



# Profile of Tirbanibulin for the Treatment of Actinic Keratosis

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**ABSTRACT:** Actinic keratosis (AK) is a chronic disease resulting from deleterious effects of long-term, cumulative, epidermal exposure to ultraviolet (UV) light. UV-induced mutations in p53, ras, and p16 genes lead to the emergence of abnormal epidermal actinic keratosis (AKs) cells, which proliferate while avoiding apoptosis and may lead to invasive squamous cell carcinoma. There are both lesion-targeted and field-directed topical treatments. This review is of new and emerging information on tirbanibulin and tirbanibulin 1% ointment, which is approved for topical field treatment of actinic keratosis on the face and scalp. Potent antiproliferative and proapoptotic activities result from tirbanibulin's inhibition tubulin polymerization and disruption of microtubule formation and Src kinase signaling. Tirbanibulin 1% ointment is an effective treatment of facial and scalp AK after five consecutive once-daily applications, as measured by complete and partial clearance and percent reduction in the number of lesions. Localized skin reactions are usually mild to moderate, resolving within a month. The short and well-tolerated course of therapy results in very high patient adherence to the treatment regimen

**KEY WORDS:** Tirbanibulin ointment, actinic keratosis, field therapy

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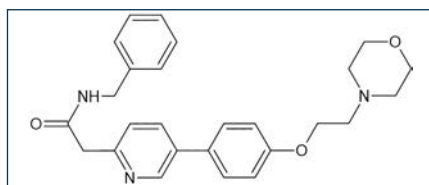
nuclear pleomorphism, and disordered keratinocyte maturation.<sup>4,6</sup> Alterations at the molecular level in specific genes, such as p53,7-10, and changes in gene expression profiles<sup>11</sup> confirm a similar genetic evolution of AK and SCC. Insights into the genomic landscape of actinic keratoses and their progression to cutaneous SCC (cSCC) were recently achieved with whole exome sequencing of 37 AKs. Forty-four significantly mutated AK driver genes were identified and confirmed to be similarly altered in cSCC. Integration with gene expression datasets confirmed that dysregulated of tumor growth factor-beta (TGF- $\beta$ ) signaling may represent an important event in AK to cSCC progression.<sup>7</sup>

The natural history of AK lesions encompasses regression, persistence, or progression to *in-situ* or invasive SCC. The overall risk of progression of an AK lesion is low; however, the disease is chronic with patients having multiple AK lesions at any point in time and developing new lesions over time, which increases a patient's overall risk of developing invasive disease.<sup>12,13</sup> In a study of nearly 500,000 people, half of which had AK and the other half of which were matched controls without AK, it was clearly detected that AK increased the risk of developing cSCC. The yearly risk of developing SCC was double in patients with AK (1.97% vs 0.835%) than in controls and was triple after 10 years of follow-up (17.1% vs 5.7%).<sup>14</sup> Beyond the risk, modeled mathematically, of a patient with 7 to 8 AK lesions developing invasive

**A**ctinic keratosis (AK) is a commonly occurring skin disease that results from cumulative ultraviolet (UV) irradiation.<sup>1</sup> Estimates approximate that 60 percent of people over 40 years of age with a history of UV exposure have at least one AK lesion<sup>2</sup> and that AK affects 58 million people in the United States, leading to treatment costs (in 2004) in excess of \$1,000,000,000.<sup>3</sup> AK is

a clinical diagnosis of scaly, rough, pink-to-red papules on sun-exposed skin. Histopathologic examination is warranted when there is a concern of squamous cell carcinoma (SCC).<sup>4,5</sup>

AK falls within a continuum from sun-damaged skin to AKs to *in-situ* SCC to invasive SCC. Intraepidermal AK cells exhibit histopathologic features detected in invasive SCC, including atypical keratinocytes,



**FIGURE 1.** Molecular structure of tirbanibulin

SCC (6.1– 10.2% spanning 10 years),<sup>15</sup> there are data that most SCCs arise from AK lesions, with an AK lesion being concomitant or contiguous with SCC in 65 to 97 percent of reviewed cases.<sup>13,16–18</sup> The need to treat AK is supported by the histologic, molecular genetic, and epidemiologic relationship between AK and risk of developing SCC.<sup>5,19,20</sup>

Treatment of AK is usually classified as lesion-directed or field-directed therapy. Investigators who biopsied and examined clinically normal skin adjacent to biopsy-proven AK lesions found that in 75 percent of the “normal” skin there was histological evidence of AK. These “subclinical” lesions of AK indicate the presence of “field cancerization,” which requires field therapy, rather than solely targeted therapy, to treat not only the clinically visible but also the affected, albeit normal appearing, intervening areas between AK lesions.

