Tradipitant Improves Worst Itch and Disease Severity in Patients with Chronic Pruritus Related to Atopic Dermatitis

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Background

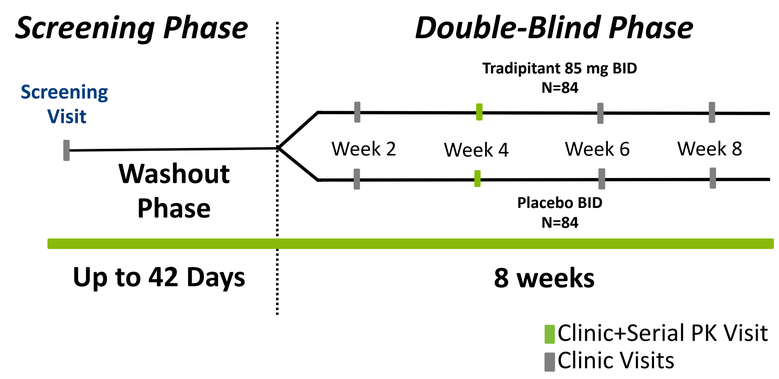
- Atopic dermatitis (AD) is a chronic inflammatory condition caused by a hypersensitivity reaction in the skin and is characterized by intense pruritus that is not relieved by scratching[1,2]
- Substance P (SP) and the neurokinin-1 receptor (NK1R) have been implicated in itch related to AD[3]
- Tradipitant is a potent and selective NK1R antagonist
- A previous study in chronic itch related to AD that is refractory to antihistamines and/or steroids showed a significant relationship between plasma concentration of tradipitant and reduction in itch
- This study, VP-VLY-686-2102, tested the efficacy of a higher daily dose of tradipitant (85 mg BID) in chronic itch associated with atopic dermatitis

Methods

Inclusion Criteria and Randomization

- Chronic (≥ 6 weeks) itch related to AD, refractory to treatment by patient history
- Average itch score by visual analog score (VAS) of ≥ 70 mm (out of 100 mm)
- Verbal response score (VRS) of ≥ 3 on at least 1 of the past 3 days prior to randomization.
- SCORAD of < 80
- Patients were randomized to either 85 mg tradipitant or placebo (1:1) BID

Figure 1. Study Design : Randomized, placebo-controlled, double-blind



Assessments of Pruritus

- Worst and Average itch severity by VAS every two weeks in the clinic
- VRS every two weeks in the clinic
- Twice-daily diary questionnaires to report worst and average itch by numeric rating scale (NRS)

Assessments of Disease

- SCORAD and EASI every two weeks
- Patient Benefit Index (PBI) and SKINDEX-16 scales
- Clinician Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C) for both itch and disease

Results

Table 1. Study Demographics

All Randomized Subjects	Tradipitant (N=84)	Placebo (N=84)	Total (N=168)
Gender - n (%)			
Male	32 (38.1)	31 (36.9)	63 (37.5)
Female	52 (61.9)	53 (63.1)	105 (62.5)
Age (years)			
Mean (min,max)	41 (18,66)	39 (18,64)	40 (18,66)
Race - n (%)			
White	49 (58.3)	57 (67.9)	106 (63.1)
Black or African American	24 (28.6)	18 (21.4)	42 (25.0)
Asian	6 (7.1)	5 (6.0)	11 (6.5)
American Indian or Alaska Native	0	1 (1.2)	1 (0.6)
Native Hawaiian or Other Pacific Islander	2 (2.4)	0	2 (1.2)
Other	3 (3.6)	3 (3.6)	6 (3.6)
Itch VAS			
Average Mean (SD)	81.3 (10.8)	80.3 (8.7)	80.8 (9.8)
Worst Mean (SD)	85.1 (10.0)	82.7 (10.0)	83.9 (10.0)
SCORAD			
Mean (SD)	47.4 (13.0)	45.7 (13.7)	46.5 (13.3)

Table 2. Intent-to-Treat Analysis at Week 8

Continuous	ITT population			
Analyses performed using MMRM		Tradipitant	Placebo	p-value
A. Itch Outcomes	Average Itch VAS	-41.5	-35.8	0.306
	Worst Itch VAS	-44.2	-30.6	**0.019**
	Worst Itch NRS Night	-3.4	-2.4	**0.029**
	Worst Itch NRS Day	-3.3	-2.5	0.074
B. Disease Outcomes	SCORAD Total	-21.3	-13.6	**0.008**
	Objective SCORAD	-13.3	-7.2	**0.005**
	Subjective SCORAD	-8.1	-6.7	0.157
C. General Impression Outcomes	CGI-C	2.6	3.3	**0.007**
	PGI-C Itch	2.6	3.2	**0.025**
	PGI-C AD	2.7	3.4	**0.007**
D. Quality of Life Outcomes	PBI	1.7	1.2	**0.038**
	SKINDEX 16	-34.8	-26.6	0.102

Categorical	ITT population			
Analyses performed using Fisher's Exact test		Tradipitant	Placebo	p-value
A. Itch Outcomes	Worst Itch VAS ≥ 40	52.60%	34.70%	**0.037**
	Worst Itch VAS ≥ 30	56.60%	38.90%	**0.049**
B. Disease Outcomes	SCORAD ≥ 50%	44.00%	20.80%	**0.004**
	EASI ≥ 75%	21.10%	11.10%	0.067

