Motion Sifnos: A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy of Tradipitant in Subjects Affected by Motion Sickness during Travel

Document Type:	Clinical Study Protocol
Sponsor:	Vanda Pharmaceuticals Inc. 2200 Pennsylvania Ave. NW Suite 300E Washington, DC 20037 USA
Study Product:	tradipitant (VLY-686)
Protocol Number:	VP-VLY-686-2401
Study Phase:	II
IND Number:	141315
NCT Number:	NCT03772340

Date: 03 18 2019
Status: Final

Name of Sponsor/Company:
Vanda Pharmaceuticals Inc.

Name of Investigational Product:
Tradipitant/VLY-686

Name of Active Ingredient:
Tradipitant/VLY-686

Title of Study: Motion Sifnos: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in subjects affected by motion sickness during travel

Study Center(s): 1

Studied Period:	**Phase of Development:**
First subject enrolled: December 2018 Estimated study duration: Four months	Phase II

Number of Subjects (planned): Approximately 150 affected subjects will be randomized and assigned to tradipitant 170 mg or placebo in a 1:1 ratio. Treatment assignments will be made according to a randomization schedule. Vehicle travel assessment will occur either in a motor vehicle (2A) or a boat (2B).

Diagnosis and Main Criteria for Inclusion: Adult males or females aged 18-75, inclusive, with a history of motion sickness who meet inclusion criteria.

Investigational Product, Dosage and Mode of Administration: Tradipitant 170 mg PO or placebo once approximately 60 minutes before entering the vehicle.

Duration of Treatment: If motor vehicle travel, one drive lasting approximately 120-240 minutes. If boat travel, one trip lasting approximately 90-300 minutes on the moving vessel.

Reference Therapy, Dosage and Mode of Administration: Placebo capsules will be provided in size and appearance identical to those containing tradipitant and will be administered orally.

Primary Objectives:

1. To assess the effects of tradipitant 170 mg on the symptoms of motion sickness during vehicle travel as measured by the MSSS.

Secondary Objectives:

1. To assess the effects of tradipitant 170 mg on the symptoms of motion sickness as measured by subjective parameter MSAQ.
2. To assess the effects of tradipitant 170 mg on the symptoms of motion sickness as measured by subjective parameter LTMSQ.
3. To assess the effects of tradipitant 170 mg on the symptoms of motion sickness as measured by subjective parameter SDQ.
4. To assess the effects of tradipitant 170 mg on the symptoms of motion sickness as measured by subjective parameter PGI-S.
5. To assess the effects of tradipitant 170 mg on the symptoms of anxiety as measured by STAI-6.
6. To assess the safety and tolerability of a single oral dose of tradipitant 170 mg.

Overall Design: This is a randomized, double-blind placebo-controlled trial to investigate the efficacy and safety of a single 170 mg oral dose of tradipitant in motion sickness affected male and female subjects during vehicle travel.

The screening phase will consist of the subject taking the motion sickness eligibility questionnaire (MSEQ) to assess their susceptibility to motion sickness. Following this questionnaire, the subject will be interviewed to understand their history of motion sickness. If the subject meets pre-defined criteria as being eligible based on the motion sickness eligibility questionnaire and interview, they will proceed to the next step of a screening visit at a clinical site with a physician and simultaneously a lab visit for a blood draw. If the subject passes the medical visit screen and blood draw based on inclusion and exclusion criteria they will proceed to the evaluation phase.

Eligible subjects will be randomized 1:1 to tradipitant 170 mg or placebo. Eligible subjects will be instructed to take tradipitant 170 mg or placebo approximately 60 minutes prior to entering the vehicle. Vehicle travel assessment will occur either in a motor vehicle (2A) or boat (2B). Subjects will be driven on a pre-determined route for approximately 120-240 minutes during motor vehicle travel or approximately 90-300 minutes during boat travel. The MSSS questionnaire will be completed approximately every 30 minutes of vehicle travel and the STAI-6 will be completed at the beginning of vehicle travel, prior to drug administration.

After the completion of the vehicle travel, subjects will complete several questionnaires including a motion sickness severity scale questionnaire (MSSS), a travel questionnaire for the subject to assess the likelihood of their travel experience to induce motion sickness based on experience scored from 1-9 (LTMSQ), a motion sickness assessment questionnaire (MSAQ), a questionnaire to record the duration of symptoms (SDQ), the 6-item Spielberger State-Trait Anxiety Inventory (STAI-6), and the Patient Global Impression of Severity Questionnaire (PGI-S). All questionnaires will be submitted for analysis. Subjects will then return for an EOS visit within 7 days of visit 2.

