# A RANDOMIZED, CONTROLLED PHASE I STUDY TO EVALUATE THE SENSITIZING POTENTIAL OF TIRBANIBULIN OINTMENT 1% 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]
- All substances that come into contact with human skin must be evaluated for the potential to cause irritation and/or sensitization as repeat exposure in a sensitized individual can result in an inflammatory reaction (allergic contact dermatitis)[2]
- Here, we report results from a Phase I, randomized, single-center, controlled, evaluator-blinded, within-subject comparison study (KX01-AK-006) evaluating the sensitizing potential of tirbanibulin ointment 1%. Results showed that tirbanibulin ointment 1% did not induce contact sensitization and was not associated with any systemic adverse events (AEs) but did result in local application site irritation

## OBJECTIVES

- The primary objective was to determine the potential of tirbanibulin to induce sensitization by repeated topical application to the skin of healthy subjects using a standard human repeat insult patch test (RIPT) design
- Safety was assessed by the reporting of AEs

## METHODS

### Study design

- Healthy adults (aged ≥18 years) of any Fitzpatrick Skin Type or race were enrolled in the study
- Prior to selecting dosing conditions for this RIPT study, a pilot study of the tolerability of tirbanibulin under occlusive, semi-occlusive, and open conditions was conducted. Results supported the use of open-patch conditions for the RIPT study
- Tirbanibulin ointment 1%, vehicle, and 0.9% saline (negative control) were applied to three adjacent, randomly assigned, 2 $cm^2$ sites on either the left or right side of the infrascapular area of a subject's back under open patch conditions and left in place for 48–72 hours
- Subjects received 10 applications of test product over approximately 6–8 weeks: nine during the Induction Phase (3 per week), followed by a rest period of 10–14 days, and one application for 48 hours to a naïve site on the opposite side of the back during the Challenge Phase
- Sites were evaluated prior to application during the Induction Phase and at 30 minutes, 24, 48, and 72 hours following removal during the Challenge Phase

### Study evaluations

- All randomized subjects who completed the Induction Phase (nine treatment applications plus a minimum of eight post-baseline evaluations) were included in the Cumulative Irritancy Population, and all subjects who completed both the Induction Phase and Challenge Phase (one treatment application plus all four evaluations) were included in the Sensitization Population
- A trained evaluator blinded to the treatment graded dermal reactions that included erythema, papules, edema, vesicular eruptions, glazed appearance, peeling/cracking/fissures, serous exudate, petechial erosions and scabs following each application
- Response grades were assigned to numerical scores per protocol for statistical analyses and decisions on discontinuations (score ≥3) of a treatment site
- The total cumulative irritation score for each subject and product were calculated by summing each subject's nine scores across the Induction Phase. Mean cumulative irritancy was defined as the average of the total cumulative irritation scores during the Induction Phase
- The Safety Population used for AE analysis was all randomized subjects who received at least one application of any study product

## RESULTS

### Baseline characteristics

- Of the 298 subjects screened, 261 were randomized and received at least one treatment application (tirbanibulin, n=198; vehicle and saline, n=231)
- In total, 232 (88.9%) and 229 (87.7%) subjects were included in the Cumulative Irritancy Population and the Sensitization Population, respectively
- Subjects that were discontinued from the study (n=32) were either lost to follow-up (n=16), voluntarily withdrew from the study (n=14), or were discontinued due to an AE or serious AE (SAE) unrelated to treatment (n=2)
- Subject demographics and baseline characteristics are presented in **Table 1**

### Table 1. Summary of subject demographics and baseline characteristics

| | Safety Population[a] (N=261) | Cumulative Irritancy Population[b] (N=232) | Sensitization Population[c] (N=229) |
|---|---|---|---|
| Mean (SD) age, years | 46.7 (15.3) | 48.1 (15.0) | 48.2 (15.0) |
| Gender, n (%) | | | |
| Female | 204 (78.2) | 183 (78.9) | 180 (78.6) |
| Male | 57 (21.8) | 49 (21.1) | 49 (21.4) |
| Race, n (%) | | | |
| White | 149 (57.1) | 132 (56.9) | 132 (57.6) |
| Asian | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Black or African American | 110 (42.1) | 98 (42.2) | 95 (41.5) |
| Multiracial: Black or African American and White | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 52 (19.9) | 44 (19.0) | 44 (19.2) |
| Not Hispanic or Latino | 209 (80.1) | 188 (81.0) | 185 (80.8) |
| Fitzpatrick Skin Type,[d] n (%) | | | |
| I | 7 (2.7) | 6 (2.6) | 6 (2.6) |
| II | 76 (29.1) | 70 (30.2) | 70 (30.6) |
| III | 58 (22.2) | 51 (22.0) | 51 (22.3) |
| IV | 52 (19.9) | 47 (20.3) | 47 (20.5) |
| V | 58 (22.2) | 49 (21.1) | 47 (20.5) |
| VI | 10 (3.8) | 9 (3.9) | 8 (3.5) |

