TIRBANIBULIN OINTMENT 1% FOR ACTINIC KERATOSIS (AK): RESULTS FROM TWO PHASE 3 STUDIES WITH 1-YEAR FOLLOW-UP

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BACKGROUND

- Actinic keratosis (AK) are precancerous lesions that if left untreated may lead to invasive cutaneous squamous cell carcinoma[1]
- Tirbanibulin (KX2-391, KX01) is a synthetic, highly selective, novel inhibitor of tubulin polymerization and Src kinase signaling developed as a first-in-class topical formulation for the treatment of AK[2]
- Previous Phase I and II studies demonstrated that tirbanibulin ointment 1% was effective against AK lesions on the forearm, face and scalp. Local skin reactions (LSRs) were mostly transient and mild-to-moderate in severity, and tirbanibulin was well tolerated[3,4]

OBJECTIVE

- Here we present results from two Phase 3, double-blinded, vehicle-controlled, randomized, parallel-group, multicenter studies (KX01-AK-003 and KX01-AK-004) that evaluated the efficacy and safety of tirbanibulin vs. vehicle in adults with AK lesions on the face or scalp

METHODS

- Adult participants with 4–8 typical, visible AK lesions in a 25 cm^2 treatment area on the face or scalp were enrolled (2:1)
- Participants were randomized to receive either tirbanibulin ointment 1% or vehicle (1:1); treatment was self-applied once-daily for 5 consecutive days and left in place for ~12 hours
- Primary efficacy endpoint: complete (100%) clearance of AK lesions at Day 57
- Secondary efficacy endpoint: partial (≥75% reduction of AK lesions) clearance
- Safety assessments included: adverse events (AEs) and monitoring of LSRs including erythema, flaking/scaling, crusting, swelling, vesicles/pustules, and erosions/ulcers as graded on a 4-point scale (0 [absent] to 3 [severe]); composite LSR score was the sum of all six LSR grades (possible range: 0–18)
- Participants with complete AK clearance at Day 57 were followed for 1 year post-Day 57 to assess safety and presence of ≥1 AK lesion in previously treated area. Transparencies with location of AK lesions at Baseline were used to determine if lesions were new (i.e., at sites distinct from lesions at Baseline) or recurred (i.e., lesions present at Baseline, cleared by Day 57, and reappeared at Follow-up)

RESULTS

Study participants

- Overall 702 participants were enrolled from 62 study sites in the US (n=351 at 31 sites per study where each site participated in only one study; **Table 1**); over 99% of participants were treatment compliant

Table 1. Demographics and baseline characteristics (ITT population)

	KX01-AK-003 (n=351)		KX01-AK-004 (n=351)	
	Tirbanibulin (n=175)	Vehicle (n=176)	Tirbanibulin (n=178)	Vehicle (n=173)
Mean age, years	69.5	70.2	69.1	70.2
Male, n (%)	147 (84)	154 (88)	158 (89)	150 (87)
Caucasian, n (%)	175 (100)	175 (99)	177 (99)	173 (100)
Fitzpatrick Skin Type I or II, n (%)	123 (70)	142 (81)	126 (71)	120 (69)
Median baseline AK lesion count	6	6	6	6
Treatment area face:scalp ratio	119:56	121:55	119:59	118:55

ITT, intent-to-treat

Efficacy

- Complete (100%) and partial (≥75%) clearance rates were significantly higher with tirbanibulin vs. vehicle in both studies (P<0.0001) and in all subgroup analyses (P<0.01) (**Table 2**)
- Median (%) reduction in AK lesion count to Day 57 was greater with tirbanibulin vs. vehicle (KX01-AK-003: -5.0 [-83%] vs. -1.0 [-20%]; KX01-AK-004: -5.0 [-100%] vs. -1.0 [-25%])

Table 2. Complete (100%) and partial (≥75%) clearance rates of AK lesions (ITT population)

	KX01-AK-003 (n=351)			KX01-AK-004 (n=351)		
	Tirbanibulin (n=175)	Vehicle (n=176)	P-value	Tirbanibulin (n=178)	Vehicle (n=173)	P-value
100% clearance, n (%)	77 (44%)	8 (5%)	<0.0001[a]	97 (54%)	22 (13%)	<0.0001[a]
Face	50%	6%	<0.0001[b]	61%	14%	<0.0001[b]
Scalp	30%	2%	<0.0001[b]	41%	11%	0.0003[b]
≥75% clearance, n (%)	119 (68%)	29 (16%)	<0.0001[a]	136 (76%)	34 (20%)	<0.0001[a]
Subgroup analysis						
Age						
<65 years old	45%	2%	<0.0001[b]	63%	10%	<0.0001[b]
≥65 years old	44%	5%	<0.0001[b]	51%	13%	<0.0001[b]
Gender						
Female	61%	14%	0.0007[b]	85%	13%	<0.0001[b]
Male	41%	3%	<0.0001[b]	51%	13%	<0.0001[b]
Baseline AK lesion count						
4–6 AK lesions	49%	6%	<0.0001[b]	61%	13%	<0.0001[b]
7–8 AK lesions	31%	2%	<0.0001[b]	42%	11%	0.0002[b]
Fitzpatrick Skin Type						
I or II	45%	5%	<0.0001[b]	54%	13%	<0.0001[b]
III, IV, V, or VI	42%	3%	<0.0001[b]	56%	13%	<0.0001[b]

ITT, intent-to-treat
[a]Based on a Cochran-Mantel-Haenszel test stratified by treatment location
[b]Based on a Pearson Chi-square test within each subgroup

