Satisfied	n (%)	n (%)
6. Very Satisfied	n (%)	n (%)
7. Extremely Satisfied	n (%)	n (%)
8. Don't know / not applicable	n (%)	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)	n (%)
EPQ2: How satisfied are you with this treatment's ability to improve your patient's skin texture (i.e., how the skin feels in terms of roughness, bumpiness, scaliness) as a result of the treatment, in the original AK treated area?	**Mean (SD), Median Min,Max**	**Mean (SD), Median, Min,Max**
1. Extremely Dissatisfied	n (%)	n (%)
2. Very Dissatisfied	n (%)	n (%)
3. Dissatisfied	n (%)	n (%)
4. Somewhat Satisfied	n (%)	n (%)
5. Satisfied	n (%)	n (%)
6. Very Satisfied	n (%)	n (%)
7. Extremely Satisfied	n (%)	n (%)
8. Don't know / not applicable	n (%)	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)	n (%)

Table 2.18 Subgroup Analysis of Clinician Satisfaction with Treatment Ability to Improve How Skin Looks in the Original Treated Area

% Extremely/Very Satisfied Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		

Yes		
No		
p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.19 Subgroup Analysis of Patient Satisfaction with Treatment Ability to Improve Skin Texture in the Original Treated Area

% Extremely/Very Satisfied Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.20 Clinician Relative Satisfaction of Tirbanibulin in Comparison with Other Topical Medications for AK in the Original Treated Area

Domain	Week 8 (N=x)
EPQ3: Compared to your patient's 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®) that the patient experienced in the original AK treated area?	**Mean (SD), Median,Min,Max**
1. Duration of skin reactions was much shorter with tirbanibulin	n (%)
2. Duration of skin reactions was somewhat shorter with tirbanibulin	n (%)
3. Duration of skin reactions was the same with tirbanibulin	n (%)
4. Duration of skin reactions was somewhat longer with tirbanibulin	n (%)
5. Duration of skin reactions was much longer with tirbanibulin	n (%)
(1 / 2) Duration of skin reactions was much / somewhat shorter with tirbanibulin	n (%)
(3) Duration of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Duration of skin reactions was somewhat / much longer with tirbanibulin	n (%)
EPQ4: Compared to your patient's 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®) that the patient experienced in the original AK treated area?	**Mean (SD), Median,Min,Max**
1. Severity of skin reactions was much better with tirbanibulin	n (%)
2. Severity of skin reactions was somewhat better with tirbanibulin	n (%)
3. Severity of skin reactions was the same with tirbanibulin	n (%)
4. Severity of skin reactions was somewhat worse with tirbanibulin	n (%)
5. Severity of skin reactions was much worse with tirbanibulin	n (%)
(1 / 2) Severity of skin reactions was much / somewhat better with tirbanibulin	n (%)
(3) Severity of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Severity of skin reactions was much / somewhat worse with tirbanibulin	n (%)
EPQ5: Compared to your patient's previous experience with treatment X, how would you rate the impact on patient's daily activities (such as shopping, bathing, social engagements, scheduling vacations, activities at work, attendance at work, etc.) due to skin reactions associated with tirbanibulin (Klisyri®) use in the original AK treated area?	**Mean (SD), Median,Min,Max**
1. Much better with tirbanibulin	n (%)
2. Somewhat better with tirbanibulin	n (%)

3. Same with tirbanibulin	n (%)
4. Somewhat worse with tirbanibulin	n (%)
5. Much worse with tirbanibulin	n (%)
(1 / 2) Much / somewhat better with tirbanibulin	n (%)
(3) Same with tirbanibulin	n (%)
(4 / 5) Somewhat / much worse with tirbanibulin	n (%)
EPQ6: Compared to your patient's 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?	**Mean (SD), Median,Min,Max**
1. Ease of use & convenience was much better with tirbanibulin	n (%)
2. Ease of use & convenience was somewhat better with tirbanibulin	n (%)
3. Ease of use & convenience was the same with tirbanibulin	n (%)
4. Ease of use & convenience was somewhat worse with tirbanibulin	n (%)
5. Ease of use & convenience was much worse with tirbanibulin	n (%)
(1 / 2) Ease of use & convenience was much / somewhat better with tirbanibulin	n (%)
(3) Ease of use & convenience was the same with tirbanibulin	n (%)
(4 / 5) Ease of use & convenience was somewhat / much worse with tirbanibulin	n (%)
EPQ7: Compared to your patient's 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 patient's daily life, etc.) with tirbanibulin (Klisyri®) treatment?	**Mean (SD), Median,Min,Max**
1. My satisfaction is much better with tirbanibulin	n (%)
2. My satisfaction is somewhat better with tirbanibulin	n (%)
3. My satisfaction is same with tirbanibulin	n (%)
4. My satisfaction is somewhat worse with tirbanibulin	n (%)
5. My satisfaction is much worse with tirbanibulin	n (%)
(1 / 2) My satisfaction is much / somewhat better with tirbanibulin	n (%)
(3) My satisfaction is same with tirbanibulin	n (%)
(4 / 5) My satisfaction is somewhat / much worse with tirbanibulin	n (%)

Note: *EPQ3 – EPQ7 only asked if patient was indicated using a topical treatment for AK prior to the start of the study. Treatment X refers to this topical treatment(s) and was piped in from the baseline clinician survey.

Table 2.21 Subgroup Analysis of Clinician's Relative Satisfaction of Tirbanibulin, Regarding Duration of Skin Reactions

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.22 Subgroup Analysis of Clinician's Relative Satisfaction of Tirbanibulin, Regarding Severity of Skin Reactions

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.23 Subgroup Analysis of Clinician's Relative Satisfaction of Tirbanibulin, Regarding its Impact on Daily Activities

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.24 Subgroup Analysis of Clinician's Relative Satisfaction of Tirbanibulin, Regarding its Convenience / Ease of Use

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.25 Subgroup Analysis of Clinician's Overall Satisfaction with Tirbanibulin Relative to Previous Topical Treatments

% Much / Somewhat Better Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.26 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin in the Original Treated Area

EPQ8 What factors influenced your response to the previous question about your overall satisfaction with tirbanibulin (Klisyri®)? **Selected**

Domain	Week 8 N=x	Week 24 N=x
[EPQ8r1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc.	n (%)	n (%)
[EPQ8r2] **Product effectiveness**: Impact on skin appearance.	n (%)	n (%)
[EPQ8r3] **Product effectiveness:** Impact on AK lesion clearance.	n (%)	n (%)
[EPQ8r4] **Product effectiveness:** Amount of time it takes to start working.	n (%)	n (%)
[EPQ8r5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve.	n (%)	n (%)
[EPQ8r6] **Product side-effects:** Number and type of local skin reactions.	n (%)	n (%)
[EPQ8r7] **Product side-effects:** Severity of the local skin reactions.	n (%)	n (%)
[EPQ8r8] **Product tolerability:** Ability to adhere to treatment dose, or intensity.	n (%)	n (%)
[EPQ8r9] **Other:** EPQ8r9oe	n (%)	n (%)

