TRADIPITANT

AMENDMENT 1 TO VP-VLY-686-3102

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

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VP-VLY-686-3102, Amendment 1

Approved by the following:

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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 the United States

Studied Period:	**Phase of Development:**
Date first patient enrolled: October 2019 Estimated study duration: 1 year	III

Number of Patients (planned):

Approximately 200 patients randomized (100 per arm, 1:1 randomization scheme), diagnosed with mild atopic dermatitis with treatment-resistant pruritus (i.e. pruritus duration of at least 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. Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) rating of 1 or 2;
   c. Presence of excoriations at screening and baseline visits (i.e. SCORing Atopic Dermatitis index excoriation score > 0).
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 childbearing 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 screening visit or 1 month prior to randomization, whichever is earlier, 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. An AD or immune-related biologic for less than 5 half-lives (if known) or 16 weeks prior to the baseline visit.
c. *Note: For clarity, an example of such biologics would be drugs such as dupilumab (approved by the FDA for treatment of AD) and fezakinumab (a biologic being investigated in AD).*

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;
7. Patient has made a suicide attempt and/or had suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 2 years, 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. Randomization in a previous tradipitant clinical trial;
15. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress;
16. 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 orally administered twice daily.

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 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), Healthy 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 Two Hundred (200) patients diagnosed with mild atopic dermatitis, who satisfy the eligibility 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: **<u>Efficacy:</u>** 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) • Healthy Days Core Module (4 questions) (HRQOL-4) **<u>Safety:</u>** • 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.

1. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and specialist terms

Abbreviation	Description
ACE	Angiotensin converting enzyme
AD	Atopic Dermatitis
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (also known as SGPT)
Anti-HCF	Positive Hepatitis C Antibody Test
AST	Aspartate Aminotransferase (also known as SGOT)
$AUC_{0-\infty}$	Area under the concentration/time curve extrapolated to infinity
AUC_{0-24}	Area under the concentration/time curve extrapolated to 24 hours post dosing
BID	Twice a day
BMI	Body Mass Index
bpm	Beats per Minute
β-HCG	Beta-Human Chorionic Gonadotropin
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
CL/F	Oral Clearance
Cm	Centimeter
C_{max}	The highest observed plasma concentration
CMH	Cochran-Mantel-Haenszel test
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DDSS	Daily diary sleep scale
dL	Deciliter

Abbreviation	Description
DLQI	Dermatology Life Quality Index
DNDP	Division of Neuropharmacological Drug Products
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EASI	Eczema Area and Severity Index
EC	Ethical Committee
EC_{50}	Half maximal effective concentration
EC_{90}	90 percent effective concentration
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
e.g.	For example
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
g	Gram(s)
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
HbA1C	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HDPE	High-Density Polyethylene
HRQOL-4	Healthy Days Core Module (4 questions)
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ID	Identification
i.e.	In other words
IgE	Immunoglobulin E
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISQ	Insomnia Symptom Questionnaire

Abbreviation	Description
IWRS	Interactive Web Response System
kg	Kilogram
kU/L	Kilounits per Unit
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
m	Meters
mg	Milligram
min	Minute
mg	Milliliter
mL	Millimeter
mmHg	Millimeters of Mercury
MMRM	Mixed Effect Model Repeat Measurement
NDA	New Drug Application
NK	Neurokinin
NKA	Neurokinin A
NKB	Neurokinin B
NOAEL	No-Observed Adverse Effect Level
NRS	Numerical Rating Scale
OTC	Over the Counter
PA	Pruritus Assessment
PBI	Patient Benefit Index
PBQ	Patient Benefits Questionnaire
PD	Pharmacodynamic
PDE4	Phosphodiesterase-4 Inhibitor
PE	Physical Examination
PET	Positron Emission Tomography
PG	Pharmacogenetic
PGI-C	Patient Global Impression of Change
pH	Hydrogen ion concentration
PK	Pharmacokinetic

Abbreviation	Description
POEM	Patient-Oriented Eczema Measure
PNQ	Patient Needs Questionnaire
QT	Time Between the Start of the Q Wave and the End of the T Wave in the Heart's Electrical Cycle
RBC	Red blood cell
RO	Receptor Occupancy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCORAD	SCORing Atopic Dermatitis
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase (also known as AST)
SGPT	Serum Glutamic Pyruvic Transaminase (also known as ALT)
SOC	System Organ Class
SOPs	Standard Operating Procedures
SP	Substance P
$T_{1/2}$	Time Required for the Plasma Drug Concentration to Decrease by One Half
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach C_{max}
ULN	Upper Limit of Normal
UV	Ultraviolet
U.S.	United States
VAS	Visual Analogue Scale
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
VRS	Verbal Rating Scale
WBC	White Blood Cell
WI-NRS	Worst Itch Numerical Rating Scale
WOCBP	Women of Childbearing Potential

3. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to United States (U.S.) and international standards of Good Clinical Practice (GCP) (Food and Drug Administration [FDA] and International Conference on Harmonization [ICH] guidelines), applicable local government regulations, and Institutional research policies and procedures.

3.1. Background

Atopic dermatitis (AD) is a chronic inflammatory condition that affects people of all ages but is more prevalent in children. The prevalence of AD varies worldwide with incidence ranging from 1-20%. Some of the countries with the highest incidence of AD include Nigeria, the United Kingdom and New Zealand[1]. AD is caused by a hypersensitivity reaction in the skin and is characterized by intense pruritus that is not relieved by scratching[2,3]. Pruritus represents one of the most burdensome symptoms of AD and it has a dramatic impact on the individual's quality of life[3].

Currently, topical emollients, corticosteroids, calcineurin inhibitors, and systemic and ultraviolet phototherapy are used regularly for the treatment of AD[3,4]. More recently, topical PDE4 inhibitors and biologic treatments that directly target the immune component of AD have been developed. Despite the availability of these treatments, Wei et al. (2017) has reported that based on Eczema Area and Severity Index (EASI) 53% of clear/almost clear, 53% of mild, 62% of moderate, and 77% of severe/very severe AD patients report inadequate control of their AD[5]. The currently available therapies improve AD through clearing of the skin by targeting improvement in lesion severity. Targeting AD improvement through reduction in pruritus remains a significant unmet medical need. Therefore, tradipitant, an orally administered safe and well-tolerated systemic treatment, which improves AD through reduction in pruritus could fill this great need.

The mammalian tachykinins (neurokinin [NK]) are a family of peptide neurotransmitters that share a common C-terminal sequence. This group includes substance P (SP), neurokinin-A (NKA), and neurokinin-B (NKB). SP exerts its effects by binding to the NK-receptors: SP preferentially binds to the neurokinin type-1 (NK-1) receptor and, with lower affinity, to the NK-2 and NK-3 receptors. NK-1 receptor is expressed in the central nervous system (CNS) and the skin[6]. The SP receptor is a G protein-coupled receptor, which, upon binding of SP, activates several second messenger systems, protein kinases, and transcription factors including calcium, inositol triphosphate, p42/44 and p38 stress-regulated kinases, and protein kinase C[7–9]. SP is the most abundant NK and is involved in the regulation of many physiological processes. SP is believed to be a major mediator in the itching observed in atopic dermatitis. Thus, medications targeting the NK-1 receptor have good therapeutic potential for the treatment of pruritus.

A previous study utilizing aprepitant, an NK-1 receptor antagonist, revealed a novel mechanism through which binding of the NK-1 receptor could significantly decrease chronic pruritus in patients with therapy refractory pruritus[10]. In VP-VLY-686-2101, Vanda investigated a similar mechanism to assess the safety and efficacy of tradipitant, a potent NK-1 receptor antagonist, in treatment-resistant pruritus associated with AD. This was a 4-week randomized, double-blind, placebo-controlled study conducted in Germany using 100 mg tradipitant dosed once a day in the evening. Although this earlier study failed to demonstrate an overall intent-to-treat (ITT) population improvement in the primary endpoints, a subsequent planned analysis of

pharmacokinetic (PK) exposure-response relationship demonstrated a significant benefit on itch corresponding with highest exposure of tradipitant.

Following this finding of exposure-response relationship, study VP-VLY-686-2102 was designed and conducted to test a higher 170 mg daily dose (85 mg BID) in the treatment of pruritus in the atopic dermatitis population. This study was an 8-week, multi-center, randomized, double-blind, placebo-controlled study of 168 patients that completed in September 2017. In the study, patients were randomized (1:1) to either tradipitant 170 mg or placebo. Tradipitant was shown to improve itch and disease severity.

Tradipitant (VLY-686), formerly known as LY686017, is a potent and selective inhibitor of human cell membrane NK-1 receptor binding *in vitro*. Tradipitant is currently being assessed clinically to determine its efficacy in treating patients suffering from atopic dermatitis.

3.2. Tradipitant Relevant Data Summary

For a thorough review, refer to the tradipitant Investigator's Brochure.

3.2.1. Nonclinical Pharmacology and Toxicology

Several in vitro and in vivo safety pharmacology studies (in rodents and dogs) were performed to assess the effect of tradipitant on the cardiovascular (CV), gastrointestinal (GI), respiratory, and central nervous (CNS) systems. The safety parameters evaluated in these studies were also monitored clinically. It was concluded that secondary pharmacological effects related to CNS, respiratory, GI, or CV functioning would not be expected at clinical doses ≤800 mg.

Animal toxicology studies (a single-dose study in rats; a 13-week repeat-dose study in mice; 1-, 3-, and 6-month repeat-dose studies in rats; 1- and 3-month repeat-dose studies in dogs; a fertility and embryo-fetal development study in rats; an embryo-fetal development study in rabbits; and in vitro and in vivo genetic tests) showed no treatment-related mortality or marked toxicity up to and including the no-observed adverse effect level of dosing (NOAEL) of 1500 mg/kg. Tradipitant was not teratogenic and did not induce changes in reproduction or fertility at doses ≤1000 mg/kg. Liver and thyroid enlargement and elevation of serum gamma-glutamyltransferase (GGT) were observed in the rat studies and associated with hepatocellular hypertrophy and thyroid hyperplasia, yet there was no evidence of hepatocellular injury. In the 6-month study, these changes were reversible after a 4-week recovery period. These findings were considered secondary to microsomal enzyme induction. In dogs, elevation of serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) were observed and considered consistent with hepatic microsomal enzyme induction because they were not accompanied by histologic evidence of liver injury. Exposure-based margins of safety for oral administration of ≤100 mg of tradipitant to humans are 23-fold and 2.9-fold, relative to rats after a single dose and 6 months of treatment, respectively; 40-fold, relative to mice after 13 weeks of treatment; and 66-fold, relative to dogs after 3 months of treatment.

Liver enzymes will be monitored in the planned clinical studies. No risk of particular severity or seriousness is anticipated.

Results of an in vitro 3T3 neutral red uptake phototoxicity test indicate that VLY-686 is predicted to have no phototoxic potential.

3.2.2. Clinical

The clinical development of tradipitant was initiated by Eli Lilly in 2003. Eli Lilly completed 5 clinical trials testing for efficacy in translational models for irritable bowel syndrome, anxiety, and alcohol dependence. In addition, six clinical pharmacology studies have been completed with tradipitant.