Counter to the evidence that field therapy is needed to address both visible and subclinical AK lesions, targeted cryotherapy is by far the most common treatment of AK in the United States (US). Survey data representing approximately 57.9 million AK visits in the US indicated that cryotherapy was administered in 50.8 percent of AK visits and field therapies (e.g., 5-fluorouracil [5FU], imiquimod, ingenol mebutate, photodynamic therapy) in less than 3.2 percent of visits.<sup>22</sup>

For limited numbers of AK lesions, cryosurgery, most commonly utilizing liquid nitrogen as the cryogen, is effective and the most frequently used method in the US.<sup>23–25</sup> Unfortunately, to be effective, the required duration

of freezing at the extremely low temperature of liquid nitrogen is lethal to normal melanocytes in the epidermis and often results in loss of pigment in the treated areas.<sup>26</sup> Relying on targeted treatment limited to visible lesions that avoids perilesional subclinical lesions results in significant recurrences, which may be due, in part, to subclinical AK lesions becoming visible AKs over time.<sup>27–29</sup>

United States Food and Drug Administration (FDA)-approved field therapies, which include 5FU, imiquimod, diclofenac, and tirbanibulin, address field cancerization in AK by eliminating transformed cells in the treated field. It is not surprising that during such field treatments new visible lesions that were not present at baseline arise and resolve, suggesting effectiveness for subclinical lesions.<sup>28,30,31</sup> Patient adherence is challenging due to required large number of applications (as many as 180) and prolonged (up to 4 months) treatment and to the resulting localized erythema, scaling, edema, erosions, and discomfort (e.g., burning, itching). To achieve greater patient adherence and persistence, greater regimen simplicity and greater tolerability has been the goal of using modified dosing schedules, lower drug concentrations, and novel formulations,<sup>31–33</sup> as well as sequential treatment employing both lesion- and field-directed methods, to achieve greater effectiveness.<sup>34–40</sup>

Shergil et al<sup>41</sup> reported that the majority (63%) of patients being treated topically for AKs did not adhere to their treatment regimen, primarily due to local skin reactions and treatment being excessive and not simple. Experts have suggested that keeping AK field treatment short and simple could improve patient adherence.<sup>41,42</sup> Of the available US Food and Drug Administration (FDA)-approved, topically applied AK field therapies and dosing regimens, the number of applications range from as few as two to as many as 180 and require up to four months duration of

therapy. Following ingenol mebutate, with its once-daily application for 2 to 3 days, being removed from the market, tirbanibulin 1% ointment, approved for once-daily application for five consecutive days, is the shortest topical AK therapy available. Ninety-nine-percent patient adherence rates have been reported in large Phase III studies using this short, simple regimen of tirbanibulin 1% ointment. The mostly mild-to-moderate severity local skin reactions (LSRs) reported in these studies peak at three days following completion of all applications and quickly resolve.

This article reviews the mechanisms of action of tirbanibulin and highlights clinical studies and data supporting the efficacy, safety, tolerability, and patient acceptance of tirbanibulin 1% ointment for the treatment of AK.

## MECHANISMS OF ACTION

Tirbanibulin is a novel synthetic chemical entity (Figure 1) that has shown potent antiproliferative and antitumoral effects *in vitro* and *in vivo* by inducing cell cycle arrest and ultimately apoptotic cell death. These effects have been attributed to the ability of tirbanibulin to reversibly bind to the colchicine-binding site on  $\beta$ -tubulin<sup>43</sup> and inhibit tubulin microfilament polymerization (Figure 2).<sup>44</sup> Additional studies are needed to confirm whether tirbanibulin also binds to  $\beta$ -tubulin and/or a novel site on the  $\alpha$ - $\beta$ -tubulin heterodimer.<sup>44</sup> Immunofluorescence staining has shown that tirbanibulin effectively disrupts the cellular MTs network immortalized keratinocyte CCD 1106 KERTr cells and HeLa cells. Tirbanibulin appears to induce complete cell cycle arrest at G2/M phase<sup>43</sup> and trigger signals of programmed cell death by activating both intrinsic and extrinsic apoptotic pathways via Bcl-2, cleavage of caspase 8 and 9, and activation of caspase 3, in colon cancer HT-29 cells.