Table 2.27 Top-3 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin in the Original Treated Area at Week 8

EPQ8A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[EPQ8Ar1]. Product convenience: Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar2] Product effectiveness: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar3] Product effectiveness: Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar4] Product effectiveness: Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar5] Product side-effects: Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar6] Product side-effects: Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar7] Product side-effects: Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar8] Product tolerability: Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8A r9] Other: (N=x) EPQ8Ar9oe	n (%)	n (%)	n (%)	

Note: Data pulled from patient DCF

Table 2.28 Top-3 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin in the Original Treated Area at Week 24

EPQ8A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[EPQ8Ar1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8A r9] **Other: (N=x)** EPQ8Ar9oe	n (%)	n (%)	n (%)	

Table 2.29 Unscheduled Patient Encounters Reported at Week 8

Domain	Week 8 (N=x)
[US1_1r1] Number of unscheduled in-person clinic visits:	n (%)
[US1_1r2] Number of unscheduled tele-health visits:	n (%)
[US1_1r3] Number of unscheduled phone calls:	n (%)

Table 2.30 Prior AK Treatment (To-Date) Including within the Past 6 Months

Character TH2 and TH3 (Start date prior to Klisyri®; End date within the past 6 months or No end date)	**Baseline (N=x)**
TH2A checked AND TH3=No Has not use any AK medication	n (%)
Topical medication **[TH2r1]** 5-Fluorouracil (5-FU) **[TH2r2]** Salicylic acid **[TH2r3]** Imiquimod **[TH2r4]** Ingenol mebutate **[TH2r5]** Diclofenac **[TH2r6]** Other [TH2r6oe] A B C	n (%)
Oral medication: **[TH2r7]** Isotretinoin Other A B C	n (%)
Other therapies: **[TH2r8]** Photodynamic therapy **[TH2r9]** Cryosurgery/Cryotherapy **[TH2r10]** Chemical/acid peel **[TH2r11]** Curettage **[TH2r12]** Laser therapy **Other:** A B C	n (%)

Note: Data from Clinician DCF; X patients had missing data; The denominator for the percentages is the number of patients with available data (N=X)

Table 2.31 AK Concomitant Medication Use During the 8-Week Observation Period

Character TH3 with no end date TH3Ar6na checked (end date after Klisyri® start date within the 8 week period) Add Variables from week-8 - start date within 8 week period	N=X n (%)
Has not used any acne medication TH3 = No	
Topical medication	
5-Fluorouracil (5-FU)	
Salicylic acid	
Imiquimod	
Ingenol mebutate	
Diclofenac	
Other	
Oral medication	
Isotretinoin	
Other	
Other therapies	
Photodynamic therapy	
Cryosurgery/Cryotherapy	
Chemical/acid peel	
Curettage	
Laser therapy	
Other	

Table 2.32 Non-AK Concomitant Medication Use During the 8-Week Observation Period

Character TH4	N=x
TH4 = No Is not currently on any concomitant medication to manage conditions other than AK medication	
Add Variables from Week-8	
<<categories from WHO ATC classifications>>	
A	n (%)
B	n (%)
C	n (%)
D	n (%)
E	n (%)

Note: Data from Clinician DCF; X patients had missing data; The denominator for the percentages is the number of patients with available data (N=X). This concomitant non-AK medication use correspond to use of medications at any time during the study observation period, overlapping with **Klisyri®** medication use.

Table 2.33 Clinician Likelihood of Retreatment with Tirbanibulin

Domain	Week 8 (N=x)	Week 24 (N=x)
PT3: In case you need to retreat patient for AK, how likely are you to consider tirbanibulin (Klisyri®) again?	**Mean (SD), Median,Min,Max**	**Mean (SD), Median,Min,Max**
1. Very Unlikely	n (%)	n (%)
2. Somewhat Unlikely	n (%)	n (%)
3. Neutral	n (%)	n (%)
4. Somewhat Likely	n (%)	n (%)
5. Very Likely	n (%)	n (%)
1 / 2 Very / Somewhat Unlikely	n (%)	n (%)
3 Neutral	n (%)	n (%)
4 / 5 Somewhat / Very Likely	n (%)	n (%)

Table 2.34 Subgroup Analysis of Clinician Likelihood of Retreatment with Tirbanibulin

% Somewhat / Very Likely Subgroups	Week 8 n (%)	Week 24 n (%)
Gender		
Male		
Female		
p-value		
Age Group		
≤ 49 years		
50 – 64 Years		
≥ 65 years		
p-value		
AK Treatment Location		
Face		
Scalp		
Both		
p-value		
Fitzpatrick Skin Type		
I / II		
III / IV / V / VI		
p-value		
Skin Photodamage		
Absent/mild		
Moderate/Severe		
p-value		
History of Skin Cancer		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Cryosurgery		
Yes		
No		
p-value		
Prior Treatment Experience: Use of Other Topical Treatments		
Yes		
No		

p-value		
Prior Treatment Experience: Treatment Naïve at Baseline		
Yes		
No		
p-value		

P-values correspond to difference between strata within respective time periods.

Table 2.35 Patient Treatment Details, If Retreated After Week 8: Clinician Reported

Domain	Week 24 (N=x)
RMH2: I started a new AK treatment for this patient within the past 16 weeks, following patient's Week-8 visit.	
RHM2 = 2 No	n (%)
RMH2Ar1: Tirbanibulin (Klisyri®)	n (%)
RMH2Ar2: Another topical treatment	n (%)
A [OTE1r1]	
RMH2Ar3: Another treatment (which is not topical)	n (%)
A [NTR1r1]	

Note: Data from Clinician DCF, from week-24.

Table 2.36 Reason for Retreatment, If Retreated with After Week 8

		Week 24			
Domain	**Statistics**	**Retreated with Klisyri® (RMH2Ar1) (N=x)**	**Retreated with Another Topical Treatment (RMH2Ar2) (N=x)**	**Retreated with Non-Topical Treatment (RMH2Ar3) (N=X)**	**Total**
Why was this patient re-treated?					
1. To manage newly emerged AK lesions	n (%)	RTE1_5r1	OTE1r7r1	NTR1r7r1	
2. To re-treat original* treated AK lesions	n (%)	RTE1_5r2	OTE1r7r2	NTR1r7r2	
3. Other	n (%)	[RTE1_5r3oe]	[OTE1r7r3oe]	[NTRr7r3oe]	

Note: Data from Clinician DCF, from week-24.

