TRADIPITANT
VP-VLY-686-3101

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY STUDY OF THE NEUROKININ-1 RECEPTOR ANTAGONIST VLY-686 IN PATIENTS WITH ATOPIC DERMATITIS

Document Type:	Clinical Study Protocol
Sponsor:	Vanda Pharmaceuticals Inc. 2200 Pennsylvania Ave. NW Suite 300E Washington, DC 20037 USA
Study Product:	tradipitant (VLY-686)
Protocol Number:	VP-VLY-686-3101
Study Phase:	III
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SYNOPSIS

Name of Sponsor/Company:
Vanda Pharmaceuticals Inc.

Name of Investigational Product:
tradipitant (VLY-686)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Efficacy Study of the Neurokinin-1 Receptor Antagonist VLY-686 in Patients with Atopic Dermatitis

Study center(s): Multicenter in North America

Studied period:	**Phase of development:**
Date first patient enrolled: July 2018 Estimated study duration: 6 months	III

Number of patients (planned):

Approximately 350 patients randomized (175 per arm, 1:1 randomization scheme), diagnosed with atopic dermatitis with treatment-resistant pruritus (i.e. pruritus duration of > 6 weeks despite the use of antihistamines or corticosteroids)

Inclusion Criteria:

1. Ability and acceptance to provide written informed consent; and sufficiently fluent in English to participate in the trial;
2. Male and non-pregnant, non-lactating female patients aged 18 – 70 years (inclusive);
    a. *Note: Principal investigators are advised to enroll a patient population that reflects the demographics of the overarching United States population. Demographics in this context refer to age, sex, race, and ethnicity.*
3. Diagnosed with atopic dermatitis
    a. ≥ 1% body surface area (BSA) of AD involvement at the screening and baseline visits;
    b. Presence of excoriations at screening and baseline visits (i.e. SCORing Atopic Dermatitis index excoriation score > 0)
    c. *Note: Principal investigators are advised to enroll a patient population that reflects the severity distribution of the overarching atopic dermatitis population seen in the United States population. Severity in this context refers to mild, moderate, and severe atopic dermatitis.*
4. Suffering from chronic pruritus with pruritus being actively present for at least 6 weeks prior to screening despite the use of antihistamines or corticosteroids;
5. Worst Itch Numerical Rating Scale (WI-NRS) score ≥ 5 points at the screening and baseline visit;

6. Daily diary reporting Worst Itch Numerical Rating Score (WI-NRS) average score for maximum itch severity ≥ 7 points between screening and baseline visits;
    a. *Note: WI-NRS average score for maximum itch severity will be determined based on the average of the 50% worst daily NRS scores for maximum itch severity (the daily scores ranging from 0 to 10) during the screening period (between visits 1 and 2). A minimum diary compliance of 70% during the screening phase (between Visits 1 and 2) is required before randomization. For patients who do not have at least 70% diary compliance preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 45-day maximum duration for screening.*
7. Patients with Body Mass Index (BMI) of ≥18 and ≤40 kg/m^2 (BMI = weight (kg)/ [height (m)]^2);
8. Patients must agree to the following study restrictions:
    a. Males of procreative capacity (not surgically sterile) will use an acceptable method of contraception from randomization through 1 month following the last dose of study medication. Examples of acceptable contraception for males include abstinence, use of a barrier method, or surgically-sterilized or post-menopausal partner.
    b. Females of child-bearing potential (not surgically sterile or post-menopausal, defined as 12 months with no menses without a medical cause) will use an acceptable method of contraception from the earlier of screening or 1 month prior to randomization through 1 month after the last dose of study medication. Examples of acceptable methods of contraception for females include abstinence, the use of 2 independent barrier methods, hormonal contraception plus 1 barrier method, or surgically sterilized partner.
9. Willing and able to comply with all study requirements and restrictions;
10. Willing to not participate in any other interventional trial for the duration of their participation;
11. Patients must be in good health as determined by past medical history, physical examination, electrocardiogram, clinical laboratory tests, and vital signs.

