

Patient- and Clinician-Reported Outcomes for Tirbanibulin in Actinic Keratosis in Clinical Practice Across the United States (PROAK)

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ABSTRACT

Background: The Patient-Reported Outcomes in Actinic Keratosis (PROAK) study evaluated patient- and clinician-reported outcomes (PRO; ClinRO) during 24 weeks of follow-up among adult patients with actinic keratosis (AK) on the face or scalp who were administered tirbanibulin 1% ointment in real-world community practices in the United States.

Methods: Quality of life (QoL) was assessed by Skindex-16 at week (W) 8. Additionally, effectiveness (Investigator Global Assessment [IGA]), PRO and ClinRO (Treatment Satisfaction Questionnaire for Medication and Expert Panel Questionnaire), safety, and tolerability were assessed at W8 and W24.

Results: The safety population included 300 patients; the full analysis set included 290 patients (278 patients at W24). At W8, a statistically significant difference ($P < 0.03$) was observed for Skindex-16 domains in all assessed subgroups. Clinicians and patients reported high global satisfaction (mean [SD] scores of 74.9 [23.9] and 72.0 [24.6], respectively) at W24. Overall skin appearance improved from baseline to W24 (83.6% clinicians; 78.5% patients). IGA success (IGA score of 0-1) was achieved by 71.9% of patients at W24 with a similar % at W8 (73.8%) suggesting a stable effectiveness over time. About 5% of patients reported at least one adverse event, 4% reported at least one serious adverse event and no patients reported serious adverse drug reactions. At W8, the most frequently reported local skin reactions were mild/moderate erythema (47.6%) and flaking/scaling (49.6%).

Conclusions: Treatment with tirbanibulin demonstrated effectiveness in the management of AK lesions and a favorable safety and tolerability profile. Furthermore, QoL was improved as early as W8, and both patients and clinicians reported high levels of treatment satisfaction, independently of patients' characteristics.

Keywords: actinic keratosis; field treatment; tirbanibulin; patient-reported outcomes; clinician-reported outcomes; real-world evidence

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INTRODUCTION

Actinic keratoses (AKs) are epithelial lesions caused by ultraviolet radiation and cumulative sun exposure that have the potential to progress to invasive as squamous cell carcinoma (SCC) if left untreated.¹⁻⁵ AKs appear mainly in visible areas impairing patients' quality of life (QoL).^{3,6} Moreover, QoL can also be compromised by treatment characteristics, treatment-induced local skin reactions (LSR), and recurrence rates, impacting treatment adherence and leading to poor outcomes.^{2,4,7} Patient-reported outcomes (PRO)

and clinician-reported outcomes (ClinRO) inform about patients' health status and experience with treatment.⁵ Comparing patient and clinician perspectives contributes to better patient management, enhancing clinician-patient communication.^{7,8}

Tirbanibulin is a reversible tubulin polymerization inhibitor with potent anti-proliferative and anti-tumoral effects. It was approved by the United States (US) Food and Drug Administration for the topical treatment of AK on the face or scalp in 2020 and by the European Medicines Agency in 2021.^{2,9}

Tirbanibulin demonstrated efficacy, safety, and tolerability in prior Phase II and III clinical trials after daily application for 5 consecutive days.^{3,10} Moreover, results from the interim analysis of Patient-Reported Outcomes in Actinic Keratosis (PROAK) (NCT05260073), an observational, single-arm, prospective, multicenter, phase IV study, demonstrated that tirbanibulin improved QoL as per SKINDEX-16 questionnaire, as early as week 8 (W8), and both clinicians and patients reported high levels of treatment satisfaction, compared to patient's previous treatments.¹¹

This final analysis of the PROAK study aimed to evaluate PROs and ClinROs for effectiveness and safety after a follow-up period of 24 weeks among adult patients with AKs on the face or scalp who were administered tirbanibulin in real-world community practice in the US.

MATERIALS AND METHODS

Study Design

PROAK study design has been published previously.^{6,11} Briefly, this single-arm, multi-center, prospective, cohort study included adult patients (≥ 18 years), diagnosed with AK on the face or scalp who initiated treatment with tirbanibulin in real-world community practice in the US. Clinicians and patients filled out surveys and clinical assessments regarding safety, effectiveness, PRO and ClinRO of tirbanibulin at baseline, W8 and week 24 (W24).

PROAK was performed at 32 private dermatology practices across the US according to the Declaration of Helsinki and consistent with the International Council for Harmonization. An independent ethics committee reviewed the study. All patients signed an informed consent form.

Outcomes

Patient-reported QoL was measured by Skindex-16^{12,13} at W8.¹¹ Skindex-16 domain scores were also assessed in subgroups of patients according to gender, age, AK treatment location, Fitzpatrick skin type, skin photodamage, history of skin cancer, and prior treatment experience (cryosurgery, other topical treatments, and treatment naïve at baseline).

Other assessments were satisfaction with tirbanibulin measured using the Treatment Satisfaction Questionnaire for Medication (TSQM-9)¹⁴ and Expert Panel Questionnaire (EPQ)⁸, treatment effectiveness measured by Investigator's Global Assessment (IGA), severity of skin photodamage, safety and tolerability at W8 and W24. TSQM-9 and EPQ scores were assessed also in subgroups of patients. Clinicians used an adapted version of TSQM-9.

EPQ consists of eleven questions: items 1 to 9 related to treatment satisfaction answered by both patients and clinicians;

and items 10 and 11 answered only by clinicians. Item 10 assessed AK responses (IGA) (0 [completely cleared] to 4 [not cleared]). Achieving an IGA score of 0-1 ($\geq 75\%$ clearance of AK lesions) at W8 was defined as IGA success; IGA success was similarly computed for W24. Item 11 assessed the patient's skin photodamage severity (0 [absent] to 3 [severe]).

Tirbanibulin safety and tolerability were monitored throughout the study, and adverse events (AEs), treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), and serious ADRs were documented. Clinicians scored the LSRs and took photographs to evaluate the progression of the LSRs.

Statistical Analysis

Timepoints were W8 and W24. No missing data imputation was performed. All study variables were analyzed descriptively using summary statistics, including percentage for categorical variables, and mean, standard deviation (SD), minimum, and maximum for continuous variables. The differences in outcome measures for discrete variables were analyzed using chi-squared tests (including the McNemar Test). The differences in mean scores for continuous variables were assessed using a t-test (including paired t-test). P-value < 0.05 was considered statistically significant for all analyses. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 300 patients were enrolled in the study and included in the safety population. Ten patients were excluded due to voluntary consent withdrawal or loss to follow-up and due to missing data at W8. Finally, 290 patients were included in the full analysis set (FAS) population for W8 analysis. Between W8 and W24, another 12 patients withdrew their consent, were lost to follow-up, or had missing data. Therefore, the analytic population for W24 included 278 patients. All patients completed the treatment course (tirbanibulin once daily for 5 consecutive days).

Patients were mainly male (68.6%), mean age (SD) of 66.3 (11.4) year-old, 71.4% of patients had a Fitzpatrick skin type II, 61.7% had a history of skin cancer and 76.9% had moderate/severe skin photodamage. A 77.9% of patients were diagnosed with AK on the face and 79.0% of patients received previous treatments for AK. A full description of patient baseline characteristics was already presented.¹¹

QoL Assessed by Skindex-16

At W8, a statistically significant ($P < 0.0001$) decrease in scores from baseline was observed for all Skindex-16 domains.¹¹ After dividing the sample by subgroups, a statistically significant difference ($P < 0.03$) was observed for all Skindex-16 domains in all subgroups, except for the subgroup ≤ 49 years in the

functioning domain (mean score of 16.4 at baseline vs 6.4 at W8, $P=0.0886$), mainly due to the limited sample size for this subgroup of patients (Table 1).

Treatment Satisfaction Assessed by TSQM-9 and EPQ

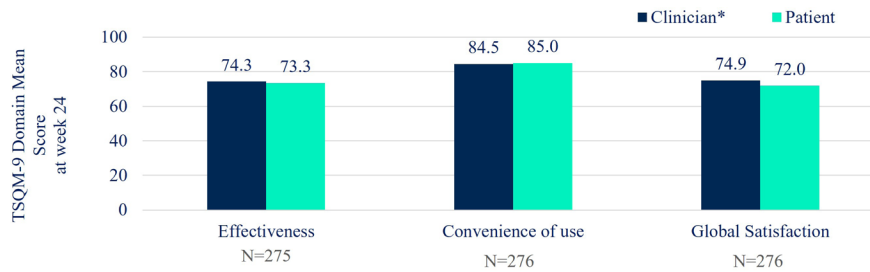
Patient's and clinician's satisfaction with tirbanibulin (TSQM-9) was high at W8¹¹ and remained high at W24 (Figure 1). At W24, both clinicians and patients (N=276 each) reported the highest satisfaction in the convenience of use subscale with mean (SD)

scores of 84.5 (15.6) and 85.0 (14.6) (TSQM-9 score range 0-100), respectively. The mean (SD) score on the effectiveness subscale was 74.3 (21.2) for clinicians and 73.3 (21.3) for patients (N=275 each); the mean (SD) score on the global satisfaction subscale was 74.9 (23.9) for clinicians and 72.0 (24.6) for patients (N=276 each). After dividing the sample by subgroups, no significant differences were observed for most PRO and ClinRO at W8 and W24 (Table 2).

TABLE 1.

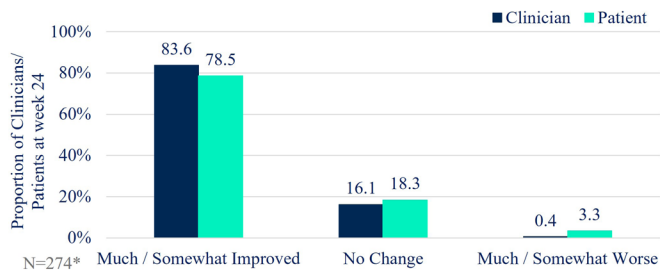
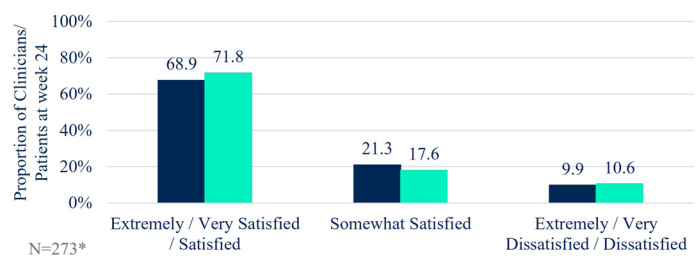
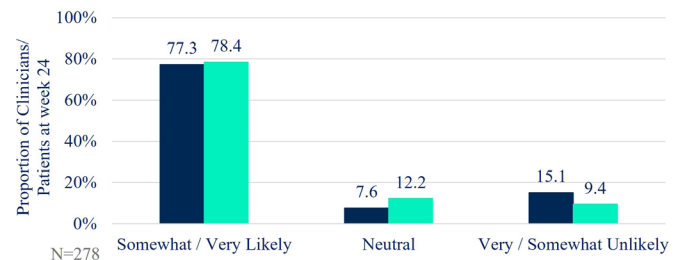
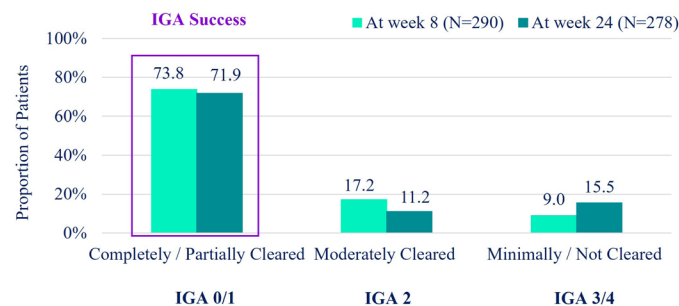
Skindex-16 Domain Scores at Baseline and W8 Across Subgroups of Patients									
Subgroups	Symptoms			Emotions			Functioning		
	Baseline	W8	P-value	Baseline	W8	P-value	Baseline	W8	P-value
	n, Mean	n, Mean		n, Mean	n, Mean		n, Mean		
Gender									
Male	198, 22.6	198, 8.5	<0.0001	195, 38.9	195, 11.7	<0.0001	199, 14.1	199, 4.5	<0.0001
Female	91, 21.6	91, 7.1	<0.0001	91, 36.7	91, 16.6	<0.0001	91, 15.1	91, 5.0	0.0004
Age Group									
<49 years	26, 27.1	26, 8.2	0.0104	26, 43.4	26, 16.2	0.0017	26, 16.4	26, 6.4	0.0886
50–64 years	86, 24.0	87, 6.5	<0.0001	86, 38.8	86, 15.1	<0.0001	87, 13.5	87, 4.7	0.0007
≥65 years	177, 20.8	177, 8.7	<0.0001	174, 37.1	174, 12.0	<0.0001	177, 14.6	177, 4.3	<0.0001
AK Treatment Location									
Face	188, 22.4	188, 6.9	<0.0001	186, 39.6	186, 13.7	<0.0001	189, 15.0	189, 4.4	<0.0001
Scalp	64, 25.5	64, 7.7	<0.0001	63,11.0	64, 10.8	<0.0001	64, 14.6	64, 3.8	0.0009
Fitzpatrick Skin Type									
I / II	228, 23.3	228, 8.7	<0.0001	225, 37.3	225, 13.7	<0.0001	229, 15.1	229, 5.0	<0.0001
III / IV / V / VI	61, 18.6	61, 5.5	0.0003	61, 42.0	61, 11.8	<0.0001	61, 11.7	61, 3.3	0.0046
Skin Photodamage									
Absent/Mild	65, 24.1	65, 5.1	<0.0001	64, 36.4	64, 10.3	<0.0001	65, 13.2	65, 3.9	0.0013
Moderate/ Severe	222, 21.5	222, 8.9	<0.0001	220, 38.9	220, 14.0	<0.0001	223, 14.9	223, 4.8	<0.0001
History of Skin Cancer									
Yes	179, 22.1	179, 8.0	<0.0001	177, 39.4	177, 11.9	<0.0001	179, 15.9	179, 4.3	<0.0001
No	105, 21.7	105, 7.6	<0.0001	104, 35.2	104, 14.7	<0.0001	106, 12.0	106, 5.1	0.0024
Prior Use of Cryosurgery									
Yes	184, 22.3	184, 7.1	<0.0001	182, 37.9	182, 10.9	<0.0001	185, 13.6	185, 3.8	<0.0001
No	105, 22.3	105, 9.7	<0.0001	104, 38.6	104, 17.6	<0.0001	105, 15.9	105, 6.0	0.0003
Prior Use of Other Topical Treatments									
Yes	111, 21.9	111, 9.1	<0.0001	110, 37.9	110, 13.7	<0.0001	111, 15.4	111, 4.6	<0.0001
No	178, 22.5	178, 7.4	<0.0001	176, 38.3	176, 13.0	<0.0001	179, 13.8	179, 4.7	<0.0001
Treatment Naïve at Baseline									
Yes	61, 23.4	61, 9.6	0.0021	60, 38.5	60, 18.7	<0.0001	61,14.9	61, 6.8	0.0273
No	228, 22.0	228, 7.6	<0.0001	226, 38.1	226, 11.9	<0.0001	229, 14.3	229, 4.1	<0.0001

AK, actinic keratosis; W, week.

FIGURE 1. Clinicians and patients reported satisfaction with tirbanibulin at W24. TSQM-9.

*Adapted from patient-version of TSQM-9.

TSQM, treatment satisfaction questionnaire for medication; W, week.

FIGURE 2. Clinicians and patients' satisfaction with treatment (A, B, and C) and likelihood to consider tirbanibulin again (D) at W24. Clinician-reported overall improvement (E) at W8 and W24 EPQ**A. Rating of overall appearance of skin****B. Rating of satisfaction with improvement in "how skin looks"****C. Rating of satisfaction with improvement in "skin texture"****D. Likelihood to consider tirbanibulin to treat AK lesions in future****E. Clinician-reported overall improvement in AK**

*At W24, response categories of "don't know/ not applicable" were excluded from the analysis.

AK, actinic keratosis; EPQ, expert panel questionnaire; IGA, investigator's global assessment.

TABLE 2.

Subgroup Analysis of Patient and Clinician TSQM-9 Domain Scores at W24								
Subgroups	Patient TSQM-9 domain scores				Clinician TSQM-9 domain scores			
	W24 (N=278)				W24 (N=278)			
	N	Effectiveness	Convenience	Global Satisfaction	N	Effectiveness	Convenience	Global Satisfaction
		Mean	Mean	Mean		Mean	Mean	Mean
Gender								
Male	190	71.8	83.3	70.3	187	72.7	84.0	73.5
Female	88	76.7	88.5	75.6	88	77.8	85.5	77.9
P-value	--	0.0720	0.0064	0.0993	--	0.0603	0.4671	0.1496
Age Group								
<49 years	25	73.3	85.1	72.3	25	81.3	88.9	83.1
50–64 Years	80	78.3	87.6	76.7	80	76.3	89.8	77.9
≥65 years	173	71.0	83.7	69.8	170	72.4	81.4	72.3
P-value	--	0.0391	0.1494	0.1145	--	0.0873	<0.0001	0.0436
AKTreatment Location^								
Face	181	74.7	86.2	73.4	181	75.6	84.2	75.8
Scalp	60	74.4	84.5	71.7	57	75.0	85.3	74.6
Both	37	64.7	79.6	65.6	37	67.4	84.4	70.9
P-value	--	0.0304	0.0413	0.2156	--	0.0997	0.8925	0.5139
Fitzpatrick Skin Type								
I / II	223	72.9	84.7	71.9	221	73.9	83.0	74.0
III / IV / V / VI	55	75.0	86.0	72.2	54	76.0	90.4	78.7
P-value	--	0.5286	0.5689	0.9427	--	0.5153	0.0016	0.1913
Skin Photodamage*								
Absent/Mild	62	75.4	86.6	73.4	60	81.2	86.3	80.4
Moderate/Severe	214	72.8	84.5	71.6	213	72.3	84.0	73.3
P-value	--	0.4111	0.3314	0.6154	--	0.0038	0.2936	0.0396
History of Skin Cancer**								
Yes	175	72.9	84.2	71.5	173	72.2	83.8	73.2
No	99	75.1	86.8	73.9	98	78.8	86.2	79.4
P-value	--	0.3973	0.1548	0.4323	--	0.0137	0.2248	0.0377
Prior Use of Cryosurgery								
Yes	180	75.4	85.0	71.4	177	75.2	85.4	74.8
No	98	72.8	84.9	73.1	98	72.9	82.8	75.2
P-value	--	0.5062	0.9790	0.5794	--	0.3810	0.1755	0.8977
Prior Use of Other Topical Treatments								
Yes	110	73.3	84.7	70.2	108	73.1	83.8	74.4
No	168	73.4	85.1	73.2	167	75.2	84.9	75.2
P-value	--	0.9806	0.8143	0.3248	--	0.4336	0.5540	0.7708
Treatment Naïve at Baseline								
Yes	55	75.4	85.6	75.7	55	75.1	84.7	77.3
No	223	72.8	84.8	71.1	220	74.2	84.4	74.3
P-value	--	0.4314	0.7330	0.2111	--	0.7826	0.9299	0.4099

P-values, calculated by chi-squared test, correspond to the difference between strata within respective time periods.

^AMutually exclusive; ^{*}2 patients have missing data for Skin Photodamage; ^{**}5 patients have missing data for history of skin cancer.

AK, actinic keratosis; W, week.

According to select EPQs with available data at W24, PROs and ClinRO were aligned. 83.6% of clinicians and 78.5% of patients (from N=274 each) considered overall skin appearance to be much/somewhat improved with tirbanibulin at W24 (Figure 2A). Furthermore, 68.5% of clinicians and 73.3% of patients (from N=273 each) were extremely/very satisfied with the improvement in how skin looked (Figure 2B), and 68.9% of clinicians and 71.8% of patients (from N=273 each) were extremely/very satisfied with skin texture improvement (Figure 2C). 77.3% of clinicians and 78.4% of patients (from N=278 each) would consider tirbanibulin again to treat AK lesions in the future, if needed (Figure 2D).

Based on the IGA, the proportion of patients with completely/partially cleared AK lesions in the treated area (IGA success) was 73.8% at W8 and it was sustained over time, as depicted by the IGA success of 71.9% at W24. When comparing the subgroups, at W8, statistically significant differences in IGA success were observed in gender subgroups (70.4% of males vs 81.3% of females, $P=0.0488$), AK treatment location subgroups (81.5% of patients with AKs on face vs 64.1% on scalp vs 48.7% on both, $P<0.0001$), and skin photodamage subgroups (83.1% of patients with absent/mild skin photodamage vs 70.9% of patients with severe/moderate skin photodamage, $P=0.0491$).

Moreover, the reduction of skin photodamage severity from baseline to W24 was statistically significant ($P<0.0001$). Similarly, the reduction of skin photodamage severity at W8 and W24 was statistically significant ($P<0.04$) in all subgroups, except for the subgroup ≤ 49 years at W24 ($P=0.0689$), mainly due to the low sample in this subgroup.

Safety

During the study, 15 patients (5.0%) reported at least one AE (mild in 4.0% of patients, moderate in 0.7% of patients, and severe in 0.3% of patients). Six patients (2.0%) reported at least

one SAE, and no patients reported serious ADR. SAEs were not related to treatment and were hospitalized for pneumothorax due to lung biopsy (one patient [0.3%]), slip and fall accident (one patient [0.3%]), Bowen's Disease (one patient [0.3%]), SCC (three patients [1.0%]) and basal cell carcinoma (BCC; two patients [0.7%]). It is important to note that one patient reported three different SAEs and two patients reported both SCC and BCC. SCC was reported in 2.3% of patients, and BCC in 1.3% of patients. Only one patient had a confirmed location as the same as the treatment (scalp). For all other patients, the location was different from the treated area. All cases were considered not related to treatment. No patients discontinued the study due to AEs or ADRs. Safety results are aligned with Phase III trials.³

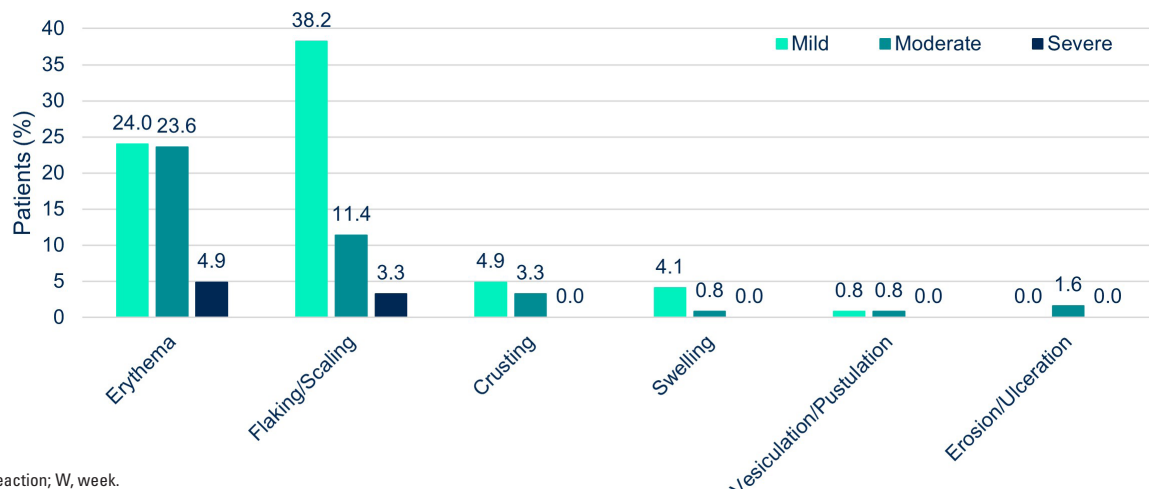
Tolerability

At W8, most reported LSRs were erythema (47.6% mild/moderate and 4.9% severe) and flaking/scaling (49.6% mild/moderate and 3.3% severe). Other LSRs were reported in 1.6-8% of patients (8.1% crusting, 4.9% swelling, 1.6% vesiculation/pustulation, 1.6% erosion/ulceration) and were mild/moderate (Figure 3). The mean (min-max) LSR composite score (range 0-18) was 0.9 (0.0-11.0). Scarring was observed in one patient (0.8%), hypopigmentation was observed in six patients (4.9%) and hyperpigmentation was observed in four patients (3.3%).

Clinical Cases

Photographs of the evolution of the AK lesions were taken in ten patients. Three patients were selected for demonstration (Figure 4). Patient 1 was a 61-year-old male treated with tirbanibulin for AKs on his face. The patient had previously been treated for AK with cryosurgery. Patient 2 was a 70-year-old male treated for AKs on the face. The patient had previously been treated for AKs with cryosurgery. Patient 3 was a 69-year-old male treated for AKs on the scalp. The patient had previously been treated for AKs with cryosurgery. All three patients achieved IGA success by W8.

FIGURE 3. Patients with LSRs at W8 after tirbanibulin administration



LSR, local skin reaction; W, week.

FIGURE 4. Clinical appearance at baseline and after the use of tirbanibulin for facial AKs.

DISCUSSION

PROAK study evaluated PROs and ClinPRO among adults with AKs on the face or scalp treated with tirbanibulin in real-world community practice in the US until W24.

QoL impairment at baseline is not insignificant and sometimes it is underestimated, resulting in a real unmet need from patients' perspective. In this study, baseline Skindex-16 scores in the three domains were quite high compared to maximum values. The impact of tirbanibulin on health-related QoL, assessed by Skindex-16, showed that tirbanibulin improved patients' QoL as early as at W8, significantly reducing the AK burden.¹¹ This trend was also observed when assessing Skindex-16 scores by a subgroup of patients. All comparisons were significant supporting the effectiveness of tirbanibulin, independent of gender, age, AK location, Fitzpatrick skin type, skin photodamage, history of skin cancer, or prior treatment experience. To our knowledge, this is the first study assessing the impact of AK treatment on health-related QoL using Skindex-16 in a subgroup of patients.

Moreover, regarding satisfaction with treatment, assessed by TSQM-9, both clinicians and patients reported high levels of global satisfaction and agreed on the effectiveness and convenience of tirbanibulin at W24, reinforcing the results obtained at W8.¹¹ In an open-label clinical study,¹⁵ patients appreciated the convenience of imiquimod use (TSQM score >60) although the overall satisfaction scores <60. High levels of satisfaction with treatment were also reported when assessed by subgroups of patients, with no significant differences observed in most of the outcomes, neither at W8 nor at W24. A previous study using TSQM-1.4 for subgroups based on a number of lesions at baseline (<6 and ≥6), age (<65 years and ≥65 years), sex, Fitzpatrick skin type (I–III), and anatomical location of the lesion (face or scalp) demonstrated that short treatment duration is an important factor for patient satisfaction.¹⁶

AK-EPO⁸ was used for the first time in this study assessing ClinRO and PRO satisfaction and tirbanibulin effectiveness. At W24 clinicians and patients were still highly satisfied with the overall skin appearance, and the improvement in skin appearance and texture, and showed a high willingness to reconsider tirbanibulin again. These results reinforce those obtained at W8¹¹ and highlight the benefits of tirbanibulin for the optimal management of AKs.

In addition, effectiveness as measured by ≥75% lesion clearance was stable over time, with 73.8% patients at W8 and 71.9% patients at W24, and consistent with the results of the Phase III trials.³ Regarding the subgroups, significant differences in IGA success were observed in male vs female patients, in patients with AKs on the face vs scalp, and in the subgroup of patients with absent/mild photodamage vs severe/moderate

skin photodamage. In a phase IV trial,¹⁶ patients with higher Fitzpatrick skin types (II and III) and with facial lesions appeared to be more likely to achieve complete clearance at W17.

Regarding safety and tolerability, tirbanibulin was well tolerated and showed a good safety profile, aligned with Phase III trials.³ In this study, only 4% of patients reported at least one SAE considered not related to treatment, and none discontinued treatment due to AEs. Moreover, most reported LSRs were mild/moderate erythema and flaking/scaling. A small percentage of patients had observed a minimal change in pigmentation and/or scarring was observed in the treatment field. In contrast, commonly prescribed topical treatments for AK on the face or scalp are associated with LSRs of severe intensity and high discontinuation rates.^{1,2,17} In a post-hoc, exploratory analysis of pooled data from two multicenter, randomized phase III studies comparing topical 5-fluorouracil (5-FU) 4% once daily or 5% twice daily for 4 weeks,¹⁷ patients treated with 5-FU 5% and 5-FU 4% reported severe erythema (47% and 37%, respectively), severe scaling/dryness or crusting (both 25% and 18%), severe stinging/burning (27% and 18%) and severe pruritus (22% and 13%). Similarly, studies with imiquimod reported values of 32% for the prevalence of severe erythema and 9% for severe scabbing/scrutiny.¹

CONCLUSION

In real-world community practice, once-daily tirbanibulin ointment for 5 consecutive days demonstrated effectiveness, favorable safety, and tolerability profile in the treatment of AK on the face or scalp, as evidenced in Phase III clinical trials.³ Patients reported a significant reduction in AK burden as per Skindex-16, as early as W8, independently of gender, age, AK location, Fitzpatrick skin type, skin photodamage, history of skin cancer, and prior treatment experience. Patients' and clinicians' satisfaction with tirbanibulin was high both at W8 and W24, and both reported a high likelihood to reconsider tirbanibulin, if needed. Finally, clearance of ≥75% of AK lesions (effectiveness) was stable over time, highlighting the clinical benefits of tirbanibulin for optimal management of AKs.

DISCLOSURES

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