PHASE I STUDY TO EVALUATE THE POTENTIAL OF TIRBANIBULIN OINTMENT 1% TO INDUCE A PHOTOTOXICITY SKIN REACTION IN HEALTHY SUBJECTS

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SYNOPSIS

- Tirbanibulin (KX2-391, KX-01) is a synthetic, highly selective, novel inhibitor of tubulin polymerization and Src kinase signaling being developed as a first-in-class topical formulation for the treatment of actinic keratosis[1]
- An *in vitro* study showed that tirbanibulin ointment 1% absorbs light within the natural range of sunlight (290–400 nm); therefore, it is necessary to determine its potential to cause a phototoxic reaction
- This poster presents results from a Phase I, 4-day randomized, controlled, double-blinded, within-subject comparison study (KX01-AK-008) evaluating the potential for tirbanibulin ointment 1% to induce a phototoxic skin reaction. Results showed that there was no evidence that tirbanibulin ointment 1% induced phototoxicity

OBJECTIVES

- The primary objective was to determine the phototoxic potential of tirbanibulin ointment 1% when topical application to healthy skin was followed by light exposure
- Safety was assessed by evaluation of any adverse events (AEs)

METHODS

Study design

- Healthy adults (aged ≥18 years) with Fitzpatrick Skin Types I–III, and no prior history of photosensitivity or photoallergy were enrolled in the study
- Prior to product application, the minimal erythemal dose (MED) was determined for each subject
- On Day 1, four 2 cm^2 sites (different from those used to determine the MED) were marked on the infrascapular region of each subject's back: tirbanibulin and vehicle (ointment containing no active drug substance formulated with the excipients glycerol monostearate and propylene glycol) were applied to two randomly assigned sites each under semi-occlusive patch conditions
- Approximately 24 hours after study product application, the patches were removed (Day 2) and one application site for each product was subsequently irradiated (16 J/cm^2 of UVA radiation followed by 0.5 times the MED of UVA/UVB [full spectrum] radiation) and one site remained non-irradiated. An additional pre-designated site that served as an untreated control was also irradiated

Study evaluations

- Erythema (scored as 0 [no reaction] to 3 [marked/severe erythema]) and edema (scored as 0 [no reaction] to 2 [definite edema with erosions/vesicles]) were evaluated in all sites before irradiation, and at 24 hours (Day 3) and 48 hours (Day 4) after irradiation by a reviewer blinded to treatment
- The parameter used for phototoxicity was mean dermal response (the sum of erythema and edema scores on Days 3 and 4). Erythema and edema must have been observed for a reaction to be suspected as phototoxic
- AEs were reported throughout the study

RESULTS

Baseline characteristics

- Thirty-one subjects were enrolled and completed the study (**Table 1**)
- The mean (standard deviation [SD]) age of subjects was 52.2 (12.2) years
- Subjects were White and mostly female with a Fitzpatrick Skin Type of II or III
- The mean (SD) MED on Day 1 was 45.5 (14.9) seconds

Phototoxicity outcomes

- A summary of dermal responses by response scores are summarized in **Table 2**
  - The maximum dermal response score was 2 (moderate erythema) and was observed in 3 (9.7%) subjects on Day 3 and 6 (19.4%) subjects on Day 4 at the tirbanibulin irradiated site; no subjects reported edema and therefore none met the criteria for phototoxicity
- There was no significant difference in mean dermal response score between: tirbanibulin irradiated or non-irradiated sites (p=0.5977), vehicle irradiated and non-irradiated sites (p=0.3796), or tirbanibulin and vehicle irradiated sites (p=0.0803); however, there was a statistically significant difference observed between tirbanibulin and vehicle non-irradiated sites (p=0.0364), suggestive of local irritation associated with tirbanibulin
- The mean dermal response scores of all tirbanibulin and vehicle sites (irradiated and non-irradiated) were significantly greater than the irradiated untreated control site (all p<0.0001)