Exclusion Criteria:

1. Chronic pruritus due to condition other than atopic dermatitis (AD);
2. Superinfection of AD;
3. Unwilling or unable to follow medication restrictions described in Section 7.2, or unwilling or unable to sufficiently washout from use of restricted medication.
4. Under medical treatment for a skin disease with a therapy listed in the prohibited medications section in Table 3 that may influence the results of the study;
5. Have been treated with the following therapies:

a. An investigational drug, including placebo, within 8 weeks or within 5 half-lives (if-known), whichever is longer, prior to the baseline visit or
b. A biologic for less than 5 half-lives (if known) or 16 weeks prior to the baseline visit

6. Recent history (within six months of screening) of drug or alcohol abuse as defined in DSM-5 Diagnostic Criteria for Drug and Alcohol Abuse and/or a positive drug or alcohol screen at the Screening visit and Baseline;
7. Patient has ever made a suicide attempt and/or had suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) or patient is at risk of suicide at Screening or Baseline, in the opinion of the Investigator;
8. Any medical procedure requiring general anesthetic within three months of the Baseline Visit or any procedure requiring sedation within one month of the baseline visit;
9. Current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal, gastrointestinal or metabolic dysfunction unless currently controlled and stable, including (but not limited to) the following:
    a. Uncontrolled diabetes mellitus defined as HbA1c >7%;
    b. Positive hepatitis C antibody test (anti-HCF);
    c. Positive hepatitis B surface antigen (HBsAg);
10. History (including family history) or current evidence of congenital long QT syndrome or known acquired QT interval prolongation;
11. History of intolerance and/or hypersensitivity to medications similar to tradipitant and its accompanying excipients;
12. Indication of impaired liver function (values for AST, ALT, or bilirubin > 2 times the Upper Limit of Normal (ULN);
13. Has a creatinine level > 1.25x ULN
14. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress;
15. Any other sound medical reason as determined by the Investigator including any condition which may lead to an unfavorable risk-benefit of study participation, may interfere with study compliance or may confound study results.

Investigational product, dosage and mode of administration:

A single oral capsule of tradipitant 85 mg or matching placebo will be orally administered twice daily for a total daily dose of 170 mg.

Duration of treatment (Randomization Phase): 8 weeks

Reference therapy, dosage and mode of administration:

Placebo capsules will be provided in size and appearance identical to those containing VLY-686 and will be administered orally.

Objectives:

Primary Objective:

- To evaluate the efficacy of VLY-686 in reducing worst itch in patients with chronic pruritus in atopic dermatitis as measured by Worst Itch Numerical Rating Scale (WI-NRS) at Week 8.

Secondary Objectives:

- To evaluate the efficacy of VLY-686 in improving disease severity in patients with atopic dermatitis as measured by the validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD).
- To evaluate the efficacy of VLY-686 in improving disease severity in patients with atopic dermatitis as measured by the SCORing Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI).
- To evaluate the proportion of patients with improvement of WI-NRS $\geq$ 4-point reduction.
- To evaluate the proportion of patients with improvement on SCORAD index of at least 50%, 75% or 90% improvement.
- To evaluate the proportion of patients with improvement on the EASI of at least 50%, 75% or 90% improvement.
- To assess the efficacy of tradipitant on global measures of improvement as measured by Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C).
- To assess the efficacy of tradipitant on quality of life as measured by the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Healthly Days Core Module (4 questions) (HRQOL-4), Insomnia Symptom Questionnaire (ISQ) and Patient Benefit Index - Pruritus (PBI-P).
- To explore the safety and tolerability of multiple oral doses of VLY-686.

Pharmacogenomic Sub-Study:

- Identify genetic markers that correlate with response to tradipitant treatment.
- Identify genetic markers that correlate with adverse events that may occur upon treatment with tradipitant.
- To identify genetic markers that are associated with atopic dermatitis and/or pruritus and disorders/diseases associated with NK-1 receptors.
- To identify genetic markers that are associated in the metabolism, distribution, and/or excretion of tradipitant and its metabolites.

Overall Design:

This is multicenter, randomized, double-blind, placebo-controlled study to be conducted in the United States. Approximately Three Hundred and Fifty (350) patients diagnosed with atopic dermatitis, who satisfy the selection criteria for the study, will be randomized to receive either tradipitant 85 mg or matching placebo BID.

The study is divided into two phases: the pre-treatment phase and the evaluation phase. The pre-treatment phase includes a screening and a baseline visit where patients' eligibility for the study will be assessed. Washout of medications will occur during the screening phase.

The evaluation phase includes 8 weeks of randomized, double-blind, placebo-controlled treatment. In-clinic evaluations will occur at Screening, Baseline, and Weeks 2, 4, 6, and 8.