- Study H8R-EW-HJAC was a dose-escalation study in healthy male subjects designed to assess the safety and pharmacokinetics of tradipitant. Doses ranged from 1 to 800 mg. A sub-proportional increase in exposure was observed with an increase in dose, most notably at doses greater than 30 mg. The oral clearance (CL/F) increased with dose level and, in general, the median terminal half-life ($T_{1/2}$) was similar across all doses, suggesting dose-dependent changes in bioavailability.
- Study H8R-EW-HJAD was a multiple-dose study with an escalating dosing regimen (1, 10, 30, and 100 mg once-daily dosing) over 28 days designed to assess the safety and tolerability of tradipitant. Consistent with the biphasic elimination of tradipitant, steady-state was reached within 7 days of daily dosing, and the exposure accumulated about 40% relative to a single dose of 1 mg. PET imaging with the radiopharmaceutical [^{11}C]GR205171 was used to quantify the relationships between oral doses, plasma concentration, and the occupancy of cerebral NK-1 receptors by tradipitant, demonstrating a dose- and concentration-dependent increase in frontal cortex receptor occupancy (RO). The maximum percent RO was 93% and was determined 24 hours after the last 100 mg dose on Day 28. The RO did not decrease substantially from 24 to 72 hours during the washout phase following 100 mg. The plasma concentration required to produce half maximal RO (EC_{50}) and 90% maximal RO (EC_{90}) was estimated to be about 2 ng/mL and 27 ng/mL, respectively.
- Study H8R-EW-HJAE was a single-dose, randomized, 2-way crossover study in healthy male subjects designed to assess the effect of a high-fat meal on the pharmacokinetics of tradipitant. Administration of 10 mg of tradipitant in the fed state increased C_{max} and $AUC_{0-\infty}$ approximately 2- and 1.5-fold, respectively, and delayed the median T_{max} by 2 hours relative to the fasted state.
- Study H8R-MC-HJAK was an open-label study in healthy male subjects to assess metabolism and disposition of a single oral dose of [^{14}C]VLY-686. It demonstrated that tradipitant was extensively metabolized via hepatic mechanisms. In addition to tradipitant, 24 metabolites were detected by radioactivity and/or by mass spectrometry in various matrices. Over 13 days, the mean total recovery of radioactivity was approximately 88%, with 81% of the dose recovered in feces and 7% of the dose recovered in urine. The fecal profiles showed that a very small percentage of excreted radioactivity was due to tradipitant, suggesting that drug had been absorbed and that its metabolites had been excreted, presumably via the bile.
- Study H8R-MC-HJAP was performed to characterize any potential PK, pharmacodynamic (PD), or adverse effect interactions between tradipitant and ethanol. Ethanol co-administered with tradipitant has a small but clinically irrelevant effect on tradipitant PK (9.3% increase for C_{max} and 14% increase for AUC_{0-24}). There was no clear or consistent effect of tradipitant given at a dose of 50 mg daily for 7 days on

postural stability or cognition functions compared to placebo and no clear or consistent adverse interaction effects between tradipitant and ethanol on postural stability or cognitive function in healthy subjects. Overall, there was no indication in this study that tradipitant given at dose of 50 mg daily for 7 days had an adverse PK or PD interaction with ethanol.

- Study VP-VLY-686-1101 was conducted to investigate the anti-pruritic potential of oral doses of VLY-686 20 mg, 50 mg or 100 mg compared to placebo after intradermal injections of the pruritogen, substance P. Due to the baseline itch severity scores before treatment with placebo being significantly higher than the baseline scores before the 3 ascending doses of VLY-686, the results of this study are uninterpretable. The VLY-686 plasma concentrations versus time curves could not be extrapolated to infinity for any subject as sampling times only went out to 24 hours post-dose. Therefore, AUC0-∞, $T_{1/2}$ and λZ could not be calculated. In general, the PK characteristics for VLY-686 observed in this study were similar to those observed in Study H8R-EW-HJAC.
- Study VP-VLY-686-2101 was a proof of concept study conducted in atopic dermatitis patients with chronic pruritus. Although a statistically significant difference from placebo was not seen in the overall intent to treat population, a PK/PD correlation was demonstrated in the tradipitant treated group. Based on this PK analysis, individuals with higher tradipitant exposure at the time of their pruritus assessment had a statistically and clinically meaningful difference from placebo as measured on a 100 mm Visual Analog Scale (VAS) for itch.
- Study VP-VLY-686-2102 was conducted in patients with treatment-resistant pruritus diagnosed with atopic dermatitis to evaluate the efficacy of tradipitant relative to placebo in reducing symptoms of chronic pruritus in patients with atopic dermatitis. This study showed that treatment with tradipitant over 8 weeks relieved the worst itch symptoms in these patients as well as improved multiple measures of disease severity and quality of life.

In clinical studies, tradipitant has been administered as a single dose up to 800 mg and up to 8 weeks at a daily dose of 170 mg. In clinical pharmacology studies, the median time to maximum blood concentration ranged from 0.5 to 4 hours. The elimination half-life ranged from 10 to 36 hours.

4. TRIAL OBJECTIVES AND RATIONALE

4.1. Objectives

4.1.1. Primary

- 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.

4.1.2. Secondary

- 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 SCORing Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI).
- 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), Healthy 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.

4.2. Rationale

4.2.1. Study Rationale

This study is a phase III study to evaluate the efficacy of tradipitant 85 mg BID in reducing worst itch and in improving disease severity in patients with mild atopic dermatitis. Increasing evidence points to the involvement of NK-1 receptors of keratinocytes in the pathogenesis of pruritus. In addition another NK-1 receptor antagonist, namely aprepitant, has previously been shown to reduce itch intensity in patients with treatment-refractory pruritus[10]. Thus, NK-1 receptor antagonists, like tradipitant, are promising potential therapeutics for treating pruritus.

In VP-VLY-686-2102, 168 patients with treatment-resistant pruritus associated with atopic dermatitis were randomized to receive either tradipitant 85 mg or matching placebo BID over 8

weeks of treatment. In this study, 24-hour worst itch measured by change from baseline as a visual analog scale (VAS) was significantly improved versus placebo at the last visit on week 8 (day 56) compared to placebo. In addition, other continuous measure scales showed statistically significant improvement over placebo in the ITT population at the last visit including: nighttime worst itch as measured by a 11-point numerical rating scale (NRS) in the daily diary, total SCORAD, objective subscale of SCORAD, CGI-C, PGI-C itch, PGI-C AD, and PBI-P. The primary end point of the study, the 24-hour average itch VAS change from baseline, demonstrated a numerical difference that was consistent across all visits. Numerical improvements in the tradipitant arm versus placebo were also seen in verbal response scale (VRS) measuring itch, daytime worst itch NRS, and the subjective subscale of SCORAD, but did not reach statistical significance.

4.2.2. Rationale for Dose and Study Design

Study VP-VLY-686-2101 was conducted in patients with atopic dermatitis using a 100 mg daily dose that did not result in an improvement in the disease parameters studied including worst and average itch. In this study, PK data was collected and analyzed for a potential exposure-response relationship. Patients in this study were dosed with tradipitant in the evening and it was observed that patients assessed in the morning had blood concentrations of tradipitant approximately twice that of those assessed in the afternoon. These patients assessed in the morning, with higher blood concentrations of tradipitant, reported increased improvement in pruritus and related outcomes when compared to placebo patients also assessed in the morning. Patients assessed in the afternoon, with lower blood concentrations of tradipitant, did not show an improvement when compared to placebo patients assessed in the afternoon.

A PK analysis of healthy patients in study VP-VLY-686-1102 receiving 85 mg of tradipitant BID showed a modeled half-life of approximately 48 hours with a range between about 24 and 173 hours. Therefore, a wide variation in exposures was expected in VP-VLY-686-2102. The PK profile from VP-VLY-686-1102 and the concentration-effect relationship observed in study 2101, lead to the increase in dose of tradipitant in study VP-VLY-686-2102 to 170 mg daily.

PK data was also collected in the 2102 study, and subsequent analysis indicated that the patients in this study had a sufficient range of exposures across the treated population for efficacy in the ITT analysis. In addition, with this higher dose, no further exposure-response relationship was observed which indicates that a higher dose than 170 mg daily is unlikely to be more effective. Safety results between the 2101 and 2102, as measured by TEAE rates were similar indicating that the safety profile of 170 mg vs 100 mg was comparable.

4.2.3. Risk and Benefit

The potential benefit for patients, if randomized to tradipitant, is the possibility of experiencing less pruritus and improvement in AD severity while participating in this study. Nonclinical and clinical data to date have not indicated any likely toxicity at doses to be used in this study, and the drug has been well-tolerated in previous clinical studies. The most commonly reported adverse events (≥ 2% and 1.25x placebo) in previous clinical studies were somnolence, dizziness, fatigue, and dry mouth. Nonetheless, as tradipitant is an experimental compound, there may be unforeseen risks associated with its use.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan: Description

This is multicenter, randomized, double-blind, placebo-controlled study to be conducted in the United States. Approximately Two Hundred (200) patients with mild atopic dermatitis, who satisfy the eligibility criteria for the study, will be randomized in a 1:1 ratio 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 as described in Section 7.2. The evaluation phase includes 8 weeks of randomized double-blind treatment. In-clinic evaluations will occur at the screening visit (V1), the baseline visit (V2), and visits at weeks 2, 4, 6, and 8 (V3-6, respectively).

5.1.1. Pre-treatment Phase

The pre-treatment phase includes the screening and baseline visits. Informed consent must be obtained prior to the initiation of medication washout. The pre-treatment phase will be at least 14 days and no longer than 45 days.

5.1.1.1. Screening Visit (Visit 1)

During the Screening Visit (Visit 1), the following assessments will be performed to assess the patient's eligibility, following informed consent: medical history, full physical examination (PE) (excluding genitourinary examination unless clinically indicated), vital signs and body measurements, resting 12-lead ECG, Screening/Baseline C-SSRS, clinical laboratory assessments (hematology, chemistry, and urinalysis), coagulation, HbA1c, Hepatitis B/C screen, drug and alcohol screen, a serum pregnancy test for women of child bearing potential (WOCBP), cytokine panel sample, Pruritus assessment (including WI-NRS and VRS) and SCORAD. Demographic, IgE, prior and concomitant medication and adverse event information, EASI, vIGA-AD, Medical History of Atopy Questionnaire, POEM, DLQI, ISQ, and HRQOL-4 assessment will also be obtained at this visit. Blood samples for pharmacogenetic (PG) and filaggrin testing will also be collected. Lastly, daily diary distribution information and instruction will occur at this visit. The screening visit may be conducted over multiple days. Tests performed to determine a patient's eligibility must be conducted within 30 days of randomization.

Patients that meet preliminary eligibility criteria (or that are expected to meet additional eligibility criteria) will be instructed to discontinue use of relevant medications according to Section 7.2. Patients will be given a daily diary to complete during the screening period prior to Visit 2 (Baseline, Day 0).

Patients who do not meet eligibility criteria will be considered screen failures. Screen failures due to insufficient time for an adequate washout from concurrent medications, as described in Section 7.2.1, may be given the opportunity for reconsideration at a later time (re-screening) at the discretion of the Investigator. Rescreening is not permitted for any scale or item that is related to the primary or secondary outcomes or any safety parameter.

5.1.1.2. Baseline Visit (Visit 2)

On Day 0 (Visit 2/Baseline), the following assessments will be performed to assess the patient's eligibility: SCORAD, Pruritus assessment, Since Last Visit C-SSRS, urine pregnancy test for WOCBP, an abbreviated PE if clinically indicated, and concomitant medication and adverse event review. The following assessments will also be performed during this visit: vital signs and body weight measurements, a drug and alcohol screen, clinical laboratory assessments (hematology, chemistry, and urinalysis), IgE collection, resting 12-lead ECG, EASI, vIGA-AD, PBI-P (PNQ), Medical History of Pruritus Questionnaire, POEM, DLQI, ISQ, HRQOL-4, and baseline PK sample draw. In addition, the patient diary will be reviewed for compliance and additional training will occur as necessary. Photography will also occur at this visit. Patients continuing to meet all eligibility criteria will be randomized to receive either 85 mg tradipitant or matching placebo twice daily for 8 weeks, and will be given enough study medication to last until the next visit. Patients who are randomized will begin taking study medication in the evening of Day 0 (Baseline/Visit 2). Twice daily dosing will begin the day following the baseline visit.

