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ORIGINAL RESEARCH

Holistic Value Assessment of Tirbanibulin for Actinic Keratosis: European Multi-Criteria Decision Analysis

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ABSTRACT

Introduction: Actinic keratosis (AK) is a prevalent, chronic skin condition and a precursor to cutaneous squamous cell carcinoma. Effective, patient-friendly therapies that target both visible and subclinical lesions are essential. Tirbanibulin, a topical microtubule inhibitor, is the latest treatment approved in the USA and European Union (EU) for treating non-hyperkeratotic, non-hypertrophic AK on the face and scalp. This study aimed to assess the overall value of tirbanibulin for treating AK on the face or scalp across Germany, Italy, and Spain and to identify key value drivers using a multi-stakeholder perspective.

Methods: This study used a multi-criteria decision analysis (MCDA) to assess the holistic value of tirbanibulin compared with 5-fluorouracil 4% (5FU-4%) across Germany, Italy, and Spain. The validated EVIDEM MCDA framework (tenth edition) included eleven criteria related to disease burden, treatment benefits, evidence quality, and comparative outcomes. A total of 18 participants—dermatologists, payers, and patients—evaluated the treatments in a two-phase process. Phase 1 involved weighing the criteria, and

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phase 2 involved scoring clinical, economic, and patient-reported evidence for both treatments. Results from both phases were used to calculate an estimated value. The approach supports transparent, stakeholder-informed decision-making for AK treatment.

***Results*:** All criteria were rated as relevant, with the greatest importance assigned to "comparative safety/tolerability," "quality of evidence," and "comparative efficacy." Tirbanibulin received positive scores across all criteria, particularly for "expert consensus/guidelines," "quality of evidence," and "size of the affected population." The final estimated value of tirbanibulin was 0.622 on a −1 to +1 scale, indicating high perceived value. Value estimations were consistent across stakeholder types, with slight country-level variations.

***Conclusions*:** Overall, participants recognized tirbanibulin as a valuable treatment for AK, on the basis of robust evidence, favorable safety/tolerability and patient-reported outcomes (PRO) profiles, and alignment with clinical guidelines, with similar efficacy compared with 5FU-4%.

PLAIN LANGUAGE SUMMARY

Actinic keratosis is a very common skin condition caused by many years of sun exposure; while it is not always serious, it can sometimes develop into a type of skin cancer called squamous cell carcinoma, and because actinic keratosis often returns after treatment, there is a real need for safe and effective options that can help manage it over the long term. To address the limited evidence available on how newer treatments compare with existing alternatives, this study in Germany, Italy, and Spain explored the overall value of a topical treatment called tirbanibulin versus an older option, 5-fluorouracil 4%, for people with actinic keratosis on the face or scalp. Researchers used a structured approach called multi-criteria decision analysis, which looks beyond effectiveness alone and considers multiple factors such as safety, quality of evidence, and how well a treatment fits into everyday clinical practice; 18 participants—dermatologists, payers, and patients with actinic keratosis—reviewed the evidence and scored both treatments across these criteria. Overall, tirbanibulin was rated positively across all areas and was particularly valued for being safe and well tolerated, supported by strong scientific evidence, and recommended in expert guidelines, achieving a high overall value score of 0.62 on a scale from −1 to +1. These findings suggest that tirbanibulin is a valuable option for managing actinic keratosis, giving patients and clinicians an evidence-backed, clinically supported treatment choice that can help address the ongoing challenge of long-term disease control.

Keywords: Keratosis, actinic; Tirbanibulin; Decision support techniques; Health care evaluation mechanisms; Europe

Key Summary Points

Why carry out this study?

Actinic keratosis is a common, chronic, sun-related condition that recurs and can progress to cutaneous squamous cell carcinoma, supporting the need for safe, patient-friendly long-term treatments.

In Europe, evidence comparing newer topical therapies with established options remains limited when safety, evidence quality, patient experience, and real-world feasibility are considered alongside effectiveness.

This study used multi-criteria decision analysis to compare topical tirbanibulin with topical 5-fluorouracil 4% for non-hyperkeratotic, non-hypertrophic lesions on the face or scalp, on the basis of evidence review and scoring by 18 stakeholders from Germany, Italy, and Spain.

What was learned from the study?

Tirbanibulin scored 0.622 on a −1 to +1 scale and was rated positively across domains, driven by safety and tolerability, evidence quality, and guideline alignment, with efficacy close to neutral versus topical 5-fluorouracil 4%.

Stakeholders prioritized safety and tolerability, evidence strength, and fit in routine care beyond lesion clearance, indicating these factors may influence adoption and reimbursement when efficacy differences are small.

Multi-criteria decision analysis transparently integrates clinician, payer, and patient perspectives and highlights research needs, including longer-term control and prevention of progression to cutaneous squamous cell carcinoma.

INTRODUCTION

Actinic keratosis (AK), or solar keratosis, is a chronic, recurrent skin condition caused by cumulative ultraviolet (UV) exposure. Lesions typically present as scaly, crusty, or discolored patches under 1 cm, often surrounded by photodamaged skin. While often asymptomatic, AK can cause itching, burning, or bleeding [1–6]. The condition is highly prevalent, with incidence varying by age, geography, and UV exposure [7–10]. A 2022 meta-analysis reported a global incidence of 1928 cases per 100,000 person-years [11], a figure expected to rise with aging populations and increased UV exposure [16].

