Contact Sensitization and Phototoxic and Photoallergic Potential of Tirbanibulin 1% Ointment in Healthy Volunteers

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Tirbanibulin 1% ointment is approved for the topical treatment of actinic keratosis, applied once daily for 5 days. Three phase 1 randomized, single-center, controlled, within-subject comparison studies were conducted to evaluate the sensitization (KX01-AK-006), phototoxic (KX01-AK-008), and photoallergic (KX01-AK-009) potential of tirbanibulin 1% ointment in healthy adults. In KX01-AK-006 and KX01-AK-009, subjects received repeated applications of tirbanibulin or vehicle for induction (followed by irradiation in KX01-AK-009) and an additional application for the challenge on naïve sites. In KX01-AK-008, subjects received single applications, followed by irradiation. Sensitization was defined as a reaction scoring 3 at naïve sites, recurring at rechallenge. Photoallergy was assessed based on the dermal response of erythema + edema at naïve sites. Phototoxicity was assessed based on the average dermal response score (days 3–4). Adverse events were collected. In KX01-AK-006, none of the 229 subjects scored 3 at naïve sites. In KX01-AK-008, none of the 31 subjects developed edema, not meeting the criteria for phototoxicity. In KX01-AK-009, none of the 59 subjects showed reactions compatible with photoallergy. Mild-to-moderate contact irritations were reported. The evidence provided by these phase 1 studies showed that tirbanibulin 1% ointment lacks sensitization and phototoxic or photoallergic potential, and supports the safety of its topical application.

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INTRODUCTION

Tirbanibulin (Klisyri, Almirall, Barcelona, Spain) is a first-in-class, antiproliferative, and pro-apoptotic agent that is approved for the treatment of actinic keratosis (AK) of the face and scalp (European Medicines Agency, 2021; Food and Drug Administration, 2020). Klisyri has been formulated as a tirbanibulin 1% ointment intended for topical application (once daily for 5 days) on these light-exposed body sites and has been shown to absorb light within the range of natural sunlight (290–400 nm). Therefore, the development program included three phase 1 studies in healthy volunteers assessing contact sensitization potential after repeated application, phototoxic and photoallergic potential, and safety. Collective results for these studies are reported in this paper.

RESULTS

For the three studies, the disposition of subjects is shown in Figure 1, and their demographic and baseline characteristics are summarized in Table 1.

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Abbreviations: AE, adverse event; AK, actinic keratosis; MED, minimal erythemal dose

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KX01-AK-006 (sensitization study)

Cumulative irritancy. A summary of mean and total irritation scores during the induction phase and pairwise comparisons are provided in Table 2. Both scores were significantly higher at tirbanibulin-treated sites than at the vehicle- and saline-treated sites.

Dermal responses and sensitization. During the challenge phase, the maximum dermal response score at the tirbanibulin-treated site was 1 (mild erythema) in 33 subjects (14.4%; 95% confidence interval = 10.1–19.6) and 2 (moderate erythema, minimal edema, or minimal papular response) in five subjects (2.2%; 95% confidence interval = 0.7–5.0). The remaining 191 subjects had a maximum score of 0 (no response). No subjects had a maximum response of 3 at the tirbanibulin-treated site. Vehicle- and saline-treated sites showed no dermal response except in one subject (1.4%; 95% confidence interval = 0.0–2.4), who had a maximum response score of 2 at the vehicle-treated site.

Safety. Adverse events (AEs) are summarized in Table 3. None were treatment related, and the most frequent were headache, nasopharyngitis, and rhinorrhea. Two subjects were discontinued from the study owing to an AE: one had a serious AE of mild dyspnea after 10 applications of the study products, which resolved in 10 days, and the remaining subject had moderate nausea after two applications, which resolved in 5 days.