5.1.2. Evaluation Phase

5.1.2.1. Visit 3

Patients will return to the clinic on Day 14. Study visits need to occur within ± 3 days. The following safety assessments will be performed: adverse event review, vital signs and body measurements, an abbreviated PE (if clinically indicated), resting 12-lead ECG, drug and alcohol screen, clinical laboratory assessments, Since Last Visit C-SSRS, and urine pregnancy test for WOCBP. A blood sample for determination of IgE levels and PK will also be collected during the visit. The following efficacy assessments will be performed: Pruritus Assessment, SCORAD, EASI, vIGA-AD, PBI-P (PBQ), PGI-C, CGI-C, and DLQI. In addition, the following will occur: concomitant medication review, study medication collection, accountability, compliance review, and dispensation, and diary compliance review. The last dose of study medication should be taken in the morning prior to study visit.

5.1.2.2. Visit 4

Patients will return to the clinic on Day 28. Study visits need to occur within ± 3 days. The following safety assessments will be performed: adverse event review, vital signs and body measurements, an abbreviated PE (if clinically indicated), resting 12-lead ECG, drug and alcohol screen, Since Last Visit C-SSRS, clinical laboratory assessments (hematology, chemistry, and urinalysis) and urine pregnancy test for WOCBP. A blood sample for determination of IgE levels and PK will also be collected during the visit. The following efficacy assessments will be performed: Pruritus Assessment, SCORAD, EASI, vIGA-AD, PBI-P (PBQ), PGI-C, CGI-C, POEM, DLQI, ISQ, and HRQOL-4. In addition, the following will occur: concomitant medication review, study medication collection, accountability, compliance review, and dispensation, and diary compliance review. Photography will also occur at this visit. Last dose of study medication should be taken in the morning prior to study visit.

5.1.2.3. Visit 5

Patients will return to the clinic on Day 42. Study visits need to occur within ± 3 days. The following safety assessments will be performed: adverse event review, vital signs and body

measurements, an abbreviated PE (if clinically indicated), 12-lead resting ECG, drug and alcohol screen, Since Last Visit C-SSRS, and urine pregnancy test for WOCBP. A blood sample for determination of IgE levels and PK will also be collected during the visit. The following efficacy assessments will be performed: Pruritus Assessment, SCORAD, EASI, vIGA-AD, PBI-P (PBQ), PGI-C, CGI-C, and DLQI. In addition, the following will occur: concomitant medication review, study medication collection, accountability, compliance review, and dispensation, and diary compliance review. Last dose of study medication should be taken in the morning prior to study visit.

5.1.2.4. End of Study or Early Termination (Visit 6)

At the End of Study Visit (Day 56 ± 3 days) or at the time of early termination, patients will return to the clinic to complete all of the assessments listed for V6. The following safety assessments will be performed: adverse event review, vital signs and body measurements, a full PE, resting 12-lead ECG, clinical laboratory assessments (hematology, chemistry, and urinalysis), drug and alcohol screen, Since Last Visit C-SSRS, and serum pregnancy test for WOCBP. A blood sample for determination of IgE levels and PK and a blood draw for the cytokine panel sample will also be collected during the visit. The following efficacy assessments will be performed: Pruritus Assessment, SCORAD, EASI, vIGA-AD, PBI-P (PBQ), PGI-C, CGI-C, POEM, DLQI, ISQ, and HRQOL-4. Photography will also occur at this visit. In addition, the following will occur: concomitant medication review, study medication collection, accountability, and compliance review, and diary compliance review. The last dose of study medication should be taken in the morning prior to study visit.

Table 2: 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[4]	X	X	X	X		X
Coagulation[4]	X					
IgE collection	X	X	X	X	X	X
Cytokine Panel[5]	X					X
Filaggrin Analysis[6]	X					
Pharmacogenetic (PG) sample[6]	X					
Pharmacokinetic (PK) sample		X	X	X	X	X
Resting 12-lead ECG	X	X	X	X	X	X
Vital signs and body measurements[7]	X	X	X	X	X	X
Physical Examination (PE)[8]	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[9]	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
Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)	X	X	X	X	X	X
Patient Benefit Index – Pruritus (PBI-P)[10]		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**
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[11]		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 elevated liver enzymes are present at any study visit, an unscheduled visit to redraw chemistry and coagulation samples will be completed prior to the next scheduled visit.

5 If the V1 cytokine panel sample is missed, the sample should be drawn at the next in-clinic visit (ex. V2).

6 If either the V1 Filaggrin or PG sample is missed or unable to be performed for any reason, the samples should be drawn at the next in-clinic visit (ex. V2).

7 Body height will only be collected at V1; body weight will be collected at V1, V2, and V6.

8 An abbreviated physical examination will be performed at V2-V5 ONLY if clinically indicated.

9 The Baseline C-SSRS will occur at V1. The Since Last Visit C-SSRS will occur at all other visits.

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

11 Patients will be instructed to take their first dose of study medication on the evening of Day 0 (V2).

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

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Patient Inclusion Criteria

Patients will be considered eligible for participation in the study if the following criteria are satisfied:

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. Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) rating of 1 or 2;
    c. Presence of excoriations at screening and baseline visits (i.e. SCORAD index excoriation score > 0);
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 Score (WI-NRS) ≥ 5 points at the screening and baseline visit;
6. Daily diary reporting of Worst Itch Numerical Rating Score (WI-NRS) average score for maximum itch severity ≥ 7 points between screening and baseline visits;
    a. *Note: Worst Itch 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 childbearing 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 screening visit or 1 month prior to randomization, whichever is earlier, 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.

6.2. Patient Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

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. An AD or immune-related biologic for less than 5 half-lives (if known) or 16 weeks prior to the baseline visit.
   c. *Note: For clarity, an example of such biologics would be drugs such as dupilumab (approved by the FDA for treatment of AD) and fezakinumab (a biologic being investigated in AD).*
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;
7. Patient has made a suicide attempt and/or had suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 2 years, 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);
13. Has a creatinine level > 1.25x ULN;
14. Randomization in a previous tradipitant clinical trial;
15. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress;
16. 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.

6.3. Patient Withdrawal Criteria

The term "discontinuation" refers to the randomized patient's premature withdrawal from the study before completing all scheduled evaluations.

Patients may voluntarily withdraw from the study at any time for any reason. Patients may also be discontinued from the study for any of the following reasons:

- If in the Investigator's judgment, continuation in the study may prove harmful to the patient. Such a decision may be precipitated by adverse events, including changes in vital signs, physical examination, ECG, or laboratory tests. The Investigator will maintain autonomy in making medical/safety decisions regarding the patient's continued participation in the trial. Clinically notable abnormalities in vital signs or laboratory tests are provided in Appendices 22.2 and 22.1, respectively, to guide clinical focus regarding a patient's continued participation;
- Noncompliance.

For patients withdrawing from the study prematurely, all efforts will be made to perform the Visit 6 Early Termination procedures.

Documented reason: It will be documented whether or not each patient completed the clinical study. For patients who do not complete the clinical study, the primary reason for discontinuation will be documented in the CRF. Possible reasons for discontinuation include:

1. protocol deviation (including noncompliance to study requirements)
2. adverse event(s) (including abnormal laboratory values, and abnormal test procedures)
3. pregnancy

4. lost to follow-up
5. death
6. patient withdrew consent
7. unsatisfactory therapeutic effect
8. other (specify).

Patients who discontinue because of an AE, abnormal laboratory value, or abnormal test result will be followed until resolution, or for 30 days, whichever is less. Events which are stable after 30 days will not require additional follow up.

7. TREATMENT OF PATIENTS

7.1. Dosing

Patients will be dispensed study medication under double-blind conditions at the study visits indicated in the Schedule of Evaluations (Table 2). Patients will be instructed to take one capsule of study medication every day in the morning prior to or at 9:00 am and one capsule of study medication every day in the evening approximately 12 hours later (± 1 hour). Study medication should be taken with food. Each capsule will contain either 85 mg of tradipitant or matching placebo. The date and time of the last dose before V3, V4, V5, and V6 should be documented in the paper source and EDC at the time of visit.

7.2. Concomitant Medications

The administration of concomitant medication (including OTC medication) will be clearly documented in the paper source and on the concomitant medication CRF page.

In general, concomitant medications with primarily CNS activity and/or medications that may interfere with the assessment of the efficacy and safety of tradipitant are not allowed in this protocol. Prohibited medications and treatments are listed in Table 3. Unless otherwise noted in Section 7.2.1, medications are prohibited from one week prior to the baseline visit through the end of study participation. Questions regarding the use of concomitant medications not listed should be directed to the medical monitor.

7.2.1. Medication Washout

Patients taking any of the following medications at screening will be required to discontinue the medication and enter a washout period during the screening phase. The length of the washout period for specific medications is measured from randomization and is listed below. Any medication for the treatment of atopic dermatitis and/or pruritus, not listed below, requires a 2-week washout period.

7.2.1.1. Medications requiring a 4-week washout period

- Systemic steroids
- Immunosuppressants
- Cytotoxic treatment

7.2.1.2. Medications requiring a 2-week washout period

- Topical calcineurin inhibitors
- Topical antibiotics
- Topical steroids
- Antihistamines
- Antiseptic preparations

- Any medication for the treatment of atopic dermatitis and/or pruritus not otherwise listed.

Table 3: List of Prohibited Medications and Treatments

Drug , Drug Class, or Treatment Name
Acamprosate
Angiotensin-Converting-Enzyme (ACE) Inhibitor (e.g., captopril, fosinopril, lisinopril, ramipril, zofenopril)
Antibiotics, topical
Anticonvulsants (e.g., carbamazepine, clonazepam, diazepam, felbamate, gabapentin, lamotrigine, levetiracetam, phenytoin, pregabalin, primidone, topiramate, tiagabine, oxcarbazepine, zonisamide)
Antidepressants (unless on a stable dose for at least 3 months)
Antihistamines (topical or systemic)
Antiseptic preparations (prescribed for daily use or atopic dermatitis)
Antipsychotics
Benzodiazepines/Hypnotics (unless on a stable dose for at least 3 months)
Calcineurin inhibitors (topical or systemic)
Camphor (topical)
Capsaicin (topical)
Corticosteroids (systemic and topical; inhaled corticosteroids, corticosteroid nasal sprays and eye drops are permitted)
Cytotoxic therapy (e.g., methotrexate)
Dietary/Herbal supplements with CNS activity (e.g., St John's Wort, tryptophan, melatonin, kava)
Disulfiram
Dupixent
Eucrisa
Elidel
Immunosuppressants (e.g., Azathioprine, Cyclosporin A)
Lithium
Monoamine oxidase inhibitors (MAOIs)
Menthol
Opiate antagonists (e.g., naltrexone, naloxone, nalmefene)
Opiate agonists and analgesics (e.g., codeine, hydrocodone, methadone, morphine, alfentanil, meperidine, propoxyphene)
Phenol (topical)
Polidocanol (topical; use as a sclerosant is permitted)
Pramoxine (topical)
Psychostimulants (unless on a stable dose for at least 3 months)
Urea (topical)
UV Light Therapy
Varenicline (unless on a stable dose for at least 3 months)
Yohimbine
*any other medication that could interfere with the assessment of efficacy of tradipitant

7.2.2. Allowed Emollients

Topical application of moisturizers, lotions, or emollients without active anti-inflammatory or antipruritic substances are allowed for use throughout the study period. The patient should use the emollient used prior to enrolling into the study throughout the study period. Patients should not introduce a new emollient during the study period.

7.3. Treatment Compliance

Compliance in this study will be assessed by the Investigator. The Investigator will consider patient interviews and diaries as well as returned capsules when assessing compliance. Patients who were not fully compliant will be re-educated by the Investigator or study staff on the importance of taking the study medication daily at the scheduled time.

7.4. Treatment Assignment

7.4.1. Patient ID Assignment

Patient Identification (ID): Each patient who signs an informed consent form should receive a patient identification number. The patient identification number (ID) consists of a 3-digit site number (Site No.) and a 4-digit patient number (Patient No.). The Site No. and Patient No. will be separated by a hyphen (XXX-XXXX).

