Differential Effect Size of Tradipitant in Atopic Dermatitis According to Baseline IgE Levels

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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
- 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
- IgE levels have been associated with the etiology of AD[4]
- More recently, IgE levels have been used to further classify AD into subtypes[5]
- Given this, we prospectively collected baseline IgE samples in all patients from VP-VLY-686-2102 knowing this would allow us to extensively explore the role of IgE levels at baseline and response to treatment in terms of disease severity and worst pruritus

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

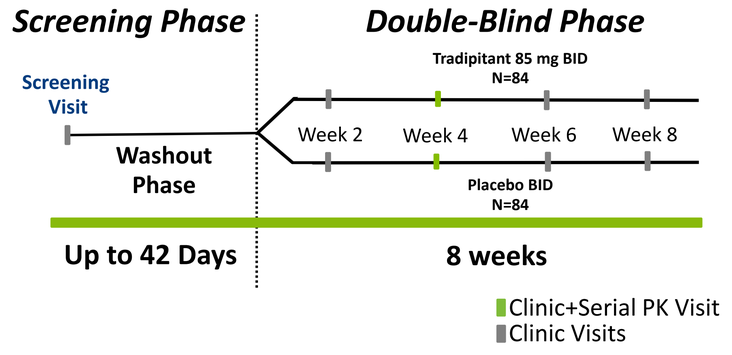
Assessments of Pruritus

- 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

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



Baseline IgE Collection

- IgE was collected at randomization visit

Post-hoc IgE Analysis

- Baseline IgE levels were classified as high or low based on a threshold value of 100 kU/L

Results

Figure 1. Time course of response for Worst Itch VAS and SCORAD in IgE subgroups

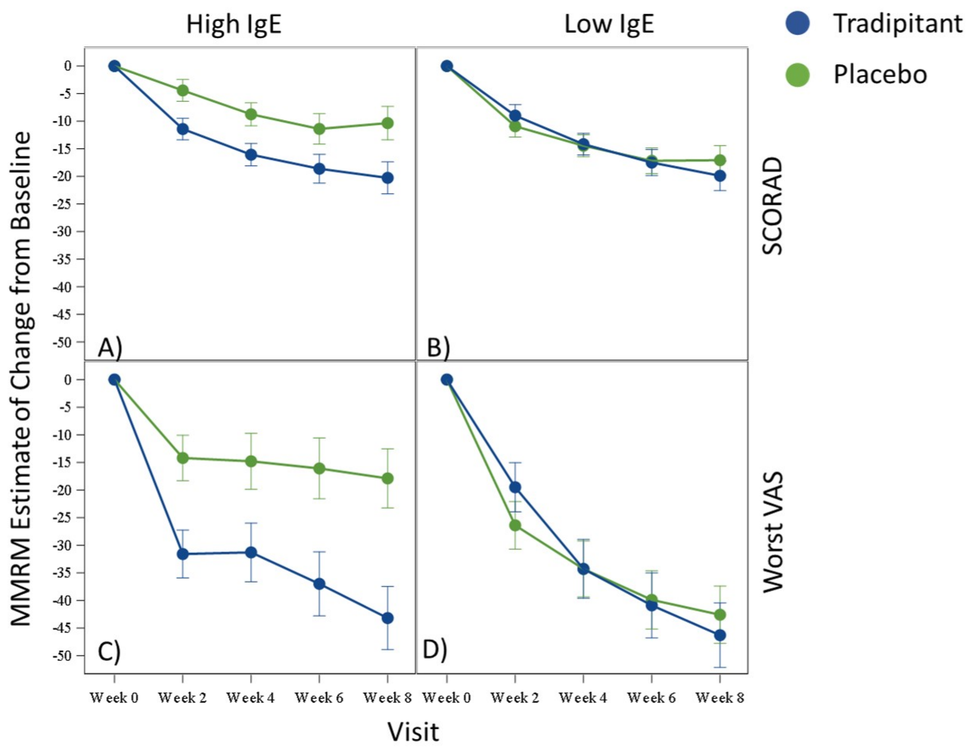


Figure 1. Increased response in the placebo arm observed in Low IgE atopic dermatitis patients. A) In the High IgE group SCORAD (disease severity) was significantly different in tradipitant treated patients compared to placebo treated patients, all time points are significantly different (p<0.05). B) In the Low IgE group an increased placebo response was seen in SCORAD. C) In the High IgE group Worst VAS (itch) was significantly different in tradipitant treated patients compared to placebo treated patients, all time points are significantly different (p<0.05). D) In the Low IgE group an increased placebo response was seen in Worst VAS.