Src family kinases (SFKs) are a family of nine nonreceptor tyrosine kinases<sup>45</sup>

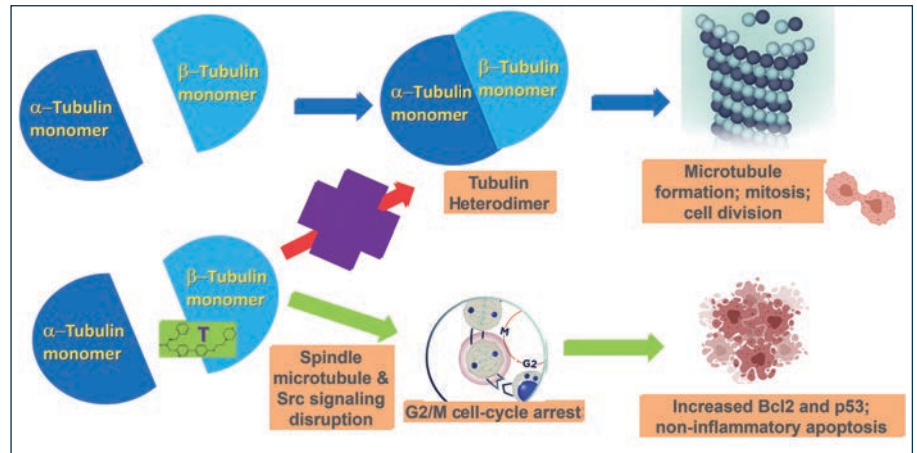
involved in vascular epithelial growth factor and angiogenesis.<sup>46,47</sup> Elevated Src expression has been observed in AK and SCC, suggesting that increased signaling is necessary for keratinocyte migration and squamous carcinoma invasion.<sup>48</sup> Tirbanibulin was shown to significantly down-regulate phospho-Src (p-Src) and Src signaling molecules and disrupt SFKs signaling in various cancer cell lines and tumor xenografts in mice.<sup>49</sup> Whether the effects of tirbanibulin on Src signaling result from its direct binding to Src or secondary to its disruption of cellular microtubule networks is unclear.

### CLINICAL DATA

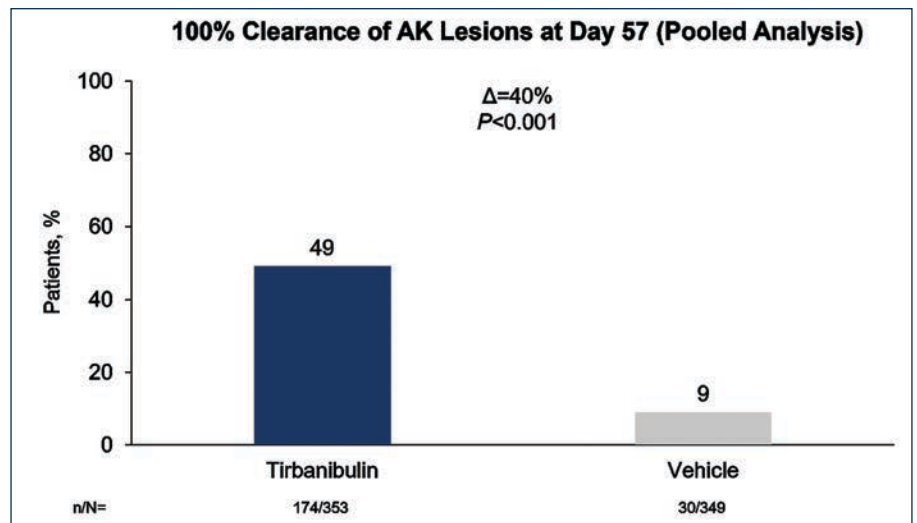
Over 700 adult patients with 4 to 8 nonhypertrophic AKs in a contiguous area of 25cm<sup>2</sup> on the face (68%) or scalp (32%) were randomized (1:1) in two identical Phase III trials to determine the tolerability and efficacy of tirbanibulin 1% ointment for AK compared to the ointment vehicle.<sup>50</sup> The trials were carried out with the subjects and investigators/evaluators blinded to the randomized treatment. The average composite subject was a 70-year-old man with Fitzpatrick Skin Type I or II with facial AKs. Subjects received five consecutive days of once-daily treatment to the targeted 25cm<sup>2</sup> field with either tirbanibulin (n=353) or vehicle control (n=349). Subjects with complete (100%) clearance of AK lesions in the treatment area at Day 57 were assessed for AK lesion recurrence every three months for a total of 12 months post-Day 57.