Site No.: Vanda Pharmaceuticals Inc. (or designee) will assign a unique, three-digit number to the site.

Patient No.: Patient numbers will be assigned to each patient starting with 2001 (i.e. 2001, 2002, 2003 …). The ID for a patient who discontinues from the study for any reason after having been assigned an ID will not be reassigned.

7.4.2. Randomization

Randomization will be performed through a centralized, web-based, validated system that automates the assignment of patients to randomization numbers. The randomization scheme will be reviewed and approved by Vanda Pharmaceuticals Inc. or designee. For study medication dispensation, the Investigator or designee will access the randomization system to determine which study medication bottle the patient will be assigned.

8. STUDY MEDICATION MATERIALS AND MANAGEMENT

8.1. Study Medication

Tradipitant capsules are white opaque, hard gelatin capsules provided at a strength of 85 mg. The 85 mg capsule formulation also contains spray-dried lactose monohydrate, microcrystalline cellulose (Avicel PH102 and PH200), povidone, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate as excipients. Placebo capsules will be provided in size and appearance identical to those containing tradipitant.

8.2. Study Medication Packaging and Labeling

Medication labels will comply with US regulations. The storage conditions for the study medication will be described on the medication label.

Study medication capsules will be provided in high-density polyethylene (HDPE) bottles with a child-resistant cap containing desiccant. Each bottle will contain 36 capsules. At each dispensing visit (refer to Table 2), one new bottle of medication will be dispensed to the patient. Patients should be instructed to bring the study medication bottle along with any unused capsules to the site at his/her next visit. Each bottle will have a two-part label. The second part of the label will be attached to the patient's source documents before the bottle is dispensed to the patient.

8.3. Study Medication Storage

Study medication should be stored at 20-25 °C with excursions permitted to 15-30 °C. Capsules should not be crushed or broken, but should be swallowed whole. Study medication will be dispensed to only randomized patients at the study site.

8.4. Study Medication Accountability

Vanda Pharmaceuticals Inc. is responsible for assuring that the quality of the study medication is adequate for the duration of the study.

Study medication should be used in accordance with the protocol, under the supervision of the Investigator or delegated by the Investigator to the site pharmacist or other personnel trained to store and dispense investigational medications.

The Investigator or designee is responsible for logging receipt of each shipment of study medication, confirming the actual shipment contents, and indicating the status of each bottle.

The Investigator must agree to supply study medication only to patients enrolled in the study. It is the responsibility of the Investigator to ensure that a current record of study drug disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount of study medication received

- Medication bottle number
- Dates of medication inventory movement
- Amount dispensed
- Initials of person responsible for each medication inventory entry

Accurate recording of all study medication administration (including dispensing and dosing) will also be made in the appropriate section of the patient's CRF and source documents.

Vanda Pharmaceuticals Inc. or its designee will instruct the Investigator on the return, destruction, or transfer of unused study medication.

If any study medication was lost or damaged, its disposition should be documented in the patient's source documents as well as the drug accountability record. Study medication supplies will be retained at the clinical site until instructions for return, destruction, or transfer of the supplies are received from Vanda Pharmaceuticals Inc. or its designee.

9. STUDY ASSESSMENTS

9.1. Study Assessments per Visit

9.1.1. Screening Visit (Visit 1, up to Study Day -45)

The following evaluations will be performed **after** the patient signs the informed consent form:

- Assess eligibility
- Demography
- Medical History and relevant treatment history
- Full PE (excluding pelvic, rectal, and breast examinations unless clinically indicated)
- Clinical laboratory assessments (hematology, chemistry, and urinalysis)
- Coagulation
- HbA1c
- Hepatitis screen
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis C antibody (anti-HCV)
- IgE collection
- Cytokine Panel Sample
- Serum β-HCG for WOCBP
- PG blood sample
- Filaggrin test blood sample
- Drug and alcohol screen
- Resting 12-lead ECG
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse) and body measurements (height and weight)
- Adverse Events
- Screening/Baseline C-SSRS
- Prior/current medications
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Medical History of Atopy Questionnaire

- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Insomnia Symptom Questionnaire (ISQ)
- Healthy Days Core Module (4 questions) (HRQOL-4)
- Patient diary distribution and instruction

9.1.2. Baseline Visit (Visit 2, Study Day 0)

- Continue eligibility assessment (as applicable)
- Abbreviated PE (if clinically indicated)
- Clinical laboratory assessments (hematology, chemistry, and urinalysis)
- IgE collection
- Urine pregnancy for WOCBP
- Baseline pharmacokinetic sample
- Drug and alcohol screen
- Resting 12-lead ECG
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse) and body measurements (weight only)
- Adverse Events
- Since Last Visit C-SSRS
- Concomitant Medication
- Medical History of Pruritus Questionnaire
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Patient Benefit Index – Pruritus (Patient Needs Questionnaire) (PBI-P (PNQ))
- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Insomnia Symptom Questionnaire (ISQ)
- Healthy Days Core Module (4 questions) (HRQOL-4)
- Photography

- Randomization
- Review daily diary compliance
- Study medication instruction and dispensation (first dose will be administered on evening of Day 0)

9.1.3. Visit 3 (Study Day 14 ± 3 days)

- Urine pregnancy for WOCBP
- Drug and alcohol screen
- IgE collection
- Pharmacokinetic (PK) sample
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse)
- Abbreviated PE (if clinically indicated)
- Clinical laboratory assessments (hematology, chemistry, and urinalysis)
- Resting 12-lead ECG
- Adverse Events
- Since Last Visit C-SSRS
- Concomitant medications
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Patient Benefit Index – Pruritus (Patient Benefits Questionnaire) (PBI-P (PBQ))
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Change (CGI-C)
- Dermatology Life Quality Index (DLQI)
- Review daily diary compliance
- Study medication collection and review of compliance
- Study medication dispensation

9.1.4. Visit 4 (Study Day 28 ± 3 days)

- Urine pregnancy for WOCBP
- Clinical laboratory assessments (hematology, chemistry and urinalysis)
- Drug and alcohol screen
- IgE collection
- Pharmacokinetic (PK) sample
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse)
- Abbreviated PE (if clinically indicated)
- Resting 12-lead ECG
- Adverse Events
- Since Last Visit C-SSRS
- Concomitant medication
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Patient Benefit Index – Pruritus (Patient Benefits Questionnaire) (PBI-P (PBQ))
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Change (CGI-C)
- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Insomnia Symptom Questionnaire (ISQ)
- Healthy Days Core Module (4 questions) (HRQOL-4)
- Photography
- Review daily diary compliance
- Study medication collection and review of compliance
- Study medication dispensation

9.1.5. Visit 5 (Study Day 42 ± 3 days)

- Urine pregnancy for WOCBP

- Drug and alcohol screen
- IgE collection
- Pharmacokinetic (PK) sample
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse)
- Abbreviated PE (if clinically indicated)
- Resting 12-lead ECG
- Adverse Events
- Since Last Visit C-SSRS
- Concomitant medication
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Patient Benefit Index – Pruritus (Patient Benefits Questionnaire) (PBI-P (PBQ))
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Change (CGI-C)
- Dermatology Life Quality Index (DLQI)
- Review daily diary compliance
- Study medication collection and review of compliance
- Study medication dispensation

9.1.6. Visit 6 (Study Day 56 ± 3 days) End-of-Study or Early Termination

- Full PE (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Laboratory evaluations (hematology, chemistry and urinalysis)
- Drug and alcohol screen
- Serum β-HCG for WOCBP
- IgE collection
- Cytokine Panel Sample
- Pharmacokinetic (PK) blood sample
- Resting 12-lead ECG

- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse) and weight
- Adverse Events
- Since Last Visit C-SSRS
- Concomitant medication
- Pruritus Assessment (including WI-NRS and VRS)
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Patient Benefit Index – Pruritus (Patient Benefits Questionnaire) (PBI-P (PBQ))
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Change (CGI-C)
- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Insomnia Symptom Questionnaire (ISQ)
- Healthy Days Core Module (4 questions) (HRQOL-4)
- Photography
- Review daily diary compliance
- Study medication collection and review

9.1.7. Unscheduled visits

Unscheduled visits may be performed at any time at the discretion of the Investigator.

9.2. Guidance for Taking Study Medication

Patients should take study medication every 12 hours (± 1 hour) at the same times each day. The morning dose of study medication should be taken prior to or at 9:00 am. Medication should be taken with food. In the event a patient is unable to take their study medication dose with food, the dose should not be skipped.

If the patient misses a dose of medication, patients should take the dose as soon as possible, and then take their next dose at the originally scheduled dosing time. If dosing does not occur by the next dosing interval, the missed dose can be taken together with the next scheduled dose. Patients should never take more than two (2) doses at one time, and should not exceed three (3) doses in any 24-hour period. Deviations from the 12-hour dosing interval will be closely monitored for compliance assessment.

10. ASSESSMENT OF EFFICACY

10.1. Efficacy Scales

The following rating scales will be used in this study to assess efficacy:

- Assessments of pruritus include:
  - Diary Worst Itch Numeric Rating Scale (WI-NRS) Itch Scale for worst 24-hour itch
  - Verbal Rating Scale (VRS) for itching, burning, and stinging
  - Site Worst Itch Numeric Rating Scale (WI-NRS) for worst 24-hour itch
- SCORing Atopic Dermatitis (SCORAD) index
- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)
- Daily Diary Sleep Scale (DDSS)
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Change (CGI-C)
- Patient Benefit Index – Pruritus (PBI-P)
- Patient Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Insomnia Symptom Questionnaire (ISQ)
- Healthy Days Core Module (4 questions) (HRQOL-4)

Note: Applicable assessments should be rated by the same rater between visits as much as possible to decreased inter-rater variability.

10.1.1. Pruritus Assessment

10.1.1.1. Patient Diary

Patients will be required to complete a questionnaire once daily using an electronic device (computer, phone, tablet, etc.). The patient will complete the screening portion of the diary for at least 14 days prior to randomization and will complete the evaluation phase portion of the diary between Visit 2 (Baseline) and Visit 6 (End of Study or Early Termination). The diary questionnaire will include questions related to pruritus symptoms (diary WI-NRS) and sleep disturbance due to pruritus (DDSS).

A minimum diary compliance of 70% during the screen phase (between Visits 1 and 2) is required before randomization. For patients who do not have at least 70% 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.

Patients will be instructed on using the ePRO to record their daily diary at the screening visit. Patients will complete the questions daily through the last study visit. Clinical sites will receive alerts when patients do not complete their ePRO diary items. Sites will be expected to contact patients who have missed 2 consecutive eDiary entries to encourage patient compliance.

10.1.1.2. Verbal Rating Scale (VRS)

The VRS will be completed by the patient during the study visits indicated in the Schedule of Evaluations (Table 2) for itching, burning, and stinging. Responses will be measured on a 5-point Likert scale in which 1 = not present, 2 = weakly present, 3 = moderately present, 4 = severely present, and 5 = very severely present[11].

10.1.1.3. Itch Numeric Rating Scale (NRS)

The NRS will be completed by the patient during the study visits Schedule of Evaluations (Table 2). Responses will be measured on a scale of 0 – 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'.

10.1.2. Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)

The vIGA-AD is a validated assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (absence) to 4 (severe). Please see the vIGA-AD training guide for specific instructions and reminders.

10.1.3. SCORing Atopic Dermatitis (SCORAD)

Throughout this protocol, when the SCORAD is described as an assessment to be performed, investigators should perform the full SCORAD index. The Objective SCORAD is a subset of the SCORAD index and will be analyzed as described in the Statistical Analysis Plan.