Table 2.37 Area of Tirbanibulin Treatment, If Retreated with After Week-8

Character	Week 24 If retreated with Klisyri® (N=x)
AK3A1: What is the AK treatment area you have identified for the patient, to apply tirbanibulin (Klisyri®)?	
Left	
Face	n (%)
Scalp	n (%)
Right	
Face	n (%)
Scalp	n (%)
Center	
Face	n (%)
Scalp	n (%)
Unknown	
Face	n (%)
Scalp	n (%)
Overall	
Face (any area)	n (%)
Scalp (any area)	n (%)

Note: Data from Clinician DCF, from week-24.

Table 2.38 Tirbanibulin Treatment Characteristics if Retreated after Week 8

Character	Week 24 If retreated with Klisyri® (N=x)
TH1B: Prescription dose	
1. 1% tirabanibulin, single-dose packets	n (%)
2. Other, please specify [TH1Br2oe]	n (%)
a. X	
TH1C: Prescription frequency	
1. Once daily for 5 consecutive days	n (%)
2. Other, please specify: [TH1Cr2oe]	n (%)
a. X	
RTE1_4: Treatment Status	
1. Patient completed the planned treatment course	n (%)
2. Discontinued due to treatment side-effect	n (%)
3. Discontinued due to treatment intolerability	n (%)
4. Discontinued due to lack of effectiveness	n (%)
5. Discontinued due to other reasons: [RTE1_4r5oe]	n (%)
6. Don't know / Not applicable	n (%)
RTE1_5: **Why was this patient re-treated**	
RTE1_5r1: To manage newly emerged AK lesions	n (%)
RTE1_5r2: To re-treat original* treated AK lesions	n (%)
RTE1_5r3: Other reason: [RTE1_5r3oe]	n (%)

Note: Data from Clinician DCF, from week-24.

Table 2.39 Treatment Satisfaction Questionnaire for Medication: Clinician Scores, If Retreated with Tirbanibulin after Week 8

Domain	Week 24 If retreated with Klisyri® N=xx
Effectiveness	
	Mean (SD) Median Min, Max
Convenience	
	Mean (SD) Median Min, Max
Global Satisfaction	
	Mean (SD) Median Min, Max

Note: Data from Clinician DCF, from week-24.

Instructions for TSQM Scoring:

Variables TS1 - TS9

TSQM			
Scoring Steps	**Global Satisfaction Score**	**Effectiveness Score**	**Convenience Score**
1	Sum TS7 TS8 TS9	Sum TS1 TS2 TS3	Sum TS4 TS5 TS6
2	Subtract 3	Subtract 3	Subtract 3
3	Divide 14	Divide 18	Divide 18
4	Multiple 100	Multiple 100	Multiple 100
	Output: Average Score per patient		

Table 2.40 Clinician Satisfaction with Tirbanibulin, If Retreated with Tirbanibulin after Week 8 (looks/texture)

Domain	Week 24 If retreated with Klisyri® (N=x)
EPQ1_2: How satisfied are you with this treatment's ability to improve how your patient's skin looks (example: reduced redness, discoloration, crusting, scaling), in the original AK treated area?	**Mean (SD), Median, Min,Max**
1. Extremely Dissatisfied	n (%)
2. Very Dissatisfied	n (%)
3. Dissatisfied	n (%)
4. Somewhat Satisfied	n (%)
5. Satisfied	n (%)
6. Very Satisfied	n (%)
7. Extremely Satisfied	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)
EPQ2_2: How satisfied are you with this treatment's ability to improve your patient's skin texture (i.e., how the skin feels in terms of roughness, bumpiness, scaliness) as a result of the treatment, in the original AK treated area?	**Mean (SD), Median, Min,Max**
1. Extremely Dissatisfied	n (%)
2. Very Dissatisfied	n (%)
3. Dissatisfied	n (%)
4. Somewhat Satisfied	n (%)
5. Satisfied	n (%)
6. Very Satisfied	n (%)
7. Extremely Satisfied	n (%)
(1 / 2) Extremely/Very Dissatisfied	n (%)
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)
(6 / 7) Very/Extremely Satisfied	n (%)

Note: Data from Clinician DCF, from week-24.

Table 2.41 Clinician Relative Satisfaction of Tirbanibulin in Comparison with Other Topical Medications for AK, If Retreated with Another Topical Treatment after Week 8

Domain	Week 24 if retreated with another topical (N=X)
RS1: Compared to your patient's 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®) that the patient experienced in the original AK treated area?	**RS1** **Mean (SD), Median,Min,Max**
1. Duration of skin reactions was much shorter with tirbanibulin	n (%)
2. Duration of skin reactions was somewhat shorter with tirbanibulin	n (%)
3. Duration of skin reactions was the same with tirbanibulin	n (%)
4. Duration of skin reactions was somewhat longer with tirbanibulin	n (%)
5. Duration of skin reactions was much longer with tirbanibulin	n (%)
(1 / 2) Duration of skin reactions was much / somewhat shorter with tirbanibulin	n (%)
(3) Duration of skin reactions was the same with tirbanibulin	n (%)
(4 / 5) Duration of skin reactions was somewhat / much longer with tirbanibulin	n (%)
EPQ4: Compared to your patient's 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®) that the patient experienced in the original AK treated area?	**RS2** **Mean (SD), Median,Min,Max**
1. Severity of skin reactions was much better with tirbanibulin	n (%)
2. Severity of skin reactions was somewhat better with tirbanibulin	n (%)
3. Severity of skin reactions was the same with tirbanibulin	n (%)
4. Severity of skin reactions was somewhat worse with tirbanibulin	n (%)
5. Severity of skin reactions was much worse with tirbanibulin	n (%)
(1 / 2) Severity of skin reactions was much / somewhat better with tirbanibulin	n (%)
(3) Severity of skin reactions was the same with tirbanibulin	n (%)

(4 / 5) Severity of skin reactions was much / somewhat worse with tirbanibulin	n (%)
EPQ5: Compared to your patient's previous experience with treatment X, how would you rate the impact on patient's daily activities (such as shopping, bathing, social engagements, scheduling vacations, activities at work, attendance at work, etc.) due to skin reactions associated with tirbanibulin (Klisyri®) use in the original AK treated area?	RS3 **Mean (SD), Median,Min,Max**
1. Much better with tirbanibulin	n (%)
2. Somewhat better with tirbanibulin	n (%)
3. Same with tirbanibulin	n (%)
4. Somewhat worse with tirbanibulin	n (%)
5. Much worse with tirbanibulin	n (%)
(1 / 2) Much / somewhat better with tirbanibulin	n (%)
(3) Same with tirbanibulin	n (%)
(4 / 5) Somewhat / much worse with tirbanibulin	n (%)
EPQ6: Compared to your patient's 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?	RS4 **Mean (SD), Median,Min,Max**
1. Ease of use & convenience was much better with tirbanibulin	n (%)
2. Ease of use & convenience was somewhat better with tirbanibulin	n (%)
3. Ease of use & convenience was the same with tirbanibulin	n (%)
4. Ease of use & convenience was somewhat worse with tirbanibulin	n (%)
5. Ease of use & convenience was much worse with tirbanibulin	n (%)
(1 / 2) Ease of use & convenience was much / somewhat better with tirbanibulin	n (%)
(3) Ease of use & convenience was the same with tirbanibulin	n (%)
(4 / 5) Ease of use & convenience was somewhat / much worse with tirbanibulin	n (%)
EPQ7: Compared to your patient's 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 patient's daily life, etc.) with tirbanibulin (Klisyri®) treatment?	RS5 **Mean (SD), Median,Min,Max**

