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

Authors: Vasilios M. Polymeropoulos, MD
Austin Anderson
Maggie Gibson

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

IND Number: 141315

Date: 11 19 2019
Status: Final
Number of Pages: 69

SIGNATURE PAGE FOR VANDA PHARMACEUTICALS INC.

VP-VLY-686-3401

Approved by the following:

Program Lead: _____ 11/20/2019

Vasilios Polymeropoulos, M.D. Date

Director of Medical Analytics

Medical Director: _____ 11/20/19

Christos Polymeropoulos, M.D. Date

Senior Medical Director

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	
Studied Period: First participant enrolled: December 2019 Estimated study duration: Eight 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 MSSS.

Secondary Objectives:

1. To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter MSSS.
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 Motion Sickness Severity Scale (MSSS) questionnaire 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: Motion sickness symptoms including vomiting will be assessed by the MSSS, 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 MSSS 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. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (also known as SGPT)
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase (also known as SGOT)
AUC	Area Under the Plasma Concentration-time Curve
$AUC_{0-\infty}$	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
BUN	Blood Urea Nitrogen
C	Celsius
CFR	Code of Federal Regulations
CINV	Chemotherapy-Induced Nausea and Vomiting
CL/F	Oral Clearance
C_{max}	The highest observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CRF	Case Report Form

Abbreviation	Description
CRO	Clinical Research Organization
CV	Cardiovascular
DNDP	Division of Neuropharmacological Drug Products
dL	Deciliter
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethical Committee
EC_{50}	Half maximal effective concentration
EC_{90}	90 percent effective concentration
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
e.g.	For example
eCLcr	Estimated Creatinine Clearance
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
g	Gram(s)
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
HDL	High Density Lipoprotein
HDPE	High-Density Polyethylene

Abbreviation	Description
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
i.e.	In other words
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
IWRS	Interactive Web Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
ms	Milliseconds
MSAQ	Motion Sickness Assessment Questionnaire
MSEQ	Motion Sickness Eligibility Questionnaire
MSSS	Motion Sickness Severity Scale

Abbreviation	Description
NDA	New Drug Application
NK	Neurokinin
NKA	Neurokinin A
NKB	Neurokinin B
NOAEL	No-Observed Adverse Effect Level
OC	Observed Cases
OTC	Over the Counter
PD	Pharmacodynamic
PE	Physical Examination
PET	Positron Emission Tomography
PG	Pharmacogenetic
pg	Picograms
PGI-S	Patient Global Impression of Severity
pH	Hydrogen ion concentration
PK	Pharmacokinetic
PONV	Post-Operative Nausea and Vomiting
QD	One a day
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

Abbreviation	Description
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
U.S.	United States
WBC	White Blood Cell
WHO	World Health Organization
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

Motion sickness is a constellation of symptoms resulting from being in a moving automobile, boat or airplane [1]. Nausea and vomiting are the cardinal symptoms of motion sickness [2]. The symptoms of motion sickness further include but are not limited to: stomach awareness, pallor, headache, sweating, dizziness, a sensation of warmth, and drowsiness [3]. Motion sickness has been reported to affect up to 30% of the population [4]. The prevalence of motion sickness in one epidemiological study during bus travel found 28% of passengers reported feeling ill while 13% reported experiencing nausea [5]. Motion sickness is thought to be caused by a mismatch between multiple sensory inputs and the processes of interpreting this movement. The sensory conflict theory describes motion sickness as arising due to a mismatch between the perception of motion by the visual, vestibular, and somatosensory systems [6].

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, the most abundant NK, preferentially binds to the neurokinin type-1 (NK-1) receptor and is involved in the regulation of many physiological processes [7]. NK-1 receptors have been mapped in the central nervous system and were found to have a broad distribution in the brain, including the mid-brain, basal ganglia, hypothalamus, and limbic system. Neurokinin receptors are also widely distributed in the gut, the bronchial tree, and the vascular system [8].