AK is the primary precursor to cutaneous squamous cell carcinoma (cSCC), responsible for approximately 65% of invasive cases [12]. Although the per-lesion transformation risk is low (0–0.075% annually), multiple lesions (more than five) raise the cumulative 10-year cSCC risk to around 17%. Recurrence, defined as the reappearance of lesions at previously treated sites or the development of new lesions in the same area, is common, with up to 75% requiring retreatment within a year [6, 7, 10, 13]. Beyond physical symptoms, AK also negatively affects quality of life and mental health, largely owing to its visible nature and cancer risk [2, 14, 15].

The primary goals of management are to reduce lesion burden and to prevent disease progression. Although there is no definitive cure, treatment strategies focus on achieving long-term disease control [16]. Therapeutic decisions are guided by the number and distribution of lesions, the extent of field cancerization (area of the skin with both clinical and subclinical lesions), patient comorbidities, and individual preferences.

According to the 2024 European consensus guidelines, lesion-directed therapies are recommended for clinically evident lesions, while field-directed therapies, such as topical agents, are first-line for multiple or subclinical lesions, as they target both visible and hidden abnormalities. Current clinical guidelines recognize topical agents as the gold standard for field-directed therapy [1, 3, 6, 17–22].

Tirbanibulin 1% ointment is a short, 5-day topical therapy for AK that selectively targets precancerous keratinocytes without causing necrosis or significant inflammation. It has a dual mechanism of action: it acts as an

antiproliferative agent by inhibiting microtubule polymerization and disrupts Src kinase signaling, both of which contribute to halting abnormal cell growth. Tirbanibulin is approved by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The EMA authorized it in July 2021 for treating non-hyperkeratotic, non-hypertrophic AK on the face or scalp in adults, for areas up to 25 cm^2. The FDA initially approved the same indication in December 2020, also limited to 25 cm^2, and expanded this in June 2024 to include treatment areas up to 100 cm^2 [23–25].

In recent years, the treatment landscape for AK has broadened with new therapeutic options [26]. As healthcare systems aim to optimize budgets and allocate resources effectively, it is essential that decision-makers assess these options not only for their clinical efficacy and safety but also for their broader societal and system value. Above all, treatment choices should reflect outcomes that matter to patients, ensuring their voices are central to the evaluation of value. To this date, evidence on comparative value of tirbanibulin against alternative therapies remains limited.

Traditional economic evaluations, particularly cost-effectiveness analyses, have guided funding decisions but often fall short in capturing the full range of factors that shape value perceptions. Moreover, these approaches typically overlook broader considerations and fail to incorporate the perspectives of all relevant stakeholders, including patients, clinicians, and society at large. To overcome these limitations, multi-criteria decision analysis (MCDA) has emerged as a complementary tool, offering a structured, transparent approach to integrate diverse criteria into healthcare decision-making. By enabling explicit consideration of clinical, economic, ethical, and societal aspects, MCDA supports more balanced, legitimate decisions [27–30]. In dermatology—and particularly for chronic, recurrent conditions like AK—MCDA can add meaningful insight [30–32]. However, its application in evaluating AK treatments remains limited.

The objectives of this study were to (1) assess the holistic value of tirbanibulin as field treatment for non-hyperkeratotic, non-hypertrophic AK of the face or scalp and (2) to identify the key value drivers, across three European countries: Germany, Italy, and Spain. It aimed to capture the perspectives of clinicians, payers, and patients to facilitate evidence-based decision-making.

METHODS

MCDA Framework

For the qualitative assessment of the perceived value of an AK treatment, the study adapted the core model of the tenth edition of the Evidence and Value: Impact on Decision-Making (EVIDEM) MCDA framework. This methodology includes three sequential steps for adaptation: (1) first, relevant criteria were selected from the EVIDEM core model and adapted on the basis of their applicability to the AK disease and treatment context; (2) a tailored framework was developed by defining these selected criteria, and related sub-criteria, specifically for AK; (3) and third, the framework was validated through input from participating clinical experts [33–35]. As a result, three domains with 11 criteria from the EVIDEM core model were included (Table 1):

1. Disease-related criteria: “burden of disease,” “size of affected population,” and “unmet medical needs.”
2. Non-comparative treatment-related criteria: “quality of evidence,” “alignment with clinical expert consensus,” “type of therapeutic benefit,” and “type of preventive benefit.”
3. Comparative treatment-related criteria: “efficacy/effectiveness,” “safety/tolerability,” “patient-reported outcomes (PROs),” and “cost consequences.”