Figure 2. Comparison of placebo response for Worst Itch VAS and SCORAD in Low and High IgE subgroups at week 8

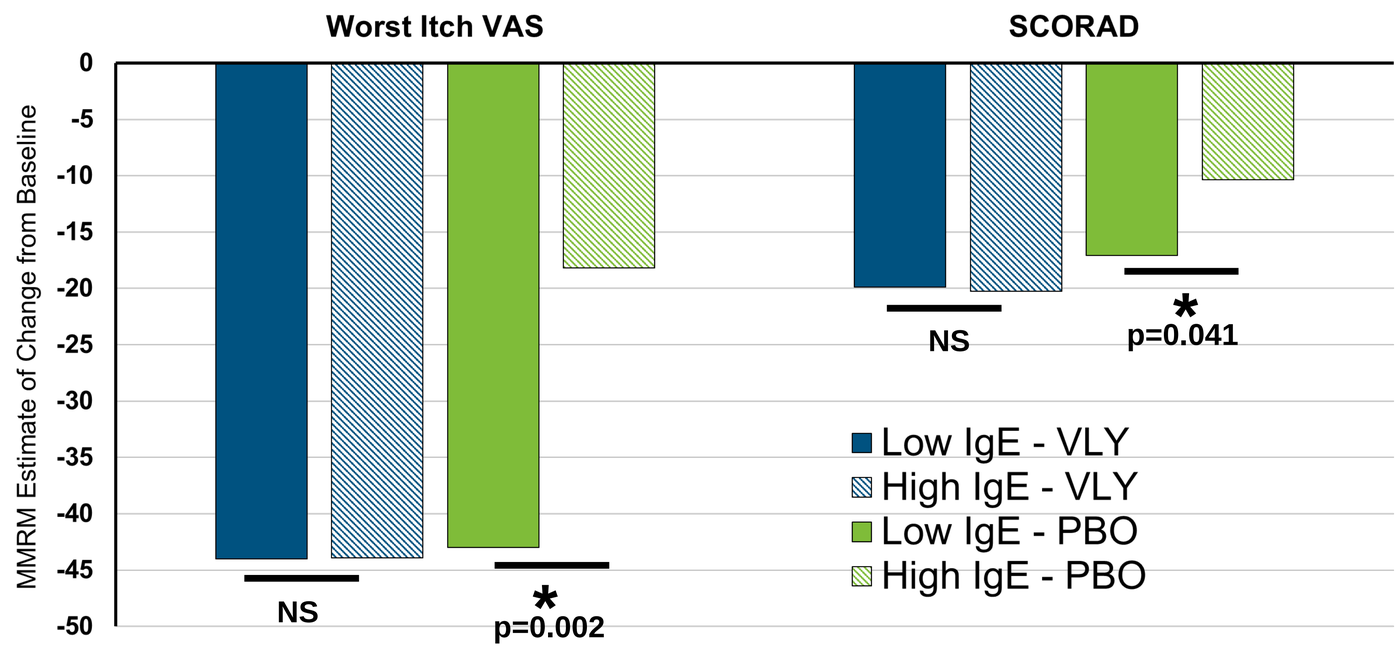


Figure 2. Increased placebo response at week 8 in placebo treated Low IgE Atopic Dermatitis Patients. No difference in treatment effect was seen in Worst Itch VAS and SCORAD in both Low and High IgE patients treated with tradipitant. The magnitude of change from baseline in the Low IgE placebo group was statistically higher than that of the High IgE placebo group at week 8 for both Worst Itch VAS and SCORAD. (Worst Itch VAS; p=0.002 and SCORAD; p=0.041)