KX01-AK-008 (phototoxicity study)

Dermal responses and phototoxicity. No subjects developed edema; therefore, none met the criteria for phototoxicity. The

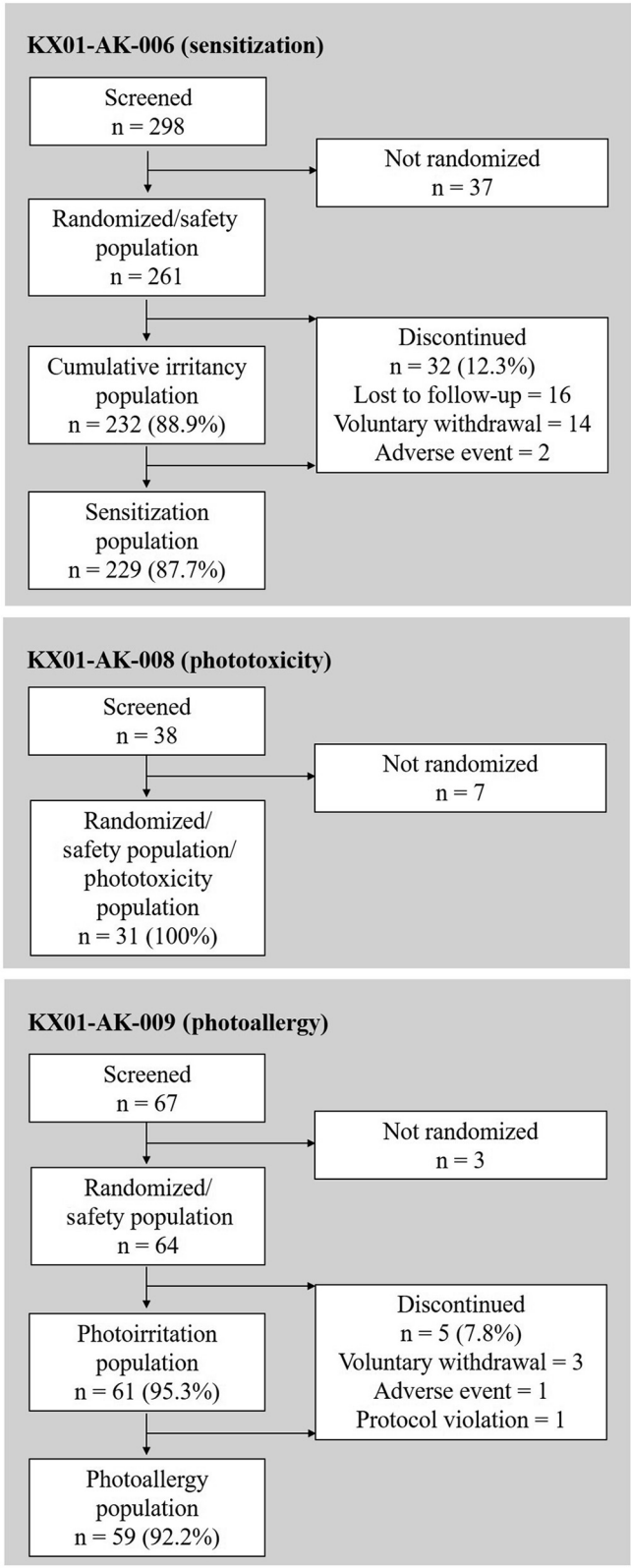

Figure 1. Subject disposition. Percentages are relative to the number of randomized subjects in each study. In KX01-AK-006 (sensitization study), 298 subjects were screened, and 261 of them were randomized and included in the safety population. A total of 32 subjects discontinued the treatment, and 229 were included in the sensitization population. In KX01-AK-008 (phototoxicity study), 38 subjects were screened, and 31 of them were randomized and included in the safety population or phototoxicity population. Finally, in KX01-AK-009 (photoallergy study), 67 subjects were screened, and 64 of them were randomized and included in the safety population. A total of five subjects discontinued the treatment, and 59 were included in the photoallergy population.

