KX2-391 Ointment 1%, a Novel Dual Src/Tubulin Inhibitor, in the Treatment of Adults with Actinic Keratosis in Two Pivotal Phase III Studies

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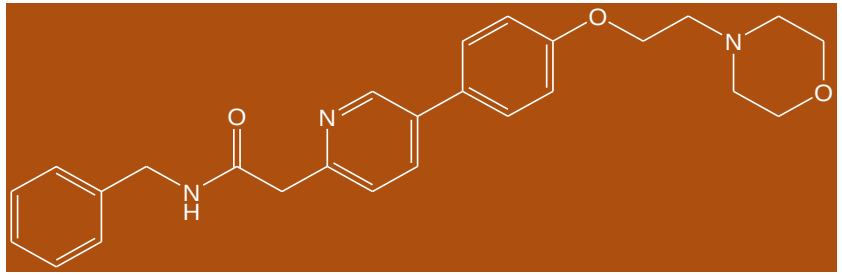
KX2-391 Mechanism of Action

- Novel small molecule compound with differentiated mechanisms of actions:
  - (1) inhibition of Src Kinase activity
  - (2) inhibition of tubulin polymerization

→ Upregulate apoptosis in proliferating cells



KX2-391 Ointment 1% =
KX2-391 free base + glyceryl monostearate + propylene glycol

Molecular Weight: 431.53 g/mole
Other names: KX01

Two Identical Phase III Efficacy and Safety Studies of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis (AK)
(KX01-AK-003 and KX01-AK-004)

Study Design: Double-blind, vehicle-controlled, randomized, parallel group, multicenter

- Treatment area: 25 cm^2 with 4-8 typical visible AK lesions on face or scalp
- KX2-391 ointment 1% vs Vehicle at 1:1 ratio
- Once daily treatment for 5 consecutive days; self-application; left in place ~12 hrs

Objectives: (A) Primary efficacy endpoint: 100% clearance of AK at Day 57
(B) Safety (local skin reaction and AEs, etc.)
of KX2-391 ointment 1% versus vehicle in adults with AK

Enrolled 351 subjects in 31 US sites per study (total of 702 subjects from 62 US sites)

Over 99% compliance with treatment

Demography and Baseline Characteristics - Intent-To-Treat (ITT) Population

	KX01-AK-003 N=351		KX01-AK-004 N=351	
Number of Subjects (% of Subjects in ITT Population)	KX2-391 N=175	Vehicle N=176	KX2-391 N=178	Vehicle N=173
Mean Age (years)	69.5	70.2	69.1	70.2
Gender: Male	147 (84%)	154 (88%)	158 (89%)	150 (87%)
Race: White	175 (100%)	175 (99%)	177 (99%)	173 (100%)
Fitzpatrick Skin Type I/II	123 (70%)	142 (81%)	126 (71%)	120 (69%)
Median Baseline AK lesion counts	6	6	6	6
Treatment area: Face to Scalp	119:56	121:55	119:59	118:55

Demographics/baseline characteristics - similar between treatment groups for both studies

Efficacy Results of KX2-391 in Field Treatment of AK - Intent-To-Treat (ITT) population

Study	KX01-AK-003			KX01-AK-004		
% of Subjects in ITT Population (Number of Subjects)	KX2-391 N=175	Vehicle N=176	p-value	KX2-391 N=178	Vehicle N=173	p-value
100% AK Clearance	**44% (N=77)**	**5% (N=8)**	**<0.0001**	**54% (N=97)**	**13% (N=22)**	**<0.0001**
Face	50%	6%	<0.0001	61%	14%	<0.0001
Scalp	30%	2%	<0.0001	41%	11%	0.0003
≥75% AK Clearance	68%	16%	<0.0001	76%	20%	<0.0001

Two of 702 subjects (both in Vehicle group) discontinued prior to Day 57 and were considered non-responders

