Poster #36

PHASE I PHOTOALLERGY STUDY OF TIRBANIBULIN OINTMENT 1% IN HEALTHY SUBJECTS

Jonathan Dosik,[1] David Cutler,[2] Jane Fang[2]

[1]TKL Research Inc., Fair Lawn, NJ, USA; [2]Athenex Inc., Buffalo, NY, USA

BACKGROUND

- 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 actinic keratosis (AK)[1]
- As tirbanibulin ointment 1% is formulated for topical use and absorbs light at a wavelength within the range of natural sunlight (290–400 nm), it was necessary to determine the potential of this product to cause a photoallergic reaction after application to the skin
- 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.[2,3] These studies supported the further development of the 5-day clinical regimen of tirbanibulin ointment 1% in treating AK on the face/scalp
- Results from two Phase III studies (KX01-AK-003/KX01-AK-004), demonstrated that tirbanibulin ointment 1% self-administered once-daily for 5 days resulted in higher rates of complete lesion clearance at Day 57 compared with placebo (KX01-AK-003: 44% vs. 5%, P<0.0001; KX01-AK-004: 54% vs. 13%, P<0.0001) and was well tolerated, potentially making it a valuable new addition to AK treatment[4] (**See EADO 2020 Poster #35**)
- Here, we present results from a 6-week, Phase I, randomised, double-blind, single-centre, within-subject comparison study (KX01-AK-009) evaluating the potential of tirbanibulin ointment 1% to induce a photoallergic skin reaction in healthy subjects

OBJECTIVES

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

METHODS

- Healthy adults (aged ≥18 years) with Fitzpatrick Skin Types I–III and no prior history of photosensitivity or photoallergy were enrolled at one centre in the USA
- Eight application sites (2 cm^2 each) were marked on each subject's back; during the study, tirbanibulin ointment 1% or vehicle ointment (glycerol monostearate and propylene glycol) were applied to the sites according to a randomised sequence
- During the 3-week Induction Phase, tirbanibulin or vehicle ointment was applied to 2 sites twice each week for 24 hours under open-patch conditions (6 applications)
- Application sites were evaluated and one site for each study product was irradiated with 2 times the subject's minimal erythemal dose using the full Xenon lamp spectrum
- All sites were re-evaluated 48- to 72-hours post-irradiation; irradiated versus non-irritated sites were compared for each subject
- Dermal reactions were assessed for erythema (0=no reaction; 1=mild but definite; 2=moderate; 3=marked/severe), oedema (0=no reaction; 1=mild but definite; 2=definite with erosion/vesiculation) and other signs of irritation
- Following a 2-week rest period, subjects entered the Challenge Phase where study products were applied to 2 naïve sites for 24 hours under open-patch conditions
- All sites were evaluated. One application site per study product, and one untreated site were irradiated; sites were examined for dermal reactions at 24-, 48- and 72-hours post-irradiation. If a cutaneous response was observed during the Challenge Phase indicating possible photosensitisation, a Rechallenge would be performed
- AEs were assessed

RESULTS

Baseline characteristics

- In total, 67 subjects were screened and 64 were randomised; subject demographics and Baseline characteristics are shown in **Table 1**
- All 64 subjects were assessed for safety, 61 completed the Induction Phase, and 59 completed the Challenge Phase
- Five (7.8%) subjects discontinued from the study: three voluntarily withdrew, one discontinued due to an AE, and one due to a protocol violation

Table 1. Subject Demographics and Baseline Characteristics

	Randomised subjects (n=64)
Mean (SD) age, years	55.8 (10.5)
Gender, n (%)	
Female	57 (89.1)
Male	7 (10.9)
Race, n (%)	
White	64 (100.0)
Ethnicity, n (%)	
Hispanic or Latino	10 (15.6)
Not Hispanic or Latino	54 (84.4)
Fitzpatrick Skin Type,[a] n (%)	
I	2 (3.1)
II	27 (42.2)
III	35 (54.7)
MED on Day 1 (seconds)[b]	
n	62
Mean (SD)	59.0 (17.7)
Minimum, maximum	31.0, 94.0

[a]Type I, always burns easily, never tans; Type II, always burns easily, tans minimally; Type III, burns moderately, tans gradually; [b]MED is defined as the length (in time) and intensity of light exposure required to produce a minimal erythemal reaction 16–24 hours after irradiation
MED, minimal erythemal dose; SD, standard deviation

Dermal responses (photoirritation) during the Induction Phase

- Mean dermal response scores were below 0.5 for each study product and irradiation status (**Table 2**)
- There was no statistically significant difference between mean dermal response scores for tirbanibulin-treated and vehicle-treated irradiated sites (p=0.8036) indicating that tirbanibulin did not cause photoirritation