Tradipitant (VLY-686), formerly known as LY686017, is a potent and selective inhibitor of human cell membrane NK-1 receptor binding *in vitro*. In preclinical and clinical studies, tradipitant produces a long-lasting blockade of brain NK-1 receptors. Although the distinct pathways of nausea and vomiting are largely undetermined, a definitive role of SP acting at NK-1 receptors in the nucleus tractus solitarus has been confirmed [9]. Previous clinical studies have demonstrated the efficacy of NK-1 antagonism in the prevention of chemotherapy induced and post-operative nausea and vomiting (CINV and PONV) [10]. Motion Sifnos (VP-VLY-686-2401) demonstrated the efficacy of tradipitant in treating motion sickness.

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. In a neonatal toxicity study in the Han Wistar Rat, juvenile Han Wistar rats were given doses of tradipitant in groups of 15, 50 or 150 mg/kg/day for up to 90 days. No adverse signs or toxicity in male or female rats was observed. Minimal hepatocyte hypertrophy in the liver and minimal follicular hypertrophy was observed in the thyroids during microscopic observation after at least 11 weeks of treatment. These changes were not observed after a 4-week recovery period. A carcinogenicity study with transgenic rasH2 mice for 26 weeks showed no toxicologically significant findings at doses up to 1500 mg/kg/day and no evidence of carcinogenicity. In a study of the effects of tradipitant in pre and postnatal development of CD rats, there were no apparent effects of treatment up to and including the maximum dose of 1000 mg/kg/day.

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. In addition to clinical pharmacology studies, Eli Lilly completed clinical trials testing for efficacy in translational models for irritable bowel syndrome, anxiety, and alcohol dependence. Vanda Pharmaceuticals Inc. has completed additional clinical pharmacology studies as well as a clinical trial testing for efficacy in chronic pruritus associated with atopic dermatitis, and gastroparesis.

- 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 wash-out 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-686-1102 was a single-site, open-label, single-sequence study in 24 healthy male and female subjects to assess the effect of tradipitant administration on CYP3A4 using midazolam pharmacokinetics as a marker. Midazolam 10 mg was administered alone and then with 85 mg tradipitant following 12 days of Q12H tradipitant dosing. There was no alteration in the pharmacokinetics of midazolam. This suggests that tradipitant has no net effect on the CYP3A4/5 enzyme. Overall, the study data indicate that repeated oral doses of 85 mg tradipitant administered Q12H is generally safe and well-tolerated in male and female healthy subjects.
- 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 a proof of concept study in atopic dermatitis patients with chronic pruritus. This study was designed to assess the decrease in VAS in patients treated with tradipitant over an 8-week period of 85 mg BID dosing compared to placebo. The total enrollment was 150 patients. Tradipitant was shown to improve itch and disease severity based on the VAS for itch.
- Study VP-VLY-686-2301 was a, randomized double-blind placebo-controlled study to assess the efficacy of tradipitant in relieving symptoms of gastroparesis. Patients received tradipitant 85 mg BID or placebo over a 4-week period. The total enrollment was 152 patients. Tradipitant met the primary endpoint of the study of change in nausea score as measured by patient daily diaries and also met the related endpoint of improvement in the number of nausea free days.
- Study VP-VLY-686-2401 was a, randomized double-blind placebo-controlled study to assess the efficacy of tradipitant in participants with motion sickness. Participants received tradipitant 170 mg PO or placebo 60 minutes prior to boat travel with an enrollment target of 150 participants. Tradipitant was shown to prevent vomiting and to treat the symptoms of motion sickness.
- Study VP-VLY-686-3101 is an on-going multicenter, randomized double-blind placebo-controlled study to assess the efficacy of tradipitant in patients with atopic dermatitis. Patients will be receiving tradipitant 85 mg PO BID or placebo over an 8-week period with an enrollment target of 500 patients.