Table 1. Baseline demographics

	Low IgE			High IgE		
	Tradipitant (N=36)	Placebo (N=34)	Total (N=70)	Tradipitant (N=38)	Placebo (N=37)	Total (N=75)
Gender - n (%)						
Male	15 (41.7)	11 (32.4)	26 (37.1)	16 (42.1)	14 (37.8)	30 (40.0)
Female	21 (58.3)	23 (67.6)	44 (62.9)	22 (57.9)	23 (62.2)	45 (60.0)
Age (years)						
Mean (min,max)	43.42 (14.2)	41.97 (13.3)	42.72 (13.7)	39.86 (12.7)	36.7 (13.6)	38.3 (13.1)
Itch VAS						
Average Mean (SD)	78.2 (10.0)	80.8 (8.3)	79.5 (9.2)	83.1 (11.6)	80.4 (9.0)	81.7 (10.4)
Worst Mean (SD)	82.61 (8.7)	82.90 (8.4)	82.75 (8.5)	86.79 (10.7)	82.79 (10.3)	84.82 (10.6)
SCORAD						
Mean (SD)	45.12 (12.9)	42.48 (12.8)	43.82 (12.8)	50.99 (13.02)	47.81 (14.0)	49.42 (13.5)

Table 2. IgE Analysis at Week 8

		ITT			High IgE		
Continuous		**Tradipitant**	**Placebo**	**p-value**	**Tradipitant**	**Placebo**	**p-value**
A. Itch Outcomes	Average Itch VAS	-41.5	-35.8	0.306	-41.9	-26.9	0.068
	Worst Itch VAS	-44.2	-30.6	**0.019**	-43.9	-18.2	**0.002**
	Worst Itch NRS Night	-3.4	-2.4	**0.029**	-3.8	-1.6	**0.001**
	Worst Itch NRS Day	-3.3	-2.5	0.074	-3.7	-1.6	**0.002**
B. Disease Outcomes	SCORAD Total	-21.3	-13.6	**0.008**	-20.3	-10.3	**0.022**
	Objective SCORAD	-13.3	-7.2	**0.005**	-11.7	-5.4	**0.049**
	Subjective SCORAD	-8.1	-6.7	0.157	-8.7	-5.6	**0.044**
C. General Impression Outcomes	CGI-C	2.6	3.3	**0.007**	2.6	3.5	**0.008**
	PGI-C ITCH	2.6	3.2	**0.025**	2.7	3.5	**0.045**
	PGI-C AD	2.7	3.4	**0.007**	3	3.9	**0.019**
D. Quality of Life Outcomes	PBI	1.7	1.2	**0.038**	1.7	0.99	0.051
Categorical							
A. Itch Outcomes	Worst Itch VAS ≥ 40	52.6%	34.7%	**0.037**	50.0%	21.6%	**0.016**
	Worst Itch VAS ≥ 30	56.6%	38.9%	**0.049**	57.9%	21.6%	**0.002**
B. Disease Outcomes	SCORAD ≥ 50%	44.0%	20.8%	**0.004**	47.4%	10.8%	**0.001**
	EASI ≥ 75%	21.1%	11.1%	0.067	23.7%	5.4%	**0.047**

Result Summary

- Primary endpoint of average itch measured by VAS failed to meet significance
- Worst itch measured by VAS and disease severity scores showed statistically significant, clinically meaningful improvement in the High IgE subgroup (**Table 2**)
- Increased response in the placebo arm was observed in Low IgE atopic dermatitis patients (**Figure 1**)
- Placebo response in both Worst Itch VAS and SCORAD was significantly increased in the Low IgE subgroup (**Figure 2**)
- 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)

Conclusions

- **Patients with Low IgE receiving placebo appear to have a significant response which may be a result of having a course of disease which seems to remit over the course of this 8 weeks study**
- **The response rate in patients receiving tradipitant was comparable in both IgE subgroup analyses**
- **Baseline IgE levels in AD patients represents a potentially useful enrichment factor for future clinical studies**
- **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.
4. Stone SPM, Muller SAM, Gleich GJ, Roches. IgE Levels in Atopic Dermatitis. Arch Dermatol. 1973 Dec; 108; 806-811.
5. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. J. Allergy Clin. Immunol. 2003 April; 112 (3):252-262.

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