10.1.3.1. SCORAD Index

The European Task Force on Atopic Dermatitis developed the SCORAD index to create a consensus on assessment methods for AD, so that study results of different trials can be compared. To measure the extent of AD, the rule of nines is applied on a front⁄back drawing of the patient's inflammatory lesions. The extent can be graded 0–100. The intensity part of the SCORAD index consists of six items: erythema, edema/papulation, excoriation, lichenification, oozing⁄crust, and dryness. Each item can be graded on a scale 0–3. The subjective items include the severity of average itch and the average sleep disturbance experienced in past 72 hours. Both subjective items can be graded on a 10 cm visual analog scale. All items should be filled out in the SCORAD evaluation form and the EDC should be used for calculations. In the case that access to the EDC is unavailable, the SCORAD index formula is: A⁄5 + 7B⁄2 + C. In this formula A is defined as the extent (0–100), B is defined as the intensity (0–18), and C is defined as the subjective symptoms (0–20). The maximum SCORAD index score is 103[12]. Please see the SCORAD training guide for specific instructions and reminders.

10.1.3.2. Objective SCORAD

The Objective SCORAD, a subset of the SCORAD index, includes intensity and extent. Please enter into the EDC at the visit to generate calculated score. The Objective SCORAD formula is A/5 + 7B/2. The maximum Objective SCORAD score is 83[12].

10.1.3.3. Subjective SCORAD

The Subjective SCORAD, a subset of the SCORAD index, includes the subjective symptom assessments: pruritus and sleep disturbance. The maximum Subjective SCORAD score is 20[12].

10.1.4. Eczema Area and Severity Index (EASI)

The EASI is a composite index, including the assessment of disease severity and percent of involved body surface area in four body regions (head/neck, upper extremities, trunk, and lower extremities).

The proportion allocated to each body region depends on the patient's age:

- In patients older than 8 years, proportions are 10% for head/neck, 20% for upper extremities, 30% for trunk and 40% for lower extremities;
- In patients aged less than 7 years, proportions are 20% for head/neck, 20% for upper extremities, 30% for trunk, and 30% for lower extremities.

The percentage body surface involvement (0-100%) is determined for each of the four body regions. These values are then entered into the EDC system, and the EDC system will translate the % body surface area (BSA) into a region score (0 to 6) based on the table below.

0	1	2	3	4	5	6
No Involvement	<10%	10% - 29%	30% - 49%	50% - 69%	70% - 89%	90% - 100%

The EASI also includes an assessment of the severity of four clinical signs: 1) erythema, 2) induration/papulation, 3) excoriation, and 4) lichenification, each on a scale from 0 to 3 based on the table below.

Severity	Absent	Mild	Moderate	Severe
Scale	0	1	2	3

These scores will be entered into the EASI eCRF in the EDC system. The EDC will determine the final EASI score. The EASI's minimum score is 0 and the maximum is 72. The algorithm for calculating the EASI uses, for each body region, is the sum of the clinical sign scores multiplied by the region score, multiplied by the proportional factor.

The total EASI score is the sum of the four body-region scores. EASI was developed to be effective in assessing patients with mild to severe AD, both in pediatric and adult populations[13]. Please see the EASI training guide for specific instructions and reminders.

10.1.5. Patient Global Impression of Change

The PGI-C is a 7-point rating scale where the patient rates their own improvement in symptoms relative to the baseline assessment. It is rated as 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

10.1.6. Clinician Global Impression of Change

The CGI-C is a 7-point rating scale where Investigators rate the patients' improvement in symptoms relative to the baseline assessment. It is rated as 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

10.1.7. Patient Benefit Index (PBI)

The questionnaire 'Patient Benefit Index for skin diseases' (PBI) provides a method for assessing patient-relevant benefit in conformity with the regulatory requirements including a single benefit score, computed by weighting treatment benefits with their importance prior to treatment. The PBI was developed and validated for skin diseases in general, but a range of disease-specific PBI versions has been developed in the meantime (e.g. PBI-V for patients with vitiligo, PBI-HE for patients with chronic hand eczema and PBI-P for patients with pruritus)[14,15]. PBI-P will be utilized for this protocol.

The PBI includes two questionnaires[16]:

- The 'Patient Needs Questionnaire' (PNQ) is filled in before therapy. In the version for pruritus (PBI-P) it consists of 27 standardized items on treatment needs such as 'no longer to experience itching' and 'to have fewer side-effects'. The patients rate the importance of each need by indicating whether each need is 'not at all', 'somewhat', 'moderately', 'quite' or 'very' important.
- The 'Patient Benefit Questionnaire' (PBQ) is filled in during or after therapy. It consists of the same items as the PNQ, but the instruction differs: here, patients rate the extent to which the treatment needs have been achieved by therapy by indicating if the treatment has benefited the patient by rating 'not at all', 'somewhat', 'moderately', 'quite' or 'very'.

10.1.8. Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess eczema disease symptoms[16]. The measure is a response to 7 items (dryness, itching, flaking, cracking, sleep disturbance, bleeding, and weeping) based on frequency during the past week (0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = everyday) with a scoring system of 0 to 28. The total score reflects disease-related morbidity.

10.1.9. Patient-Reported Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QOL)[17]. The measure is a response to 10 questions (0 to 3 where 0 is “not at all” and 3 is “very much"). The responses assess QOL over the past week, with an overall scoring system of 0 to 30 (higher indicates worse QOL).

10.1.10. Insomnia Symptom Questionnaire (ISQ)

The ISQ is a 13-item, validated questionnaire used in clinical practice and clinical trials to assess sleep symptoms during the past month[18]. The measure is a response to 13 items; the first 5 of which are rated on a scale of 0 to 5 where 0 is “never” and 5 is “always”. Items 6 through 13 are measured on the scale from 0 to 4 where 0 is “not at all” and 4 is “extremely”. The responses assess the frequency and duration of sleep symptom criteria, as well as daily impairment due to sleep loss.

10.1.11. Healthy Days Core Module (4 questions) (HRQOL-4)

The Healthy Days Core Module (4 questions) (CDC HRQOL-4) is a 4-item quality of life questionnaire that has been in the used in the State-based Behavioral Risk Factor Surveillance System since 1993[19]. The questionnaire assesses overall quality of life and well-being.

10.2. Photography

During visits 2, 4, and 6, a representative lesion with high or worst excoriations and half body body photographs will be taken. Patients will need to remove clothing for proper photographs to be taken. Undergarments, including underwear and bras, will remain on for these photos.

The face will not be photographed and any tattoos/identifying marks will be covered by a blinded third party vendor before viewed by the sponsor.

The study specific photography manual includes instructions for photography.

10.3. Pharmacokinetic Assessment

Pharmacokinetic (PK) blood draws will occur at Visits 2, 3, 4, 5, and 6. During these visits, a single blood sample (5 mL) will be drawn for pharmacokinetic analysis. The PK blood sample will be collected from all patients into appropriately labeled tubes containing lithium heparin.

Samples (5 mL) will be centrifuged for 10 minutes at approximately 1500xg within 2 hours of sampling. Immediately after centrifugation, split the resulting plasma (~ 2.5 mL) into the aliquots, T1/T2 (tradipitant), in pre-labeled polypropylene tubes, and store frozen at ≤ -20 °C until sending to analytical lab for analyses. The samples should be shipped under frozen condition to PPD Central Laboratories (Highland Heights, Kentucky).

The concentration of tradipitant, and its major metabolites, in plasma will be determined by QPS (Newark, DE, USA), using a fully validated High Performance Liquid Chromatography Mass Spectrometric method.

The shipping address and instructions for shipment of PK samples will be provided separately.

Plasma concentrations of tradipitant and its major metabolites will be obtained for the purpose of population pharmacokinetic analysis and pharmacokinetic-pharmacodynamic analysis. The population pharmacokinetic analysis may be provided in a separate report.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety assessments should be conducted as specified in the Schedule of Evaluations (Table 2). These assessments include the regular monitoring and recording of all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry and urinalysis values, vital signs, body measurements and suicidal ideation and behavior; and the performance of physical examinations and electrocardiograms. Any amendments to this protocol that change the schedule of visits and procedures will be included in the clinical study report for this protocol.

11.1.1. Safety ECG

A full standard 12-lead ECG will be performed (after the patient has rested for approximately 15 minutes) and centrally read at as specified in Table 2.

11.1.2. Laboratory Evaluations

The Schedule of Evaluations (Table 2) shows the days at which blood will be collected for clinical laboratory tests and other assessments and urine for the urinalysis.

The table below (Table 4) presents the clinical laboratory tests to be performed.

Clinical laboratory tests will be performed by a certified laboratory that will forward laboratory data to both the site and Vanda Pharmaceuticals Inc. or its designee.

Values considered to be potentially clinically notable are provided in Appendix 22.1 for the Investigator's guidance. Any laboratory test result from an enrolled patient that the Investigator considers clinically significant may be repeated once to rule out laboratory error. For tests where a persistent abnormality is considered to be drug related, repeat analyses will be performed until the cause is determined and either a return to normality occurs or the Investigator deems the abnormality to be of no clinical significance. Any laboratory test result that the Investigator considers clinically significant must also be recorded as an adverse event.

Table 4: Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count (RBC), hemoglobin, hematocrit, platelets, Nucleated Red Blood Cell (CBC), RBC Morphology, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Mean Platelet Volume (MPV) and white blood cell (WBC) count with differential (neutrophils, lymphocytes, immature granulocytes, monocytes, eosinophils, basophils), coagulation (to include Partial Thromboplastin Time (PTT), Prothrombin Time (PT), International Normalized Ratio (INR), D-Dimer, Fibrinogen)
Chemistry	
Electrolytes	sodium, potassium, chloride, magnesium, bicarbonate

Category	Parameters
Liver function test	alkaline phosphatase, aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), total bilirubin, gamma-glutamyltransferase (GGT)
Renal function parameters	blood urea/blood urea nitrogen (BUN), creatinine (including creatinine clearance calculation)
Other	glucose, calcium, albumin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine kinase, IgE, TSH, T4
Urinalysis	
Gross and chemical exam	color, appearance, specific gravity, pH, protein, glucose, ketone, blood, nitrite
Reflexive microscopic exam (will be done if any of the urinalysis testing is not negative)	RBC, WBC, epithelial cells, bacteria, casts, crystals

11.1.2.1. Additional Laboratory Evaluations

- Serum pregnancy test at Visits 1 and 6
- Urine pregnancy test at Visits 2, 3, 4, and 5
- Hepatitis B/C screen at Visit 1
- Drugs of abuse and alcohol at Visits 1, 2, 3, 4, 5, and 6
- HbA1c measurement at Visit 1
- IgE measurement at every visit
- Cytokine panel at Visits 1 and 6
- Filaggrin analysis at Visit 1

11.1.3. Vital Signs and Body Measurements

11.1.3.1. Vital Signs

Vital signs will be taken as specified in the Schedule of Evaluations (Table 2). Measurements will include the following:

- Oral body temperature
- Respiratory rate
- Semi-supine blood pressure (systolic and diastolic)
- Semi-supine pulse/heart rate

After the patient signs the informed consent, vital sign values that the Investigator considers clinically significant will be recorded as AEs. Vital sign values considered to be potentially clinically notable are provided in Appendix 22.2 for the Investigator's guidance. The recording must be in the form of a clinical sign, symptom, or diagnosis, and not a mere description of the vital sign abnormality. Measurements will be repeated at medically appropriate intervals until they return to acceptable levels.

11.1.3.2. Body Measurements

Body measurements include the following assessments:

- Body weight (at Visit 1, Visit 2, and Visit 6)
- Height (at Visit 1 only)

11.1.4. Medical History and Physical Examinations

A medical history will be taken at Visit 1 (Screening). A full PE (excluding pelvic, rectal and breast examinations unless clinically indicated) will be performed at Visit 1 (Screening) and Visit 6. An abbreviated physical examination may be conducted as necessary based on clinician assessment (e.g. change in health status or AE) at Visits 2-5. This abbreviated exam should include only the body systems deemed clinically relevant by the investigator. Documentation of the PE will be included in the source documentation at the investigational site.