Table 2. Mean Dermal Response Scores During the Induction Phase

	Tirbanibulin		Vehicle	
	Irradiated (n=61)	Non-irradiated (n=61)	Irradiated (n=61)	Non-irradiated (n=61)
Mean dermal response score[a] (SD)	0.414 (0.32)	0.075 (0.14)	0.406 (0.32)	0.003 (0.01)
P-values[b]				
vs tirbanibulin, irradiated	-	<0.0001[c]	**0.8036**	<0.0001[c]
vs tirbanibulin, non-irradiated		-	<0.0001[c]	0.0312[c]
vs vehicle, irradiated			-	<0.0001[c]
vs vehicle, non-irradiated				-

[a]Mean of the mean dermal response scores at each evaluation time point during the Induction Phase, where the dermal response scores are the sum of the erythema and oedema scores for each subject; [b]P-values are from an analysis of variance of the average numerical score over all Induction Phase evaluations, with effects of subject and treatment, using Fischer's least significant differences; [c]Significant difference in cumulative irritation score between products with P<0.05. SD, standard deviation

Dermal responses (photosensitisation) during the Challenge Phase

- At ~24-, 48- and 72-hours post-irradiation, most subjects had a maximal dermal response score of 0 at both tirbanibulin- and vehicle-treated, and irradiated and non-irradiated sites (**Table 3**)
- The maximal dermal response score overall was 1, most commonly observed at ~72 hours; at this time point, for tirbanibulin-treated sites, dermal response scores of 1 were reported in 10 (16.9%) and 7 (11.9%) subjects whose sites were irradiated and not irradiated, respectively
- No photosensitisation was observed (and so no re-challenges were performed)

Table 3. Proportions of Subjects with Different Dermal Response Scores Before and After Irradiation During the Challenge Phase

	Tirbanibulin		Vehicle		Untreated
	Irradiated (n=59)	Non-irradiated (n=59)	Irradiated (n=59)	Non-irradiated (n=59)	Irradiated (n=59)
Dermal response score[a]					
Pre-application, n (%)					
0	59 (100.0)	59 (100.0)	59 (100.0)	59 (100.0)	0
0 hours (pre-irradiation/24 hours post-application)[b], n (%)					
0	59 (100.0)	59 (100.0)	59 (100.0)	58 (98.3)	58 (98.3)
1	0	0	0	1 (1.7)	1 (1.7)
24 hours (post-irradiation/48 hours post-application)[b], n (%)					
0	56 (94.9)	55 (93.2)	58 (98.3)	59 (100.0)	57 (96.6)
1	3 (5.1)	4 (6.8)	1 (1.7)	0	2 (3.4)
48 hours (post-irradiation/72 hours post-application)[b], n (%)					
0	57 (96.6)	59 (100.0)	56 (94.9)	59 (100)	58 (98.3)
1	2 (3.4)	0	3 (5.1)	0	1 (1.7)
72 hours (post-irradiation/96 hours post-application)[b], 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)

[a]Sum of erythema and oedema scores; [b]All time points are ±4 hours

Safety outcomes

- In total, six treatment-emergent AEs were reported (onset date on or after the first study product administration date): three were mild (bruising, n=2; cold symptoms, n=1) and three were moderate (cold symptoms, sinus headache, upper respiratory tract infection; all n=1)
- There were no treatment-related AEs and no serious AEs
- One AE (upper respiratory tract infection) led to study discontinuation

CONCLUSIONS

- There was no difference in mean dermal responses between the tirbanibulin- and vehicle-treated irradiated sites during the Induction Phase, confirming a lack of photoirritation
- There was also no evidence of photosensitisation with tirbanibulin ointment 1% or vehicle ointment during the Challenge Phase and therefore, no evidence of tirbanibulin causing a photoallergic reaction

REFERENCES

1. Smolinksi MP, et al. J Med Chem. 2018;61:4707-4719
2. DuBois J, et al. Phase I study of tirbanibulin ointment 1%, a novel Src phosphorylation and tubulin polymerization inhibitor, in subjects with actinic keratosis. Poster presented at the 6th Annual Practical Symposium, Beaver Creek, CO, USA, August 8–11, 2019
3. DuBois J, et al. Phase II study of tirbanibulin ointment 1%, a novel Src phosphorylation and tubulin polymerization inhibitor, for actinic keratosis. Poster presented at the 6th Annual Practical Symposium, Beaver Creek, CO, USA, August 8–11, 2019
4. Blauvelt A, et al. Tirbanibulin ointment 1% for actinic keratosis(AK): Results from two Phase 3 studies with 1-year follow-up. Poster presented at the Maui Derm Virtual Congress, June 24–27, 2020

DISCLOSURES

This study was sponsored by Athenex, Inc.

ACKNOWLEDGEMENTS

Editorial support, under the direction of the authors, was provided by Gemma Turner, MSci, 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 European Association of Dermato Oncology (EADO) virtual congress, 12–14 October 2020