- Study VP-VLY-686-3301 is an on-going multicenter, randomized double-blind placebo-controlled study to assess the efficacy of tradipitant in patients with gastroparesis. Patients will be receiving tradipitant 85 mg PO BID or placebo over an 8-week period with an enrollment target of 400 patients.

In clinical studies, tradipitant has been administered as a single dose up to 800 mg, up to 12 days at a daily dose of 170 mg, up to 4 weeks at a daily dose of 100 mg, up to 12 weeks at a daily dose of 170 mg, and at single one-time dosing of 170 mg. Following 12 days of twice daily 85 mg tradipitant administration in 24 healthy volunteers, the median time to maximum plasma concentration ranged from 2 to 6 hours and the geometric mean (%CV) elimination half-life was 34 (41%) hours.

4. TRIAL OBJECTIVES AND RATIONALE

4.1. Objectives

4.1.1. Primary

- 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 MSSS.

4.1.2. Secondary

- To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter MSSS.
- To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter MSAQ.
- To assess the effects of tradipitant 85 mg and 170 mg on the symptoms of motion sickness as measured by subjective parameter PGI-S.
- To assess the safety and tolerability of a single oral dose of tradipitant 85 mg and 170 mg.

4.1.3. Exploratory

- To identify genetic markers that correlate with response to tradipitant treatment.
- To identify genetic markers that correlate with adverse events that may occur upon treatment with tradipitant.
- To identify genetic markers that are associated with motion sickness and other 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.
- To assess the effects of tradipitant on individual symptoms of motion sickness as represented in the MSAQ.
- To collect more information to help understand the constellation of motion sickness symptoms, preferred therapies, and participant's attitudes towards motion sickness.

4.2. Rationale

4.2.1. Study Rationale

Tradipitant is a novel NK-1 receptor antagonist with proven efficacy in the treatment of motion sickness, as demonstrated in VLY-686-2401 (the Motion Sifnos study). In the Motion Sifnos study, 126 participants, distributed over seven individual boat trips in the Pacific Ocean, were randomized to 170 mg tradipitant or placebo. Participants taking tradipitant were protected from vomiting as compared to the placebo group in the ITT population, and exhibited a dramatic improvement in prevention of vomiting and treatment of motion sickness symptoms when only examining boat trips in rough sea conditions.

Other NK-1 receptor antagonists include maropitant, a NK-1 receptor antagonist approved for the prevention of vomiting due to motion sickness in dogs and cats [11]. The crossover study showed that the therapy reduced the occurrence of vomiting in over 75% of dogs as compared to placebo. Another NK-1 receptor antagonist, aprepitant, is approved for postoperative nausea and vomiting (PONV) in adults [12]. Currently, tradipitant is being tested in clinical trials for the treatment of nausea and vomiting in patients with gastroparesis. This study will inform further about the protective effects of tradipitant in the treatment of motion sickness.

Motion sickness has been estimated to affect up to 30% of the population, and currently available therapies are not effective for all patients and some of the medications used have significant side effect profiles [4].

4.2.2. Rationale for Dose and Study Design

In a multiple-dose PET clinical study, frontal cortex receptor occupancy was recorded at 93% following 7 days of 100 mg daily dosing. Based on the PET study findings, it is estimated that a dose of approximately 85 mg daily would achieve 90% brain receptor occupancy 24-hours post steady-state dosing. A target brain NK-1 receptor occupancy of 90% is based on a published study comparing the efficacy of two different doses in aprepitant, an NK-1 receptor antagonist approved for CINV and PONV, in which a greater antiemetic effect was observed at a dosing regimen which reached 90% receptor occupancy than a dosing regimen reaching 80% receptor occupancy [10].

