Motion Syros: 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-686-3401
Study Phase:	III
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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 Syros: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in participants affected by motion sickness during travel	
Study Center(s): Approximately 10-15	
Studied Period: First participant enrolled: February 2020 Estimated study duration: Forty months	**Phase of Development:** Phase III
Number of Participants (planned): Approximately 300 affected participants will be randomized and assigned to tradipitant 85 mg, tradipitant 170 mg, or placebo in a 1:1:1 ratio. Treatment assignments will be made according to a randomization schedule.	
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, tradipitant 85 mg PO, or placebo once approximately 60 minutes before entering the vehicle.	
Duration of Treatment: One boat trip lasting approximately 120-300 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. The 170 mg tradipitant dosage will consist of two tradipitant 85 mg capsules. The 85 mg tradipitant dosage will consist of one 85 mg tradipitant capsule and one placebo capsule. The placebo group will consist of two capsules matching in appearance to the 85 mg tradipitant capsules.	

Primary Objectives:

1. To assess the effects of tradipitant 85 mg and 170 mg on the prevention of vomiting from motion sickness during vehicle travel as measured by Vomiting Assessment (VA).

Secondary Objectives:

1. To assess the effects of tradipitant 85 mg and 170 mg on nausea severity as measured by subjective parameter Nausea Assessment (NA).
2. To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter MSAQ.
3. To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter PGI-S.
4. To assess the safety and tolerability of a single oral dose of tradipitant 85 mg and 170 mg.

Overall Design: This is a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of a single 85 mg or 170 mg oral dose of tradipitant in motion sickness affected male and female participants during vehicle travel.

The screening phase will consist of the participant taking the motion sickness eligibility questionnaire (MSEQ) to assess their susceptibility to motion sickness. Following this questionnaire, the participant will be interviewed to understand their history of motion sickness. If the participant 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 participant passes the medical visit screen and blood draw based on inclusion and exclusion criteria they will proceed to the evaluation phase.

Eligible participants will be randomized 1:1:1 to tradipitant 85 mg, 170 mg, or placebo. Eligible participants will be instructed to take tradipitant 85 mg, 170 mg, or placebo approximately 60 minutes prior to entering the boat. Boat travel will last approximately 120-300 minutes. The Vomiting Assessment (VA) and Nausea Assessment (NA) questionnaires will be completed approximately every 30 minutes of vehicle travel.

After the completion of the vehicle travel, the participant will complete the Patient Global Impression of Severity Questionnaire (PGI-S) and the Motion Sickness Assessment Questionnaire (MSAQ).

All questionnaires will be submitted for analysis. Participants will then return for an EOS visit within 7 days of Visit 2.

Statistical Methods: Prevention of vomiting will be assessed by the VA, with the other questionnaires serving as secondary endpoints. The percentage of vomiting will be assessed by CMH test adjusting for the trips, and nausea severity measured by NA will be assessed by analysis of variance with the treatment group and trip 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 100 participants per arm (300 total) will provide around 96% power to detect a 26% difference in vomiting between tradipitant and placebo assuming 50% of participants on placebo will vomit and 24% of participants on tradipitant will vomit.

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 unless specified otherwise. 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.

Multiplicity adjustments will be used to control study wise type I error at 5%. The details will be provided in the SAP.

1.2.2. Participant Populations for Analysis

Three participant populations will be defined:

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

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

Per-Protocol population (PP population): Any participant 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. Participant Disposition

Study completion and reasons for discontinuation for all randomized participants 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 participants 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 participant will be counted only once.

1.3. Efficacy Data Analysis

1.3.1. Primary Outcome and Methodology

The primary endpoint is the percentage of vomiting as assessed by the VA questionnaire. The primary analysis method is CMH test adjusting for trips. The primary efficacy analysis will be based on the ITT population.

As there are two active doses, the higher dose 170 mg will be tested first. Vomiting rate in the 85 mg group will only be tested if the test in 170 mg group is positive.

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

1.3.2. Secondary Efficacy Analysis

The continuous secondary endpoints from NA as well as those from other questionnaires (MSAQ, PGI-S) will be analyzed by an analysis of variance (ANOVA) model with the main effects of treatment group and trip. The categorical secondary endpoints 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 participants 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 participant 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 participants 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 participants 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 participants 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 participants 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 participant. These data will also be summarized for each treatment group by presenting participants 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.