PHASE I MAXIMAL USE PHARMACOKINETIC STUDY OF TIRBANIBULIN OINTMENT 1% IN SUBJECTS WITH ACTINIC KERATOSIS

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SYNOPSIS

- Tirbanibulin 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].
- In Phase I/II studies, tirbanibulin was minimally absorbed and systemic exposure was low when applied topically.
- 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 Phase I, open-label, uncontrolled, non-randomised, maximal use pharmacokinetic (PK) study (KX01-AK-007) evaluating the systemic exposure and safety of tirbanibulin ointment 1% (5 days) applied to the face/balding scalp of adults with AK.

OBJECTIVES

- The primary objective was to determine the PK of tirbanibulin ointment 1% under maximal use conditions.
- Secondary objectives were to evaluate the safety and tolerability of tirbanibulin ointment 1% and to determine the PK of tirbanibulin metabolites.

METHODS

Study design

- Subjects (aged ≥18 years) with ≥6 clinically typical, visible and discrete AK lesions on 25 cm^2 of the face/balding scalp were enrolled in the study.
- Subjects self-applied sufficient tirbanibulin to cover the treatment area (25 cm^2 area of the face/balding scalp) from the 250 mg sachet once-daily for 5 consecutive days. Subjects were instructed to avoid touching or wetting the treatment area for at least 12 hours after drug application.

Study evaluations

Pharmacokinetics

- PK blood sampling (for tirbanibulin and its inactive metabolites [KX2-5036 and KX2-5163]) occurred on Days 1, 3 and 4 at 0 (pre-dose) and on Day 5 at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours post-the Day 5 application.

Safety

- Adverse events (AEs) were assessed.
- LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration; scale of 0–3 [absent–severe]) were evaluated on Days 1, 6, 8, 15 and 29; and LSR composite scores were calculated as the sum of all individual LSR scores at each visit with the possible range of 0–18.

RESULTS

Baseline characteristics

- In total, 18 subjects (face, n=9; scalp, n=9) were enrolled and completed the study (**Table 1**).
- The mean (standard deviation, SD) age of subjects was 66.4 (9.42 [range: 43–83]) years.
- Subjects were White, predominantly male (83.3%) with Fitzpatrick skin type I–III (94.4%) and a mean (SD) baseline AK lesion count of 8.2 (2.43 [range: 6–14]).
- Mean (SD) dose applied was 137 (44.9) mg among the combined subject group (~55% of the full dose possible, 250 mg).

Table 1. Subject demographics and baseline characteristics

	Face (n=9)	Scalp (n=9)	Combined (n=18)
Mean Age (SD), years	71.1 (6.92)	61.8 (9.58)	66.4 (9.42)
Gender: Female, n (%)	3 (33.3)	0	3 (16.7)
Male, n (%)	6 (66.7)	9 (100)	15 (83.3)
Race: White, n (%)	9 (100)	9 (100)	18 (100)
Ethnicity, n (%)			
Hispanic or Latino	0	2 (22.2)	2 (11.1)
Not Hispanic or Latino	9 (100)	7 (77.8)	16 (88.9)
Fitzpatrick Skin Type,[a] n (%)			
I	2 (22.2)	2 (22.2)	4 (22.2)
II	2 (22.2)	2 (22.2)	4 (22.2)
III	5 (55.6)	4 (44.4)	9 (50.0)
IV	0	1 (11.1)	1 (5.6)
Mean (SD) Baseline AK lesion count	8.4 (2.46)	7.9 (2.52)	8.2 (2.43)

[a]Type I: always burns easily, never tans; Type II: always burns easily, tans minimally; Type III: burns moderately, tans gradually; Type IV: burns minimally, always tans well. AK, actinic keratosis; SD, standard deviation.

Pharmacokinetics

Tirbanibulin

- Using an LC-MS/MS bioanalytical assay (lower limit of quantification [LLOQ] of 0.01 ng/mL), all subjects had measurable but low concentrations of tirbanibulin at troughs (**Figure 1**).
- By the observed C_{trough} plateau, the pre-dose concentration C_{trough} data demonstrated that steady-state was achieved following the third dose (72 hours) of once-daily, 5 days of dosing.
- On Day 5, mean (SD) C_{max} was 0.258 (0.231) ng/mL (0.598 nM), median t_{max} was 6.91 h, and mean (SD) $AUC_{0\text{-}24h}$ was 4.09 (3.15) ng·h/mL (**Table 2**).

Tirbanibulin metabolites

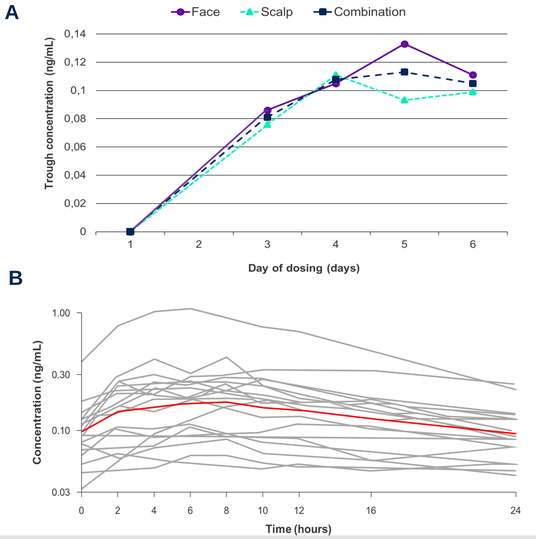
- For the majority of subjects, plasma concentrations for the main tirbanibulin metabolites KX2-5036 (n=14/18) and KX2-5163 (n=13/18) were below the LLOQ of 0.05 ng/mL.

Table 2. Tirbanibulin plasma PK parameters following 5 days of consecutive topical dosing

	Face (n=9)	Scalp (n=9)	Combined (n=18)
Mean (SD)			
C_{max} (ng/mL)	0.340 (0.297)	0.176 (0.102)	0.258 (0.231)
t_{max}[a] (h)	6.0 (2.0, 9.8)	7.8 (2.0, 10.0)	6.91 (2.0, 10.0)
$AUC_{0\text{-}24}$ (h*ng/mL)	5.0 (3.9)	3.18 (1.92)	4.09 (3.15)

[a]For t_{max}, median (min, max) are reported. $AUC_{0\text{-}24}$, area under the curve from 0-24 hours; C_{max}, maximum plasma concentration; PK, pharmacokinetic; t_{max}, time of maximum concentration.

Figure 1. (A) Mean trough plasma concentrations of tirbanibulin at Days 1, 3, 4 and 5; (B) Individual plasma concentrations of tirbanibulin with overall mean on Day 5 post-dose



Safety

Adverse events

- Four subjects (face, n=1; scalp, n =3) experienced a total of 5 treatment-emergent AEs (TEAEs); all were unrelated to treatment.
- One subject in the scalp-treated group experienced a treatment-related TEAE (mild skin dryness; resolved spontaneously).
- There were no serious AEs, severe AEs, deaths or TEAEs leading to study discontinuation.

Local skin reactions

- LSRs on the treatment area were mostly transient, all were mild-to-moderate erythema and flaking/scaling that peaked around Day 8 (mean [SD] composite score: 3.4 [1.76]) before resolving or returning to baseline.

CONCLUSIONS

- Under maximal use conditions, low systemic exposure of tirbanibulin with subnanomolar plasma concentrations for both parent drug and metabolites was confirmed.
- Tirbanibulin ointment 1% for 5 days was well tolerated for the treatment of AK on the face/balding scalp.

REFERENCES

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