The primary efficacy endpoint was complete (100%) clearance of AK lesions in the treatment area, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area, and the secondary endpoint was partial (≥75%) clearance of AK lesions in the treatment area.

**Efficacy (pooled).** Statistically significant higher Day 57 clinical endpoint complete and partial responses (Figures 3 and 4) were achieved in those receiving tirbanibulin



**FIGURE 2.** Mechanism of action of tirbanibulin (T)<sup>43,44</sup>



**FIGURE 3.** Percent of patients with complete clearance of actinic keratosis (AK) lesions after treatment with tirbanibulin 1% ointment vs. vehicle control treatment, once daily for 5 days—Data are from the intent-to treat population and included both face and scalp treatment areas. Patients who discontinued before the Day 57 assessment were considered treatment failures. Significance determined by Cochran-Mantel-Haenszel method stratified by treatment group.<sup>50</sup>

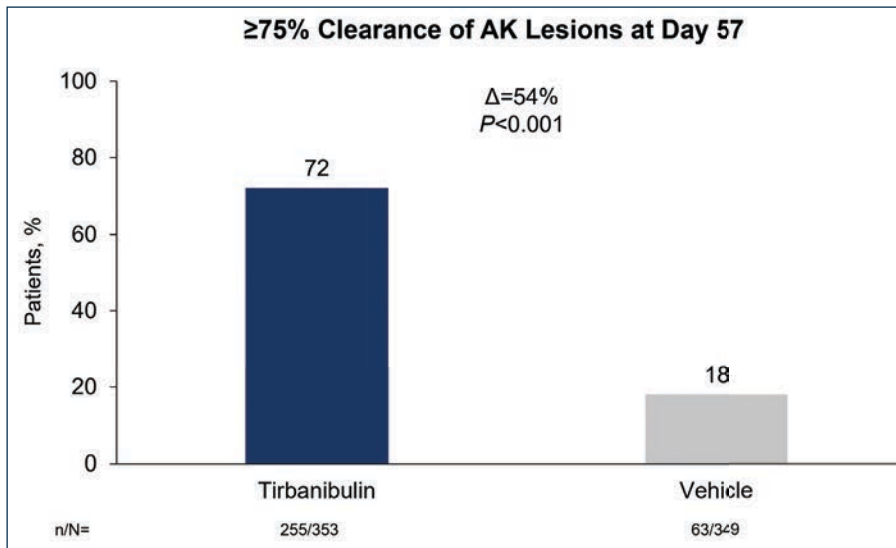
Δ: difference between treatment groups; n/N: number of patients with 100% clearance/total number of patients

treatment compared to those receiving vehicle. Median percent reduction from baseline, an important, unique endpoint being independent of the starting number of AK lesions, was higher (83%) in the active treatment arm compared with vehicle (20%).<sup>50</sup>

Consistent with the knowledge that AK lesions on the face have been found to be more responsive to all approved field therapies than

AK lesions on the scalp, tirbanibulin treatment also exhibited significantly enhanced effectiveness rates on facial AK lesions, compared to vehicle (Table 1). Subgroup analyses revealed the efficacy of tirbanibulin to be consistent across sex and in those above or below 65 years of age.<sup>50</sup>

**Phototoxicity and contact sensitization.** Clinical studies in



**FIGURE 4.** Percent of patients with at least 75% clearance of actinic keratosis (AK) lesions after treatment with tirbanibulin 1% ointment vs. vehicle control treatment once daily for 5 days—Data are from the intent-to-treat population and included both face and scalp treatment areas. Patients who discontinued before the Day 57 assessment were considered treatment failures. Significance determined by Cochran-Mantel-Haenszel method stratified by treatment group.<sup>50</sup>

Δ: difference between treatment groups; n/N: number of patients with ≥75% clearance/total number of patients