1. My satisfaction is much better with tirbanibulin	n (%)
2. My satisfaction is somewhat better with tirbanibulin	n (%)
3. My satisfaction is same with tirbanibulin	n (%)
4. My satisfaction is somewhat worse with tirbanibulin	n (%)
5. My satisfaction is much worse with tirbanibulin	n (%)
(1 / 2) My satisfaction is much / somewhat better with tirbanibulin	n (%)
(3) My satisfaction is same with tirbanibulin	n (%)
(4 / 5) My satisfaction is somewhat / much worse with tirbanibulin	n (%)

Note: *EPQ3 – EPQ7 only asked if patient was indicated using a topical treatment for AK prior to the start of the study. Treatment X refers to this topical treatment(s) and was piped in from the baseline clinician survey.

Note: Data from Clinician DCF, from week-24.

Table 2.42 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin, If Retreated after Week 8

EPQ8 What factors influenced your response to the previous question about your overall satisfaction with tirbanibulin (Klisyri®)? **Selected**

Domain	Week-24 if retreated with another topical treatment (N=X)	Week 24 If retreated with Klisyri® (N=x)
Product convenience: Length of treatment, frequency, and easiness to take, etc.	[RS6r1] n (%)	[EPQ8_2r1] n (%)
Product effectiveness: Impact on skin appearance.	[RS6r2] n (%)	[EPQ8_2r2] n (%)
Product effectiveness: Impact on AK lesion clearance.	[RS6r3] n (%)	[EPQ8_2r3] n (%)
Product effectiveness: Amount of time it takes to start working.	[RS6r4] n (%)	[EPQ8_2r4] n (%)
Product side-effects: Amount of time it takes for local skin reactions to resolve.	[RS6r5] n (%)	[EPQ8_2r5] n (%)
Product side-effects: Number and type of local skin reactions.	[RS6r6] n (%)	[EPQ8_2r6] n (%)
Product side-effects: Severity of the local skin reactions.	[RS6r7] n (%)	[EPQ8_2r7] n (%)
Product tolerability: Ability to adhere to treatment dose, or intensity.	[RS6r8] n (%)	[EPQ8_2r8] n (%)
Other:	[RS6r9] n (%) [RS6r9oe]	[EPQ8_2r9] n (%) EPQ8r9oe

Note: Data from Clinician DCF, from week-24.

Table 2.43 Top-3 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin at Week 24, If Retreated with Tirbanibulin after Week-8

EPQ8A Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[EPQ8Ar1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8A5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[EPQ8Ar9] **Other: (N=x)** EPQ8Ar9oe	n (%)	n (%)	n (%)	

Note: Data from Clinician DCF, from week-24.

Table 2.44 Top-3 Factors Influencing Overall Clinician Satisfaction with Tirbanibulin at Week 24, If Retreated with Another Topical Treatment after Week 8

RS6 Among the list of factors that influenced your overall satisfaction with tirbanibulin (Klisyri®), please identify the three most important factors and rank them on a scale of importance from 1 to 3, where 1 is the first most important factor, 2 is the second most important factor and 3 is the third most important factor to you, by entering a number in the boxes next to only those factors in the following list.

Domain	Rank 1	Rank 2	Rank 3	Average Rank
[RS6Ar1]. **Product convenience:** Length of treatment, frequency, and easiness to take, etc. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar2] **Product effectiveness**: Impact on skin appearance. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar3] **Product effectiveness:** Impact on AK lesion clearance. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar4] **Product effectiveness:** Amount of time it takes to start working. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar5] **Product side-effects:** Amount of time it takes for local skin reactions to resolve. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar6] **Product side-effects:** Number and type of local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar7] **Product side-effects:** Severity of the local skin reactions. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar8] **Product tolerability:** Ability to adhere to treatment dose, or intensity. **(N=x)**	n (%)	n (%)	n (%)	
[RS6Ar9] **Other: (N=x)** RS6Ar9oe	n (%)	n (%)	n (%)	

Note: Data from Clinician DCF, from week-24.

Table 2.45 Unscheduled Patient Encounters Reported at Week 24, If Retreated after Week 8

	Week-24			
Domain	**Retreated with Klisyri (RMH2Ar1)** (N=x)	**Retreated with Another Topical Treatment (RMH2Ar2)** (N=x)	**Retreated with Non-Topical Treatment (RMH2Ar3)** (N=X)	**Total** (N=X)
[US1_1r1] Number of unscheduled in-person clinic visits:	n (%)	n (%)	n (%)	n (%)
[US1_1r2] Number of unscheduled tele-health visits:	n (%)	n (%)	n (%)	n (%)
[US1_1r3] Number of unscheduled phone calls:	n (%)	n (%)	n (%)	n (%)

7.3 Tables for Comparison of Patient and Clinician data

For tables comparing patient and clinician data, the FAS dataset is used for analysis only in the instances patient data has corresponding clinician week 12 data. All data tables in this section pertain to FAS population.

Table 3.1 Overall Appearance in Original Treatment Area: Patient and Clinician
7.1.10 & 7.2.13

Question	Statistics	Week 8		Week 24	
		PER1 Patient (N=x)	AK8_2 Clinician (N=x)	PER24_1 Patient (N=x)	AK8_2 Clinician (N=x)
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?	Mean (SD), Median, Min, Max				
	n (%)				
1. Much Worse	n (%)				
2. Somewhat Worse	n (%)				
3. No Change	n (%)				
4. Somewhat Improved	n (%)				
5. Much Improved	n (%)				
(1 / 2) Much / Somewhat Worse	n (%)				
(3) No Change	n (%)				
(4 / 5) Somewhat / Much Improved	n (%)				

Table 3.2 Treatment Satisfaction Questionnaire for Medication Scores in the Original Treatment Area: Patient and Clinician
7.1.12 & 7.2.15

Domain	Statistics	Week 8 Patient (N=x)	Week 8 Clinician (N=x)	Week 24 Patient (N=x)	Week 24 Clinician (N=x)
Effectiveness					
	Mean (SD) Median Min, Max				
Convenience					
	Mean (SD) Median Min, Max				
Global Satisfaction					
	Mean (SD) Median Min, Max				

