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## BACKGROUND

- Actinic keratoses (AK) are precancerous lesions that if left untreated may lead to invasive cutaneous squamous cell carcinoma<sup>1</sup>
- Tirbanibulin (KX2-391) is a synthetic, highly selective, novel inhibitor of tubulin polymerisation and Src kinase signalling developed as a first-in-class topical formulation for the treatment of AK<sup>2</sup>
- Previous Phase I and II studies showed that tirbanibulin ointment 1% for 5 days 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.<sup>3,4</sup> These studies supported the further development of the 5-day clinical regimen of tirbanibulin ointment 1% in treating AK on the face/scalp

## OBJECTIVES

- Here we present results from two Phase III, double-blinded, vehicle-controlled, randomised, parallel-group, multicentre 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 subjects with 4–8 typical, visible AK lesions in a 25 cm<sup>2</sup> treatment area on the face or scalp were enrolled (2:1)
- Subjects were randomised 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)
- Subjects 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 a previously treated area. Transparencies with the 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 subjects

- Overall 702 subjects 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 subjects 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
<b>100% clearance, n (%)</b>	<b>77 (44%)</b>	<b>8 (5%)</b>	<b>&lt;0.0001<sup>a</sup></b>	<b>97 (54%)</b>	<b>22 (13%)</b>	<b>&lt;0.0001<sup>a</sup></b>
Face	50%	6%	<0.0001 <sup>b</sup>	61%	14%	<0.0001 <sup>b</sup>
Scalp	30%	2%	<0.0001 <sup>b</sup>	41%	11%	0.0003 <sup>b</sup>
<b>≥75% clearance, n (%)</b>	<b>119 (68%)</b>	<b>29 (16%)</b>	<b>&lt;0.0001<sup>a</sup></b>	<b>136 (76%)</b>	<b>34 (20%)</b>	<b>&lt;0.0001<sup>a</sup></b>
<b>Subgroup analysis</b>						
<b>Age</b>						
<65 years old	45%	2%	<0.0001 <sup>b</sup>	63%	10%	<0.0001 <sup>b</sup>
≥65 years old	44%	5%	<0.0001 <sup>b</sup>	51%	13%	<0.0001 <sup>b</sup>
<b>Gender</b>						
Female	61%	14%	0.0007 <sup>b</sup>	85%	13%	<0.0001 <sup>b</sup>
Male	41%	3%	<0.0001 <sup>b</sup>	51%	13%	<0.0001 <sup>b</sup>
<b>Baseline AK lesion count</b>						
4–6 AK lesions	49%	6%	<0.0001 <sup>b</sup>	61%	13%	<0.0001 <sup>b</sup>
7–8 AK lesions	31%	2%	<0.0001 <sup>b</sup>	42%	11%	0.0002 <sup>b</sup>
<b>Fitzpatrick Skin Type</b>						
I or II	45%	5%	<0.0001 <sup>b</sup>	54%	13%	<0.0001 <sup>b</sup>
III, IV, V or VI	42%	3%	<0.0001 <sup>b</sup>	56%	13%	<0.0001 <sup>b</sup>

<sup>a</sup>Based on a Cochran-Mantel-Haenszel test stratified by treatment location<sup>b</sup>Based on a Pearson Chi-square test within each subgroup

AK, actinic keratosis; ITT, intent-to-treat

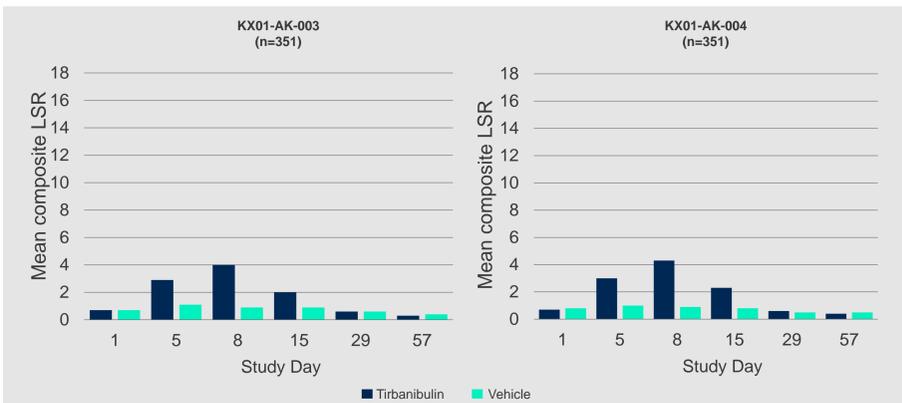
### Safety

- Treatment-related treatment-emergent AEs (TEAEs) were reported in 56 subjects receiving tirbanibulin (KX01-AK-003, n=20 [11%]; KX01-AK-004, n=36 [20%]) and 35 subjects 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 was reported, 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

LSR, local skin reaction

**Table 3. Maximal Post-Baseline Severe (Grade 3) LSRs (Safety Population)**

	KX01-AK-003 (N=351)		KX01-AK-004 (N=351)	
	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

LSR, local skin reaction

### 1-year Follow-up (Pooled data)

- A total of 174 subjects 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 estimated rate of subjects with ≥1 AK lesion in a tirbanibulin-treated area up to 1-year post-Day 57 was 73% (the estimated rate was 74% for KX01-AK-003 and 72% for KX01-AK-004); 27% of subjects had sustained AK clearance at 1-year
- 58% of subjects with ≥1 AK lesion in the treated area during Follow-up had recurred lesions and 42% had only new lesions (**Figure 2**)
- When only subjects with recurred lesions were considered, Kaplan–Meier estimated rate of recurrence was 47%
- When AK lesions were observed during Follow-up, 86% subjects had ≤2 AK lesions and 57% had 1 lesion in the treatment area
- 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<sup>a</sup>)**

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

AK, actinic keratosis

## CONCLUSIONS

- Tirbanibulin ointment 1% for 5 days was shown to be well tolerated and effective in two large Phase III studies, potentially making it a valuable new addition to AK treatment
- Statistically significant differences were demonstrated in all subgroups analysed 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 subjects completed the full 5-day self-application of tirbanibulin
- At 1-year Follow-up, the estimated rate of subjects having any AK (recurred or new) in the tirbanibulin-treated areas among complete responders at Day 57 was 73%. When only subjects with recurred lesions at the same sites at Baseline were considered, the estimated rate was 47%

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## DISCLOSURES

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