Table 1. Subject demographics and baseline characteristics

	Number of randomized subjects (N=31)
Mean (SD) age, years	52.2 (12.2)
Gender, n (%)	
Female	24 (77.4)
Male	7 (22.6)
Race, n (%)	
White	31 (100.0)
Black or African American	0
Asian	0
American Indian or Alaskan Native	0
Native Hawaiian or Other Pacific Islander	0
Other	0
Ethnicity, n (%)	
Hispanic or Latino	4 (12.9)
Not Hispanic or Latino	27 (87.1)
Fitzpatrick Skin Type,[a] n (%)	
Type I	0
Type II	12 (38.7)
Type III	19 (61.3)
MED on Day 1 (seconds)[b]	
Mean (SD)	45.5 (14.9)
Median	38.0
Minimum, Maximum	32.0, 76.0

[a]Type I: always burns easily, never tans; Type II: always burns easily, tans minimally; Type III: burns moderately, tans gradually
[b]MED is expressed as seconds of exposure to a solar simulator with the output set to 661 µw/cm^2 UVB/UVA [full spectrum]
MED, minimal erythema dose; SD, standard deviation

Table 2. Summary of dermal response scores by response scores (Phototoxicity Analysis Population)[a]

	Tirbanibulin		Vehicle		Untreated
Response score[b]	Irradiated (N=31)	Non-irradiated (N=31)	Irradiated (N=31)	Non-irradiated (N=31)	Irradiated (N=31)
0 hours (Day 2), n (%)					
0	22 (71.0)	22 (71.0)	18 (58.1)	17 (54.8)	31 (100.0)
1	9 (29.0)	9 (29.0)	13 (41.9)	14 (45.2)	0
24 hours (Day 3), n (%)					
0	5 (16.1)	8 (25.8)	5 (16.1)	8 (25.8)	24 (77.4)
1	23 (74.2)	18 (58.1)	25 (80.6)	21 (67.7)	7 (22.6)
2	3 (9.7)	5 (16.1)	1 (3.2)	2 (6.5)	0
48 hours (Day 4), n (%)					
0	8 (25.8)	8 (25.8)	11 (35.5)	13 (41.9)	22 (77.4)
1	17 (54.8)	19 (61.3)	19 (61.3)	18 (58.1)	7 (22.6)
2	6 (19.4)	4 (12.9)	1 (3.2)	0	0
Average of 24 & 48 hours					
Mean (SD)	0.94 (0.54)	0.89 (0.57)	0.77 (0.43)	0.69 (0.48)	0.23 (0.40)
Least square mean (SD)	0.94 (0.54)	0.89 (0.57)	0.77 (0.43)	0.69 (0.48)	0.23 (0.40)
p-values[c]					
vs tirbanibulin, irradiated	-	0.5977	0.0803	0.0092	<0.0001
vs tirbanibulin, non-irradiated		-	0.2194	0.0364	<0.0001
vs vehicle, irradiated			-	0.3796	<0.0001
vs vehicle, non-irradiated				-	<0.0001
vs untreated, irradiated					-

[a]Includes all randomized subjects who completed the study
[b]Response score is the sum of erythema and edema
[c]p-values are from an analysis of variance of the average numerical score (sum of erythema and edema) at 24 and 24 hours (Days 3 and 4), with effects of subjects and treatment, using Fisher's least significant differences
SD, standard deviation

Safety outcomes

- One AE was reported in one subject (headache). The event was considered mild and possibly related to study products
- There were no serious or severe AEs or treatment-emergent AEs that led to study discontinuation

CONCLUSIONS

- There were no differences in mean dermal response scores between irradiated and non-irradiated sites for tirbanibulin and vehicle; therefore, tirbanibulin ointment 1% did not induce phototoxicity

REFERENCE

1. Smolinski MP, et al. *J Med Chem*. 2018;61:4704-4719

DISCLOSURES

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