For the comparative criteria, 5-fluorouracil 4% (5FU-4%) was selected as the comparator, as it is the second most recently approved treatment

Table 1 MCDA Framework Core Model (Quantitative Criteria)

	Criteria	Sub-criteria	Definition
Disease-related criteria	Disease severity	• Effect of disease on life-expectancy • Effect of disease on morbidity (includes disability and function) • Effect of disease on patients' quality of life	• Severity of actinic keratoses as a health condition with respect to mortality, morbidity, disability, function, impact on quality of life, clinical course (i.e., acuteness, clinical stages, possibility of turning into skin cancer)
	Size of affected population	• Prevalence • incidence	• Number of people affected by the condition in your country in terms of incidence (annual number of new cases) and/or prevalence (proportion of the population affected at a certain point in time)
	Unmet needs	• Unmet needs in efficacy • Unmet needs in safety • Unmet needs in patient-reported outcomes • Patient demand	• Shortcomings of existing treatments in their ability to prevent, cure, or ameliorate the health condition (actinic keratoses); also include shortcomings with respect to safety, patient-reported outcomes, and convenience
Treatment-related criteria	Quality of evidence	• Validity • Relevance • Completeness of reporting • Type of evidence	• Extent to which evidence "product "A" is relevant to the decision-making body (in terms of population, disease stage, comparator interventions, outcomes, etc.) and valid with respect to scientific standards (i.e., study design, etc.) and conclusions (i.e., agreement of results between studies). This includes consideration of uncertainty (e.g., conflicting results across studies and limited number of studies and patients). Complete reporting of evidence is a prerequisite to assess coherence and validity

Table 1 continued

Criteria	Sub-criteria	Definition
Expert consensus/clinical practice guidelines	• N/A	• Concurrence of "product A" (or similar alternatives) with the current consensus of experts on what constitutes state-of-the-art practices in the management of actinic keratoses; guidelines are usually developed via an explicit process and are intended to improve clinical practice
Type of preventive benefit of drug A	• Prevention or risk reduction of skin cancer	• Nature of the preventive or risk reduction benefits provided by drug A for skin cancer, from a public-health perspective
Type of therapeutic benefit of drug A	• Treatment of actinic keratosis	• Nature of the curative clinical benefit provided by drug A at the patient level
Comparative efficacy/effectiveness: drug A versus drug B	• Magnitude of clearance rate achieved • Rapidity in onset of clearance rate improvement • Rate of recurrence	• Capacity of "drug A" to improve clearance rates in patients with actinic keratoses above and beyond beneficial changes produced by the relevant comparative treatment ("drug B")
Comparative safety/tolerability: drug A versus drug B	• Adverse events • Serious adverse events • Fatal adverse events • Short-term safety • Long-term safety • Tolerability	• Capacity of "drug A" to produce a reduction in treatment-related harmful or undesired health effects compared with the alternative relevant comparative treatment ("drug B")
Comparative patient-perceived health/patient-reported outcomes	• Improvement in health-related quality of life • Impact on dignity • Convenience/ease of use/mode and setting of administration • Impact on mental wellbeing	• Capacity of "drug A" to produce beneficial changes in patient-perceived health and patient-reported outcomes (e.g., quality of life) above and beyond beneficial changes produced by the alternative relevant comparative treatment ("drug B"); also includes improvement in convenience to patients

Table 1 continued

Criteria	Sub-criteria	Definition
Comparative cost consequences (drug A versus drug B—cost of intervention	• Net cost of drug A • Acquisition cost • Implementation/maintenance cost • Potential cost savings	• Net cost of financing drug A (excluding other spending). This represents the differential between the expected expenditures for drug A and the alternative relevant comparative treatment ("drug B"). This also includes potential cost savings that may result from replacement of other treatments(s) currently covered

MCDA multicriteria decision analysis, *N/A* not applicable

for use in patients with non-hyperkeratotic and non-hypertrophic AK after tirbanibulin.

Literature Review and Matrix Development

A systematic literature review was conducted to gather relevant information on the burden and management of AK in Europe, as well as clinical, economic, and patient-reported evidence for tirbanibulin and 5FU-4% (January 2018 to September 2024). Evidence was sourced from both public and proprietary databases, including major biomedical literature repositories such as PubMed/MEDLINE. In addition to database searches, supplementary targeted searches of gray literature were performed. These included queries through Google Scholar, websites of relevant patient associations, scientific societies, and official regulatory or health technology assessment (HTA) bodies. Findings were synthesized into an evidence matrix, which structured the available data across the 11 selected criteria. This matrix was translated to German, Italian, and Spanish and subsequently used for scoring during the MCDA.

Participants and Process

A total of eighteen ($n = 18$) participants were recruited for the MCDA panel. Each national group included two dermatologists with experience in AK management, two payer representatives (experienced pharmacists involved in the evaluation of specialist-prescribed retail medicines, serving in primary care and/or regional health system roles Italy and Spain, and statutory sickness fund representatives in Germany), and two patients with a confirmed AK diagnosis. Clinicians were identified via professional networks, while patients and payers were recruited through a specialized third-party agency for healthcare research.

This study is a non-interventional expert MCDA workshop with multidisciplinary professionals. It involves no intervention on human subjects, no administration of medicinal products or devices, and no collection of patient data; therefore, it falls outside the scope of

clinical trial/device investigation requirements and is not human-subjects biomedical research.

This non-interventional, survey-based study was conducted in accordance with the principles of the Declaration of Helsinki. All participants (clinicians, payers, and patients) provided informed consent before participation. The study involved no clinical procedures or collection of identifiable personal data. All participants signed a participation agreement (including data-processing terms) and informed consent, and the analysis dataset contains only aggregated/anonymized responses (contact/payment details are stored separately per the agreement and privacy notice). Given the absence of identifiable/sensitive data in the analytical dataset and the safeguards in place, formal institutional review board (IRB)/research ethics committee (REC) review is not required.