Table 3.3 Satisfaction with Tirbanibulin in the Original Treated Area (looks/texture): Patient and Clinician
7.1.14 & 7.2.17

Questions	Statistics	Week 8		Week 24	
		Patient (N=x)	Clinician (N=x)	Patient (N=x)	Clinician (N=x)
How satisfied are you with this treatment's ability to improve how your skin looks (example: reduced redness, discoloration, crusting, scaling) in the original AK treated area?	**Mean (SD), Median, Min,Max**	PT1	EP1	PT1	EP1
1. Extremely Dissatisfied	n (%)				
2. Very Dissatisfied	n (%)				
3. Dissatisfied	n (%)				
4. Somewhat Satisfied	n (%)				
5. Satisfied	n (%)				
6. Very Satisfied	n (%)				
7. Extremely Satisfied	n (%)				
(1 / 2) Extremely/Very Dissatisfied	n (%)				
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)				
(6 / 7) Very/Extremely Satisfied	n (%)				

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 AK treated area?	**Mean (SD), Median, Min,Max**	**PT2**	**EPQ2**	**PT2**	**EPQ2**
	n (%)				
1. Extremely Dissatisfied	n (%)				
2. Very Dissatisfied	n (%)				
3. Dissatisfied	n (%)				
4. Somewhat Satisfied	n (%)				
5. Satisfied	n (%)				
6. Very Satisfied	n (%)				
7. Extremely Satisfied					
(1 / 2) Extremely/Very Dissatisfied	n (%)				
(3 / 4 / 5) Dissatisfied/Somewhat Satisfied/Satisfied	n (%)				
(6 / 7) Very/Extremely Satisfied	n (%)				

Table 3.4 Relative Satisfaction of Tirbanibulin in Comparison with Other Topical Medications for AK in the Original Treated Area: Patient and Clinician
7.1.17 & 7.2.20

Domain	Statistics	Week 8 Patient (N=x)	Week 8 Clinician (N=x)
Compared to your [patient's] 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?	**Mean (SD), Median,Min,Max**	TT1	EPQ3
1. Duration of skin reactions was much shorter with tirbanibulin			
2. Duration of skin reactions was somewhat shorter with tirbanibulin	n (%)		
3. Duration of skin reactions was the same with tirbanibulin	n (%)		
4. Duration of skin reactions was somewhat longer with tirbanibulin	n (%)		
5. Duration of skin reactions was much longer with tirbanibulin	n (%)		
(1 / 2) Duration of skin reactions was much / somewhat shorter with tirbanibulin	n (%)		
(3) Duration of skin reactions was the same with tirbanibulin	n (%)		
(4 / 5) Duration of skin reactions was somewhat / much longer with tirbanibulin	n (%)		
Compared to your [patient's] 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?	**Mean (SD), Median,Min,Max**	TT2	EP4
1. Severity of skin reactions was much better with tirbanibulin	n (%)		

2. Severity of skin reactions was somewhat better with tirbanibulin 3. Severity of skin reactions was the same with tirbanibulin 4. Severity of skin reactions was somewhat worse with tirbanibulin 5. Severity of skin reactions was much worse with tirbanibulin (1 / 2) Severity of skin reactions was much / somewhat better with tirbanibulin (3) Severity of skin reactions was the same with tirbanibulin (4 / 5) Severity of skin reactions was much / somewhat worse with tirbanibulin	n (%) n (%) n (%) n (%) n (%) n (%) n (%)		
Compared to your [patient's] 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? 6. Much better with tirbanibulin 7. Somewhat better with tirbanibulin 8. Same with tirbanibulin 9. Somewhat worse with tirbanibulin 10. Much worse with tirbanibulin (1 / 2) Much / somewhat better with tirbanibulin (3) Same with tirbanibulin (4 / 5) Somewhat / much worse with tirbanibulin	**Mean (SD), Median,Min,Max** n (%) n (%) n (%) n (%) n (%) n (%) n (%) n (%)	**TT3**	**EP5**
Compared to your [patient's] 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®)	**Mean (SD), Median,Min,Max**	**TT4**	**EP6**

treatment? 6. Ease of use & convenience was much better with tirbanibulin 7. Ease of use & convenience was somewhat better with tirbanibulin 8. Ease of use & convenience was the same with tirbanibulin 9. Ease of use & convenience was somewhat worse with tirbanibulin 10. Ease of use & convenience was much worse with tirbanibulin (1 / 2) Ease of use & convenience was much / somewhat better with tirbanibulin (3) Ease of use & convenience was the same with tirbanibulin (4 / 5) Ease of use & convenience was somewhat / much worse with tirbanibulin	 n (%) n (%) n (%) n (%) n (%) n (%) n (%) n (%)		
Compared to your [patient's] 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? 6. My satisfaction is much better with tirbanibulin 7. My satisfaction is somewhat better with tirbanibulin 8. My satisfaction is same with tirbanibulin 9. My satisfaction is somewhat worse with tirbanibulin 10. My satisfaction is much worse with tirbanibulin (1 / 2) My satisfaction is much / somewhat better with tirbanibulin (3) My satisfaction is same with tirbanibulin (4 / 5) My satisfaction is somewhat / much worse with tirbanibulin	**Mean (SD), Median,Min,Max** n (%) n (%) n (%) n (%) n (%) n (%) n (%) n (%)	**TT5**	**EPQ7**

Table 3.5 Tirbanibulin Retreatment Likelihood: Patient and Clinician
7.1.26 & 7.2.33

Domain	Statistics	Week 8 Patient (N=x)	Week 8 Clinician (N=x)	Week 24 Patient (N=x)	Week 24 Clinician (N=x)
PT3: In case you need to be retreated for AK, how likely are you to consider tirbanibulin (Klisyri®) again?	**Mean (SD), Median, Min,Max**				
Very Unlikely	n (%)				
Somewhat Unlikely	n (%)				
Neutral	n (%)				
Somewhat Likely	n (%)				
Very Likely	n (%)				
Very / Somewhat Unlikely	n (%)				
Neutral	n (%)				
Somewhat / Very Likely	n (%)				

7.4 Tables from Clinician DCF: Safety Data Analysis

These analyses will use Safety Population dataset.

All patients who started the study and received at least one dose of the sareycline during the study observation period, as part of usual care. This corresponds to the entire cohort of 300 eligible patients who started the study.