Result Summary

- Primary endpoint of average itch measured by VAS failed to meet significance
- Worst itch measured by VAS and multiple other measures of itch showed statistically significant, clinically meaningful improvement (**Table 2, Figure 3**)
- Disease severity scores showed statistically significant, clinically meaningful improvement (**Table 2, Figure 4**)
- No serious adverse events (AEs) reported in the study
- There were no significant differences in the total number treatment emergent AEs (tradipitant *n*=65, placebo *n*=61)
- The majority of treatment emergent AEs were mild to moderate; severe treatment emergent AEs were reported in 1 tradipitant treated patient and 2 placebo treated patients
- No common treatment emergent AEs were identified in the treatment arm as defined by >5% incidence and having a higher frequency than placebo

Figure 2. Patient Disposition

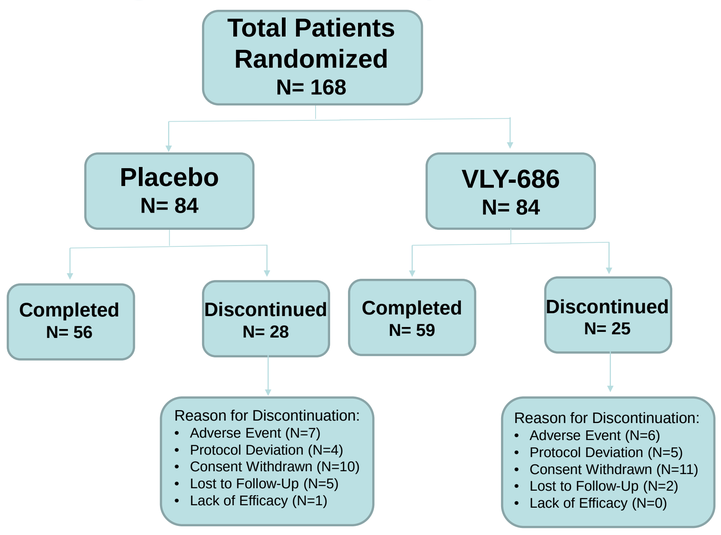


Figure 3. Time Progression - Itch

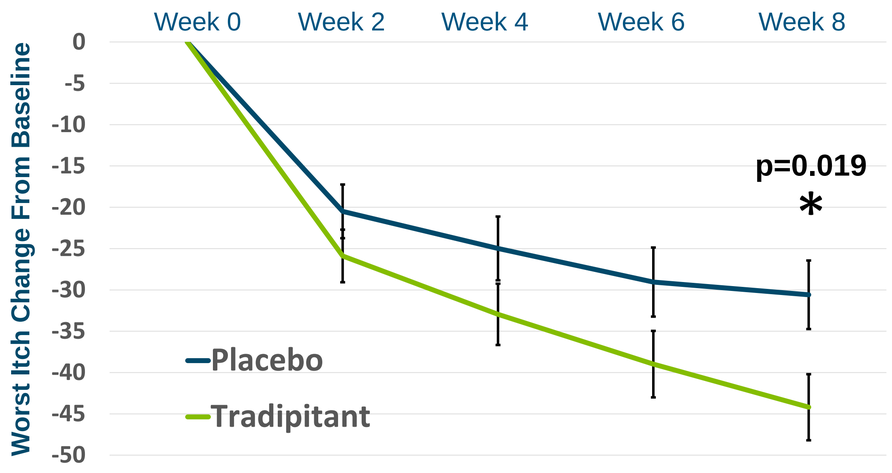
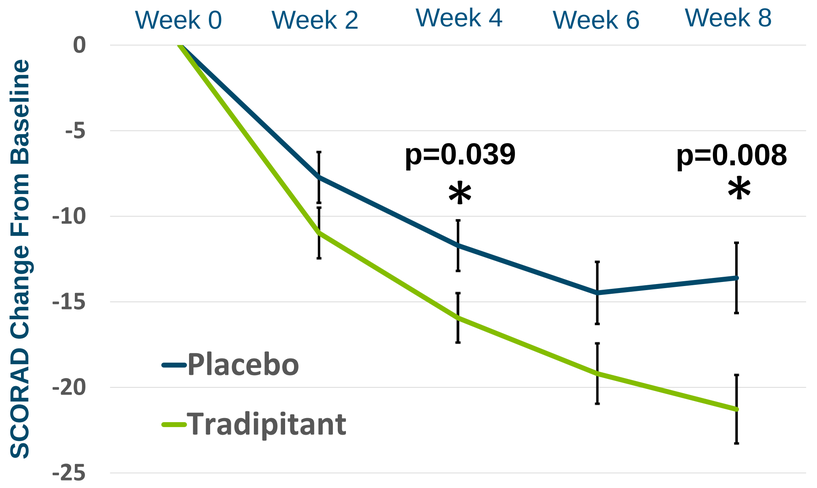


Figure 4. Time Progression - Disease



Conclusions

- **Tradipitant demonstrates efficacy in reducing the severity of a number of measures of pruritus and disease in patients with atopic dermatitis**
- **Tradipitant was safe and well tolerated**
- **Tradipitant, a potent and selective NK1R antagonist, may represent a potential novel treatment for patients with atopic dermatitis**

References

1. Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. Am Fam Physician 2012; 86(1):35-42.
2. Raap U, Stander S, Metz M. Pathophysiology of itch and new treatments. Curr Opin Allergy Clin Immunol 2011; 11(5):420-427.
3. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of Chronic Pruritus in Atopic Dermatitis: Getting the Itch Out? Clin Rev Allergy Immunol. 2016 Dec; 51(3):263-292.

Acknowledgements

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