[a]The Safety Population contained all randomized subjects who received at least one application of study product
[b]The Cumulative Irritancy Population included all randomized subjects who completed the Induction Phase
[c]The Sensitization Population included all subjects who completed the Induction and Challenge Phases
[d]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; Type V: rarely burns, tans very well; Type VI: never burns, deeply pigmented
SD, standard deviation

### Sensitization outcomes

- At the Challenge Phase, maximum dermal response scores of 1 and 2 were reported for 33 (14.4%) and 5 (2.2%) subjects treated with tirbanibulin, respectively (**Table 2**)
- A maximum dermal response score of 2 was reported for one (0.4%) vehicle-treated subject; no subjects had a maximum score of 1 or 2 at the saline patch site (**Table 2**)
- No subject had a maximum response score of 3 at any treatment site, therefore none met the criteria for possible sensitization (erythema, papules, edema or vesicular eruption)

### Irritancy outcomes

- Irritation scores of sites treated with tirbanibulin were greater compared with sites treated with vehicle or saline (p<0.0001; **Table 3**)

### Safety

- In total, 22 AEs were reported in 21 subjects; no AEs were treatment-related
- The most frequently reported AEs were headache (n=7 [2.7%]: 1 mild, 5 moderate, 1 severe), nasopharyngitis (n=6 [2.3%]: 4 mild, 2 moderate), and rhinorrhea (n=3 [1.1%]: all mild)
- One subject reported an SAE of mild dyspnea and one subject discontinued due to an AE of moderate nausea. Both AEs resolved and were not related to the study drug

### Table 2. Summary of sensitization potential during the Challenge Phase (Sensitization Population, N=229)

| Number of subjects, n (%) | Tirbanibulin | Vehicle | Saline |
|---|---|---|---|
| Response Score of 1[a,b] | 33 (14.4) | 0 | 0 |
| 95% confidence limit[c] | 10.13, 19.64 | 0, 1.60 | 0, 1.60 |
| Response Score of 2[d] | 5 (2.2) | 1 (0.4) | 0 |
| 95% confidence limit | 0.71, 5.02 | 0.01, 2.41 | 0, 1.60 |
| Response Score of 3[e] | 0 | 0 | 0 |
| 95% confidence limit | 0, 1.60 | 0, 1.60 | 0, 1.60 |
| Sensitization[f] | 0 | 0 | 0 |
| 95% confidence limit | 0, 1.60 | 0, 1.60 | 0, 1.60 |

[a]The denominator used for the percentage in this table is the total Sensitization Population
[b]Scores of 1 indicate minimal erythema, barely perceptible
[c]The 95% confidence limits are calculated using the Clopper-Pearson (exact) method
[d]Scores of 2 indicate definite erythema, readily visible; or minimal edema; or minimal papular response
[e]Scores of 3 indicate erythema and papules
[f]The recurrence of a cutaneous response of 3 or greater at Rechallenge equivalent to or more severe than that observed at Challenge was considered indicative of a sensitization reaction

### Table 3. Summary of mean and total irritation scores (Cumulative Irritancy Population, N=232)

| | Mean irritation score | | | | Total irritation score | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | LSM (SE) | B | C | Mean (SD) | LSM (SE) | B | C |
| A Tirbanibulin | 2.09 (0.66) | 2.09 (0.03) | <0.0001 | <0.0001 | 18.83 (5.96) | 18.83 (0.25) | <0.0001 | <0.0001 |
| B Vehicle | 0.06 (0.25) | 0.06 (0.03) | - | 0.282 | 0.56 (2.27) | 0.56 (0.25) | - | 0.288 |
| C Saline | 0.02 (0.09) | 0.02 (0.03) | | - | 0.19 (0.84) | 0.19 (0.25) | | - |
| p-value for overall F test | <0.0001 | | | | <0.0001 | | | |

p-values are from pairwise comparison of products from the analysis of variance with main effects of subject and product using Fisher's least significant differences; Significant difference in cumulative irritation score between products with p<0.05
LSM, least square mean; SD, standard deviation; SE, standard error

## CONCLUSIONS

- Tirbanibulin ointment 1% did not induce contact sensitization and was not associated with any systemic AEs but did result in local application site irritation

## REFERENCES

1. Smolinski MP, et al. *J Med Chem*. 2018;61:4704-4719
2. Gilmour N, et al. *Contact Derm*. 2019;80:195-200

## DISCLOSURES

This study is sponsored by Athenex, Inc. Authors are either investigators (JD), consultants (JF) or employees (DC) of Athenex, Inc.

## ACKNOWLEDGMENTS

Editorial support, under the direction of the authors, was provided by Gemma Fisher, BSc, of CMC AFFINITY, a division of McCann Health Medical Communications Ltd, Glasgow, UK, in accordance with Good Publication Practice (GPP3) guidelines and funded by Almirall, SA.

**Presented at the Fall Clinical Dermatology Conference®, October 17–20, 2019, Wynn Hotel, Las Vegas, NV, USA**