TRADIPITANT

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

Document Type:	Statistical Analysis Plan
Sponsor:	Vanda Pharmaceuticals Inc. 2200 Pennsylvania Avenue NW Suite 300E Washington, DC 20037
Study Product:	tradipitant
Protocol Number:	VP-VLY-686-3102
Study Phase:	III
IND Number:	122741
NCT Number:	NCT04140695

Date: 02 June 2022
Status: Final

1. STATISTICS

1.1. 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.

1.2. 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.

1.2.1. 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.

1.2.2. 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.

1.2.3. 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.

1.2.4. 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.

1.2.5. 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 9.3 of this protocol, will be summarized by treatment groups.

1.2.6. 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.

1.3. Efficacy Data Analysis

1.3.1. Primary Outcome and Methodology

The primary efficacy outcome measure for the double-blind phase will be the WI-NRS responder rate at Week 2. 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.

1.3.2. 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.

1.4. 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 assessments, and changes in ECGs, physical exam findings during treatment, and suicide ideation (C-SSRS) and behavior events.

1.4.1. 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.

1.4.2. 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 24.1).

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.

1.4.3. Vital Signs and Body Measurements

Data from vital signs and body measurements will be listed, clinically notable values (Appendix 24.1) 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.

1.4.4. 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.

1.4.5. 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.

1.5. 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.

1.6. Interim Analysis

No interim analyses are planned.

1.7. 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.