TRADIPITANT
VP-VLY-686-2102

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF TRADIPITANT IN TREATMENT-RESISTANT PRURITUS ASSOCIATED 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-686-2102
Study Phase:	II
IND Number:	122741
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SYNOPSIS

Name of Sponsor/Company:
Vanda Pharmaceuticals Inc.

Name of Investigational Product:
Tradipitant (VLY-686)

Name of Active Ingredient:
{2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Tradipitant in Treatment-Resistant Pruritus Associated with Atopic Dermatitis

Study center(s): Up to 30 centers in the United States

Indication:	**Phase of development:**
Chronic pruritus in subjects with atopic dermatitis	II

Number of subjects (planned):
Approximately 164 subjects randomized (82 per arm, 1:1 randomization scheme)

Inclusion Criteria:

1. Male and non-pregnant, non-lactating female subjects aged 18 – 65 years (inclusive);
2. Diagnosed with atopic dermatitis
   a. with a SCORAD index ≤ 80 at the screening and baseline visits;
   b. with atopic lesion(s) present at the screening and baseline visits;
3. Suffering from chronic pruritus with pruritus being actively present for at least 6 weeks prior to screening despite the use of antihistamines or corticosteroids;
4. Average pruritus intensity (VAS) ≥70 mm (during one of the three days preceding the screening and baseline visits);
5. Patient assessment of pruritus (VRS (1-5) item “pruritus”) ≥3 at screening and baseline visits;
6. Subjects with Body Mass Index (BMI) of ≥18 and ≤35 kg/m^2 (BMI = weight (kg)/ [height (m)]^2);
7. Subjects must agree to the following study restrictions:
   a. Males of procreative capacity (not surgically sterile via vasectomy) 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 without menses) 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, or hormonal contraception plus 1 barrier method, or surgically sterilized partner.

8. Ability to provide written informed consent;
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. Subjects 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 that may influence the results of the study; or treatment with Cyclosporin A within the past 6 months.
5. Recent history (within six months of screening) of Alcohol Use Disorder or Substance Use Disorder as defined in DSM-5 or a positive drug screen at the Screening visit;
6. Subject 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 subject is at risk of suicide at Screening or Baseline, in the opinion of the investigator;
7. 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;
8. 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);
9. History (including family history) or current evidence of congenital long QT syndrome or known acquired QT interval prolongation;
10. Exposure to any investigational medication, including placebo, within 60 days of the Baseline Visit;
11. History of intolerance and/or hypersensitivity to medications similar to tradipitant and its accompanying excipients;

12. Participation in a previous tradipitant (LY686017 or VLY-686) trial;
13. Indication of impaired liver function (including values for AST, ALT, or bilirubin > 1.5 times the Upper Limit of Normal, unless isolated bilirubin > 1.5 x ULN due solely to Gilbert's syndrome);
14. Has a creatinine level > 1.25x ULN;
15. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress;
16. Any other reason as determined by the Investigator 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. Study medication should be administered with food.

Duration of treatment: 8 weeks

Objectives:

Primary:

- To evaluate the efficacy of tradipitant relative to placebo in reducing symptoms of chronic pruritus in subjects with atopic dermatitis

Secondary:

- To evaluate the efficacy of tradipitant relative to placebo in reducing chronic pruritus
- To evaluate the efficacy of tradipitant relative to placebo in reducing atopic dermatitis disease progression
- To evaluate the efficacy of tradipitant relative to placebo in reducing the severity of sleep disruption
- To assess the efficacy of tradipitant on global measures of improvement
- To assess the efficacy of tradipitant on quality of life
- To evaluate the relationship between tradipitant's pharmacokinetics and efficacy measurements
- To explore the safety and tolerability of multiple oral doses of tradipitant.

Optional Pharmacogenetic Sub-Study:

- To identify genetic markers that correlate with response to tradipitant treatment.
- To 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 a multicenter, randomized, double-blind, placebo-controlled study to be conducted in the United States. Approximately 164 subjects with treatment-resistant pruritus 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 subjects' eligibility for the study will be assessed. Washout of medications per Section 7.2 will occur during the screening phase. The evaluation phase includes 8 weeks of randomized double-blind treatment. In clinic evaluations will occur at Screening, Baseline, and Weeks 2, 4, 6, and 8.