**TABLE 1.** Efficacy of treatment of facial and scalp actinic keratoses with tirbanibulin 1% ointment versus vehicle control treatment once daily for 5 days

EFFICACY AT DAY 57	LOCATION	TIRBANIBULIN	VEHICLE	P-VALUE
Complete (100%) Clearance	Face	55.9%	9.6%	P<0.0001
	Scalp	35.7%	6.4%	P<0.0001
Partial (≥75%) Clearance	Face	77.7%	20.5%	P<0.0001
	Scalp	60.9%	12.7%	P<0.0001
Median % reduction in AK lesion count	Face	100%	25%	P<0.0001
	Scalp	83.33%	18.33%	P<0.0001

Blauvelt A, Kempers S, Lain E, et al. Phase III trials of tirbanibulin ointment for actinic keratosis. *New Eng J Med.* 2021;384(6):512–520.

healthy subjects have reported that tirbanibulin ointment did not cause contact sensitization (n=261), phototoxic skin reactions (n=31), or photoallergic skin reactions (n=64).<sup>51</sup>

**Safety (pooled).** *Treatment-related adverse events (AEs).* AEs were few and mostly mild transient application-site pruritus (tirbanibulin vs. vehicle: 9% vs. 6%) and pain (tirbanibulin vs. vehicle: 10% vs. 3%) (Table 2). No deaths, discontinuations, or serious AEs related to tirbanibulin occurred.<sup>50,51</sup>

*LSRs.* LSRs were collected independent of AEs and included erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosions/ulcerations. LSRs were assessed by the investigators using a four-point grading scale of 0=absent, 1=mild (slightly, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Composite score was the sum of all six LSR grades with a possible range of 0 to 18.<sup>50</sup> Incidence and severity

of LSRs greater than baseline was higher with tirbanibulin versus vehicle. LSRs were mostly mild to moderate, with severe reactions observed in less than 10 percent of subjects receiving tirbanibulin.<sup>51</sup> LSRs peaked on Day 8 with tirbanibulin, decreased significantly by Day 15, and completely resolved by Days 29 to 57 (Figure 5). No significant difference was observed in LSR severity in patients younger or older than 65 years of age. No patients discontinued the study due to LSRs.<sup>50,52</sup> Complete clearance of AKs using tirbanibulin 1% ointment was associated with mild-to-moderate LSRs, with 70.2 percent of patients showing a composite LSR score of 5 or less, highlighting that complete clearance was not correlated with the severity of LSRs.<sup>53</sup>

A post-hoc analysis of the two Phase III clinical trials, in which 353 participants having 4 to 8 clinically visible AK lesions (25cm<sup>2</sup> area) were randomized to receive tirbanibulin (self-applied once daily, 5 consecutive days) was performed to assess the clearance rates of facial and scalp AK following treatment with tirbanibulin ointment 1% in different patient subgroups by body mass index (BMI), Fitzpatrick skin type, and previous AK treatment. There was no statistically significant relationship between the baseline variables of previous AK treatment (Table 3), Fitzpatrick skin type (Table 4), or BMI (29kg/m<sup>2</sup>) (Table 5) and complete (100%) and partial (>75%) clearance (CC, PC) at Day 57. In contrast, although found to be effective for both facial and scalp AK lesions, their location on the face did predict greater CC and PC success rates after two months.<sup>54</sup>

Additional post-hoc analyses of the two Phase III clinical trials evaluated CC and PC rates of AKs and severity of LSRs at time points (Day 8 earlier than end of study Day 57). At study visits (Days 8–15 to Days 29–57) CC, PC, and LSRs, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration,

were assessed. Each LSR was scored between 0 and 3 (0=absent, 3=severe). Individual scores were added together, resulting in a LSR composite score between 0 and 18. The maximum LSR composite scores reached up to Day 57 were averaged for participants achieving CC at each visit.