Subgroup Analysis of 100% Clearance at Day 57 - ITT Population

	KX01-AK-003			KX01-AK-004		
Subgroups	KX2-391	Vehicle	p-value	KX2-391	Vehicle	p-value
Female	61%	14%	0.0007	85%	13%	<0.0001
Male	41%	3%	<0.0001	51%	13%	<0.0001
<65 years old	45%	2%	<0.0001	63%	10%	<0.0001
≥65 years old	44%	5%	<0.0001	51%	13%	<0.0001
Baseline						
4-6 AK lesions	49%	6%	<0.0001	61%	13%	<0.0001
7-8 AK lesions	31%	2%	<0.0001	42%	11%	0.0002
Skin Type						
I or II	45%	5%	<0.0001	54%	13%	<0.0001
III/IV/V/VI	42%	3%	<0.0001	56%	13%	<0.0001

Statistical significant difference in 100% clearance was demonstrated for all subgroups analyzed in both studies

Safety Results - Safety Population

- KX2-391 was well tolerated
- No ocular exposure that led to ocular AEs
- No related clinically significant abnormal EKGs, PEs, vital signs or laboratory findings

Number of Subjects (% of Subjects in Safety Population)	KX01-AK-003 N=351		KX01-AK-004 N=351	
Number of subjects	KX2-391 N=175	Vehicle N=176	KX2-391 N=178	Vehicle N=173
Discontinuation of study drug [a]	1 (<1%)	0	0	0
Discontinuation prior to Day 57 – all unrelated	0	2 (1%)	0	0
Serious Adverse Events - all unrelated	0	2 (1%)	1 (<1%)	4 (2%)
Treatment-related TEAEs [b]	20 (11%)	16 (9%)	36 (20%)	19 (11%)