The value estimation process unfolded in two structured phases, with both tirbanibulin and 5FU-4% anonymized using neutral identifiers to minimize bias:

- Phase 1—criteria weighting: All participants were independently assigned relative weights to each criterion on the basis of perceived relevance to AK treatment decisions (1 = low relevance, 5 = high relevance). These individual weightings were then discussed in an online session, aiming to promote mutual understanding and consensus across stakeholder groups.
- Phase 2—evidence scoring: All participants received the evidence matrix and independently scored the evidence for each criterion. The highest scores indicate a stronger alignment of the evidence with the desired outcomes of the criterion when assessing the value of treatment for AK (Supplementary Table S1). The evidence of non-comparative treatment related criteria was scored from 0 (lowest value) to 5 (highest), while the evidence for comparative criteria used a −5 to +5 scale, where negative scores indicated superiority of the comparator and positive scores indicated superiority of tirbanibulin. A second online session was held to review the scores, clarify uncertainties, and allow participants to refine their assessments based on the group discussion. Comments and reflections were also gathered to contextualize scores.

Data Collection and Analysis

All data were collected through individual online surveys (weights, scores, and rationales). An online secured platform was used to collect answers from participants.

For each criterion, descriptive statistics were calculated, including mean, standard deviation (SD), and range. Qualitative feedback was analyzed thematically to interpret scoring rationales.

The overall value of tirbanibulin was computed using a linear additive model, combining individual criterion weights with normalized scores [34, 35]. The value estimation formula is presented below:

$$V = \sum_{x=1}^{n} V_x = \sum_{x=1}^{n} \left(\frac{\omega_x}{\Sigma^{\omega_n}} S_x \right)$$

where, V is the total estimated value of the intervention; V_x is the contribution of criterion x to the total value; W_x is the weight assigned to criterion x; ΣW_n is the sum of weights across all criteria; S_x is the normalized score for criterion x, calculated as $S_x = (\text{score}/5)$.

Results were normalized to a −1 to +1 scale. A value > 0 indicates a positive contribution to tirbanibulin's value, whilst < 0 reflects a negative contribution (relative to 5FU-4%).

Reporting of the study data was conducted according to the Discrete Choice Experiment Reporting Checklist (DIRECT), which provides consolidated guidance and minimum reporting standards for discrete choice experiments in health. Use of the DIRECT checklist ensures transparency, facilitates comparison with similar studies, and enables robust assessment of methodological quality [36].

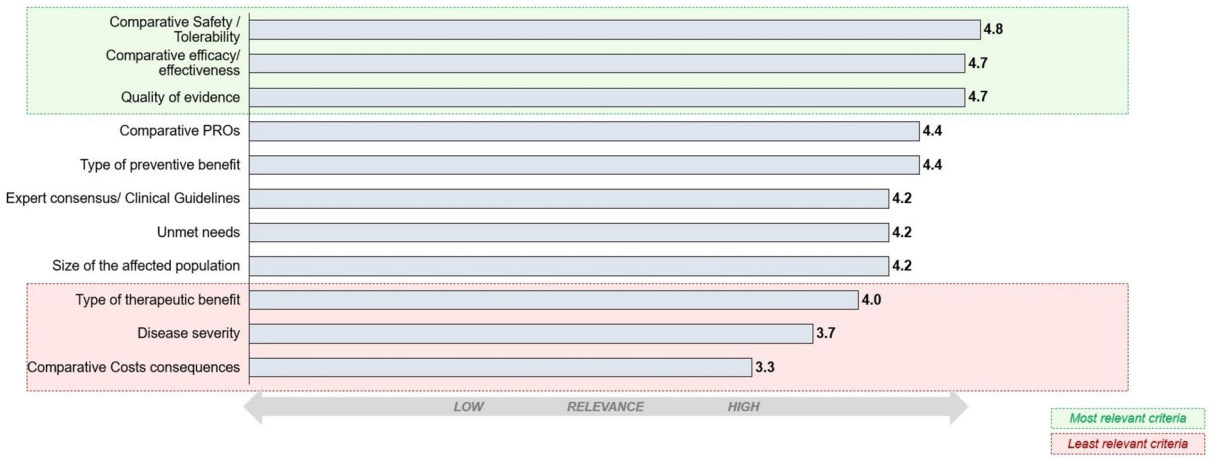

Fig. 1 Mean results of the criteria weighting (phase 1) after group discussion ($n = 18$). *PRO* patient-reported outcome