Criteria for evaluation:

Efficacy:

Efficacy assessments will include:

- Worst Itch Numerical Rating Scale (WI-NRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Eczema Area and Severity Index (EASI)
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Patient Benefit Index – Pruritus (PBI-P)
- Insomnia Symptom Questionnaire (ISQ)
- Healthly Days Core Module (4 questions) (HRQOL-4)

Safety:

- Safety and tolerability assessments will include the recording of adverse events (AEs), physical examinations, clinical laboratory evaluations, vital signs, and electrocardiograms.
- The Columbia-Suicide Severity Scale (C-SSRS) will be used to assess suicidal behavior and ideation.

Table 1: Schedule of Evaluations

Phase	Pre-Treatment		Evaluation			
Visit	V1 Screening	V2 Baseline	V3	V4	V5	V6
Study Day	Up to Day -45	Day 0	Day 14[1]	Day 28[1]	Day 42[1]	Day 56[1] or ET
Informed Consent Form (ICF)[2]	X					
Eligibility assessment	X	X				
Patient demography	X					
Medical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Adverse Event (AE) Assessment[3]	X	X	X	X	X	X
Serum β-HCG (for WOCBP)	X					X
Urine pregnancy test (for WOCBP)		X	X	X	X	
HbA1c	X					
Hepatitis B/C screen	X					
Drug and alcohol screen	X	X	X	X	X	X
Hematology, chemistry, and urinalysis	X	X		X		X
IgE collection	X	X	X	X	X	X
Cytokine Panel[4]	X					X
Filaggrin Analysis	X					X[5]
Pharmacogenetic (PG) sample	X					X[5]
Pharmacokinetic (PK) sample		X	X	X	X	X
Resting 12-lead ECG	X	X	X	X	X	X
Vital signs and body measurements[6]	X	X	X	X	X	X
Physical Examination (PE)[7]	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[8]	X	X	X	X	X	X
Medical History of Pruritus Questionnaire		X				
Medical History of Atopy Questionnaire	X					
Pruritus Assessment (incl. NRS, VRS)	X	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD) index	X	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X	X	X	X	X

Phase	Pre-Treatment		Evaluation			
Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**
Study Day	**Up to Day -45**	**Day 0**	**Day 14[1]**	**Day 28[1]**	**Day 42[1]**	**Day 56[1] or ET**
Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)	X	X	X	X	X	X
Patient Benefit Index – Pruritus (PBI-P)[9]		X	X	X	X	X
Patient Global Impression of Change (PGI-C)			X	X	X	X
Clinical Global Impression of Change (CGI-C)			X	X	X	X
Patient Oriented Eczema Measure (POEM)	X	X		X		X
Dermatology Life Quality Index (DLQI)	X	X	X	X	X	X
Insomnia Symptom Questionnaire (ISQ)	X	X		X		X
Healthy Days Core Module (4 questions) (HRQOL-4)	X	X		X		X
Daily Diary	◄———	———	———	———	———	———►
Photography		X		X		X
Randomization		X				
Study medication dispensation[10]		X	X	X	X	
Study medication collection & compliance			X	X	X	X
Daily diary distribution and instruction	X					
Patient daily diary review		X	X	X	X	X

1 within +/- 3 days

2 Informed Consent will be obtained prior to performance of any study procedure(s)

3 Adverse Event collection will begin at the time the ICF is signed

4 If V1 cytokine panel sample is missed, sample should be drawn at the next in-clinic visit.

5 Sample collected at V1. Sample collected at V6/EOS only if randomized under Protocol Amendment 1 and sample was not already collected at V2.

6 Body height will only be collected at screening (V1), body weight will be collected at visits 1, 2, and 6.

7 An abbreviated physcial axamination will be performed at V2 (Baseline) and post-baseline visits 3-5 ONLY if clinically indicated.

8 The Screening/Baseline C-SSRS will occur at V1 (Screening). The Since Last Visit C-SSRS will occur at all other visits.

9 At V2 (Baseline), the Patient Needs Questionnaire (PBI-P(PNQ)) will be administered. The Patient Benefits Questionaire (PBI-P(PBQ)) will be administered at subsequent visits.

10 Patients will be instructed to take their first dose of study medication on the evening of Day 0.

ET = Early Termination; WOCBP = Women of Child-bearing Potential; ECG = electrocardiogram; C-SSRS = Columbia Suicide Severity Rating Scale; NRS = Numeric Rating Scale; VRS = Verbal Response Scale; HbA1c= Haemoglobin A1c or glycated haemoglobin; IgE= Immunoglobulin E