11.1.4.1. Medical History of Pruritus Questionnaire

At Baseline (Visit 2), patients will also complete a questionnaire describing the history of their pruritus symptoms prior to entering the study.

11.1.4.2. Medical History of Atopy Questionnaire

At the screening visit (Visit 1), patients will complete a questionnaire describing their personal and family history of their atopy (i.e. asthma, allergy, and atopic dermatitis) prior to entering the study.

11.1.5. Pregnancy

Before enrolling a woman of childbearing potential (WOCBP) in this clinical study, Investigators must review the following information with the patient:

- Informed consent requirements
- Risk of pregnancy
- Contraceptives in current use
- Drug interactions with hormonal contraceptives
- Pregnancy prevention during the study (including abstinence)

Women using hormonal methods of birth control (e.g. oral contraceptives, patch, and steroids) must use an additional method of birth control from the screening visit or 1 month prior to randomization, whichever is earlier, during the study, and for one month after the last dose.

All WOCBP (defined as any female unless surgically sterile or postmenopausal at least 12 months) should be instructed to contact the Investigator immediately if they suspect they might be pregnant while participating in this study. Any pregnancy that occurs during study participation must be reported to Vanda Pharmaceuticals Inc. (or designee) within 24 hours of learning of its occurrence and must be followed to determine outcome. If a patient becomes pregnant, she will be discontinued from the study.

11.1.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a semi-structured clinical interview designed to systematically assess and track suicidal adverse events (behavior and ideation) throughout different settings including clinical trials. This scale was developed by researchers at Columbia University and will be administered in this study as specified in the Schedule of Evaluations (Table 2). The Screening/Baseline version of the C-SSRS will be completed at Visit 1 and the Since Last Visit version of the C-SSRS will be completed at Visits 2-6. Results from the C-SSRS will be listed for each patient. These data will also be summarized for each treatment group and for suicidal ideation events, suicidal behaviors, and completed suicides.

11.1.6.1. Guidelines on Handling Positive Results (C-SSRS)

A positive answer to any of the following questions triggers immediate referral to mental health services and patient safety precautions since it indicates a severe risk and clear need for further evaluation and clinical management*:

1. A positive answer to Question 4 or 5 in the **Severity of Ideation Subscale** indicating presence of ideation with at least some intent to die in the past one month.
2. Presence of ANY suicidal behavior (suicide attempt, interrupted attempt, aborted attempt and preparatory behavior) in **Suicidal Behavior Subscale** in the past 3 months.

A positive answer to any of the following questions in conjunction with clinical judgment triggers immediate hospitalization or calling the local police or 911 if a hospital is not available since the patient may be at high risk of suicide.

1. A positive answer to Question 5 in the **Severity of Ideation Subscale** indicating presence of ideation with intent to die in the past one month.
2. Presence of ANY suicidal behavior (suicide attempt, interrupted attempt, aborted attempt and preparatory behavior) in **Suicidal Behavior Subscale** in the past 1 week.

11.1.7. Definitions Related to Safety

11.1.7.1. Adverse Event

An ***adverse event*** (AE) is defined as any untoward medical occurrence in a clinical investigation patient that does not necessarily have causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory

* The C-SSRS informs, but does not replace, clinical judgment. If any clinician has a suspicion of suicide risk, initiate the referrals and safety measures at the level deemed appropriate.

finding), symptom, or disease temporally associated with clinical study whether or not related to the investigational product.

Clinically significant findings or changes in assessments should be recorded as AEs. Every attempt should be made to describe the AE in the form of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be reported individually.

11.1.7.2. Serious Adverse Event

AEs are classified as serious or non-serious. A ***serious adverse event*** is defined as any untoward medical occurrence that occurs during clinical study that meets one of the following criteria as shown in Table 5.

Table 5: SAE Criteria and Definitions

SAE Criteria	Definition
Death of Patient	An event that results in the death of the patient.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly/Birth Defect	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include transient interruptions of daily activities or experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome[1]	An important medical event that, based on medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of a patient, life-threatening, patient hospitalization, prolongation of existing hospitalization, congenital anomaly, or persistent or significant disability/incapacity).

[1] Important Medical Events may be classified as serious or non-serious events at the discretion of the Investigator.

All AEs that do not meet the above criteria should be classified as ***non-serious adverse events.*** Elective surgeries requiring hospitalization and hospitalizations for social reasons are not considered SAEs.

11.1.7.3. Adverse Event Follow-up

Patients with non-serious AEs that are ongoing at the patient's last study visit must be followed until resolution or for 30 days after the patient's last study visit, whichever comes first. Non-serious AE that are reported during the 7 days following the patient's last study visit will be recorded on the Adverse Events CRF and followed until resolution or for up to the 30 days after the patient's last study visit, whichever comes first. SAEs will be followed until the event resolves or the event or sequelae stabilize. SAEs that are reported within 30 days of the patient's last study visit should be reported as indicated in Section 11.1.10.

11.1.7.4. Adverse Event Reporting Period

AEs are to be recorded in the source documents from the time of the patient's informed consent signature until the end of the patient's study participation. Each AE, both serious and non-serious, will also be reported on the Adverse Events CRF. CRF Completion Instructions will be provided to each investigational site. If the patient reports or the Investigator learns of a new AE(s) up to 7 days after the patient's last study visit or a new SAE(s) up to 30 days after the patient's last study visit, the investigational site personnel will ensure that these data are recorded on the Adverse Events CRF for the study. The period during which an SAE must be reported may be extended if there is a strong suspicion that the event being reported is related to the study medication or a study procedure.

11.1.7.5. Pre-Existing Condition

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the characteristics of the condition worsen during the study period.

11.1.8. Relationship to Study Medication

Each AE is to be reported on the AE CRF. The Investigator is responsible for making an assessment of the likelihood that an AE is causally related to the study medication. The Investigator should choose one of the five choices of causality.

- **Certain:** occurs in a reasonable time after study drug administration and cannot be explained by concurrent disease or drugs. The event should respond to withdrawal of study drug (de-challenge) and recur with re-challenge when clinically plausible.
- **Probable:** occurs in a reasonable time after study drug administration and it is unlikely to be to be attributed to concurrent disease or drugs, and it has a response to de-challenge. Re-challenge information is not required to fulfill this definition.
- **Possible:** occurs in a reasonable time after study drug administration, but could be related to concurrent disease or drugs. De-challenge information may be lacking or unclear.
- **Unrelated:** the event has an improbable temporal relationship (too soon, or too late after study drug, or study drug is not taken) and is plausibly related to other drugs or underlying disease.

- **Unassessable:** available information is insufficient, contradictory, and cannot be supplemented or verified at the time of the report. **This assessment will be considered as "related" for all expedited reports until an alternative assessment is made.**

Adverse Event causality of "certain", "probable", "possible", and "unassessable" will be considered related to study medication.

11.1.9. Recording Adverse Events

11.1.9.1. Adverse Events during Study Period

At each study visit, the Investigator must seek information on AEs by questioning the patient and, as appropriate, by examining the patient. Information on all AEs should be recorded immediately in the source document and in the appropriate AE module of the CRF. All signs, symptoms, and abnormal diagnostic procedure results that are considered clearly related should be grouped and recorded in the source document as one diagnosis. All AEs occurring during the study period must be recorded.

11.1.9.2. Post-Study Adverse Event

At the last scheduled visit, the Investigator should instruct each patient to report any subsequent event(s) that the patient or the patient's personal physician believes might reasonably be related to participation in this study. The Investigator should notify the study sponsor of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. The Investigator should also notify the sponsor if they become aware of the development of cancer or a congenital anomaly in any offspring conceived subsequent to a patient's study participation.

11.1.9.3. Abnormal Laboratory Values

Abnormal laboratory values or test results should not generally be considered adverse events, unless deemed clinically significant by the Investigator. Assessment of signs or symptoms or requirement for therapeutic intervention should be considered when determining clinical significance. Record clinical significant laboratory values on the Adverse Events CRF using an appropriate diagnostic description.

11.1.10. Reporting Adverse Events

11.1.10.1. Study Sponsor Notification by Investigator

All SAEs should be reported within 24 hours to Vanda Pharmaceuticals Inc. (or designee) using the fax number or e-mail address on the Serious Adverse Event Report form. The investigator should also call the medical monitor and Vanda program lead. The Investigator will keep a copy of the SAE Report form on file at the study site. The SAE form and detailed instructions will be provided to the site.

The initial report should contain as much information about the event as possible. Follow-up reports will provide any information missing at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report). In addition, significant new

information on ongoing SAEs should be reported promptly to Vanda Pharmaceuticals Inc. (or designee).

The initial and follow-up reports should identify patients by a unique patient ID rather than by patients' names, personal identification numbers, and/or address.

At the time of the initial report, the information listed in Table 6 should be provided.

Table 6: SAE Reporting Information

• Protocol Number • Site Number • Patient ID number • Event term • Event date of onset • Date site became aware of event	• Brief narrative with relevant medical history • Action taken regarding study medication administration • Seriousness criteria met • Date event met seriousness criteria • Initial PI assessment of relationship to study medication

11.1.10.2. Reporting of Events to Regulatory Authorities and IRB/EC

The investigator or designee will submit events to the IRB/EC according to individual committee requirements. Vanda Pharmaceuticals Inc. or designee will submit expedited reports of relevant events to Regulatory Authorities as required by local and federal regulations. Events will be reviewed for medical sense, expectedness, and causality.

11.1.11. Unblinding Procedures

The patients and medical staff will not be aware of which treatment is being administered. Data will remain blinded until clinical data have been reviewed, at which time, the randomization schedule may be released for the purposes of assessment of drug safety and efficacy.

Only if a patient's medical condition warrants, such as a medical emergency for which treatment requires knowledge of what study medication was given, may the Investigator break the blind to determine if the patient received tradipitant or placebo. If possible, the Medical Monitor and Vanda should be consulted prior to unblinding. If a patient's condition were so severe that time would not permit consulting with the Medical Monitor, the patient's assigned treatment can be unblinded by the Investigator using the IWRS system. In the event that it becomes necessary to unblind a patient's treatment assignment during the study, the Investigator should contact the Medical Monitor immediately, if not prior to unblinding, and explain the reason for unblinding.

12. PHARMACOGENETIC ASSESSMENT

The purpose of this research is to use genetic information to learn more about atopic dermatitis and the effects of tradipitant. The collection of this sample for PG research is mandatory. Patients cannot participate in this study if they do not agree to the collection of their blood sample for PG research.

During the screening (V1) visit, an additional 10 mL of blood sample will be drawn into an EDTA tube and gently inverted to prevent clotting. The study personnel will label the blood sample with a coded identification number. The sample will then be placed in a -70°C (or -20°C) freezer at the site. The sample will be shipped on dry ice to a central laboratory for DNA extraction and analysis. The results of future studies could trigger the need to test the sample; therefore, the sample will be held by Vanda Pharmaceuticals Inc. at a secure location for fifty (50) years. Vanda Pharmaceuticals Inc. does not intend to use any information to identify or contact the patients.

The data gathered from this study will be collectively analyzed, and several studies will be needed to confirm any findings. Because this analysis is preliminary and cannot be easily interpretable, patients will not have access to their genetic data. Families, relatives, or study personnel will also not have access to the patient's genetic data.

Patients will not be identified by name in any reports or publications resulting from this study. Data resulting from this study will not be placed on any patient's medical record. Only authorized personnel from Vanda Pharmaceuticals Inc. or its representatives will have access to your genetic information, though the FDA or other government agencies could request copies in order to verify that the research is being carried out properly and ethically. Unless ordered by a court of law, nobody else will have access to the genetic information.

If, at any time, the patient decides he or she no longer wishes to participate in the PG research, they may contact the study doctor, who will contact Vanda Pharmaceuticals Inc. Upon receiving the patient's request, Vanda Pharmaceuticals Inc. will destroy the patient's DNA sample and send a confirmation letter to the study doctor. Any information already generated from the sample before the request will not be destroy, but no new information will be generated from it.