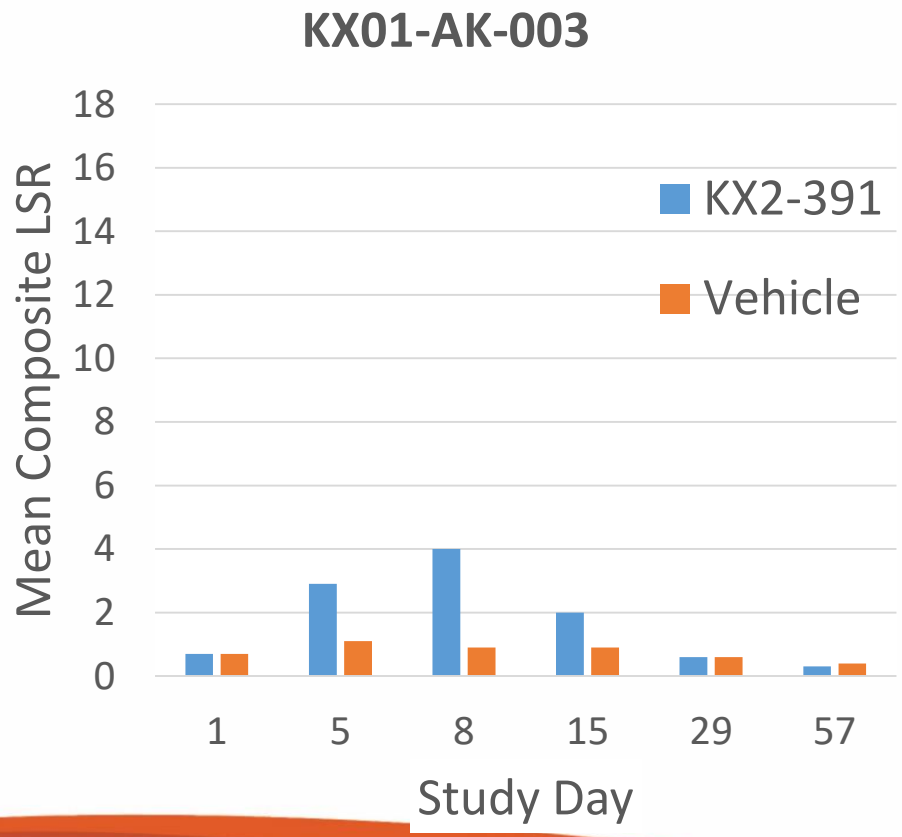
TEAE = Treatment Emergent Averse Events

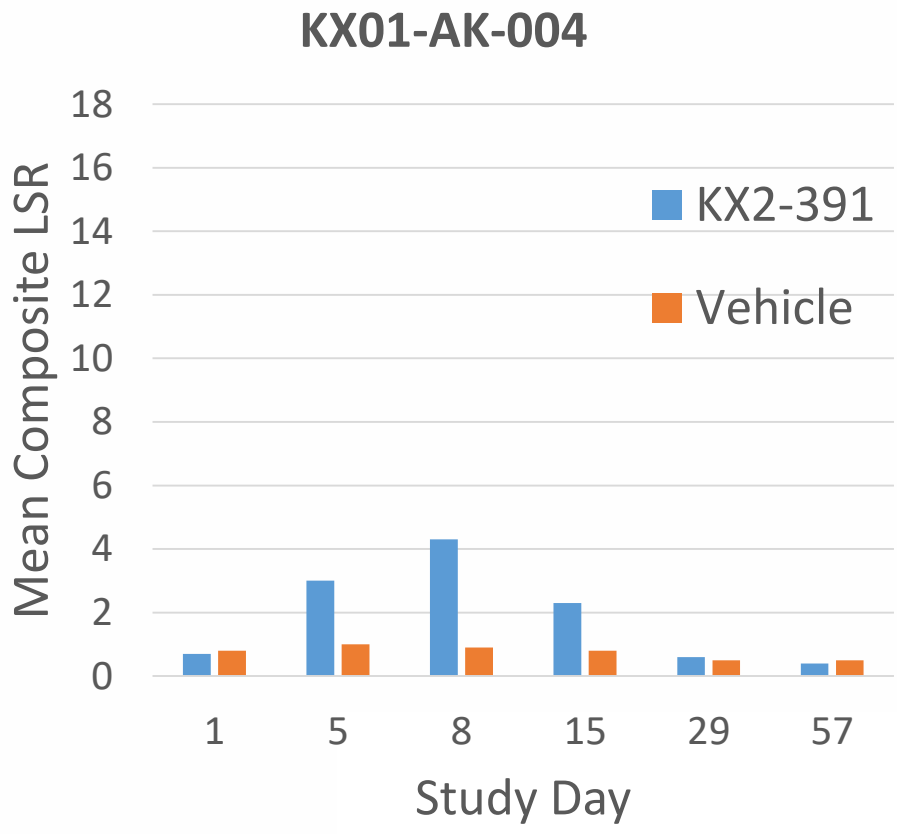
a. One subject discontinued study drug due to unrelated AE (laceration at treatment area on Day 2) but remained in the study

b. Most related TEAEs were mild-moderate transient application site pruritus or pain that required no treatment

Local Skin Reactions (LSR) – Safety Population

- 0-3 LSR grade: 0=absent; 1=mild (slightly or barely perceptible); 2=moderate (distinct presence); 3=severe (marked, intense);
- Composite LSR score is the sum of all 6 LSR (erythema, flaking/scaling, crusting, swelling, vesicles/pustules, erosions/ulcers) grades with a possible range 0-18





LSRs were mostly mild to moderate, peaked on Day 8 and resolved by Day 29

Maximal Post-Baseline LSR at Grade 3 (Severe) - Safety Population

Number of Subjects (% of Subjects in Safety Population)	KX01-AK-003		KX01-AK-004	
	KX2-391 N=175	Vehicle N=176	KX2-391 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

Conclusions

- KX2-391 ointment 1%, once daily for 5 days, resulted in higher overall complete AK clearance rates at Day 57 than Vehicle in two Phase III trials at 44% and 54%, respectively
- Statistical significant differences were demonstrated in all subgroups analyzed including for face and scalp
- Most related TEAEs were mild-moderate transient application site pruritus or pain that required no treatment
- Mean composite LSR scores were low; peaking at Day 8 and resolving by Day 29
- Completion of full 5-day self-application was at >99%