Table 4.1 Safety Analysis Population

S1: Population	N=x
Total FAS Population	n (%)
Total Safety Population	n (100%)

Note: Data from Patient DCF

Table 4.2 Study Subject Selection Criteria, Safety Population

Domain (N=X)	Yes	No
SS1r1 Diagnosed with actinic keratosis of the face and/or scalp?	n (%)	n (%)
SS1r2 Has clinically typical, visible, and discrete AK lesions?	n (%)	n (%)
SS1r3 Considered a candidate for tirbanibulin (Klisyri®) AND you plan to administer tirbanibulin (Klisyri®) treatment?	n (%)	n (%)
SS1r4 At least 18 years of age at the time of initiation of tirbanibulin (Klisyri®) treatment?	n (%)	n (%)
SS1r5 Willing to avoid excessive sun or UV exposure, and/or use relevant sunscreen protection and protective clothing during the study duration.	n (%)	n (%)
SS1r6 Able to read and write English.	n (%)	n (%)
SS1r7 Able to provide consent to participate AND is willing to comply with study procedure?	n (%)	n (%)
SS2r1 Have another dermatological condition of the face that could interfere with the actinic keratosis clinical evaluations?	n (%)	n (%)
SS2r2 Hypertrophic AK lesions, open wounds or suspected skin cancers within close proximity of the treatment area	n (%)	n (%)
SS2r3 Anticipated need for in-patient hospitalization or in-patient surgery within the next 2 months.	n (%)	n (%)
SS2r4 Have a medical chart accessible to complete baseline data collection?	n (%)	n (%)

Note: Data from Clinician DCF. The denominator for the percentage is the number of patients with available data (N=X). There are no missing data.

Table 4.3 Patient Demographic Characteristics, Safety Population

Adult Demographic Data	Total (N=x)
S1: Age	**Mean, SE (SD)** **Median** **Min, Max**
S3: Gender	
Male	n (%)
Female	n (%)
Other S3r3oe	n (%)
S4: Marital Status	
Not Married	n (%)
Not Marries, living with Partner	n (%)
Married or Civil Union	n (%)
Divorced or Separated	n (%)
Widow/Widower	n (%)
Prefer not to answer	n (%)
S5: Highest level of Education	
Less than high school diploma/degree	n (%)
High school degree or equivalent (e.g., GED)	n (%)
Some college but not degree	n (%)
Associated degree	n (%)
Bachelor's degree	n (%)
Graduate degree	n (%)
Prefer not to answer	n (%)
S6: Employment status	
Employed/Working full-time (paid)	n (%)
Employed/Working part-time (paid)	n (%)
Homemaker	n (%)
Student	n (%)
Retired	n (%)
Unemployed	n (%)
S7: Annual household income	
$20,000 or less	n (%)
$20,001-$50,000	n (%)
$50,001-100,000	n (%)
$100,001 or more	n (%)
Prefer not to answer	n (%)
S8: Regions/States	
Northeast	n (%)
Midwest	n (%)
West	n (%)

South	n (%)
S9: Number of household members	
0	n (%)
1	n (%)
2	n (%)
3	n (%)
4	n (%)
More than 4	n (%)
S14: Primary Health Insurance	
Private health insurance	n (%)
Medicaid	n (%)
Medicare	n (%)
Uninsured	n (%)
S10: Race/Ethnicity*	
S10r1: White	n (%)
S10r2: Black or African American	n (%)
S10r3: American Indian or Alaska Native	n (%)
S10r4: Asian	n (%)
S10r5: Native Hawaiian or other Pacific Islander	n (%)
S10r6: Other	n (%)
S10r7: Prefer not to answer	n (%)
S11: Hispanic, Latino, or of Spanish Origin	
Yes	n (%)
No	n (%)

Table 4.4 Patient Clinical Characteristics from Medical Chart, Safety Population

Character	Statistics	Baseline (N=XX)
PC1 Gender		
Male	n (%)	
Female	n (%)	
Other	n (%)	
PC2 Primary Health Insurance		
Private health insurance	n (%)	
Medicaid	n (%)	
Medicare	n (%)	
Uninsured	n (%)	
Other: Self Pay	n (%)	
Not available	n (%)	
PC3 Height (in inches)	N, Mean, SE (SD), Median, Min, Max	
PC4 Weight (in lbs/pound)	N, Mean, SE (SD), Median, Min, Max	
PC5 Waist circumference (in inches)	N, Mean, SE (SD), Median, Min, Max	
Body Mass Index (BMI - calculated)	N, Mean, SE (SD), Median, Min, Max	
PC6 Blood pressure (in mm HG)		
Systolic	N, Mean, SE (SD), Median, Min, Max	
Diastolic	N, Mean, SE (SD), Median, Min, Max	
PC7 Concomitant (comorbid) conditions		
None	n (%)	
Anxiety	n (%)	
Anemia or other blood disease	n (%)	
Asthma	n (%)	
Atopic dermatitis	n (%)	
Cancer (of any type)	n (%)	
Crohn's disease / IBD	n (%)	
Diabetes	n (%)	
Depression	n (%)	
Dyslipidemia/Hyperlipidemia	n (%)	
Gastroesophageal reflux disease	n (%)	
Heart disease	n (%)	
Hypertension	n (%)	
Kidney disease	n (%)	
Liver damage or disease	n (%)	

Lung disease	n (%)
Osteoarthritis, degenerative arthritis	n (%)
Other gastrointestinal disease	n (%)
Other	n (%)
X Y Z	n (%)
PC8 History of Skin Cancer	
Yes	n (%)
No	n (%)
AK2 Fitzpatrick Skin-type classification?	
Type I	n (%)
Type II	n (%)
Type III	n (%)
Type IV	n (%)
Type V	n (%)
Type VI	n (%)

Table 4.5 Tirbanibulin Treatment Characteristics for the Original Treated Area, Safety Population

Character	Baseline (N=x)
TH1B:Prescription dose	
3. 1% tirbanibulin, single-dose packets	n (%)
4. Other, please specify [TH1Br2oe]	
a. X	n (%)
TH1C:Prescription frequency	
3. Once daily for 5 consecutive days	n (%)
4. Other, please specify: [TH1Cr2oe]	
a. X	n (%)

Table 4.6 Area of Tirbanibulin Treatment for the Original Treated Area, Safety Population

Character	Baseline (N=x)
AK3A1: What is the AK treatment area you have identified for the patient, to apply tirbanibulin (Klisyri®)?	
Left	
Face	n (%)
Scalp	n (%)
Right	
Face	n (%)
Scalp	n (%)
Center	
Face	n (%)
Scalp	n (%)
Unknown	
Face	n (%)
Scalp	n (%)
Overall	
Face (any area)	n (%)
Scalp (any area)	n (%)

Table 4.7 Tirbanibulin Treatment Completion Rate for the Original Treated Area, Safety Population

Character	Week 8 (N=X)
P2: Did the patient complete 5-day treatment course of tirbanibulin (Klisyri®) at the beginning of the study? (N=X)	
Yes	n (%)
No	n (%)