Detailed instructions for PG sample collection, preparation, storage, and shipment will be included in the laboratory manual.

13. CYTOKINE PANEL ASSESSMENT

A blood sample for cytokine panel assessment will be drawn at screening (V1) and the end of evaluation phase (V6) (as well as EOS visits). The goal of this assessment is to identify changes in cytokine expression that may (1) elucidate the relationship between tradipitant treatment and treatment response or (2) identify immunomodulatory markers associated with atopic dermatitis and/or pruritus.

Detailed instructions for cytokine sample collection, preparation, storage, and shipment will be included in the laboratory manual.

14. FILAGGRIN MUTATION ANALYSIS

A blood sample for filaggrin gene mutation analysis will be drawn at Screening (V1). The goal of this assessment is to identify possible mutations to the filaggrin gene in the patient population that may elucidate further the relationship between tradipitant treatment and placebo response. Filaggrin null mutations are the characterized genetic mutation associated with atopic dermatitis.

Detailed instructions for filaggrin sample collection, preparation, storage, and shipment will be included in the laboratory manual.

15. STATISTICS

15.1. Sample Size and Accrual

A total sample size of 200 patients (100 per arm) will provide approximately 93% power to detect a 25% response rate difference, assuming 30% and 55% response rates in placebo and VLY-686 treatment groups respectively, based on a two-sided Fisher's Exact Test with a 5% significance level. In addition, 200 patients will provide about 90% power to detect a 1.2 point treatment difference in worst itch score, as measured by WI-NRS, between VLY-686 and placebo with a standard deviation (SD) of 2.6, based on a two-sided Student's T-Test with a 5% significance level.

15.2. Statistical Methods and Analysis Plan

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP). Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

15.2.1. General

Statistical analyses will be performed using two-sided tests.

Data will be summarized by treatment group (and by visit when applicable), with respect to demographic and baseline characteristics, efficacy variables, and safety variables.

Summary statistics will include the mean, N, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

For the analyses of change from baseline, only patients with a baseline and at least one (1) post-baseline measure will be included in the analysis. Unless otherwise specified, baseline is defined as the latest non-missing observation across all the visits in the screening phase, before the active study drug begins. Endpoint will be the latest non-missing observation across all the post-baseline visits in the evaluation phase.

Low enrolling sites will be pooled for analysis and the pooling algorithm will be determined prior to breaking the blind. The goal of pooling low enrolling sites is to have a sufficient number of patients per treatment group within a site for the analysis models and for the evaluation of the treatment-by-site interaction for the primary endpoint. Unless otherwise specified, the pooled sites will only be used in the analyses where the site has an effect. The actual sites rather than the pooled sites will be specified in the data listings.

Details of the model and the analyses will be specified in the SAP. All statistical analyses will be performed using SAS®, Version 9.1.3 or higher.

15.2.2. Patient Populations for Analysis

The following analysis populations will be defined for this study:

Intent-to-Treat: Any patient randomized into the study that receives a dose of study drug and that has completed at least one post-baseline efficacy measurement while on study medication;

Safety: Any patient randomized into the study that receives a dose of study drug;

Per-Protocol: Any patient who is randomized and receives the protocol required study drug exposure and required protocol processing.

Efficacy analyses will be performed on the Intent-to-Treat population and the Per-Protocol population. Safety summaries will be based on Safety set. Patient characteristics will be presented for all patients randomized.

15.2.3. Patient Disposition

Study completion and reasons for discontinuation for all randomized patients in the double-blind phase will be summarized for each treatment group. Discontinuations by reason will be tabulated by visit for each treatment group.

Time to discontinuation due to adverse events, lack of efficacy, and for any reason will be analyzed using Kaplan-Meier survival techniques; the log-rank test will be used for group comparison.

15.2.4. Demography and Other Baseline Data

Demographic data and patient characteristics at screening/baseline will be listed and summarized by treatment group for all randomized patients using descriptive statistics.

Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Past medical conditions will be defined as an onset date prior to randomization (Visit 2) and resolved (not on-going) as of Visit 2. Current medical conditions, defined as an onset date on or after the date of randomization (Visit 2) or an onset date prior to randomization (Visit 2) and unresolved (on-going) as of Visit 2, will be reported separately, but similarly to the past medical conditions. If both a past and a current (on-going) medical condition record are indicated for a condition, the condition will be presented under current medical conditions only.

15.2.5. Study Medication

The number of patients at each visit will be summarized by treatment group.

The compliance to study medication, as recorded in the CRF, will also be summarized by treatment group. The proportion of patients who are significantly noncompliant in the double-blind phase, as noted in Section 7.3 of this protocol, will be summarized by treatment groups.

15.2.6. Prior/Concomitant Therapy

Any medications or therapy present before the first dose of study medication (Visit 2) will be considered as prior medications. Concomitant medications (medications present while on study medication) will be recorded throughout the study and at early discontinuation. These medications will be coded using the WHO-drug dictionary. The number of patients from the Safety Population using prior or concomitant medications will be categorized by the WHO-drug category and preferred term, and presented for each treatment group. In any given category (e.g., drug category), a patient will be counted only once.

15.3. Efficacy Data Analysis

15.3.1. Primary Outcome and Methodology

The primary efficacy outcome measure for the double-blind phase will be the WI-NRS responder rate at Week 8. A WI-NRS (worst itch numerical rating scale) responder is defined as a patient achieving at least 4 points reduction from baseline in WI-NRS. The primary statistical method will be the CMH (Cochran–Mantel–Haenszel) test. A detailed description of the primary analysis model and the corresponding sensitivity analysis will be included in the SAP.

As stated previously, any changes in the statistical methods that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

15.3.2. Secondary Efficacy Analysis

The secondary efficacy outcomes include:

- WI-NRS;
- DDSS;
- Itch questionnaires including diary WI-NRS and VRS;
- WI-NRS responder at other time points;
- SCORAD;
- EASI;
- Proportion of patients with improvement on SCORAD index of at least 50%, 75% or 90% improvement;
- Proportion of patients with improvement on the EASI of at least 50%, 75% or 90% improvement;
- vIGA-AD;
- PGI-C;
- CGI-C;
- PBI-P;
- HRQOL-4;
- POEM;
- DLQI;
- ISQ;
- Pharmacokinetic-Pharmacodynamic correlation.

Continuous endpoints will be summarized and analyzed using MMRM (mixed effects model repeated measurement). Categorical endpoints will be analyzed by a CMH test. Details of the analysis will be described in the SAP.

Time to event data will be analyzed using the Kaplan-Meier method, and the treatment group differences will be tested by the log-rank test. Details of the analysis will be described in the SAP.

15.4. Safety Data Analysis

The primary assessment of safety will be based on the frequency of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and on the frequency of clinically notable abnormal vital signs, electrocardiograms (ECGs) and laboratory values. Other safety evaluations include changes in vital signs, changes in clinical laboratory evaluations, and changes in ECGs, physical exam findings during treatment, and suicide ideation (C-SSRS) and behavior events.

15.4.1. Adverse Events

Adverse events will be recorded throughout the study and at early discontinuation. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent adverse events will be defined as those events, which are newly occurring or worsening from baseline. In all cases, only treatment emergent adverse events will be summarized.

Treatment-emergent adverse events will be summarized within each treatment group by primary system organ class and preferred term. (***NOTE***: In any given category [e.g. body system], a patient will only be counted once.) The incidence rates of TEAEs will be analyzed as described in the SAP. Similar displays will be provided for SAE and prior (conditions ending prior to the first dose of study medication) and current (conditions present while on study medication) medical conditions.

Adverse events will further be categorized by severity, relationship to study medication, and action taken. Other information collected will be listed, as appropriate. Any event starting more than 3 days after the final dose of study medication will be excluded from the above tables and only listed, unless the event caused discontinuation.

The proportions of patients experiencing SAEs and AEs resulting in discontinuation from the study will be summarized by treatment groups.

15.4.2. Laboratory Data

Clinical Laboratory Data

The summary statistics of raw data (hematology and chemistry) and change from baseline values will be presented, as well as shift tables from baseline to post-baseline values using normal ranges. For urinalysis parameters, the number and percentage of patients falling under each category of the test will be presented.

Clinical laboratory data will be summarized for each treatment group by presenting the proportions of patients with clinically notable abnormalities (Appendix 22.1).

Clinically notable values will be identified according to the criteria identified in the FDA's "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates" (Revised

2-APR-87) provided by the FDA Division of Neuropharmacological Drug Products (DNDP). Differences in incidence rates between the treatment groups will be tested as described in the SAP.

15.4.3. Vital Signs and Body Measurements

Data from vital signs and body measurements will be listed, clinically notable values (Appendix 22.1) will be flagged, and any other information collected will be listed. Data will also be summarized by treatment group using mean change from baseline and proportions of patients with values outside the normal range, and values that were clinically notable.

15.4.4. Electrocardiogram (ECG)

Results from the ECG will be listed for each patient. These data will also be summarized for each treatment group by presenting patients with newly occurring or worsening ECG abnormalities.

15.4.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be listed for each patient. These data will also be summarized by treatment group and for suicidal ideation events, suicidal behaviors, and completed suicides. In particular, for each of the following suicide related events, the number and percent of patients with the event will be enumerated by treatment group: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead. Details of the analysis will be provided in the SAP.

15.5. Subgroup Analysis

The subgroup analysis (such as, sex, age, baseline illness severity etc.) for efficacy variables and safety variables may be conducted as described in the SAP.

15.6. Interim Analysis

No interim analyses are planned.

15.7. Deviations in Analysis from Statistical Plan and Other Issues

During the analysis and reporting process, any deviations from the statistical plan designed for this protocol will be described and justified in the final report.

16. DIRECT ACCESS TO SOURCE DOCUMENTS

16.1. Definition of Source Document

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records (ICH E6, Section 6.10) include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical or technical departments involved in the clinical trial. The Investigator is required to maintain adequate and accurate source documents that record all observations and other data pertinent to this study.

16.2. Study Monitoring

The Sponsor or CRO's monitor will maintain contact with the Investigator and designated staff between study visits. Monitoring visits to each investigational site will be conducted by the assigned monitor as frequently as stipulated in the monitoring plan. The Investigator must designate an adequate space to conduct the monitoring visit and will allocate adequate time for Vanda Pharmaceuticals Inc.'s monitoring activities. The CRFs and patient's corresponding original medical records (source documents) are to be fully available for review by the monitor.

The purposes of clinical trial monitoring are to verify that:

- the rights and well-being of the human patients are protected;
- reported trial data are accurate, complete and verifiable from source documents; and
- trial conduct is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

16.3. Audits and Inspections

In addition to routine monitoring procedures, Vanda Pharmaceuticals Inc. may request an independent Good Clinical Practice Quality Assurance contractor to perform audits of clinical research activities to evaluate compliance with principles of Good Clinical Practice.

The Investigator will ensure that the compliance or quality assurance reviewer is allowed to:

- review all of the study-related documents (e.g., study records and source documents) and study related facilities (e.g., pharmacy, diagnostic laboratory)
- discuss the conduct of the study with the Investigator

A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the CRO and Vanda Pharmaceuticals Inc. immediately that this request has been made, and promptly forward copies of the audit reports to Vanda Pharmaceuticals Inc.

17. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, Standard Operating Procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits will be made periodically by the Sponsor's (or CRO's) qualified compliance auditing team, which is an independent function from the study conduct team.

17.1. Data Collection

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. A detailed guideline on the completion of the CRF will be provided to the site. Monitors will highlight any discrepancies found in the documentation of study conduct and ensure that appropriate site personnel address the discrepancies.

17.2. Clinical Data Management

Data from the CRFs and other external data (e.g. laboratory data) will be entered into a clinical database as specified in the Sponsor (or CRO's) data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

17.3. Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

18. ETHICS

18.1. Ethics Review

This protocol and any amendments will be submitted to a properly constituted EC or IRB, in agreement with local legal prescriptions (ICH 3.1-3.4), for formal approval of the study conduct.