Criteria for evaluation:

Efficacy:

Efficacy assessments will include:

- Daily Diary Itch Scale (DDIS)
- Pruritus Visual Analogue Scale (VAS)
- Verbal Rating Scale (VRS) item "pruritus"
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area Scoring Index (EASI)
- Daily Diary Sleep Scale (DDSS)
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Skindex-16
- Patient Benefit Index (PBI)

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.

Statistical methods:

Primary Endpoint:

- Mean change from baseline in pruritus symptoms in the tradipitant group versus the placebo group

Secondary Endpoints:

- Mean change from baseline in pruritus intensity in the tradipitant group versus the placebo group

- Mean change from baseline of disease severity in the tradipitant group versus the placebo group as measured by SCORing Atopic Dermatitis (SCORAD) index
- Mean change from baseline of disease severity in the tradipitant group versus the placebo group as measured by Eczema Area Scoring Index (EASI)
- Mean change from baseline in the daily diary sleep scale(DDSS) in the tradipitant group versus the placebo group.
- Mean global improvement measured by the Clinical Global Impression-Change (CGI-C), Patient Global Impression of Change (PGI-C), Skindex-16, and the Patient Benefit Index (PBI)
- Mean change from baseline in pruritus intensity in relation to serum concentrations of tradipitant and its metabolites.

Statistical analyses will be performed using two-sided tests. The details of analysis models will be specified in the SAP.

Table 1: Schedule of Evaluations

Phase	**Pre-Treatment**		**Evaluation**			
Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6 EOS or ET**
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				
Subject demography	X					
Medical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Adverse Event (AE) assessment	X[3]	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
Hematology, chemistry, and urinalysis	X	X		X		X
IgE		X				
Pharmacogenetic (PG) sample[4]		X				
Pharmacokinetic (PK) sample(s)		X	X[5]	X[6]	X[5]	X[5]
12-lead resting ECG	X	X	X	X	X	X
Vital signs and body measurements[7]	X	X	X	X	X	X
Physical Examination (PE)	X	X[8]	X[8]	X[8]	X[8]	X
C-SSRS[9]	X	X	X	X	X	X
Medical History of Pruritus Questionnaire		X				
Pruritus Assessment (incl. VAS, VRS)[10]	X	X	X[11]	X[12]	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X	X	X	X	X
Patient Benefit Index (PBI)[13]		X	X	X	X	X
Skindex-16		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
Randomization		X				
Study medication dispensation[14]		X	X	X	X	

Phase	**Pre-Treatment**		**Evaluation**			
Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6 EOS or ET**
Study Day	**Up to Day -45**	**Day 0**	**Day 14**[1]	**Day 28**[1]	**Day 42**[1]	**Day 56**[1] **or ET**
Study medication collection & compliance			X	X	X	X
Subject daily diary distribution and instruction	X[15]					
Subject daily diary review		X	X	X	X	X
Subject daily diary collection						X

EOS = End of Study; ET = Early Termination; WOCBP = Women of Child-bearing Potential; ECG = electrocardiogram; C-SSRS = Columbia Suicide Severity Rating Scale; VAS = Visual Analog Scale; VRS = Verbal Rating Scale

[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] The PG blood sample will only be collected for subjects consenting to the PG study.
[5] The PK sample collection should occur within 15 minutes following the pruritus assessment
[6] Multiple PK samples will be collected at V4. In-clinic dosing of study medication (morning dose) will occur at V4 following a pre-dose PK blood draw.
[7] Vital signs will be collected at all visits. Height will be collected at V1(Screening). Body weight will be collected at V1 (Screening), V2 (Baseline), and V6.
[8] An abbreviated physical examination may be performed at V2 (Baseline), V3, V4, and V5 if clinically indicated.
[9] The Screening/Baseline C-SSRS will occur at V1 (Screening). The Since Last Visit C-SSRS will occur at all other visits.
[10] The baseline pruritus assessment will be completed at V1 and V2. The post-baseline pruritus assessment will be completed at V3, V4, V5, and V6.
[11] At V3, V5, and V6, the Pruritus Assessment will be conducted between 2 and 4 hours post study drug administration
[12] At V4, the Pruritus assessment will occur at 03:00 (+/- 00:30) post in-clinic study drug administration
[13] At V2 (Baseline), The Patient Needs Questionnaire (PBI-PNQ) will be administered. The Patient Benefits Questionnaire (PBI-PBQ) will be administered at subsequent visits.
[14] Subjects will be instructed to take their first dose of study medication on the evening of Day 0.
[15] The subject diary will be completed for at least 7 days prior to randomization and the duration of the evaluation phase.