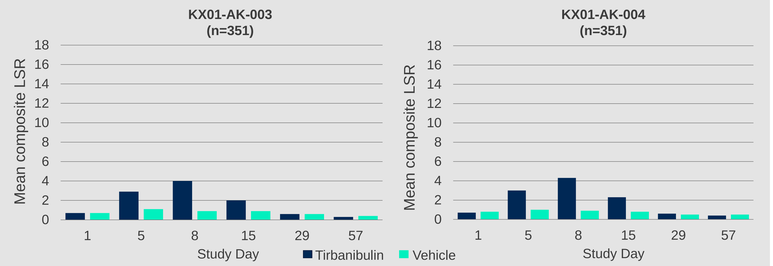
Safety

- Treatment-related treatment-emergent AEs (TEAEs) were reported in 56 participants receiving tirbanibulin (KX01-AK-003, n=20 [11%]; KX01-AK-004, n=36 [20%]) and 35 participants treated with vehicle (KX01-AK-003, n=16 [9%]; KX01-AK-004, n=19 [11%])
  - Most were mild-to-moderate, transient application site pruritus or pain that did not require treatment
- No discontinuations or serious AEs related to tirbanibulin were reported
- No ocular exposure led to ocular AEs, and there were no clinically significant abnormal electrocardiograms, laboratory findings, physical examinations, or vital signs

LSR assessments

- LSRs were mostly mild-to-moderate erythema and flaking/scaling
- Mean composite LSR scores were low for tirbanibulin, peaked on Day 8 and were resolved by Day 29 (**Figure 1**)
- The incidence of severe maximal post-baseline LSRs were low; these were mostly erythema and flaking/scaling (**Table 3**)

Figure 1. Mean composite LSR scores (Safety Population)



LSRs were graded on a 4-point scale (0=absent; 1=mild [slightly or barely perceptible]; 2=moderate [distinct presence]; 3=severe [marked/intense]). Composite LSR score is the sum of all six LSR grades (erythema, flaking/scaling, crusting, swelling, vesicles/pustules, erosions/ulcers) with a possible range of 0–18

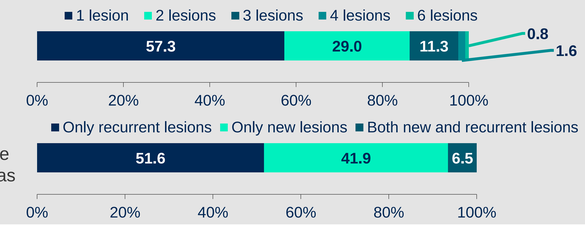
Table 3. Maximal post-baseline severe (Grade 3) LSRs (Safety Population)

	KX01-AK-003 (n=351)		KX01-AK-004 (n=351)	
n (%)	Tirbanibulin (n=175)	Vehicle (n=176)	Tirbanibulin (n=178)	Vehicle (n=173)
Erythema	5 (3)	0	17 (10)	0
Flaking/scaling	11 (6)	0	20 (11)	1 (<1)
Crusting	2 (1)	0	5 (3)	0
Swelling	1 (<1)	0	1 (<1)	0
Vesicles/pustules	1 (<1)	0	1 (<1)	0
Erosions/ulcers	0	0	0	0

1-year Follow-up (Pooled data)

- A total of 174 participants treated with tirbanibulin who achieved complete AK clearance at Day 57 entered the 1-year Follow-up Period (KX01-AK-003, n=77; KX01-AK-004, n=97)
- Kaplan-Meier estimates of rate of participants with ≥1 AK lesion in tirbanibulin-treated area up to 1-year post-Day 57 was 73%. Post-hoc analysis showed that when only participants with recurred lesions (58% of subjects with any AK lesion in the treated area during Follow-up) were considered, Kaplan-Meier estimates of participants with recurred lesions was 47%
- When AK lesions were observed during Follow-up, 86% participants had ≤2 AK lesions (57% had 1 lesion) in the treatment area; and 42% had only new lesions (**Figure 2**)
- Baseline number of lesions (>5) and previous AK treatments in the treatment area were correlated with recurrence (odds ratio, 2.1 and 3.0, respectively)
- No treatment-related AEs including skin cancers throughout 1-year Follow-up were reported

Figure 2. Recurrence distribution (Pooled tirbanibulin data; n=124[a])



[a]Participants who had recurrent or new lesions in the recurrence population
[b]An AK lesion that was at the same AK lesion location identified at Baseline and resolved at Day 57
[c]An AK lesion that was not identified in the target treatment area at Baseline and emerged during the 1-year Follow-up Period

CONCLUSIONS

- Tirbanibulin ointment 1% for 5 days was shown to be well tolerated and effective in two large Phase 3 studies, potentially making it a valuable new addition to AK treatment
- Statistically significant differences were demonstrated in all subgroups analyzed for the face and scalp
- Most treatment-related TEAEs were mild-to-moderate, transient application site pruritus, or pain that did not require treatment
- Mean composite LSR scores were low and peaked at Day 8 before resolving by Day 29
- Over 99% of participants completed the full 5-day self-application of tirbanibulin
- At 1-year Follow up, the estimated rate of participants having any AK (recurred or new) in the tirbanibulin-treated areas among complete responders at Day 57 was 73%. When only participants with recurred lesions at the same sites at Baseline were considered, the estimated rate was 47%

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DISCLOSURES

This study was sponsored by Athenex, Inc.

ACKNOWLEDGMENTS

Editorial support, under the direction of the authors, was provided by Gemma McGregor, PhD, on behalf of CMC AFFINITY, McCann Health Medical Communications in accordance with Good Publication Practice (GPP3) guidelines and was funded by Almirall, SA.

Presented at the Maui Derm Virtual Congress, June 24–27, 2020