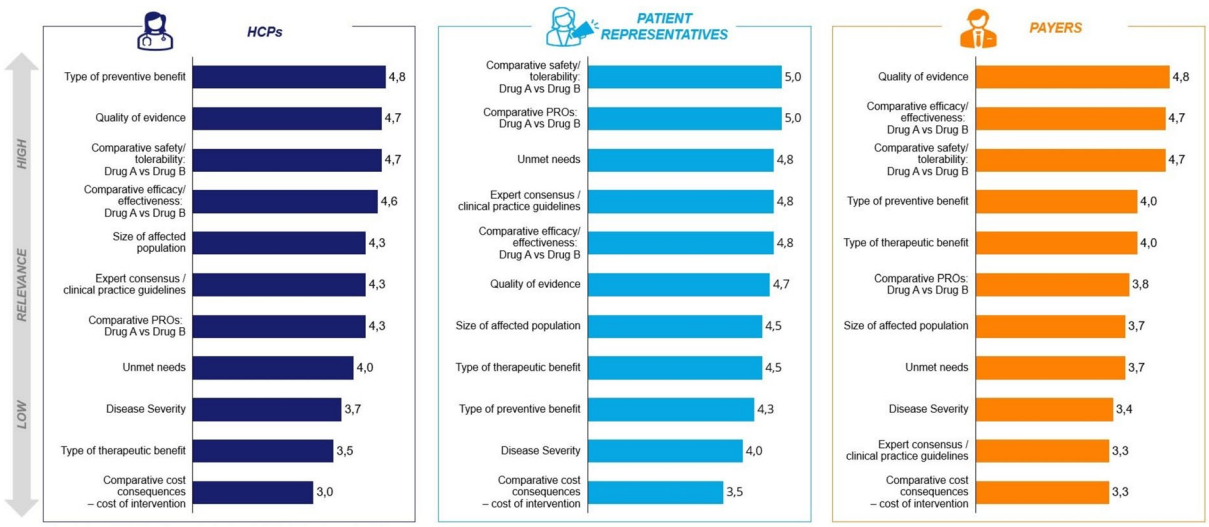

Fig. 2 Mean results of the criteria weighting (phase 1) after group discussion by participant profiles ($n = 18$). *HCP* healthcare professional, *PRO* patient-reported outcome

RESULTS

The results are presented in three sections: (1) the relative importance assigned to each evaluation criterion (weights), (2) the scoring of the available evidence for tirbanibulin per criterion (scores), and (3) the overall value estimate derived by integrating weights and scores.

Weights: Relative Importance of Each Criterion

The participants assigned all criteria with high relative importance (average weight of over 3 out of 5 for all criteria) (Fig. 1). "Comparative safety/tolerability," "quality of evidence," and "comparative efficacy/effectiveness" were

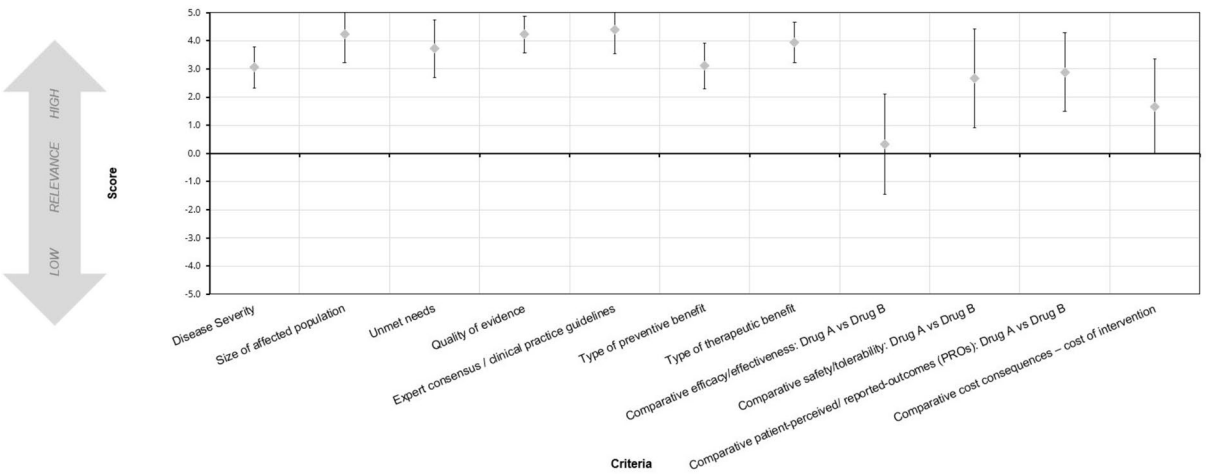

Fig. 3 Mean results for the evidence scoring (phase 2)

identified as the three most relevant criteria for assessing the value of a treatment for AK. On the contrary, "type of therapeutic benefit," "disease severity," and "comparative cost consequences" were considered the least relevant criteria.

Numerical variability in participant responses was generally low, with a median standard deviation (SD) of 0.8 across the 11 criteria. Strong agreement (SD < 1) was observed for "size of the affected population," "quality of evidence," "type of therapeutic benefit," comparative "efficacy/effectiveness," "safety/tolerability," and "PROs." The remaining criteria ("disease severity," "unmet needs," "expert consensus/clinical guidelines," "type of preventive benefit," and "cost consequences") showed slightly greater variability (SD 1.0–1.2), indicating modest differences in participant views.

When broken down by participant group, variations emerged (Fig. 2). However, "comparative safety/tolerability" was consistently ranked among the top three criteria across all groups, underscoring its perceived high importance. Conversely, "disease severity" and "comparative cost consequences" consistently appeared in the bottom three rankings for all participant types, indicating a lower perceived importance.

Scoring of Tirbanibulin

Tirbanibulin received positive scores across all 11 criteria. The criteria that received the highest scores (indicating stronger alignment with the desired outcomes) were "expert consensus/clinical guidelines" (4.5 ± 0.8), followed by "quality of evidence" (4.2 ± 0.6), and "size of the affected population" (4.2 ± 1). In contrast, the lowest scoring criteria were "efficacy/effectiveness" (0.3 ± 1.8) and "cost consequences" (1.7 ± 1.7) (Fig. 3). Results were consistent across participants, reflecting a shared perspective in the assessment of criteria.