A CC rate of 13.4 percent was achieved at Day 8, increasing during treatment to 24.7 percent (Day 15), 36.4 percent (Day 29), and 49.3 percent (Day 57). PC rate was 20.2 percent at Day 8 and gradually rose to 41.2 percent (Day 15), 62.8 percent (Day 29), and 72.2 percent (Day 57). Among patients reaching CC at each visit, baseline characteristics were similar except for a trend to higher percentage of face treatments in those achieving CC at Days 8 to 15 versus Days 29 to 57. The mean ( $\pm$ standard deviation) maximum LSR composite score reached during the follow-up was similarly low regardless of whether CC was obtained at Day 8 ( $4.7\pm 1.8$ ), Day 15 ( $4.8\pm 2.2$ ), Day 29 ( $4.9\pm 2.1$ ), or Day 57 ( $4.9\pm 2.1$ ). Although the highest CC rate with tirbanibulin was observed at Day 57, this analysis confirms that patients with AK can show much earlier responses (from Day 8). These were not accompanied by an increase in the severity of LSRs.<sup>55</sup>

**Recurrence.** For the one-year follow-up study, 174 subjects treated with tirbanibulin 1% ointment for once daily for five days who achieved CC at Day 57 were included. Post-hoc analysis of Kaplan-Meier estimates showed that at one year, 53 percent of patients maintained CC from recurrent lesions. The Kaplan-Meier estimate indicated that 27 percent remained free of any new or recurrent AK lesions in the 25cm<sup>2</sup> treated area up to one year. Patients who had more than five baseline AK lesions [OR 2.1] or had prior AK treatments to the study treatment area [OR 3.0] correlated with recurrence of any AKs. Importantly, no skin cancers were detected in the treatment area

**TABLE 2.** Investigator assessment of maximal post-baseline local skin reactions greater than baseline in the treatment area (face or scalp): pooled data from 2 Phase III controlled clinical trials

LOCAL SKIN REACTIONS	VEHICLE (N=349)			TIRBANIBULIN 1% OINTMENT (N=353)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Erythema	98 (28%)	20 (6%)	0	76 (22%)	223 (63%)	22 (6%)
Flaking/Scaling	86 (25%)	33 (9%)	1 (<1%)	92 (26%)	166 (47%)	31 (9%)
Crusting	31 (9%)	8 (2%)	0	107 (30%)	50 (14%)	7 (2%)
Swelling	15 (4%)	1 (<1%)	0	102 (29%)	32 (9%)	2 (<1%)
Vesiculation/Pustulation	3 (<1%)	0	0	25 (7%)	2 (<1%)	2 (<1%)
Erosion/Ulceration	10 (3%)	0	0	32 (9%)	9 (3%)	0

Local skin reactions were mostly mild to moderate, peaked on Day 8 and returned to baseline by Day 29. 0-3 LSR scale: 0=absent; 1=mild (slightly or barely perceptible); 2=moderate (distinct presence); 3=severe (marked, intense).

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throughout the one-year follow-up period.<sup>50</sup>

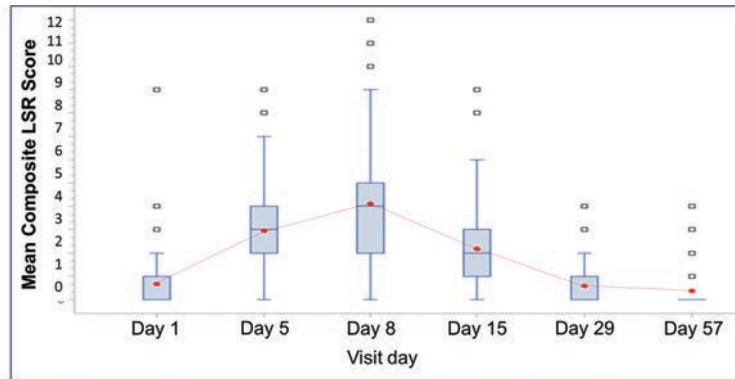
Based upon these studies, tirbanibulin was approved by the FDA as a field therapy for AK with the application of 2.5mg tirbanibulin in 250mg ointment to a 25cm<sup>2</sup> contiguous area of skin on the face or scalp once daily for five consecutive days.<sup>51</sup> The FDA accepts the defined 25cm<sup>2</sup> area as a "field" of AK lesions, but in clinical practice, treatment requires a greater area. In a recent report, a single packet of 2.5mg tirbanibulin dissolved in 250mg ointment was sufficient to be evenly applied to a patient's balding scalp, forehead, and two facial target AK lesions, for a total area of 317.82cm<sup>2</sup> (digitally measured).<sup>56</sup> As expected, LSRs peaked at Day 8 in the treatment areas and resolved by Day 39, similar to the findings in the Phase III trials. Presence of LSRs which peaked at Day 8 and resolved by Day 39 and clearance of the two target AK lesions (last to be treated at each of the 5 consecutive once-daily applications) suggest that the thin layer of

ointment applied to this large area was sufficient to penetrate and be effective.<sup>56</sup>