Table 1. Demographics and Baseline Characteristics (Safety Population)

Characteristics	KX01-AK-006 (Sensitization)	KX01-AK-008 (Phototoxicity)	KX01-AK-009 (Photoallergy)
n	261	31	64
Age (y)			
Mean (SD)	46.7 (15.3)	52.2 (12.2)	55.8 (10.5)
Median	48.0	53.0	57.0
Range	18.0–75.0	21.0–70.0	26.0–75.0
Sex, n (%)			
Female	204 (78.2)	24 (77.4)	57 (89.1)
Race, n (%)			
White	149 (57.1)	31 (100)	64 (100)
African American	110 (42.1)	0	0
Asian	1 (0.4)	0	0
Other	1 (0.4)[1]	0	0
Fitzpatrick skin type, n (%)[2,3]			
I	7 (2.7)	0	2 (3.1)
II	76 (29.1)	12 (38.7)	27 (42.2)
III	58 (22.2)	19 (61.3)	35 (54.7)
IV	52 (19.9)	0	0
V	58 (22.2)	0	0
VI	10 (3.8)	0	0
MED (seconds)[4,5]			
Mean (SD)	NA	45.5 (14.9)	59.0 (17.7)
Median	NA	38.0	NR
Minimum-Maximum	NA	32.0-76.0	31.0-94.0

Abbreviations: MED, minimal erythemal dose; NA, not applicable; NR, not reported.

[1]Mixed race.

[2]I: Always burns easily, never tans; II: always burns easily, tans minimally; III: burns moderately, tans gradually; IV: burns minimally, always tans well; V: rarely burns, tans very well; and VI: never burns, deeply pigmented.

[3]In the phototoxicity and photoallergy studies, only subjects with Fitzpatrick skin types I–III were eligible.

[4]Seconds of exposure with the output of the solar simulator set to 661 μw/cm^2 full-spectrum UVB/UVA.

[5]In KX01-AK-0009, MED was determined in 62 subjects.

maximum dermal response score before irradiation (day 2) was 1 (mild erythema) at the test sites and 0 at the control site. On days 3 and 4, the maximum score did not exceed 2 (moderate erythema) at the test sites and 1 at the control site. Mean dermal response scores for fays 3–4 and pairwise comparisons are shown in Table 4. The mean score was <1 at the test and control sites regardless of irradiation status. Within each product (tirbanibulin or vehicle), the mean score was similar at irradiated and nonirradiated sites. When comparing tirbanibulin and vehicle, the mean score was significantly higher for tirbanibulin at nonirradiated sites but similar to that for vehicle at irradiated sites. For both tirbanibulin and vehicle, mean scores at irradiated and nonirradiated sites were significantly higher than at the irradiated control.

Safety. AEs are summarized in Table 3. One subject had an AE of headache, which was considered mild and possibly related to study products. The AE resolved within the same day and did not lead to study discontinuation.

KX01-AK-009 (photoallergy study)

Photoirritation. Mean dermal response scores for the induction phase and pairwise comparisons are shown in Table 5. The mean score was <0.5 for both products regardless of irradiation status. Within each product (tirbanibulin or vehicle), the mean score was significantly higher at irradiated than at nonirradiated sites. When comparing tirbanibulin and vehicle, the mean score was significantly higher for tirbanibulin at nonirradiated sites but similar to that for the vehicle at irradiated sites.

Photoallergy. The proportion of subjects with each dermal response score at the different assessments of the challenge phase is summarized in Table 6. Twenty-four, 48, and 72 hours after irradiation, most subjects had a score of 0 (no reaction) regardless of treatment and irradiation. The maximal dermal response score overall was 1, most common at 72 hours. There were no reactions suggesting photoallergy, so no rechallenges were required.

Safety. AEs are summarized in Table 3. None were treatment related, and the most frequent was nasopharyngitis. One subject had an AE of moderate sinus headache that led to study withdrawal because the subject received a concomitant medication (aspirin) to treat the AE that was not allowed by the protocol.

DISCUSSION

The results of this series of phase 1 studies in healthy volunteers show that tirbanibulin 1% ointment has a favorable safety profile upon topical application. Of note, all the three studies were conducted with the commercially available

Table 2. Summary of Irritation Scores during Induction Phase in KX01-AK-006 (Cumulative Irritancy Population) (n = 232)

	Mean Irritation Score				Total Irritation Score			
Product Applied	Mean (SD)	LSM (SE)	*P*-Value Versus Vehicle	*P*-Value Versus Saline	Mean (SD)	LSM (SE)	*P*-Value Versus Vehicle	*P*-Value Versus Saline
Tirbanibulin	2.09 (0.66)	2.09 (0.03)	<0.001	<0.001	18.8 (6.0)	18.83 (0.25)	<0.001	<0.001
Vehicle	0.06 (0.25)	0.06 (0.03)	—	0.28	0.6 (2.3)	0.56 (0.25)	—	0.28
Saline	0.02 (0.09)	0.02 (0.03)	—	—	0.2 (0.8)	0.19 (0.25)	—	—
Overall *P*-value	<0.001				<0.001			

Abbreviations: LSM, least square mean; SE, standard error.