Overall, response variability was higher than for the weighting exercise with a mean SD of 1.1 across the eleven criteria. Criteria showing the lowest variability included "disease severity," "quality of evidence," "expert consensus/clinical guidelines" (SD: 0.6–0.8), and "preventive benefit" and "therapeutic benefit". On the contrary, comparative criteria showed the highest variability (SD: 1.0–1.8).

From a multidisciplinary perspective across Europe, tirbanibulin received positive scores across all participants to all criteria driven by convenience, favorable safety profile, and alignment with established dermatological guidelines.

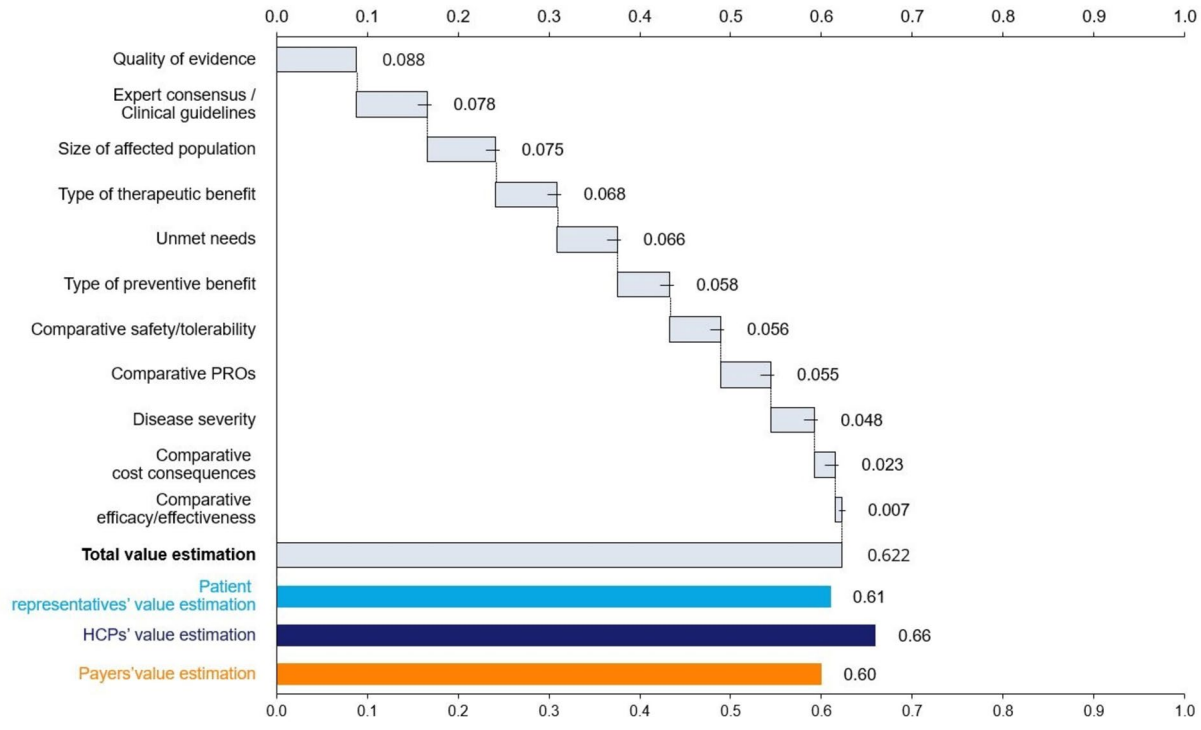

Fig. 4 Value estimation of tirbanibulin (−1 to +1 scale, total and per expert profile), and value contribution per criteria (ranked from highest to lowest contribution). *HCP* healthcare professional, *PRO* patient-reported outcome

Value Estimation: Combining Weights and Scores

Integrating weights and scores yielded a mean overall value of 0.622 for tirbanibulin on a −1 to +1 scale, with minimal variation across stakeholders (range 0.60–0.66) (Fig. 4).

From a European perspective, the criteria with the highest contribution to the final estimated value of tirbanibulin were "quality of evidence" (0.088 ± 0.02), "expert consensus/clinical guidelines" (0.078 ± 0.02), and "size of the affected population" (0.075 ± 0.02). The criteria which contributed the lowest to the value of the treatment were "comparative cost consequences" (0.023 ± 0.03) and "comparative efficacy" (0.007 ± 0.03) (Fig. 4).

A comparative view of the weights, scores, and value contributions are presented in Table 2.

Overall, participants recognized tirbanibulin as a valuable treatment for AK, on the basis of robust evidence, favorable safety and PRO profiles, and alignment with clinical guidelines, despite limited differentiation in efficacy compared with 5FU-4%.

DISCUSSION

This study is, to our knowledge, the first application of an MCDA framework to assess the value of a therapeutic intervention for AK. Tirbanibulin received a total MCDA score of 0.622 on a −1 to +1 scale, reflecting a high perceived value of tirbanibulin based on a multidimensional assessment involving clinicians, payers, and patients from three European countries. This finding is particularly relevant given the chronic and recurrent nature of AK, its rising prevalence, and the pressing need for effective, patient-friendly treatment options that address both visible and subclinical lesions, supported by robust clinical evidence.