Table 4.8 Prior AK Treatment (To-Date) Including within the Past 6 Months, Safety Population

Character TH2 and TH3 (Start date prior to Klisyri®; End date within the past 6 months or No end date)	**Baseline (N=x)**
TH2A checked AND TH3=No Has not use any AK medication	n (%)
Topical medication **[TH2r1]** 5-Fluorouracil (5-FU) **[TH2r2]** Salicylic acid **[TH2r3]** Imiquimod **[TH2r4]** Ingenol mebutate **[TH2r5]** Diclofenac **[TH2r6]** Other [TH2r6oe] A B C	n (%)
Oral medication: **[TH2r7]** Isotretinoin Other A B C	n (%)
Other therapies: **[TH2r8]** Photodynamic therapy **[TH2r9]** Cryosurgery/Cryotherapy **[TH2r10]** Chemical/acid peel **[TH2r11]** Curettage **[TH2r12]** Laser therapy **Other:** A B C	n (%)

Table 4.9 AK Concomitant Medication Use During the 8-Week Observation Period, Safety Population

Character TH3 with no end date TH3Ar6na checked (end date after Klisyri® start date within the 8 week period) Add Variables from week-8 - start date within 8 week period	N=X n (%)
Has not used any acne medication TH3 = No	
Topical medication	
5-Fluorouracil (5-FU)	
Salicylic acid	
Imiquimod	
Ingenol mebutate	
Diclofenac	
Other	
Oral medication	
Isotretinoin	
Other	
Other therapies	
Photodynamic therapy	
Cryosurgery/Cryotherapy	
Chemical/acid peel	
Curettage	
Laser therapy	
Other	

Table 4.10 Non-AK Concomitant Medication Use During the 8-Week Observation Period, Safety Population

Character TH4	N=x
TH4 = No Is not currently on any concomitant medication to manage conditions other than AK medication	
Add Variables from Week-8	
<<categories from WHO ATC classifications>>	
A	n (%)
B	n (%)
C	n (%)
D	n (%)
E	n (%)

Note: Data from Clinician DCF; X patients had missing data; The denominator for the percentages is the number of patients with available data (N=X). This concomitant non-AK medication use correspond to use of medications at any time during the study observation period, overlapping with **Klisyri®** medication use.

Table 4.11 Patient Disposition Throughout the Study

	Baseline n (%)		Week 8 n (%)		Week 24 n (%)	
(Cumulative numbers)	**Patient Survey**	**Clinician Survey**	**Patient Survey**	**Clinician Survey**	**Patient Survey**	**Clinician Survey**
Patients completing study visit						
Patients with missing surveys						
Patient Terminations/ Discontinuations						
P1Br3 Due to Adverse event associated with any medication (other than tirbanibulin (Klisyri®						
P1Br4 Due to Adverse drug reaction associated with tirbanibulin (Klisyri®)						
P1Br5 Due to Clinician decision: tirbanibulin (Klisyri®) treatment non-compliance						
P1Br6 Due to Clinician decision, Other [P1Br6oe]						
P1Br2 Patient voluntarily withdrawal of consent (for reasons other than adverse event or adverse drug reaction)						
P1Br1 Patient Lost to follow-up						
TOTAL Study Population (N)	300	300	300	300	300	300

Table 4.12 Reason for Discontinuation

	Statistics	Adverse drug reaction associated with tirbanibulin (Klisyri®)	Adverse event associated with any medication (other than tirbanibulin (Klisyri®	Clinician decision: tirbanibulin (Klisyri®) treatment non-compliance	Clinician decision, Other	Patient voluntarily withdrawal of consent (for reasons other than adverse event or adverse drug reaction)	Patient Lost to follow-up	TOTAL
Week 8	n (%)							
Week 24	n (%)							
TOTAL	n (%)							

Table 4.13 Subject Level Summary of Local Site Reactions

LSRs (Refer to annotated CRF for all other variables)	Baseline N=X	Week 8 N=X	Week 24* N=X
LSR1 Erythema (N=X)			
LSR1r1 Grade			
2. Mild	n (%)	n (%)	n (%)
3. Moderate	n (%)	n (%)	n (%)
4. Severe	n (%)	n (%)	n (%)
LSR1r4 Action taken with Tirbanibulin			
1. Drug withdrawal	n (%)	n (%)	n (%)
2. Dose Reduced	n (%)	n (%)	n (%)
3. Dose Increased	n (%)	n (%)	n (%)
4. Dose not changed	n (%)	n (%)	n (%)
5. Not Applicable	n (%)	n (%)	n (%)
LSR2 Flaking/Scaling (N=X)			
Grade			
Mild	n (%)	n (%)	n (%)
Moderate	n (%)	n (%)	n (%)
Severe	n (%)	n (%)	n (%)
Action taken with Tirbanibulin			
Drug withdrawal	n (%)	n (%)	n (%)
Dose Reduced	n (%)	n (%)	n (%)
Dose Increased	n (%)	n (%)	n (%)
Dose not changed	n (%)	n (%)	n (%)
Not Applicable	n (%)	n (%)	n (%)
LSR3 Crusting (N=X)			
Grade			
Mild	n (%)	n (%)	n (%)
Moderate	n (%)	n (%)	n (%)
Severe	n (%)	n (%)	n (%)
Action taken with Tirbanibulin			
Drug withdrawal	n (%)	n (%)	n (%)
Dose Reduced	n (%)	n (%)	n (%)
Dose Increased	n (%)	n (%)	n (%)

Dose not changed	n (%)	n (%)	n (%)
Not Applicable	n (%)	n (%)	n (%)
LSR4 Swelling (N=X)			
Grade			
Mild	n (%)	n (%)	n (%)
Moderate	n (%)	n (%)	n (%)
Severe	n (%)	n (%)	n (%)
Action taken with Tirbanibulin			
Drug withdrawal	n (%)	n (%)	n (%)
Dose Reduced	n (%)	n (%)	n (%)
Dose Increased	n (%)	n (%)	n (%)
Dose not changed	n (%)	n (%)	n (%)
Not Applicable	n (%)	n (%)	n (%)
LSR5 Vesiculation/Pustulation (N=X)			
Grade			
Mild	n (%)	n (%)	n (%)
Moderate	n (%)	n (%)	n (%)
Severe	n (%)	n (%)	n (%)
Action taken with Tirbanibulin			
Drug withdrawal	n (%)	n (%)	n (%)
Dose Reduced	n (%)	n (%)	n (%)
Dose Increased	n (%)	n (%)	n (%)
Dose not changed	n (%)	n (%)	n (%)
Not Applicable	n (%)	n (%)	n (%)
LSR6 Erosion/Ulceration (N=X)			
Grade			
Mild	n (%)	n (%)	n (%)
Moderate	n (%)	n (%)	n (%)
Severe	n (%)	n (%)	n (%)
Action taken with Tirbanibulin			
Drug withdrawal	n (%)	n (%)	n (%)
Dose Reduced	n (%)	n (%)	n (%)
Dose Increased	n (%)	n (%)	n (%)
Dose not changed	n (%)	n (%)	n (%)