Table 3. Summary of AEs (Safety Population)

Summary of AEs, n (%)	KX01-AK-006 (Sensitization)	KX01-AK-008 (Phototoxicity)	KX01-AK-009 (Photoallergy)
Safety population	261 (100)	31 (100)	64 (100)
Any AE	21 (8.0)	1 (3.2)	5 (7.8)
Serious AE	1 (0.4)	0	0
Fatal AE	0	0	0
Treatment-related AE	0	1 (3.2)	0
AE leading to product withdrawal	2 (0.8)	0	1 (1.6)
AE by SOC and preferred term			
Nervous system disorders			
Headache	7 (2.7)	1 (3.2)	0
Sinus headache	0	0	1 (1.6)
Dizziness	1 (0.4)	0	0
Infections and infestations			
Nasopharyngitis	6 (2.3)	0	2 (3.1)
Upper respiratory tract infection	0	0	1 (1.6)
Respiratory, thoracic, and mediastinal disorders			
Rhinorrhea	3 (1.1)	0	0
Dyspnea	1 (0.4)	0	0
Nasal congestion	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders			
Neck pain	1 (0.4)	0	0
Rotator cuff syndrome	1 (0.4)	0	0
Gastrointestinal disorders			
Nausea	1 (0.4)	0	0
Injury, poisoning, and procedural complications			
Contusion	0	0	1 (1.6)

Abbreviations: AE, adverse event; SOC, system organ class.

formulation of tirbanibulin, both in terms of concentration of active substance (1%) and vehicle composition (monoglycerides, diglycerides, and propylene glycol), and the study sample sizes exceeded those indicated by regulatory standards. All these contribute to the external validity of the results.

First, the inability of tirbanibulin to induce sensitization was assessed and shown through a repeated insult patch test. Mean and total irritation scores obtained during the induction phase showed that tirbanibulin 1% ointment caused contact irritation, which was significantly higher than that caused by the vehicle alone. The dermal responses observed during the challenge phase, reaching moderate erythema at most, were expected and consistent with that observed in two large, phase 3, randomized, vehicle-controlled studies with tirbanibulin in patients with AK (Blauvelt et al., 2021). Although these responses pointed to a potential for contact irritation, there was no evidence of sensitization.

The effect of UV light exposure on skin treated with tirbanibulin 1% or vehicle ointments was assessed in two studies, in which there was no evidence of phototoxicity or photosensitivity for either product. In the phototoxicity study, even though erythema was reported, no subjects developed edema after a single application of the study

Table 4. Mean Dermal Response Scores for Days 3–4 and Pairwise Comparisons in KX01-AK-008 (Phototoxicity Population) (n = 31)

	Tirbanibulin 1% Ointment		Vehicle Ointment		Untreated Control
Dermal Response	Irradiated	Nonirradiated	Irradiated	Nonirradiated	Irradiated
Mean (SD) dermal response score	0.94 (0.54)	0.89 (0.57)	0.77 (0.43)	0.69 (0.48)	0.23 (0.40)
LSM (SD) dermal response score	0.9 (0.5)	0.9 (0.6)	0.8 (0.4)	0.7 (0.5)	0.2 (0.4)
P-values:					
Tirbanibulin irradiated versus	—	0.59	0.080	0.009	<0.001
Tirbanibulin nonirradiated versus	—	—	0.22	0.036	<0.001
Vehicle irradiated versus	—	—	—	0.38	<0.001
Vehicle nonirradiated versus	—	—	—	—	<0.001

Abbreviation: LSM, least square mean.

P-values (row vs. column) are from an ANOVA of the average numerical score (sum of erythema and edema) on days 3 and 4, with effects of subject and treatment, using Fisher's least significant differences.