The value attributed to tirbanibulin was primarily driven by three key factors: (1) the

Table 2 Results of weighting (phase 1) and scoring (phase 2) and value contribution per criteria for tirbanibulin

	Criteria	Value contribution	Weight	Score	Description
Disease-related criteria	Disease severity	0.048 ± 0.02	4.7	3.1	AK was perceived as a moderately severe condition: despite not being life-threatening, concerns regarding its potential progression to SCC, the psychological, cosmetic, and quality of life impacts of AK were acknowledged. Patient representatives placed greater emphasis on these aspects than payers and HCPs. Consequently, this criterion had a modest contribution on overall tirbanibulin value
	Size of affected population	0.075 ± 0.02	4.2	4.2	The rising prevalence of AK, driven by population aging and increased sun exposure, was a key driver of perceived treatment value. Participants, particularly healthcare professionals, assigned high importance to this criterion, often giving it near-maximum scores owing to the substantial and growing disease burden. In contrast, German payers were more reserved, considering prevalence less critical within the context of health technology assessment
	Unmet needs	0.066 ± 0.03	4.2	3.7	Participants acknowledged a medium–high level of unmet need, characterized by delayed diagnosis, high recurrence, high levels of toxicity, and lack of personalized care. Patient representatives placed particular emphasis on gaps in patient education and disease awareness

Table 2 continued

	Criteria	Value contribution	Weight	Score	Description
Treatment-related criteria	Quality of evidence	0.088 ± 0.02	4.7	4.2	This was the highest contributing criterion to tirbanibulin's total value, receiving high weights and scores from all groups. Participants widely regarded the clinical evidence as robust due to the existence of RCTs complemented with locally relevant RWE. This criterion's high weight and favorable scoring underscore the central role that strong evidence plays in value determination
	Expert consensus/clinical practice guidelines	0.078 ± 0.02	4.2	4.4	The alignment between the use of tirbanibulin and European dermatological guidelines was consistently viewed as a key value indicator. All stakeholder groups, especially HCPs, considered this alignment to be a critical enabler of clinical adoption. The broad consensus across countries further reinforced the criterion's relevance
	Type of preventive benefit of drug A	0.058 ± 0.02	4.4	3.1	While tirbanibulin is effective in lesion clearance, its long-term preventive effect, particularly in reducing SCC risk, was challenged owing to high recurrence rates. As such, this criterion contributed moderately to overall value. Stakeholder groups uniformly rated preventive benefit as important but weighed it less than other criteria owing to the current lack of conclusive long-term data proving impact of tirbanibulin on SCC incidence

Table 2 continued

Criteria	Value contribution	Weight	Score	Description
Type of therapeutic benefit of drug A	0.068 ± 0.01	4	3.9	Tirbanibulin's therapeutic benefit was characterized by its short treatment course, ease of use, and tolerability, which were recognized as enablers for higher patient adherence, therefore contributing moderately to its overall value. Particularly, HCP participants highlighted these aspects as key differentiators from traditional therapies
Comparative efficacy/effectiveness: drug A versus drug B	0.007 ± 0.03	4.7	0.3	This criterion was considered the most relevant by participants. However, tirbanibulin received a low score primarily because participants perceived its clinical effectiveness as comparable to that of 5-FU 4%. The absence of direct head-to-head comparative trials further limited payers' ability to draw firm conclusions regarding tirbanibulin's relative efficacy. As a result, despite the recognized importance of efficacy, this criterion contributed the least to the overall tirbanibulin value, representing a limited, though not negative, impact
Comparative safety/tolerability: drug A versus drug B	0.056 ± 0.04	4.8	2.7	Comparative safety and tolerability received a high weight across stakeholder groups, highlighting its perceived importance in AK treatment decision-making. However, the score assigned to tirbanibulin on this criterion was only moderate. This was largely due to the recognition that tirbanibulin demonstrated a favorable safety profile and fewer LSR compared with 5-FU4%; nonetheless, the perception of the magnitude of the comparative benefit differed between payers (lower benefit) and patients and HCPs (higher benefit). As a result, this criterion contributed moderately to the overall value estimate

Table 2 continued

Criteria	Value contribution	Weight	Score	Description
Comparative patient-perceived health/patient-reported outcomes	0.055 ± 0.03	4.4	2.9	Although it received a high weight, its score was moderate due to lack of reported AK-specific PRO data. The higher adherence and convenience of tirbanibulin compared with 5-FU4% contributed positively to its perceived value. Therefore, this criterion made a moderate contribution to the overall value estimate
Comparative cost consequences (drug A versus drug B—cost of intervention	0.023 ± 0.03	3.3	1.7	This criterion received the lowest weight among all criteria, reflecting its limited perceived importance in the overall value assessment. The medium score assigned was largely due to the absence of robust, locally relevant economic data, which made it difficult for participants to fully evaluate tirbanibulin's cost implications. While stakeholders recognized that tirbanibulin's improved tolerability and lower discontinuation rates compared with 5-FU4% might result in indirect cost savings, the overall contribution of comparative cost consequences to tirbanibulin's value estimation was marginal

AK actinic keratosis, *HCP* healthcare provider, *LSR* local skin reactions, *MCDA* multicriteria decision analysis, *N/A* not applicable, *PRO* patient reported outcomes, *RCT* randomized controlled trial, *RWE* real-world evidence, *SCC* squamous cell carcinoma

quality of the clinical evidence supporting its efficacy and safety; (2) its short treatment regimen, which enhances patient adherence and satisfaction; and (3) alignment with expert clinical guidelines, particularly in the context of increasing AK prevalence and unmet clinical needs. These drivers are consistent with criteria identified in prior MCDA studies across dermatological indications, including moderate-to-severe psoriasis and atopic dermatitis, where treatment convenience, health-related quality of life (HRQoL), and stakeholder alignment were also major contributors to perceived value [30–32].