All patients for this study will be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a patient by the investigative site, using the EC/IRB-approved consent form, must be obtained before that patient is submitted to any study procedure. This consent form must be signed by the patient, or patient's legally acceptable surrogate, and the Investigator-designated research professional obtaining the consent.

18.2. Ethical Conduct of the Study

This study is to be conducted according to US and international standards of Good Clinical Practice, as described in the following documents:

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice.

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56).
3. Declaration of Helsinki (current)

18.3. Written Informed Consent

Prior to any study procedures being performed, patients and persons conducting the consent process will be required to sign and date the IRB/EC approved informed consent, and each patient will be given a copy. In addition, this information should be recorded in the patient's medical record. The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki, US 21 CFR Part 50.25, ICH GCP, and in accordance with any local regulations. The Investigator is responsible for the preparation, content, and IRB/EC approval of the consent form. The consent form must be approved by the IRB/EC and be acceptable to the study Sponsor or designee. The consent form must be written in language fully comprehensible to the prospective patient. The Investigator or designee will give the patient adequate opportunity to read the consent form and to discuss any questions.

19. DATA HANDLING AND RECORD KEEPING

Throughout this study, all data will be linked to the electronic CRF via the unique patient identification number. However, patients' initials and date of birth may also be collected in accordance with local and/or country regulations, and used to assist the Sponsor or designee with verification of data. These data will be blinded in corresponding analyses. Medical records of consented patients will be reviewed by the Sponsor or designee including, but not limited to, laboratory test results, ECG reports, hospital admission and discharge summaries for admissions occurring during a patient's participation in the study, and autopsy reports for deaths occurring during the study. The Sponsor and/or designee accessing the records will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patient identities.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the patient before the patient is entered into the study.

19.1. Retention of Records

It is the Investigator's responsibility to retain essential study documents for at least 2 years after the last approval of a marketing application in his/her country for the investigational product and until there are no pending or contemplated marketing applications in his/her country, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product and they have written approval from the sponsor to dispose of the study documents. These documents should be retained for a longer period if required by an agreement with the sponsor or if legally required. In such an instance, it is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator must receive Sponsor approval prior to destroying any records associated with the study.

20. ADMINISTRATIVE PROCEDURES

20.1. Changes to the protocol

Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol shall be conducted as described. Any significant protocol deviation must be documented in the source documents.

Any change or addition to this protocol requires a written protocol amendment that must be approved by Vanda Pharmaceuticals Inc. prior to IRB/EC and regulatory agency submission. The Investigators must sign the amendment before implementation.

Substantial amendments require approval from the regulatory authority and/or the responsible ethics committee. Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the patients, or
- the scientific value of the trial, or
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial.

In addition, if amendments affect the informed consent, a revised informed consent has to be submitted to the responsible ethics committee, before changes in study procedures are implemented. These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Vanda Pharmaceuticals Inc. in the interests of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the Vanda Pharmaceuticals Inc. monitor and the IRB/EC should be notified.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or Ethical Committee approval but the Ethical Committee must be kept informed of such administrative changes.

20.2. Discontinuation of Study

Vanda Pharmaceuticals Inc. reserves the right to discontinue any study for administrative reasons at any time. If appropriate, reimbursement for reasonable expenses will be made.

20.3. Publication of Results

Manuscript(s) for publication, texts of presentations, abstracts of papers, and similar material should be submitted to Vanda Pharmaceuticals Inc. for review and comment at least sixty (60) days prior to submission for publication, public dissemination, or review by a program committee. Upon request from Vanda Pharmaceuticals Inc., the site shall remove any confidential information (other than study results) prior to submitting or presenting the materials. Vanda Pharmaceuticals Inc. shall notify the Investigator in writing within sixty (60) days of receipt of such draft whether

it contains information deemed to be confidential or information that if published within thirty (30) days would have an adverse effect on Sponsor's business interests, including but not limited to a patent application in which Vanda Pharmaceuticals Inc. owns an interest. In the latter case, Vanda Pharmaceuticals Inc. may request a delay and Investigator agrees to delay publication or presentation for a period not exceeding ninety (90) days. An independent joint publication may be authored by Investigators from the multiple sites. The Investigator, therefore, agrees not to independently publish the results of the study before the publication of such multi-site paper, if applicable. No party heretofore mentioned shall use any other party's name, or Vanda Pharmaceuticals Inc.'s name, in connection with any advertising, publication, or promotion without prior written permission.

20.4. Investigator Agreement

This protocol is being provided to me for conducting a clinical trial for Vanda Pharmaceuticals Inc. The information contained in the protocol is confidential and proprietary to Vanda Pharmaceuticals Inc. Study documents provided by Vanda Pharmaceuticals Inc. (protocols, Investigator's Brochures, and other material) will be stored appropriately to ensure their confidentiality.

I may disclose the contents of this protocol to study personnel under my supervision and my Institutional Review Board or Ethical Committee for the purpose of conducting this trial only.

The information provided by Vanda Pharmaceuticals Inc. to me may not be disclosed to others without direct written authorization from Vanda Pharmaceutical Inc., except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined and according to the moral, ethical, and scientific principles governing the Declaration of Helsinki and the principles of GCP and applicable local requirements.

I understand that should the decision be made by Vanda Pharmaceuticals Inc. to terminate prematurely or suspend the clinical trial at any time, with or without cause, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the clinical trial, I will immediately communicate such decision in writing to Vanda Pharmaceuticals Inc.

By my signature below, I attest that I have read, and understood, and agree to abide by the conditions, instructions, and restrictions contained in this protocol.

Investigator

Name: _____

Signature: _____

Date: _____

Site Name: _____

Site Number: _____

Protocol Number: **VP-VLY-686-3102 Amendment 1, 12 March 2020**

21. REFERENCES

1. DaVeiga, S. P. Epidemiology of atopic dermatitis: a review. *Allergy asthma Proc.* **33,** 227–34 (2012).

2. Berke, R., Singh, A. & Guralnick, M. Atopic dermatitis: an overview. *Am.Fam.Physician* **86,** 35–42 (2012).

3. Raap, U., Stander, S. & Metz, M. Pathophysiology of itch and new treatments. *Curr.Opin.Allergy Clin.Immunol.* **11,** 420–427 (2011).

4. Correale, C. E., Walker, C., Murphy, L. & Craig, T. J. Atopic dermatitis: a review of diagnosis and treatment. *Am.Fam.Physician* **60,** 1110–1191 (1999).

5. Wei, W. *et al.* Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. *J. Dermatol.* 1–8 (2017). doi:10.1111/1346-8138.14116

6. Almeida, T. A. *et al.* Tachykinins and tachykinin receptors: structure and activity relationships. *Curr.Med.Chem.* **11,** 2045–2081 (2004).

7. Fiebich, B. L., Schleicher, S., Butcher, R. D., Craig, A. & Lieb, K. The neuropeptide substance P activates p38 mitogen-activated protein kinase resulting in IL-6 expression independently from NF-kappa B. *J.Immunol.* **165,** 5606–5611 (2000).

8. Lieb, K. *et al.* Substance P and histamine induce interleukin-6 expression in human astrocytoma cells by a mechanism involving protein kinase C and nuclear factor-IL-6. *J.Neurochem.* **70,** 1577–1583 (1998).

9. Otsuka, M. & Yoshioka, K. Neurotransmitter functions of mammalian tachykinins. *Physiol Rev.* **73,** 229–308 (1993).

10. Stander, S., Siepmann, D., Herrgott, I., Sunderkotter, C. & Luger, T. A. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS.ONE.* **5,** e10968 (2010).

11. Reich, A. *et al.* Visual analogue scale: evaluation of the instrument for the assessment of pruritus. *Acta Derm.Venereol.* **92,** 497–501 (2012).

12. Oranje, A. P. Practical issues on interpretation of scoring atopic dermatitis: SCORAD Index, objective SCORAD, patient-oriented SCORAD and Three-Item Severity score. *Curr.Probl.Dermatol.* **41,** 149–155 (2011).

13. Hanifin, J. M. *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp.Dermatol.* **10,** 11–18 (2001).

14. Augustin, M. *et al.* The patient benefit index: a novel approach in patient-defined outcomes measurement for skin diseases. *Arch.Dermatol.Res.* **301,** 561–571 (2009).

15. Blome, C., Maares, J., Diepgen, T., Jeffrustenbach, S. & Augustin, M. Measurement of patient-relevant benefits in the treatment of chronic hand eczema - A novel approach. *Contact Dermatitis* **61,** 39–45 (2009).

16. Charman, C. R., Venn, A. J. & Williams, H. C. The patient-oriented eczema measure:

development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch. Dermatol.* **140,** 1513–9 (2004).

17. Finlay, A. Y. & Khan, G. K. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin.Exp.Dermatol.* **19,** 210–216 (1994).

18. Okun, M. L. *et al.* Psychometric evaluation of the insomnia symptom questionnaire: A self-report measure to identify chronic insomia. *J. Clin. Sleep Med.* **5,** 41–51 (2009).

19. Centers for Disease Control and Prevention. *Measuring Healthy Days: Population Assessment of Health-Related Quality of Life*. (2000).

22. APPENDICES

22.1. Laboratory Ranges Used to Identify Clinically Notable Abnormal Laboratory Values

Criteria for identifying laboratory values as Potentially Clinically Notable Abnormalities are based on the Guidelines for the Division of Neuropharmacological Drug Products, US Food and Drug Administration (revised on April 2, 1987).

Variable		Criterion Values	
		Standard Units	**SI Units**
Chemistry			
SGOT		≥ 3 x Upper Limit Normal	
SGPT		≥ 3 x Upper Limit Normal	
Alkaline Phosphatase		≥ 3 x Upper Limit Normal	
LDH		≥ 3 x Upper Limit Normal	
BUN		≥ 30 mg/dL	≥ 10.7 μM
Creatinine		≥ 2.0 mg/dL	≥ 176.8 μM
Uric Acid	Male	≥ 10.5 mg/dL	≥ 624.6 μM
	Female	≥ 8.5 mg/dL	≥ 505.6 μM
Bilirubin (Total)		≥ 2.0 mg/dL	≥ 34.2 μM
Hematology			
Hematocrit	Male	≤ 37%	
	Female	≤ 32%	
Hemoglobin	Male	≤ 11.5 g/dL	
	Female	≤ 9.5 g/dL	
Platelets		≤ 75,000/mm^3 or ≥ 700,000/mm^3	≤ 75 x 10^9/L or ≥ 700 x 10^9/L
Leukocytes		≤ 2,800/mm^3 or ≥ 16,000/mm^3	≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L
Eosinophils		≥ 10%	
Neutrophils		≤ 15%	
Urinalysis			
Protein		Increase of ≥ 2 units	
Glucose		Increase of ≥ 2 units	
Casts		Increase of ≥ 2 units	

22.2. Vital Signs Values

Criteria for identifying vital signs values as Potentially Clinically Notable Abnormalities are based on the Guidelines for the Division of Neuropharmacological Drug Products, US Food and Drug Administration (revised on April 2, 1987).

Variable	**Criteria**		**Change Relative to Baseline**
Heart Rate	≥ 120 bpm	and an	increased of ≥ 15 bpm
	≤ 50 bpm	and a	decrease of ≥ 15 bpm
Systolic			
Blood Pressure	≥ 180 mmHg	and an	increase of ≥ 20 mmHg
	≤ 90 mmHg	and a	decrease of ≥ 20 mmHg
Diastolic			
Blood Pressure	≥ 105 mmHg	and an	increase of ≥ 15 mmHg
	≤ 50 mmHg	and a	decrease of ≥ 15 mmHg
Temperature	≥ 38.3 °C	and a	change of ≥ 1.1 °C
	≥ 101 °F	and a	change of ≥ 2 °F
Weight	--		change of ≥ 7% body weight