Table 5. Mean Dermal Response Scores during Induction Phase and Pairwise Comparisons in KX01-AK-009 (Photoirritation Population) (n = 61)

	Tirbanibulin 1% Ointment		Vehicle Ointment	
Dermal Response	**Irradiated**	**Nonirradiated**	**Irradiated**	**Nonirradiated**
Mean (SD) dermal response score	0.41 (0.32)	0.07 (0.14)	0.41 (0.32)	0.00 (0.01)
P-values				
Tirbanibulin irradiated versus	—	<0.001	0.80	<0.001
Tirbanibulin nonirradiated versus	—	—	<0.001	0.031
Vehicle irradiated versus	—	—	—	<0.001

P-values (row vs. column) are from an ANOVA of the average numerical score over all induction phase readings, with effects of subject and treatment, using Fisher's least significant differences.

products. The mild-to-moderate dermal responses observed can be attributed to irritation rather than to phototoxicity. In addition, dermal responses at tirbanibulin 1% ointment irradiated and nonirradiated sites were similar, and the same occurred for the vehicle. This further supports a lack of phototoxic activity. In the photoallergy study, although mean dermal response scores during the induction phase were significantly higher at irradiated than at nonirradiated sites of each product, these differences cannot be considered clinically significant, given the low level of the dermal responses observed. Because dermal responses during the challenge phase were either absent or mild, a photoallergic potential of tirbanibulin 1% ointment or vehicle was ruled out.

Moreover, in these phase 1 studies, tirbanibulin 1% ointment and vehicle ointment were well-tolerated even when the number of applications exceeded those recommended on the product label. Treatment-related AEs were not reported during repeated dosing in the sensitization and photoallergy studies (up to 10 and 7 applications, respectively), and only one (mild headache) was reported after a single application in the phototoxicity study. Systemic AEs, whether considered related or unrelated to study products, were infrequent, consistent with the minimal absorption observed in a previous phase 1 maximum-use study (Yavel et al., 2022).

This favorable safety profile was obtained in three studies with different designs and including healthy volunteers only, which may limit its generalization to patients with AK. Nevertheless, the studies were modeled after standard designs, according to Food and Drug Administration guidance (Federal Register, 1999). Furthermore, a good safety profile for tirbanibulin 1% ointment has also been observed in larger clinical studies conducted for tirbanibulin in patients with AK (Blauvelt et al., 2021; Kempers et al., 2020). This is a relevant point because there is evidence (Erntoft et al., 2016; Neri et al., 2019; Shergill et al., 2013) as well as consensus among physicians (Stockfleth et al., 2015) that the tolerability of topical medications affects the QOL of patients with AK and their compliance with treatment. In a phase 2 study including 168 patients with AK who received daily applications of tirbanibulin 1% ointment for 3 or 5 days, 12 (7%) patients presented treatment-related AEs, none was serious or led to study withdrawal, and most were application-site pruritus and pain (Kempers et al., 2020). Finally, in the two phase 3 studies, 702 patients with AK applied tirbanibulin 1% or vehicle ointments daily for 5 days. The most common

Table 6. Proportion of Subjects with Each Dermal Response Score during Challenge Phase in KX01-AK-009 (Photoallergy Population) (n = 59)

	Tirbanibulin 1% Ointment		Vehicle Ointment		Untreated Control
Each Dermal Response Score	**Irradiated**	**Nonirradiated**	**Irradiated**	**Nonirradiated**	**Irradiated**
Before application, n (%)					
0	59 (100)	59 (100)	59 (100)	59 (100)	0
Before irradiation, n (%)					
0	59 (100)	59 (100)	59 (100)	58 (98.3)	58 (98.3)
1	0	0	0	1 (1.7)	1 (1.7)
24 h after irradiation, n (%)					
0	56 (94.9)	55 (93.2)	58 (98.3)	59 (100)	57 (96.6)
1	3 (5.1)	4 (6.8)	1 (1.7)	0	2 (3.4)
48 h after irradiation, n (%)					
0	57 (96.6)	59 (100)	56 (94.9)	59 (100)	58 (98.3)
1	2 (3.4)	0	3 (5.1)	0	1 (1.7)
72 h after irradiation, n (%)					
0	49 (83.1)	52 (88.1)	58 (98.3)	58 (98.3)	58 (98.3)
1	10 (16.9)	7 (11.9)	1 (1.7)	1 (1.7)	1 (1.7)

AEs were application-site pruritus or pain; most were mild or moderate, and all resolved spontaneously. No treatment-related AEs were serious or led to study withdrawal (Blauvelt et al., 2021).