Statistical Methods: Motion sickness symptoms will be assessed by the MSSS questionnaire, with the other questionnaires serving as secondary endpoints. Motion sickness symptoms as measured by MSSS will be assessed by analysis of variance with the treatment group, vehicle, and site, if more than one site, as main effects. The primary efficacy analysis will be based on the ITT population.

The statistical analyses will be detailed in the statistical analysis plan.

1. STATISTICS

1.1. Sample Size and Accrual

A sample size of up to 75 subjects per arm (150 total) will provide around 86% power to detect a 0.8 point difference in motion sickness severity between Tradipitant and Placebo, with the standard deviation of motion sickness severity assumed to be around 1.6.

1.2. Statistical Methods and Analysis Plan

1.2.1. General

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), which will be finalized prior to unblinding. Any changes in the statistical methods described in this protocol that occur prior to unblinding will be documented in the statistical analysis plan and will not require a protocol amendment.

Statistical hypothesis testing will be performed at two sided alpha level of 0.05. For continuous variables, population size (N for sample size and n for available data), the mean, the standard deviation (SD), the median, the minimum and maximum values will be tabulated. For categorical variables, population size and frequencies in each category will be tabulated.

1.2.2. Subject Populations for Analysis

Three subject populations will be defined:

Intent-To-Treat population (ITT population): Any subject randomized that received a dose of study drug and had post baseline MSSS data. ITT population are analyzed as they are randomized, regardless of which treatment a subject received.

Safety population (Safety population): Any subject randomized that received a dose of study drug. Safety population are analyzed based on the actual treatment received.

Per-Protocol population (PP population): Any subject who was randomized and received the protocol required study drug exposure and required protocol processing. Blinded clinical data will be reviewed prior to data lock to finalize the list of PP population.

The primary analyses will be performed in the intent-to-treat population. Analyses of efficacy endpoints in the PP population will provide supportive evidence. Safety summaries will be based on the Safety population.

1.2.3. Subject Disposition

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

1.2.4. Demography and Other Baseline Data

Demographic data will be tabulated by treatment group. 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.

1.2.5. Study Medication

Exposure and compliance will be tabulated by treatment groups.

1.2.6. Prior/Concomitant Therapy

Prior/concomitant therapy will be summarized.

Any medications or therapy present before the first dose of study medication 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 subjects from the Safety Set 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 subject will be counted only once.

1.3. Efficacy Data Analysis

1.3.1. Primary Outcome and Methodology

The primary endpoint is motion sickness severity assessed by the MSSS questionnaire. The primary analysis method is ANOVA with the treatment group, vehicle, and site, if more than one site, as main effects. The primary efficacy analysis will be based on the ITT population.

The statistical analyses will be detailed in the statistical analysis plan (SAP).

1.3.2. Secondary Efficacy Analysis

The secondary endpoints from other questionnaires (MSAQ, SDQ, LTMSQ, STAI-6, PGI-S) will be analyzed in the same way as the primary endpoint. Other statistical methods may also be used as deemed appropriate. The details will be provided in the SAP.

1.4. Safety Data Analysis

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 by presenting for each group the number and percentage of subjects having any treatment-emergent AE, having an AE in each body system, and having each individual AE. (Note: In any given category [e.g. body system] a subject will only be counted once.) Similar displays will be provided for 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 subjects experiencing SAEs and AEs resulting in discontinuation from the study will also be summarized.

1.4.2. Laboratory Data

The summary statistics of raw data (hematology and chemistry) and change from baseline values (means, medians, standard deviations, ranges) 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 subjects 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 subjects with clinically notable abnormalities. Clinically notable values (Appendix 20.1) 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).

1.4.3. Vital Signs and Body Measurements

Data from vital signs will be listed, clinically notable values as previously defined (Section 11.1.3) will be flagged, and any other information collected will be listed. Data will be summarized by group using mean change from baseline and proportions of subjects 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 subject. These data will also be summarized for each treatment group by presenting subjects with ECG abnormalities; shift tables; summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

1.5. Subgroup Analysis

Subgroup analysis (such as, gender, age, race etc.) for efficacy variables and safety variables may be conducted.

1.6. Interim Analysis

No interim analysis 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.