The score obtained by tirbanibulin (0.622) compares favorably with those reported in previous MCDAs in dermatology. For example, Zozaya et al. (2018) reported value scores ranging from 0.41 to 0.63 across biologics for moderate-to-severe psoriasis, while Pereyra-Rodríguez et al. (2023) identified key value drivers—such as HRQoL and symptom control—for emerging treatments in atopic dermatitis [30, 32]. The consistent structure across these studies, which adapt the EVIDEM framework to the therapeutic area under evaluation, enables cross-indication comparisons and provides a benchmark for interpreting value in dermatological care. In addition, all individual scores assigned in this MCDA—both absolute and comparative—were positive, despite the potential for negative scoring in the latter. This reinforces the overall favorable perception of tirbanibulin across the evaluated criteria.

An important strength of this study lies in the diversity and balance of the expert panel ($n=18$), which included equal representation of clinicians, payers, and patient representatives, and covered three major European markets. This geographical diversity enabled the capture of potential contextual differences in value perception within Europe. While agreement across stakeholder profiles was high (score range: 0.60–0.66), differences were observed between countries, with the highest value perception reported in Italy (0.73), followed by Spain (0.62) and Germany (0.52). These variations reflect differences in healthcare delivery and reimbursement processes. Similar findings were observed in other reflective MCDAs, such as in the evaluation of cenobamate for drug-resistant epilepsy in Spain, where regional differences in expert scoring were linked to contextual healthcare realities [37].

The analysis also underscored persistent challenges in AK management, including limited awareness of the disease and restricted access to dermatologic care in certain settings. In addition, it highlighted the need for therapeutic options with lower recurrence rates and for evaluating treatment efficacy beyond traditional endpoints such as complete and partial clearance. The latter reflects growing interest in capturing more nuanced, continuous measures of clinical benefit in AK management. For instance, Ezzedine et al. (2020) demonstrated that complete clearance rates are inversely related to baseline lesion counts, highlighting the limitations of relying solely on this endpoint and underscoring the relevance of alternative measures like percentage lesion count reduction [38–41]. These issues were recurrent themes in qualitative feedback and emerged as relevant value components. This supports the notion that MCDA frameworks are well suited not only for treatment assessment but also for identifying broader system-level gaps that impact healthcare outcomes [30].

Nevertheless, while the methodology is robust, certain methodological limitations should be acknowledged. First, MCDA inherently involves a degree of subjectivity, as both weighting and scoring are influenced by the individual experiences and perspectives. While efforts were made to mitigate bias through balanced recruitment of experts, training and structured scoring, results should be interpreted within this context. Second, the analysis provides a static assessment, reflecting a specific point in time. In practice, value perceptions may evolve owing to the emergence of new evidence, pricing changes, or shifts in health policy priorities. Third, the comparative criteria were assessed against a single comparator only, which should be considered when generalizing results. These limitations are not unique to this study and have been widely discussed in previous MCDA literature [29, 30]. Lastly, the assessment was performed leveraging only evidence for treatment field of up to 25 cm^2, excluding evidence for larger field use.

Future research should aim to expand the participant base to include broader national and regional perspectives and test the adaptability of the framework in different decision-making contexts. Replication of MCDA exercises like this one over time, incorporating additional comparators, may offer critical insights to address existing knowledge gaps regarding the comparative value of topical treatments for AK, thereby better informing healthcare and reimbursement policy in Europe. In addition, future research should aim to measure the direct preventive effect of AK treatments for cSCC.

CONCLUSIONS

This MCDA supports tirbanibulin as a high-value treatment for AK, acknowledged by expert consensus, evidence-based evaluation, and alignment with patient and payer expectations. These findings contribute to growing literature on the utility of MCDA in dermatology and reinforce its potential as a complementary tool in health-technology assessment processes.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Julio Sosa has no conflicts to declare. The remaining authors (Carola Berking, Rafael Botella, Andrea Carugno, Giovanna Gambarelli, Josep Malvehy, Elvira Moscarella, Arianna Petracca, Gregorio Romero, Eggert Stockfleth, and Jose Luis Trillo Mata) received honorarium fees from Almirall S.A. for participating in qualitative interviews conducted as part of this research. The honorarium was provided as compensation for experts' time and expertise and did not influence the content, analysis, or conclusions of the manuscript.

Ethical Approval. This study is a non-interventional expert MCDA workshop with multidisciplinary professionals. It involves no intervention on human subjects, no administration of medicinal products or devices, and no collection of patient data; therefore, it falls outside the scope of clinical trial/device investigation requirements and is not human-subjects biomedical research. This non-interventional, survey-based study was conducted in accordance with the principles of the Declaration of Helsinki. All participants (clinicians, payers, and patients) provided informed consent before participation. The study involved no clinical procedures or collection of identifiable personal data. All participants signed a participation agreement (including data-processing terms) and informed consent, and the analysis dataset contains only aggregated/anonymized responses (contact/payment details are stored separately per the agreement and privacy notice). Given the absence of identifiable/sensitive data in

the analytical dataset and the safeguards in place, formal IRB/REC review is not required.

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