In conclusion, the evidence provided by this set of phase 1 studies shows that tirbanibulin 1% ointment lacks sensitization and phototoxic or photoallergic potential, and supports the safety of its topical application.

MATERIALS AND METHODS

The three studies were approved by the institutional review board of the participating center (TKL Research, Fair Lawn, NJ) and were conducted in accordance with good clinical practice, the Declaration of Helsinki, the International Council for Harmonisation Guidelines, and applicable regulatory requirements. All subjects provided informed written consent.

KX01-AK-006 (sensitization study)

Design and objective. This was a randomized, single-center, controlled, within-subject comparison study aimed at determining the sensitization potential of tirbanibulin 1% ointment after repeated topical application.

Subjects. These included men and women aged ≥18 years and of any Fitzpatrick skin type or race as long as pigmentation allowed for discernment of erythema.

Treatment. Tirbanibulin 1% ointment, vehicle ointment, and negative control (0.9% saline) were applied at three adjacent, randomly assigned test sites (2 × 2 cm^2 each) in the left or right infrascapular area. During the induction phase, each product was applied three times weekly for 3 weeks under open-patch conditions. After a rest period (10–14 days), subjects entered the challenge phase, during which products were applied once to a naïve site on the opposite side of the back and removed 48 hours later. Subjects showing signs of contact sensitization during this phase were rechallenged at an additional naïve site ≥2 weeks later.

Assessments. Assessments were done by trained evaluators blinded to study products. During the induction phase, test sites were examined before each application, and irritancy was scored from 0 (none) to 3 (fissures/exudate/erosions and/or scabs). During the challenge phase, the naïve site was examined 30 minutes and 24, 48, and 72 hours after removal of products; dermal response was scored from 0 (none) to 3 (erythema/edema/vesicular eruption). Potential for contact sensitization was defined as dermal response scoring 3 during the challenge phase and recurring at rechallenge in at least one subject. AEs were collected during the whole study; severity and relation to study products were assessed.

Analyses. The cumulative irritancy population encompassed all subjects who completed the induction phase, the sensitization population encompassed those who completed the challenge phase, and the safety population encompassed those receiving treatment. Mean dermal response scores were calculated for each subject and product considering all nine assessments of the induction phase; these values are presented as means and SD and as least square means and standard error. Pairwise comparisons between products were conducted in the context of an ANOVA considering the subject and product effects without interactions; *P*-values were obtained using Fisher's least significant differences, with a threshold of 0.05 for significance. AEs are presented as frequencies and relative percentages. The maximum dermal response scores during the challenge phase for the tirbanibulin-treated site are presented as percentages with 95% confidence intervals. All statistical processing was performed using the SAS system (version 9.2).

KX01-AK-008 (phototoxicity study)

Design and objective. This was a randomized, single-center, controlled, within-subject comparison study aimed at determining the phototoxic potential of tirbanibulin 1% ointment after a single topical application followed by light exposure.

Subjects. These included men and women aged ≥18 years with Fitzpatrick skin types I–III and no previous history of photosensitivity or photoallergy.

Treatment. The minimal erythemal dose (MED) was first determined for each subject. An area of approximately 50 cm^2 divided into six equal sites was delimited in the infrascapular area. Sites were successively irradiated with full spectrum UV light (UVA/UVB), each site receiving a 25% greater UV dose than the preceding. Sites were evaluated 2 days after irradiation, and the lowest exposure-producing erythema was selected as MED.

To assess phototoxicity, four application sites of 2 × 2 cm^2 each (different from those used for MED determination) were delimited in each subject's infrascapular area. An additional site was delimited as control. On day 1, tirbanibulin 1% ointment and vehicle ointment were applied at two sites each, randomly assigned. The control site was left untreated. Test sites were kept under semiocclusive patch conditions for approximately 24 hours. On day 2, patches were removed, and one site per product (plus the control site) was irradiated with 16 J/cm^2 of UVA followed by 0.5 times the MED of UVA/UVB.