#### ADDITIONAL CONSIDERATIONS

Recently, the American Academy of Dermatology (AAD) released a focused update of its guidelines of care for the management of AK.<sup>57</sup> In this update, tirbanibulin is unique among all other listed topical treatments of AKs, in that it received the AAD AK guidelines committee's strongest recommendation based on the highest certainty of evidence. The use of other field therapies, including imiquimod and ingenol mebuate, following cryotherapy of AK with liquid nitrogen, have resulted in additional benefits. We look forward to future studies to determine the effectiveness and safety of sequential treatment of AK with targeted cryotherapy followed by tirbanibulin 1% ointment.

An active comparator study of the efficacies and tolerabilities of tirbanibulin 1% ointment versus 5FU preparations would help direct the clinical choice of AK treatment. If such



The length of the box represents the interquartile range (the distance between the 25th and 75th percentiles). The symbol in the box interior represents the group mean. The horizontal line in the box represents the group median.

LSRs were graded on a 4-point scale (0=absent; 1=mild [slightly or barely perceptible]; 2=moderate [distinct presence]; 3=severe [marked/intense]).

- |                    |                             |
|--------------------|-----------------------------|
| 1. Erythema        | 4. Swelling                 |
| 2. Flaking/scaling | 5. Vesiculation/pustulation |
| 3. Crusting        | 6. Erosions/ulceration)     |

**FIGURE 5.** Composite local skin reaction (LSR) scores to tirbanibulin 1% ointment once-daily treatment (Days 1–5) over time; composite score is the sum of all six LSR grades with a possible range of 0–18.; pooled results from 2 Phase III studies<sup>52</sup>

studies are undertaken, the following caveat regarding extemporaneous 5FU preparations should be noted. Investigators compared the efficacy and tolerability of 5% 5 fluorouracil cream + 0.005% calcipotriol ointment combination (FU+C) with 5% 5FU + petroleum jelly (Vaseline®, Unilever plc., London, England, United Kingdom) combination (FU+V) in the treatment of actinic keratoses.<sup>58</sup> The FU+V control resulted in zero percent of participants having CC of facial AKs and an unexpectedly low four percent developing severe erythema, possibly due to the added petroleum jelly interfering with FU absorption. A recent study comparing the skin absorption and penetration of four different 5% 5FU formulations, including FU+V, found that combining 5FU cream with petroleum jelly interfered with the 5FU penetration through skin, resulting in a 20-fold reduced eight-hour penetration of 5FU when in the presence of petroleum jelly compared to 5% 5FU cream, and a 73-percent reduction in 5FU penetration compared to the 5-FU + calcipotriol ointment combination.<sup>59</sup> These findings point to

the inappropriateness of using 5FU in petroleum jelly as a control for clinical studies, which could lead to erroneous superiority claims.

Human papillomavirus 16 (HPV 16) has been detected in periungual SCCs and the HPV 16 E7 oncoprotein up-regulates Src family kinases, which tirbanibulin has been found to inhibit. Therefore, it is intriguing, albeit not surprising, that tirbanibulin 1% ointment has been reported to be effective in the treatment of *in-situ* cSCC.<sup>60</sup> As previously discussed, SCC falls in the AK-to-SCC continuum, and therefore this possible indication for its treatment with tirbanibulin should be pursued further.

### IN SUMMARY

Tirbanibulin 1% ointment is novel as a topical field therapy for AK, both in its mechanisms of action and short treatment duration. Its antiproliferative and proapoptotic activities result in an 83-percent median reduction in the number of AK lesions from baseline. It does so in a relatively noninflammatory fashion, with LSRs being rated as mostly mild to moderate. Importantly,

the contents of a single packet of tirbanibulin 1% ointment were measured to cover more than the FDA-approved area of 25cm<sup>2</sup>, while maintaining effectiveness. At one year following once daily treatment for five days, 53 percent of the patients maintained 100-percent clearance, without recurrence of any of treated AK lesions. The findings outlined in this review suggest that tirbanibulin 1% ointment is a valuable, effective, and safe addition to our treatment armamentarium for AK.

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