Initial results of a phase 1 trial of PRA-523 for pruritus secondary to atopic dermatitis

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Introduction: Chronic itch treatment is critical in caring for atopic dermatitis (AD) patients, but current treatments offer insufficient or delayed itch relief. Non-histaminergic pruritus involves elevated cutaneous serotonin (5-HT), activating neuronal 5-HT_7 receptors which trigger co-expressed transient receptor potential ankyrin 1 (TRPA1) calcium-flux-mediated itch.

Objectives: This trial investigated the safety, tolerability, and antipruritic activity of topical PRA-523, a selective 5-HT_7 receptor antagonist, in patients with AD.

Methods: This Phase 1 analysis of an ongoing, randomized, double-blind, vehicle-controlled first-in-human Phase 1/2a trial evaluated PRA-523 versus vehicle in 15 participants with AD (validated Investigator Global Assessment for AD ≥2, Peak Pruritus Numeric Rating Scale (PP-NRS) ≥4, 2–25% Body Surface Area). During twice-daily dosing for 28 days, participants were evaluated weekly in clinic. Treatment emergent adverse events (TEAEs) and relationship to PRA-523 or vehicle, and changes from baseline in vital signs, ECG parameters and laboratory values were evaluated. On weekly visit days, modified PP-NRS (mPP-NRS) scores were measured at decelerating post-dose intervals to determine onset of "No Itch" (mPP-NRS 0–1) and change in mPP-NRS itch score levels.

Results: TEAEs occurred in 8/15 (53%) of participants. All TEAEs were mild or moderate and none were related to treatment. No serious adverse events occurred. There were no clinically significant trends identified in vital signs, ECGs, hematology, clinical chemistry, or

urinalysis. In 14 evaluable participants (PRA-523, n=10; vehicle, n=4), No Itch was achieved in 50–70% of participants in the treatment group across all visits and in 0% of participants in the vehicle group at all visits except at week 3 where 1 out of 4 participants (25%) achieved No Itch (Table 1). Summed across all visits, 31 out of 50 (62%) participant-visits in the treatment group achieved No Itch, versus 1 out of 19 (5%) participant-visits in the vehicle group. A 4-point reduction in mPP-NRS scores was achieved within a median of 15–30 minutes of dosing in the treatment group across all visits, while a 4-point reduction was inconsistent and variable in the vehicle group (with a median of 15, 60 or 240 minutes at weeks 1, 2 and 5, respectively) (Table 1).

Conclusions: Topical administration of PRA-523 cream was well-tolerated following twice-daily dosing for up to 28 days. The data demonstrated rapid onset of pruritus control and consistent pruritus control across repeat doses. By targeting the 5-HT_7 receptor and TRPA1 ion channel, topical PRA-523 utilizes a novel mechanism of action that could provide faster, superior itch relief for AD patients. Funding: Praeventix, Inc.

Table 1:

Pruritus Control Value of '0' or '1' at any mPP-NRS timepoint (n) Median time in minutes to 4-point reduction (n)			
		PRA-523	**Vehicle**
Visit 2 (Week 1)	Value of '0' or '1'	70% (7/10)	0% (0/4)
	4-point reduction	30' (7/10)	15' (1/4)
Visit 3 (Week 2)	Value of '0' or '1'	70% (7/10)	0% (0/3)
	4-point reduction	30' (5/10)	60' (1/3)
Visit 4 (Week 3)	Value of '0' or '1'	50% (5/10)	25% (1/4)
	4-point reduction	30' (5/10)	not achieved (0/4)
Visit 5 (Week 4)	Value of '0' or '1'	60% (6/10)	0% (0/4)
	4-point reduction	15' (5/10)	not achieved (0/4)
Visit 6 (Week 5)	Value of '0' or '1'	60% (6/10)	0% (0/4)
	4-point reduction	15' (1/10)	240' (1/4)