While it is hypothesized that a daily dose of 85 mg will provide adequate central receptor occupancy coverage to centrally mediate nausea and vomiting, there is some evidence to suggest that the antiemetic effects of NK-1 antagonism may also have a peripherally-mediated component involving modulation of abdominal vagal afferent activity [13]. Based on previous PK/PD studies, we believe that a dose of 170 mg administered prior to engaging in activities associated with motion sickness may be necessary for rapid onset of action. In VP-VLY-686-2401, Motion Sifnos, participants were administered a single dose of tradipitant 170 mg approximately 60 minutes before the initiation of vehicle travel. This study demonstrated a therapeutic effect for participants at this dose conferring a protective advantage for motion sickness symptoms. To understand whether there is a difference in protective effects based on dose, this study will include doses of 85 mg and 170 mg of tradipitant.

The protective effect of tradipitant was dramatic in the Motion Sifnos study in sea conditions where the wave height was above 1 meter. This wave height was indicative of rougher sea conditions and thus may be more likely to stimulate the symptoms of motion sickness. Since a stronger stimulus for illness would be more informative, this study will only have participants exposed to sea conditions that may induce more significant symptoms and thus display the protective effects of tradipitant.

The completed nonclinical and clinical safety studies with tradipitant showed a favorable safety profile. Clinical laboratory tests, vital signs, 12-lead ECG, and physical examination (PE) data showed no clinically significant alterations due to administration of tradipitant. Additionally, preclinical studies showed no evidence of a drug-related QT prolongation.

4.2.3. Risk and Benefit

The potential benefit for participants, if randomized to tradipitant, is the possibility of experiencing decreased symptoms of motion sickness while participating in this study, as observed in the Motion Sifnos 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 1.5x placebo) in previous clinical studies were somnolence, dizziness, and fatigue. Nonetheless, as tradipitant is an experimental compound, there may be unforeseen risks associated with its use.

5. STUDY DESIGN

5.1. General Design

This is a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of a single oral dose of tradipitant 85 mg or 170 mg in volunteers that have a history of experiencing the symptoms of motion sickness on prior vehicle travel, and meet inclusion criteria.

5.1.1. Screening Period

The screening period will involve interested participants taking the MSEQ, a screening survey to assess the severity of motion sickness in participants, and a detailed interview to understand the participant's history of motion sickness. The MSEQ will be available either online or as a phone survey. Participants who have demonstrated a history of motion sickness based on the questionnaire and interview will be able to proceed to an in-person medical screening visit (V1).

Participants will be identified as having symptoms consistent with motion sickness if they answer the MSEQ as detailed in MSEQ Inclusion Criteria (Appendix 20.3.2).

At the screening visit, potential participant's eligibility for the study will be assessed based on the MSEQ, interview, physical examination, vital signs, ECG, clinical laboratory tests, drug and alcohol screen, and medical history. Clinical laboratory testing will include a pharmacogenetics sample for whole genome sequencing. Participants that are WOCBP will also have urine and serum B-HCG pregnancy tests.

5.1.2. Evaluation Period

5.1.2.1. Vehicle Travel Assessment

Participants who fulfill all of the inclusion-exclusion criteria will continue into the evaluation phase of the study (vehicle travel assessment, Visit 2).

24-48 hours prior to Visit 2, an assessment will be made based on NOAA sea conditions to determine if the travel assessment visit will take place. This will be determined based on the wave height: if the wave height is predicted to be above 1 meter, then the travel assessment will proceed. If the wave height is predicted to be below 1 meter, the travel assessment will be rescheduled and participants who are not able to proceed with a rescheduled visit will have the option to withdraw consent and screen fail. During Visit 2, participants will be randomly assigned to 1 of 3 treatment groups stratified by port: 85 mg tradipitant, 170 mg tradipitant, or placebo. Participants will be assigned to take 85 mg tradipitant, 170 mg tradipitant, or placebo approximately 60 minutes prior to entering the vehicle. Throughout the duration of vehicle travel, the MSSS will be completed approximately every 30 minutes. Immediately following completion of the boat travel, participants will be instructed to complete several questionnaires to assess their travel: the MSAQ to assess the symptoms associated with motion sickness, and the Patient Global Impression of Severity Questionnaire (PGI-S).