Not Applicable	n (%)	n (%)	n (%)
LSR7 Scarring			
Present?			
Yes	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)
LSR8 Hypo-pigmentation			
Present?			
Yes	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)
LSR9 Hyper-pigmentation			
Present?			
Yes	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)

Table 4.14 Subject Level Summary of Local Site Reactions, by Patient ID

Patient ID	Study/ Survey Timepoint	LSR	Grade	Date of Baseline (yyyy/mm/dd)	Date of Onset (yyyy/mm/dd)	Status	Action Taken with tirbanibulin*

Table 4.15 Subject Level Summary of Adverse Events, Any Type

Adverse Events, Any Type	N=X n (%)
Subjects with at least 1 adverse event (any type)	
Intensity of adverse event, among Subjects with at least 1 adverse event (any type)	
Mild	
Moderate	
Severe	
Action taken with Tirbanibulin, among Subjects with at least 1 adverse event (any type)	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Subjects with at least 1 SAE or Serious ADR	
Subjects with at least 1 SAE or Serious ADR resulting in death	

Table 4.16 Subject Level Summary of 'Not-Related to Tirbanibulin' Adverse Events

'Not-Related to Tirbanibulin' Adverse Events	N=X n (%)
Subjects with at least 1 'not-related' AE	
Intensity of adverse event, among Subjects with at least 1 'not-related' AE	
Mild	
Moderate	
Severe	
Action taken with Tirbanibulin, among Subjects with at least 1 'not-related' AE	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Subjects with at least 1 SAE	
Subjects with at least 1 SAE resulting in death	

Table 4.17 Subject Level Summary of 'Not-Related' AEs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.18 Subject Level Summary of Adverse Drug Reactions

Adverse Drug Reactions	N=X n (%)
Subjects with at least 1 ADR	
Intensity of adverse event, among Subjects with at least 1 ADR	
Mild	
Moderate	
Severe	
Action taken with Tirbanibulin, among Subjects with at least 1 ADR	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Subjects with at least 1 Serious ADR	
Subjects with at least 1 Serious ADR resulting in death	

Table 4.19 Subject Level Summary of ADRs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.20 Subject Level Summary of Serious ADRs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.21 Event Level Summary of Adverse Events, Any Type

Adverse Events, Any Type	N=X n (%)
Total number of adverse event (any type)	
Intensity of adverse event, among documented adverse events (any type)	
Mild	
Moderate	
Severe	
Action taken with tirbanibulin, for documented adverse events (any type)	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Number of SAEs or Serious ADRs	
Number of SAEs or Serious ADRs resulting in death	

Table 4.22 Event Level Summary of 'Not-Related to Tirbanibulin' Adverse Events

'Not-Related to Tirbanibulin' Adverse Events	N=X n (%)
Total number of 'not-related' AE	
Intensity of adverse event, among documented 'not-related' AEs	
Mild	
Moderate	
Severe	
Action taken with tirbanibulin, for documented 'not-related' AEs	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Number of SAEs	
Number of SAEs resulting in death	

Table 4.23 Event Level Summary of 'Not-Related' AEs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.24 Event Level Summary of 'Not-Related' AEs by Patient ID

Patient ID	Study/ Survey Timepoint	Reported Term for the Adverse Event	AE Preferred Term	Primary System Organ Class	Date of Onset (yyyy/mm/dd)	Date of Resolution (yyyy/mm/dd)	Action Taken with tirbanibulin*	Intensity of Adverse Event	Is this a SAE?

Table 4.25 Event Level Summary of Adverse Drug Reactions

Adverse Drug Reactions	N=X n (%)
Total number of ADRs	
Intensity of adverse event, among documented ADRs	
Mild	
Moderate	
Severe	
Action taken with tirbanibulin, for documented ADRs	
Drug withdrawal / study discontinuation	
Other Actions:	
Dose Not Changed	
Number of Serious ADRs	
Number of Serious ADRs resulting in death	

Table 4.26 Event Level Summary of ADRs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.27 Event Level Summary of Serious ADRs by Organ Class & Preferred Term

System Organ Class: Preferred Term	N=X	Intensity	Action Taken
	n (%)	Mild, Moderate, Severe	A: Dose not changed; B: Drug withdrawn.

Table 4.28 Event Level Summary of ADRs by Patient ID

Patient ID	Study/ Survey Timepoint	Reported Term for the Adverse Event	AE Preferred Term	Primary System Organ Class	Date of Onset (yyyy/mm/dd)	Date of Resolution (yyyy/mm/dd)	Action Taken with tirbanibulin*	Intensity of Adverse Event	Is this a SAE?

Table 4.29 Subject Level Summary of Other Safety Events

Safety events	N=300
	n (%)

Table 4.30 Event Level Summary of Other Safety Events

Safety events	N=300
	n (%)

Table 4.31 Significant Protocol Deviations

TBD

7.5 Sensitivity Analyses

Analysis of clinician IGA, stratified by type of subject visit.

Table 5.1 Subgroup Analysis of IGA Success stratified by Visit Type

IGA Success / % Clear/Almost Clear	Baseline N=x	Week 8 N=x
Subject visit type		
In-person visit	n (%)	n (%)
Remote/ Tele-health visit	n (%)	n (%)

8 PATIENT QUALITATIVE INPUT FROM SITE AK01

Table summarizing verbatims from audio-input from patients at end of study from Site # AK01 will be added here.

9 CANFIELD PHOTOS OF AK PATIENTS FROM SITE AK01

A separate file will be attached, summarizing the canfield photos of AK patients from Site # AK01.

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11 APPENDICES

Appendix A: Study Schedule of Events

Appendix B: Select Study Questionnaires

Appendix C: Signature Page

Appendix D: Individual Data Listings

APPENDIX A: STUDY SCHEDULE OF EVENTS

Study Encounter (physical or virtual)	**Baseline V1**	**V2**	**End of Study V3**	**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 SAP and the attachments and provides the necessary assurances that this study analyses will be conducted according to all stipulations of the SAP.

Study CRO:

[redacted], PhD — PPD — [redacted]

CEO — Signature — Date

Almirall Approvals:

[redacted] MD — PPD — [redacted]

[redacted] — Signature — Date

Global Medical Affairs

[redacted] — PPD — [redacted]

PPD [redacted] — Signature — Date

Global Development – R&D

APPENDIX-D: INDIVIDUAL DATA LISTINGS

Individual patient data listings will be provided at the end of the study, based on data from clinician eCRFs and patient eDCFs.