Assessments. Assessments were done by trained evaluators blinded to study products. The test and control sites were evaluated before irradiation (day 2) and 24 hours (day 3) and 48 hours (day 4) after. At each site, erythema was scored from 0 (none) to 3 (marked/severe), and edema was scored from 0 (none) to 2 (definite edema with erosions/vesicles). Dermal response score on each day was the sum of erythema and edema scores. The parameter used for phototoxicity was the average dermal response score for days 3 and 4, which could range from 0 (none) to 5 (maximum response), but for a reaction to be suspected as phototoxicity, both erythema and edema had to be observed. AEs were collected during the whole study, and severity and relation to study products were assessed.

Analyses. The phototoxicity population encompassed all subjects completing the study, and the safety population encompassed all subjects receiving treatment. Average scores for days 3–4 were summarized as mean (SD) and least square means (SD), and pairwise comparisons were conducted in the context of ANOVA and considering the subject and product effects without interactions. *P*-values were obtained using Fisher's least significant differences, with a threshold of 0.05 for significance. AEs were summarized as frequencies and relative percentages.

KX01-AK-009 (photoallergy study)

Design and objective. This was a randomized, single-center, controlled, within-subject comparison study aimed at determining the photoallergic potential of tirbanibulin 1% ointment after repeated topical application followed by light exposure.

Subjects. These included men and women aged ≥18 years with Fitzpatrick skin types I–III and no previous history of photosensitivity or photoallergy.

Treatment. The MED was first determined for each subject as previously described. The study consisted of two phases. For the induction phase, four test sites of 2 × 2 cm^2 each (different from those used to assess the MED) were delimited at one side of each subject's infrascapular area. On day 1, tirbanibulin 1% ointment and vehicle ointment were randomly assigned to two sites each; one site per product was designated for irradiation. Products were applied twice weekly for 3 weeks. After each application, sites were left under open-patch conditions for approximately 24 hours, after which the sites designated for irradiation were exposed to two times the subject's MED of UVA/UVB. Subjects completing the induction phase entered a rest period (10–17 days), followed by the challenge phase, in which photoallergy was assessed. Four naïve test sites (2 × 2 cm^2 each) and an additional control site were delimited on each subject's infrascapular area. Tirbanibulin and vehicle were applied once to two randomly assigned sites each and left under open-patch conditions. Approximately 24 hours later, one site per product and the control site were irradiated. If a cutaneous response was observed, subjects could be rechallenged as soon as the reaction resolved.

Assessments. Assessments were performed by trained evaluators blinded to study products. After each application of the induction phase, sites were examined before irradiation and 48–72 hours after irradiation. During the challenge phase, sites were examined before application; before irradiation; and 24, 48, and 72 hours after irradiation. For each site and time point assessed, erythema was scored from 0 (none) to 3 (marked/severe), and edema was scored from 0 (none) to 2 (definite edema with erosions/vesicles); dermal response was the sum of erythema and edema scores. Investigators determined whether a reaction was consistent with photoallergy on the basis of dermal reactions in the challenge phase, but in general, both erythema and edema had to be present. Suspected photoallergy could be confirmed by rechallenge. AEs were collected during the whole study; severity and relation to study products were assessed.

Analyses. The photoirritation population encompassed all subjects who completed the induction phase, the photoallergy population encompassed those who completed the challenge phase, and the safety population encompassed all subjects receiving treatment. For each test/control site, dermal response scores obtained during the induction phase were averaged and summarized as mean (SD). Pairwise comparisons were conducted for these means in the context of ANOVA and considering the subject and product effects without interactions. *P*-values were obtained using Fisher's least significant differences, with a threshold of 0.05 for significance. Dermal response scores during the challenge phase and AEs were summarized as frequencies and relative percentages.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: DC, JF; Funding Acquisition: JF, LP; Investigation: JD; Methodology: DC, JF; Project Administration: JF, LP; Resources: JF; Supervision: DC, JD, JF, LP; Visualization: JF; Writing — Review and Editing: DC, JD, JF, LP

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