Figure 1: Study Schematic

Screening Period

Visit 0 (Remote):

MSEQ with interview, participants will be directed to complete the MSEQ and enter their contact information to arrange for a remote interview if qualified from the MSEQ inclusion criteria and potentially for the screening visit at the clinical site

Visit 1 (Screening):

Informed Consent

Physical examination, vital signs, ECG, demography, medical history, blood draw, drug and alcohol screen, serum and urine B-HCG pregnancy tests for WOCBP, participant ID assignment

Evaluation Period:

Visit 2 (Vehicle travel assessment):

24-48 hours before: Determination to proceed with travel assessment based on wave height above 1 meter

Upon arrival: Randomization

Approximately 60 minutes prior to vehicle travel: Administration of tradipitant 85 mg, tradipitant 170 mg, or placebo

Approximately every 30 minutes of travel: MSSS questionnaire

Immediately following vehicle travel completion: MSAQ (Motion Sickness Assessment Questionnaire), PGI-S (Patient Global Impression of Severity Questionnaire)

Visit 3 (EOS visit):

Within 7 days of vehicle travel assessment: EOS visit with clinical site including physical exam, vital signs, ECG, blood draw, serum B-HCG pregnancy test for WOCBP, adverse events query

6. SELECTION AND WITHDRAWAL OF PARTICIPANTS

6.1. Participant Inclusion Criteria

Each participant must meet the following criteria for inclusion in the study:

General

1. History of symptoms consistent with motion sickness;
2. Ability and acceptance to provide written informed consent and fluency in English;
3. Men or women between 18 – 75 years, inclusive;
4. Body Mass Index (BMI) of ≥ 18 and < 40 kg/m^2 (BMI = weight (kg)/ [height (m)]^2);
5. Males, non-fecund females (i.e., surgically sterilized, if procedure was done 6 months before screening or participant is postmenopausal for at least 2 years), or females of child-bearing potential using an acceptable method of birth control (i.e., condoms, diaphragm, spermicidal agents, cervical cap, Copper IUD) for a period of 35 days before the first dosing, during the study and for one month after the last dose and must have a negative pregnancy test at the screening visit,
    a. Note: Women using hormonal methods of birth control must use an additional method of birth control during the study and for one month after the last dose;
6. In good health as determined by a medical and psychiatric history, physical examination, electrocardiogram, and serum chemistry and hematology;
7. Normal vision, with or without corrective lenses;
8. Willing to comply with study procedures and restrictions;
9. Willing to provide a pharmacogenetic sample; and
10. Has negative test result for selected substances of abuse at screening.

6.2. Participant Exclusion Criteria

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

1. History (within the 12 months prior to screening) of psychiatric disorders including Major Depressive Disorder, Generalized Anxiety Disorder, Axis II Disorders, delirium or any other psychiatric disorder that in the opinion of the clinical investigator would affect participation in the study or full compliance with study procedures;
2. Current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal, gastrointestinal or metabolic dysfunction unless currently controlled and stable;
3. History of intolerance and/or hypersensitivity to other NK-1 receptor antagonists;
4. Clinically significant deviation from normal in clinical laboratory results, vital signs measurements, or physical examination findings at screening as determined by the clinical investigator;

5. Major surgery, trauma (including broken pelvis/legs), illness (e.g. sepsis, stroke) or immobility for 3 or more days within the past month;
6. Active cancer or cancer treatment within the past 6 months;
7. Central venous catheter in place or within the past month;
8. History of pulmonary embolism/deep vein thrombosis (DVT) or short-term blood thinner treatment as an outpatient (e.g. Coumadin, Lovenox, heparin);
9. History or first-degree family history of thrombosis or hypercoagulable state (e.g. Factor V Leiden, Factor VIII deficiency, Protein C & S deficiency);
10. Impaired liver function indicated by AST, ALT, or bilirubin > 2 times the upper limit of normal, unless there is an isolated bilirubin > 2 times the upper limit of normal due to Gilbert's syndrome;
11. Pregnancy or recent pregnancy (within 6 weeks) or women who are breastfeeding;
12. History of drug or alcohol abuse as defined in DSM-V, Diagnostic Criteria for Drug and Alcohol Abuse, within the 12 months prior to screening and/or regular consumption of alcoholic drinks (> 2 drinks/day or > 14 drinks/week);
13. Refusal to abstain from use of any prescription or OTC medication that affects motion sickness or nausea for 1 week preceding and the day of Visit 2;
14. Randomization in a previous tradipitant (VLY-686 or with Eli Lilly) trial;
15. Refusal to abstain from use of any investigational drug, including placebo, or prohibited medications specified in section 7.2.1.1 throughout the study;
16. Participant is at risk of suicide, in the opinion of the Investigator. Evidence of suicide risk could include any suicide attempt within the past year or any other suicidal behavior within the past year;
17. Unwilling or unable to follow the medication restrictions, or unwilling or unable to sufficiently wash-out from use of a restricted medication;
18. Routinely consumes caffeine including coffee, tea and/or other caffeine-containing beverages or food averaging more than 3 cups a day (24 ounces);
19. Chronic nausea caused by conditions such as irritable bowel syndrome, gastroparesis, cyclic vomiting syndrome or any other cause;
20. First-degree relative of a participant who has participated or will be participating in any portion of the study; and
21. Any other sound medical reason as determined by the clinical investigator.

6.3. Participant Withdrawal Criteria

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

Participants may voluntarily withdraw from the study at any time for any reason. Participants 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 participant. 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 participant's continued participation in the trial. Clinically notable abnormalities in vital signs or laboratory tests are provided in Appendices 20.1 and 20.2, respectively, to guide clinical focus regarding a participant's continued participation;
- Noncompliance,
- At the request of the participant.

For participants withdrawing from the study prematurely, all efforts will be made to perform Visit 3 End-Of-Study visit.

Documented reason: It will be documented whether or not each participant completed the clinical study. For participants 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. Participant withdrew consent
7. Unsatisfactory therapeutic effect
8. Other (specify).

Participants 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 PARTICIPANTS

7.1. Study Medication

7.1.1. Dosing

Randomized participants will be dispensed study medication under double-blind conditions. Each participant will be given a dose of study medication at Visit 2. Participants will be instructed to take the study medication approximately 60 minutes prior to boat travel.

7.1.2. Guidance for Taking Study Medication

Participants should take the study medication approximately 60 minutes prior to entering the boat. Study medication should be taken on an empty stomach whenever possible.

In the event that a participant vomits within 15 minutes of taking study medication and both intact capsule(s) can be identified in the emesis, a second administration of two capsules should be performed.

7.2. Concomitant Medications

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

In general, concomitant medications that may interfere with the assessment of the efficacy and safety of tradipitant are not allowed in this protocol or are allowed with specific provisions.

Questions regarding the use of concomitant medications not listed should be directed to the Medical Monitor.

7.2.1. Prohibited Medications

7.2.1.1. Prohibited Medications from Screening to EOS

The following medications are prohibited from use during the screening and treatment periods of the study. This list is not exhaustive. In the event that a study participant is on any medication or treatment that is not listed but that may interfere with the assessment of the efficacy and safety of tradipitant, the eligibility of the participant and/or use of the potential medication should be reviewed with the Medical Monitor and the Sponsor;

- NK-1 receptor antagonists (including but not limited to aprepitant, netupitant, rolapitant)
- Opioid administration more than 2 times per week
- Marijuana (illicit or medical) use (including a positive drug screen for marijuana)

- Typical and atypical antipsychotics

7.2.1.2. Prohibited Medications from 1 Week Before Randomization until End of V2

The following medications are prohibited from use beginning one week before randomization through the end of the treatment period:

- Second generation 5-HT3 receptor antagonists (including palonosetron)
- Any medication with anti-nausea, antiemetic, or prokinetic effects
- Phenergan (or promethazine) administration more than 2 times per day or Phenergan use that is not considered rescue use
- Antihistamines
- Drugs with a narrow therapeutic index: carbamazepine, cyclosporine, digoxin, ethosuximide, lithium, phenytoin, procainamide, quinidine, sirolimus, tacrolimus, theophylline, warfarin
- Strong CYP3A4 inhibitors (listed by class):

Class	Prohibited medications
Antibiotics	clarithromycin, telithromycin
Antifungals	itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals	boceprevir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, topinavir
Other	conivaptan, grapefruit juice, nefazodone

7.3. Treatment Assignment

7.3.1. Participant ID Assignment

Participant Identification (ID) - Each participant who signs an informed consent form should receive a participant identification number. The participant identification number (ID) consists of a 3-digit site number (Site No.) and a 4-digit participant number (Participant No.). The Site No. and Participant No. will be separated by a hyphen. Participant identification numbers will be assigned during the screening visit by IWRS. The participant identification number will remain the same throughout the study, and will be used to identify the participant. This 7-digit alpha numeric identifier will appear in the "Participant ID" space on the electronic CRF for a given participant.

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

Participant No. – Participant numbers will be assigned to each participant starting with 1001 (i.e. 1001, 1002, 1003 …). The ID for a participant who discontinues from the study for any reason after having been assigned an ID will not be reassigned.

7.3.2. Participant Replacement

Participants who discontinue prior to study completion will not be replaced.

7.3.3. Randomization

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

8. STUDY MEDICATION MATERIALS AND MANAGEMENT

8.1. Study Medication

Tradipitant capsules are white opaque, hard gelatin capsules provided as 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 two capsules. At Visit 2, participants will be administered two capsules of either drug or placebo, or one placebo and one drug capsule if in the 85 mg tradipitant group.

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 participants.

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 participants 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 participant's CRF.

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

9. STUDY ASSESSMENTS

9.1. Study Assessments per Visit

9.1.1. Screening Period

9.1.1.1. Visit 0 (Remote Screening)

- Study participants to complete MSEQ online or via phone, and additional phone interview if qualified

9.1.1.2. Visit 1 (Day 1 at clinical site visit following online MSEQ and interview)

- Inclusion/Exclusion Criteria
- Demographics
- IWRS for Participant ID assignment
- Medical history
- Hematology
- Chemistry
- Urinalysis
- Drug/Alcohol screen
- Serum B-HCG for all females of child bearing potential, except those who have been postmenopausal for at least 2 years or are surgically sterile
- Urine B-HCG for all females of child bearing potential, except those who have been postmenopausal for at least 2 years or are surgically sterile
- Vital signs (body temperature, respiratory rate, blood pressure, pulse, weight, and height)
- Physical examination
- ECG
- Blood draw for pharmacogenetic analysis
- Prior/concomitant medications review

9.1.2. Evaluation Period

9.1.2.1. Assessment: 24-48 hours prior to travel, wave height will be assessed to determine clearance to proceed with boat travel. If cleared, participants will proceed to Visit 2.

9.1.2.2. Visit 2- Vehicle Travel Assessment

- Upon arriving at the boat travel location, participants will be randomized.

- The participants, following randomization, will be administered either drug or placebo approximately 60 minutes prior to beginning boat travel.
- Participants will enter the boat following drug administration and sit in an assigned seat. They will be instructed to remain in their seat for the duration of travel, lasting approximately between 120-300 minutes.
- If a participant has vomited, the participant may elect with the staff they no longer wish to proceed with filling out the rest of the MSSS questionnaires. If a participant is to no longer participate in filling out the questionnaires, the staff should request the participant to fill out an additional MSSS questionnaire which will be marked by the next 30-minute time point (e.g. if a participant vomits and no longer wishes to participate at time +45 minutes from departure, they should be given the MSSS to fill out with the timestamp of +60 minutes from departure). If the participant is too ill to fill out the MSSS themselves, the staff can read the MSSS questionnaire to the participant and fill it out on their behalf. The PGI-S and MSAQ are still to be filled out at the end of travel if permissible.
- Approximately every 30 minutes participants will be reminded to complete the MSSS questionnaire.
- Participants will be prohibited from sleeping throughout the duration of the assessment.
- A medical professional will be on board for the safety of participants.
- Participants are not to exit the main cabin of the boat to the exterior standing decks, but are instructed to remain in their seats to the best of their ability. Participants will have access to restrooms on the vessel.
- The vessel will be chartered with a full staff of nautical professionals.
- Length of travel and route will be recorded. Wind speed, average wave height, wind direction, linear vertical acceleration (heave), pitch, roll, yaw, degree of vertical displacement and wave period will be recorded.
- At the completion of boat travel, participants will complete the MSAQ, and the PGI-S.

9.1.3. Visit 3- End of Study Visit

- Hematology
- Chemistry
- Urinalysis
- Serum B-HCG for all females of child bearing potential, except those who have been postmenopausal for at least 2 years or are surgically sterile
- Vital signs (body temperature, respiratory rate, blood pressure, pulse, and weight)
- Physical examination
- ECG
- Prior/concomitant medications

- Adverse events query
- EOS

Table 2: Schedule of Evaluations

	Pre-randomization		Evaluation	
Period	**Screening**		**Assessment**	**EOS**
Visit	**0**	**1**	**2**	**3**
Informed Consent Form[1]		X		
Inclusion/Exclusion Criteria		X		
MSEQ and Interview	X			
Demographics		X		
Participant ID Assignment		X		
Randomization[6]			X	
Medical History		X		
Hematology[2]		X		X
Chemistry[2]		X		X
Urinalysis[2]		X		X
Drug/Alcohol Screen		X		
Serum B-HCG (WOCBP)		X		X
Urine Pregnancy (WOCBP)		X		
MSAQ			X	
MSSS			X[3]	
PGI-S			X	
PG Blood Sample		X		
Vital Signs[4]		X		X
Physical Examination		X		X
ECG[5]		X		X
Drug Administration			X	
Adverse Events Query[7]				X
Prior/Concomitant Medications		X		X

EOS= end of study; WOCBP= women of childbearing potential; PG= Pharmacogenetic; MSSS= Motion Sickness Severity Scale; MSAQ= Motion Sickness Assessment Questionnaire; MSEQ= Motion Sickness Eligibility Questionnaire; PGI-S= Patient Global Impression of Severity Questionnaire

[1] The Study Informed Consent will be explained to the participants at the screening visit and must be signed prior to performing any procedures.

[2] Laboratory tests will be repeated as required to follow any abnormal changes.

[3] MSSS to be completed approximately every 30 minutes of travel.

[4] Body height will be recorded at screening only.

[5] A central interpretation from the provided ECG machines will be used to determine any cardiac abnormalities.

[6] Following the screening visit and review of labs participants may be randomized.

[7] Adverse event collection will begin at the time the participant is randomized.

10. ASSESSMENT OF EFFICACY

Subjective Assessments

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

- Motion Sickness Severity Scale (MSSS)
- Motion Sickness Assessment Questionnaire (MSAQ)
- Patient Global Impression of Severity Questionnaire (PGI-S)

The following rating scale will be used for screening:

- Motion Sickness Eligibility Questionnaire (MSEQ)

10.1. Subjective Assessments

Motion Sickness Severity Scale (MSSS)

The MSSS is a numerical rating scale to evaluate the symptoms of motion sickness. Responses will be measured on a 7-point scale in which 0 = no symptoms, 1 = stomach awareness or discomfort, 2 = mild nausea, 3 = moderate nausea, 4 = severe nausea, 5 = retching, and 6 = vomiting. