SKIN

ORIGINAL RESEARCH

Clinician- and Patient-reported Outcomes with Tirbanibulin 1% Treatment for Actinic Keratosis in Routine Clinical Practice Across the U.S. (PROAK Study)

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ABSTRACT

Background: Patients' experiences regarding topical actinic keratosis (AK) treatments may optimize clinical outcomes. PROAK study aimed to evaluate patient- and clinician-reported outcomes among adult patients with AK on face or scalp who were prescribed tirbanibulin in real-world clinical practice in the United States.
Methods: Key primary endpoint was quality of life (QoL) assessed by Skindex-16. Additional endpoints were tirbanibulin treatment effectiveness and satisfaction (Treatment Satisfaction Questionnaire for Medication and Expert Panel Questionnaire).
Results: 290 patients were included in this analysis. At week 8, Skindex-16 scores improved in all domains (mean change from baseline [standard deviation, SD]: -14.3 [27.8] in symptoms, -24.9 [33.0] in emotions, and -9.8 [23.7] in functioning domain). Clinicians and patients reported high global satisfaction with tirbanibulin (mean [SD] scores of 78.8 [20.1] and of 74.5 [23.5]). Overall skin appearance improved from baseline to week 8 (91.0% clinicians; 84.1% patients). In comparison with previous treatments, tirbanibulin had shorter skin reactions duration (89.2% clinicians; 73.9% patients); milder skin reaction severity (91.0% clinicians; 76.6% patients); better daily activities impact (87.4% clinicians; 64.0% patients); and was easier to use (88.3% clinicians; 71.2% patients). Investigator's Global Assessment (IGA) success (0-1) was achieved by 73.8% of the patients. Skin photodamage severity reduction from baseline to week 8 was significant (77.4% vs. 39.6%; $p<0.0001$).
Conclusions: Tirbanibulin treatment demonstrated effectiveness in AK management. Moreover, tirbanibulin improved QoL, as early as week 8, and both clinicians and patients reported tirbanibulin treatment convenience, and high levels of treatment satisfaction, compared to patient's previous treatments.

INTRODUCTION

Actinic keratoses (AKs) are dysplastic keratinocyte lesions caused by cumulative sun-exposure and ultraviolet radiation and are associated with fair skin and increasing age.[1–15] AKs are common skin lesions that affect around 58 million people in the United States (U.S.) and are one of the most frequent skin diagnoses.[2,4,8,14]

These cutaneous lesions are rough erythematous papules, particularly on face, scalp, and extremities, with potential to progress to squamous cell carcinoma.[1–3,6,7] All forms of AK must be treated and it is important to assess how to manage AK most effectively, owing to high prevalence of AK and the inability to predict which lesions will become cancerous.[2,12,16] Currently, there are two major categories of AK treatments: lesion-directed (cryosurgery and excisional therapies) and field-directed therapies (topical therapies, and photodynamic therapy [PDT]).[7,10–12,15]

Tirbanibulin is a novel synthetic chemical drug with potent antitumor and antiproliferative activity, with a simple dosage regimen that favors adherence.[2,10] It was approved by the U.S. Food and Drug Administration for treatment of AKs on December 14, 2020.[2] Phase II and III clinical trials have shown tirbanibulin to be efficacious with a favorable tolerability and safety profile on face and scalp after a short course of daily treatment for 5 consecutive days.[3,17] In Phase III clinical trials, patients treated with tirbanibulin experienced higher complete (100%) clearance (CC) levels (44% in trial 1; 54% in trial 2) than those treated with control ointment (5% trial 1; 13% trial 2; $p<0.001$ for both trials) at day 57.[3] Most common local skin reactions (LSR) were transient erythema (91% of patients) and flaking or scaling (82% of patients).[3] However, these reported outcomes may not fully capture the patient experience with the treatment.

Although clinical studies of topical treatments result in high therapeutic efficacy, in real-world, treatment length, regimen complexity, LSR presence and recurrence rates may impact treatment adherence, leading to poor outcomes.[2,6,14,18] In addition, AK lesions occur primarily on visible, sun-exposed areas, and negatively affect patients' quality of life (QoL), affecting emotional and social functioning.[19,20] Therefore, it is critical to understand patients' experiences and preferences regarding AK treatments, as their perspective may optimize adherence and clinical outcomes.[7,19]

Achievement of long-term treatment outcomes depends on patient's and clinician's treatment risk-benefit perceptions.[15,18] Moreover, patient satisfaction with treatment and QoL can affect treatment-related behaviors, such as correct and continuous use of medication.[21] Hence, patient-reported outcomes (PRO) are important measures concerning health status and medication experience coming directly from the patient.[13] PRO instruments could be categorized into AK-specific and non-specific instruments[7] and the most commonly used are Skindex and Treatment Satisfaction Questionnaire for Medication (TSQM) surveys.[15] The need of an AK-specific PRO instrument brought together a nine-person expert panel of dermatologists to develop the first AK-specific measure (Expert Panel Questionnaire [EPQ]) of PROs and clinician-reported outcomes (ClinROs) for comparative use.[16] Comparing patient and clinician perspectives may help optimize precision in AK treatment. AK-EPQ was first

implemented in this study[19] and will be used in future research studies of AK treatments.

Here, we present the interim results of PROAK (Patient-Reported Outcomes in Actinic Keratosis) study that evaluated PROs and ClinROs among adult patients with AKs on face or scalp who were prescribed tirbanibulin in real-world clinical practice in the U.S.

METHODS

Study Population and Design

PROAK is an observational, single-arm, prospective, multicenter, Phase IV study (NCT05260073) among adult patients with AK on face or scalp who have initiated treatment with tirbanibulin (as per label) in real-world clinical practices in the U.S., as part of routine care.[19] Patients were followed for 6 months post-treatment initiation.
Adults aged ≥18 years at time of treatment initiation with tirbanibulin, diagnosed with AK on face or scalp with clinically typical, visible, and discrete AK lesions, were included in the PROAK study. Patients with any dermatological condition of face or scalp that could interfere with clinical evaluations and patients with hypertrophic AK lesions, open wounds, or suspected skin cancers too close to treatment area were excluded from the study.

Patients and clinicians completed surveys and clinical assessments concerning safety and effectiveness of tirbanibulin at baseline, week 8 (timeframe for main endpoints) and week 24. Surveys results and clinical assessments at week 8 are presented here.
The study was performed at 32 private dermatology practices across the U.S. in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with the International Council for Harmonization. The study was reviewed by an independent ethics committee. All patients signed the informed consent form.

Outcomes

Primary endpoint was patient-reported QoL assessed by Skindex-16 at week 8.[22,23] Skindex-16 consists of 16 items classified into three domains: symptoms (four items: itching, burning, hurting, irritation), emotional impact (seven items: bothered about persistence/recurrence, appearance, worry about condition, frustration, embarrassment, being annoyed, feeling depressed) and functioning (five items: impact on interactions with others, desire to be with people, showing affection, daily activities, work, or other activities). Total score is the average of all items and transformed to a linear scale of 100 varying from 0 (never bothered) to 100 (always bothered). The higher the score, the more severe the impairment.

Additional endpoints included patient and clinician satisfaction with tirbanibulin treatment, assessed by TSQM-9[21] and EPQ[16] at week 8, treatment effectiveness assessed by Investigator's Global Assessment (IGA) and clinician rating of severity of skin photodamage at week 8 and week 24, safety, and tolerability (last two additional endpoints are not presented here).

TSQM-9 measured patient satisfaction with treatment on three key domains: effectiveness, convenience, and global satisfaction. Most items (from item 1 to 6 and item 9) are scored on a seven-point Likert scale from 1 (extremely dissatisfied/difficult/inconvenient) to 7 (extremely satisfied/easy/convenient). Items 7 and 8 of TSQM-9 are scored on a five-point scale from 1 (not at all confident/certain) to 5 (extremely confident/certain). TSQM-9

subscale scores are transformed to scores ranging from 0 to 100, with higher scores representing higher satisfaction on respective domains. An adapted version of TSQM-9 (same domains and scoring) was given to clinicians to measure their satisfaction with tirbanibulin treatment.

Regarding the EPQ, eleven questions were designed to measure patient and clinician's perspectives of clinical and cosmetic outcomes associated with AK, effect of treatment related LSR, and overall relative satisfaction with treatment. Items 1 to 9 were designed to be answered by both patient and clinician, whereas items 10 and 11 assess skin clearance (IGA of AK status) and photodamage, were designed to be answered by only clinicians. Clinician version of EPQ refers to clinician experience and observation of treatment effects among their patients.

Overall skin appearance was rated on a five-point adjectival response scale of 0 (much worse) to 4 (much improved) and satisfaction with 'how skin looks' and 'skin texture', on a seven-point response scale of 1 (extremely dissatisfied) to 7 (extremely satisfied) (EPQ 1-3). LSRs duration and severity, impact on daily activities, convenience and ease of use and overall satisfaction compared to previous AK treatments (EPQ 4-8) were rated on a five-point response scale from 0 (much shorter/better) to 5 (much longer/worse). Likelihood to reconsider treatment in future was rated on a five-point scale of 0 (very unlikely) to 5 (very likely) (EPQ 9). AK responses were assessed using IGA on a five-point response scale of 0 (completely cleared) to 4 (not cleared) (EPQ 10). IGA success was defined as achieving an IGA score of 0-1 (≥75% AK lesions clearance) at week 8. Clinicians assessed patient's skin photodamage severity on a four-point response scale of 0 (absent) to 3 (severe) (EPQ 11).

LSRs were graded by clinicians, and, in one site, photographs were captured to assess LSRs progression.

Statistical Analysis

Timepoint was week 8. Validated instruments (Skindex-16 and TSQM-9) were scored according to developer guidelines, reporting domain scored and overall summary scores. For all study variables and endpoints, no missing data imputation was planned. Data were presented descriptively using summary statistics, including percentage for categorical data, and mean with standard deviation (SD) and minimum and maximum for continuous data. Change from baseline (CFB) in Skindex-16 score was explored using relevant multivariate analyses. Pearson correlation coefficients were used to assess the correlation between key outcome measurements. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

A total of 300 patients were enrolled in the study. Ten of the enrolled patients were not included in the week 8 analyses due to missing data (one patient), or patient voluntary withdrawal of consent or lost to follow-up (nine patients). Therefore, a total of 290 patients with data from week 8 assessments were included in the interim analysis. Most of patients were male (68.6%) and the mean age (SD) was 66.3 (11.4) years. Overall, 77.9% of patients were diagnosed with AK on the face and 61.7% had a history of skin cancer. 71.4% of

Table 1. Baseline patient characteristics.

	Patients (N=290*)
Age, mean (SD) [min, max], years	66.3 (11.4) [30.0, 90.0]
Gender, n (%)	
Female	91 (31.4)
Male	199 (68.6)
AK location (not mutually exclusive), **n (%)**	
Face	226 (77.9)
Scalp	98 (33.8)
Primary health insurance, n (%)	
Private Insurance	121 (41.7)
Medicaid	9 (3.1)
Medicare	156 (53.8)
Uninsured	4 (1.4)
History of skin cancer, n (%)	179 (61.7)
Fitzpatrick skin type, n (%)	
Type I	22 (7.6)
Type II	207 (71.4)
Type III	54 (18.6)
Type IV	4 (1.4)
Type V	3 (1.0)
Baseline patient self-reported skin-texture, n (%)	
Dry	115 (39.7)
Smooth	138 (47.6)
Rough	57 (19.7)
Bumpy	54 (18.6)
Scaly	102 (35.2)
Blistering	1 (0.3)
Peeling	18 (6.2)

AK, actinic keratoses; SD, standard deviation.
*Ten patients were not included in the week 8 analyses: 1 patient had missing data, and 9 patients were discontinued from the study due to patient voluntary withdrawal of consent or lost to follow-up.

patients had Fitzpatrick skin type II and 47.6% of patients self-reported to have a smooth skin-texture. Patient characteristics are depicted in **Table 1**.

All patients completed their tirbanibulin treatment course (once daily for 5 days) and more than 75% of patients were treated with tirbanibulin between April and August 2022.

QoL Assessed by Skindex-16

Mean (SD) scores decreased from baseline to week 8 in all three domains: symptoms (22.3 [22.4] to 8.0 [13.8]), emotions (38.2 [27.3] to 13.3 [20.1] and functioning domains (14.4 [20.1] to 4.6 [12.0] (**Figure 1**). The mean (SD) Skindex-16 CFB in symptoms, emotions and functioning domains were -14.3 (27.8), -24.9 (33.0) and -9.8 (23.7), respectively. Decrease in scores from baseline to week 8 was statistically significant ($p<0.0001$) for all Skindex-16 domains.

Treatment Satisfaction Assessed by TSQM-9 and EPQ

Regarding TSQM-9 responses, clinician and patient satisfaction with tirbanibulin was high at week 8. Both clinicians and patients reported the highest satisfaction in the convenience of use subscale (mean [SD] scores of 85.3 [14.9] and 85.8 [14.3], respectively) followed by global satisfaction (mean [SD] scores of 78.8 [20.1] and 74.5 [23.5], respectively) and effectiveness (mean [SD] scores of 76.4 [21.5] and 73.0 [21.7], respectively) (**Figure 2**).

Regarding EPQ responses, 91.0% of clinicians and 84.1% of patients considered that overall skin appearance much or somewhat improved from baseline to week 8 using tirbanibulin (**Figure 3A**). Moreover, 79.0% of clinicians and 75.9% of patients were extremely or very satisfied with the improvement in how skin looked (**Figure 3B**) and 80.7% of clinicians and 74.8% of patients were extremely or very satisfied with skin texture improvement (**Figure 3C**).

A total of 111 out of 290 patients (38.3%) had used a topical medication in the past, with 5-fluorouracil (5-FU) being the most frequent (66.7%), followed by imiquimod (28.8%), ingenol mebutate (11.7%) and diclofenac (7.2%). Duration of skin reactions was considered much or somewhat shorter with tirbanibulin in comparison with previous topical AK medications by 89.2% of clinicians and 73.9% of patients (**Figure 4A**); 91.0% of clinicians and 76.6% of patients considered that the severity of skin reaction was much or somewhat better with tirbanibulin (**Figure 4B**); 87.4% of clinicians and 64.0% of patients considered that the impact on daily activities due to skin reactions associated with tirbanibulin use was much or somewhat better than with previous topical medications (**Figure 4C**); and 88.3% of clinicians and 71.2% of patients considered that tirbanibulin treatment was much or somewhat easier to use in comparison with other previous topical medications (**Figure 4D**). Overall satisfaction with tirbanibulin compared with previous AK treatments was rated as much or somewhat better by 82.9% of clinicians and 72.1% of patients (**Figure 4E**). Likewise, 85.2% of clinicians and 80.0% of patients reported their desire to consider tirbanibulin again, if needed, to treat AK lesions.

On the other hand, the proportion of patients with completely/partially cleared AK (IGA 0-1) was 73.8% (IGA success) at week 8. Among 288 patients with available data at both baseline and week 8, 77.4% of patients had moderate/severe skin photodamage at baseline and 39.6% of patients at week 8. Reduction of skin photodamage severity at week 8 was statistically significant ($p<0.0001$).

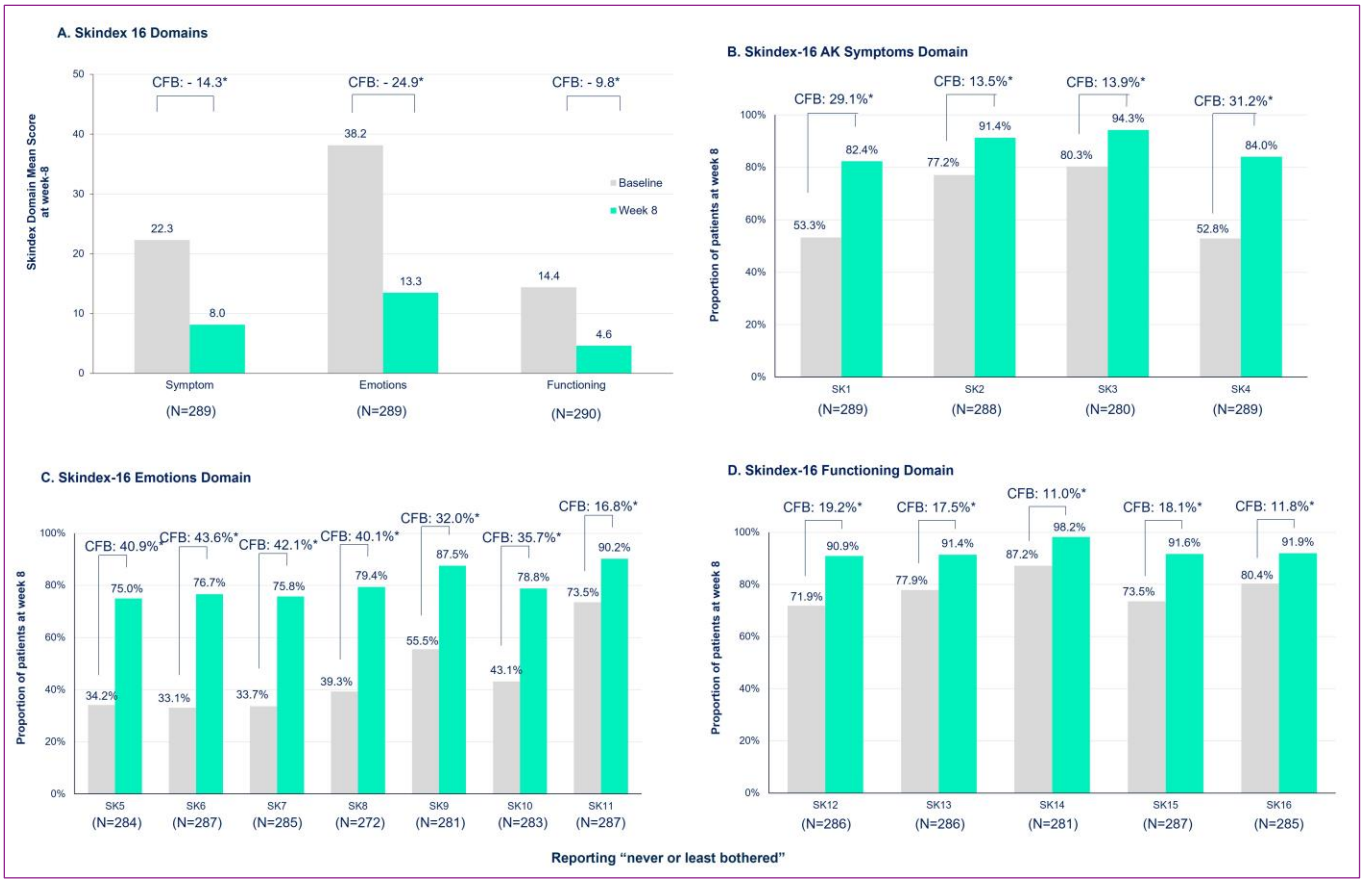

Figure 1. Evaluation of patient-reported AK symptoms, impact on emotions and functioning. SKINDEX-16 - QoL

One & four patients had missing data at baseline for Symptom & Emotions domain respectively; one patient had missing data at week-8 for Emotions domain.

Over the past week…

SK1: How often have you been bothered by **itching**?

SK2: How often have you been bothered by **burning** or **stinging**?

SK3: How often have you been bothered by your **skin condition hurting**?

SK4: How often have you been bothered by your **skin condition being irritated**?

SK5: How often have you been bothered by **persistence/recurrence** of skin condition?

SK6: How often have you **worried** about your **skin condition spreading, worsening, scarring** (etc.)

SK7: How often have you been bothered by the **appearance** of your skin condition?

SK8: How often have you been **frustrated** by your skin?

SK9: How often have you been **embarrassed** by your skin?

SK10: How often have you been **annoyed** about your skin?

SK11: How often have you been **feeling depressed** about your skin condition?

SK12: How often has your **interactions with others** been affected by your skin condition?

SK13: How often has your **interactions with others** been affected by your skin condition?

SK14: How often has skin condition made it **hard to show affection**?

SK15: How often has your skin affected your **daily activities**?

SK16: How often has skin condition made it **hard to work or do what you enjoy**?

AK, actinic keratoses; CFB, change from baseline to Week-8; QoL, quality of life.

*p<0.0001

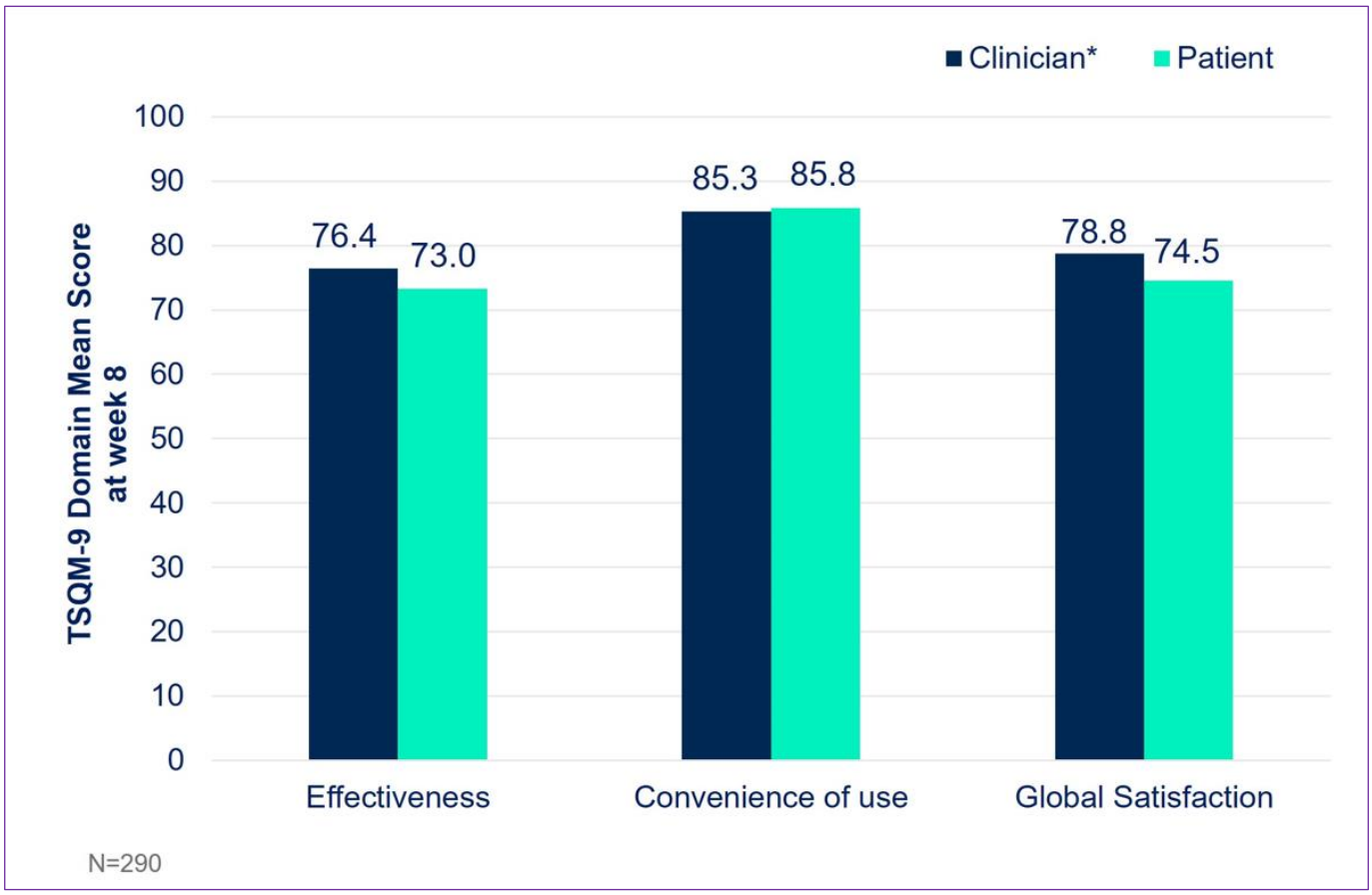

Figure 2. Clinicians' and patients' reported satisfaction with tirbanibulin treatment. TSQM-9.

TSQM, treatment satisfaction questionnaire for medication.
*Adapted from patient-version of TSQM-9.

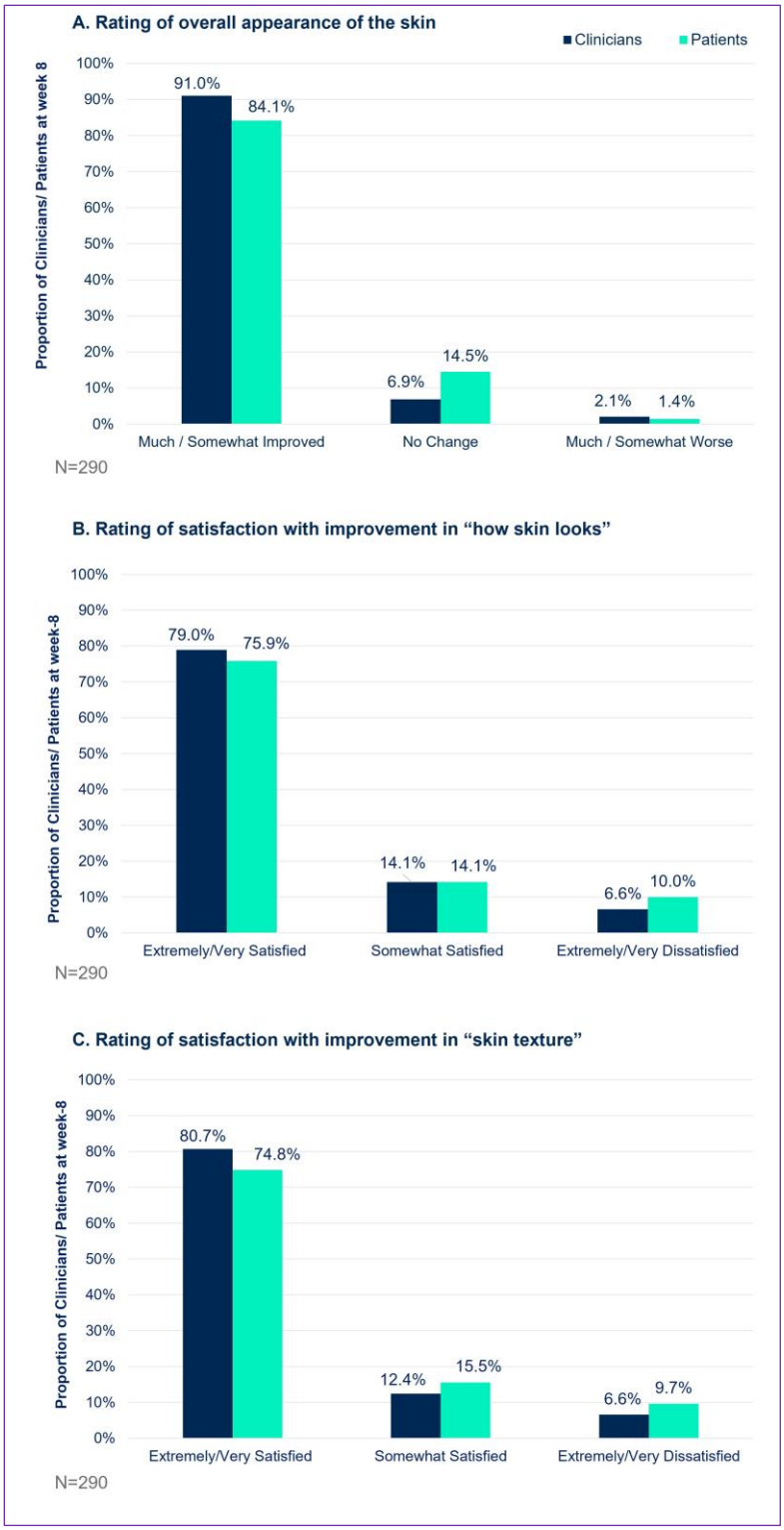

Figure 3. Clinicians and patients rating of overall appearance of the skin. EPQ.

EPQ, expert panel questionnaire.

Figure 4. Clinicians and patients' outcomes regarding tirbanibulin in comparison with other previous topical medications. EPQ.

EPQ, expert panel questionnaire.

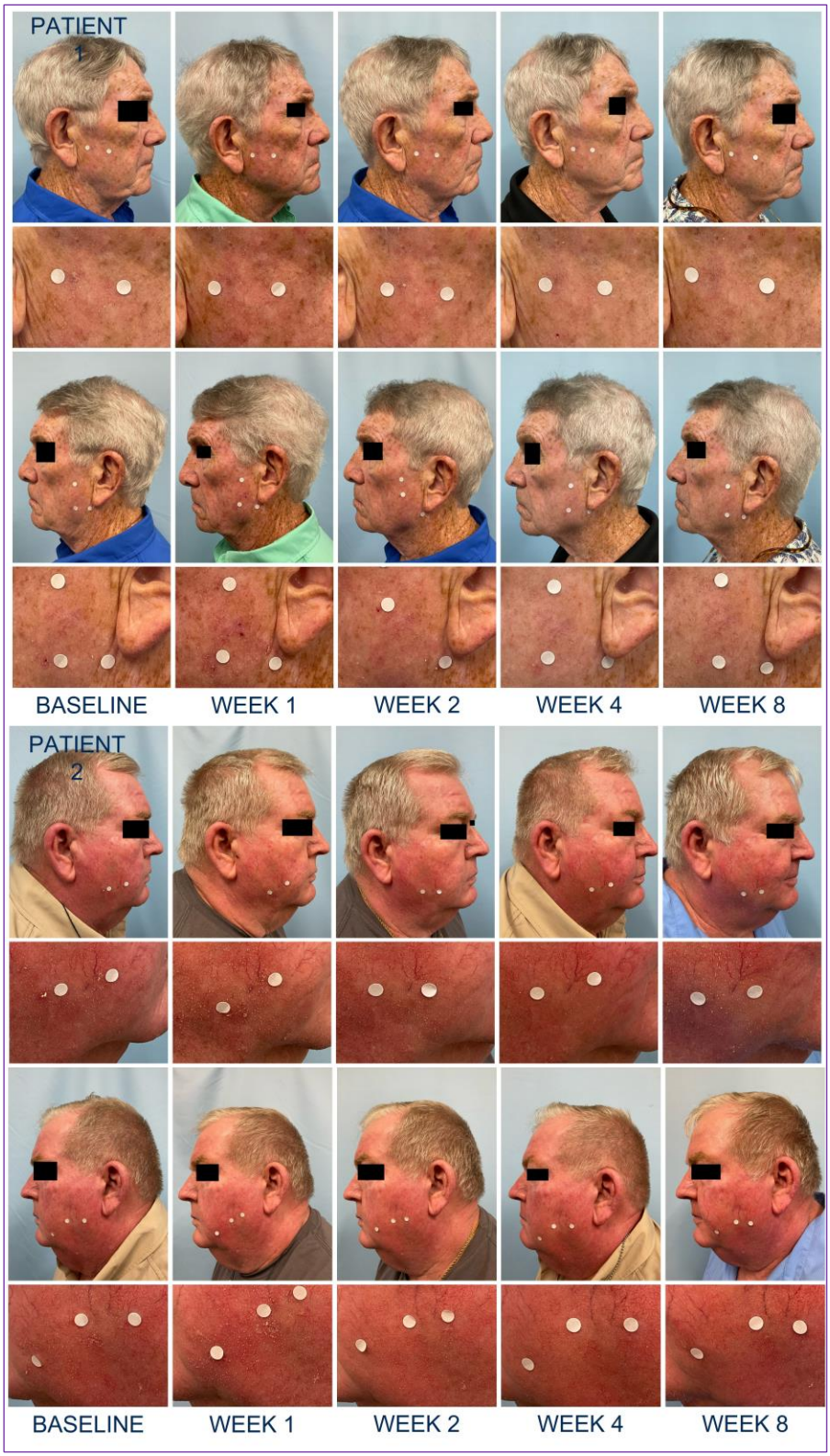

Figure 5. Clinical clearance at days baseline, week 1, week 2, week 4 and week 8 with use of tirbanibulin for actinic keratoses on face.

Photographs

Photographs were taken of ten patients. Two patients were selected for demonstration. Photographs were taken at baseline, week 1, week 2, week 4 and week 8 (**Figure 5**). Patient 1 was a 78-year-old male treated with tirbanibulin for AKs on face. The patient had previously been treated for AK with cryosurgery and 5-FU/calcipotriene. Patient 2 was a 69-year-old male treated for AKs on the face. The patient had previously been treated for AKs with cryosurgery, BLU-U PDT, and Efudex 5% cream. In both patients, CC (100%) levels were achieved before week 8.

DISCUSSION

In the real-world setting, adherence to therapy is important to achieve optimal outcomes. However, adherence can be compromised by patients' perception and satisfaction with the treatment. Hence, PROs, not always included in clinical trials, may inform clinicians about patients' preferences and what patients value the most for the AK treatment. PROAK study provides the opportunity to evaluate both PROs and ClinROs among adult patients with AKs on face or scalp treated with tirbanibulin in real-world clinical practice in the U.S.

The Skindex-16 survey was used in the PROAK study to comprehensively assess the impact of tirbanibulin on health-related QoL. Under real-world circumstances, tirbanibulin treatment improved QoL of patients, as early as in week 8, as indicated by the significant reduction of AK burden regarding symptoms, emotions, and functional impact from baseline. In this study, CFB reflects a large improvement in all the Skindex-16 domains (-14.3 in symptoms domain, -24.9 in emotions domain, and -9.8 in functioning domain). On the contrary, studies assessing health-related QoL, using Skindex-17 or Skindex-29, showed generally low impairment in patients with AK before the start of the therapy and reflected small improvements in QoL after treatment with other topical AK treatments (5-FU, imiquimod, methyl aminolevulinate, ingenol mebutate).[13,24,25]

Regarding satisfaction with treatment at week 8, assessed by TSQM-9 survey, both clinicians and patients agreed in the effectiveness and convenience of tirbanibulin treatment, reporting high levels of global satisfaction (79 and 75 mean score in clinicians and patients, respectively), higher than those reported in other studies using AK topical treatments. In the RAPID-ACT study[9], in Denmark and Sweden, patients diagnosed with AK and treated with diclofenac gel, imiquimod (3.75% or 5%) or ingenol mebutate (150 lg/g or 500 lg/g) reported, at week 3, a higher global satisfaction with imiquimod (64 TSQM-9 mean score) compared with diclofenac (61 TSQM-9 mean score) and ingenol mebutate (60 TSQM-9 mean score). On the other hand, in a phase III, multicenter, randomized study[12] in Germany and UK, overall treatment satisfaction was greater among patients with AK that received 5-FU than in patients that received vehicle (69 vs. 56 TSQM-1.4 mean score). To our knowledge, this is the first study assessing satisfaction with AK treatment using TSQM-9 in the U.S.

Furthermore, this is the first study using the new AK-EPQ survey[16]. AK-EPQ was designed to capture both ClinRO and PRO regarding AK treatment considering clinical and cosmetic outcomes associated with AK, effect of treatment related LSR, and overall satisfaction. Comparing both perspectives may help optimize AK treatment and enhance clinician-patient communication. Moreover, comparison of current and

previous AK treatments could be useful to measure the relative impact of different treatments. Therefore, the fact that both clinicians and patients better rated the attributes of tirbanibulin compared to previous treatments (shorter duration, ease of use, less LSR severity, better impact on patient's daily activities) and reported their desire to consider tirbanibulin again, highlights the benefits of this novel therapeutic option for the optimal management of AKs. Clinician-reported satisfaction with tirbanibulin treatment compared with previous AK topical medications was higher than patient-reported satisfaction, most likely due to clinicians comparing the results based on their daily experience with AK patients.

In addition, most patients and clinicians reported improvement in overall skin appearance in tirbanibulin-treated area at week 8. Moreover, clinicians reported a significant reduction in severity of skin photodamage from baseline to week 8 (77% vs. 40%; $p<0.001$) and most patients (74%) experienced IGA success (75-100% clearance). In conditions close to real clinical practice, tirbanibulin demonstrated effectiveness in AKs treatment, similar to that obtained in Phase III clinical trials of patients with AK receiving tirbanibulin or control ointment[3]. In Phase III clinical trials, at day 57, 44% and 54% of patients in the tirbanibulin group of trials 1 and 2, respectively, achieved CC (100%) of all AK lesions; whereas 68% and 76% of patients in the tirbanibulin group of trials 1 and 2, respectively, achieved partial (≥75%) clearance of AK lesions.[3]

Results may be subjected to bias such as recall bias, reporting bias, selection bias, and other biases commonly seen in real-world studies and open-label studies. Approaches such as standardized study inclusion/exclusion criteria, consecutive sampling, and geographically diverse dermatology clinics, with varied experience with oral antibiotics were employed to minimize these biases.

By contrast, this study has some strengths as to be able to assess QoL, treatment satisfaction and short-term effectiveness in daily practice tirbanibulin use in AK patients. Moreover, the newly developed AK-specific PRO and ClinRO instrument (EPQ[16]) obtains information about patient and clinician experience with AK treatments and comparing both perspectives can help to improve precision of AK treatments.

CONCLUSION

In real-world routine community practice, tirbanibulin treatment demonstrated effectiveness, as evidenced in Phase III clinical trials[3], highlighting the clinical and humanistic benefits associated with this novel therapeutic option for optimal management of AKs. Moreover, tirbanibulin improved QoL among patients with AK, as early as in week 8, and both clinicians and patients agreed in the convenience of tirbanibulin treatment, reporting high levels of treatment satisfaction and likelihood to consider its use again, if needed. Compared to patient's previous treatment, clinicians found a shorter duration and milder severity of skin reactions associated with tirbanibulin use, and a better impact in the daily activities of their patients, citing tirbanibulin as highly convenient. Tirbanibulin was better rated when compared to previous topical treatments in all questions. Finally, assessing both ClinRO and PRO among patients with AK in real-world setting is important to improve our understanding of patient burden and to inform healthcare professionals and

payers to aid their clinical and reimbursement decisions, respectively.

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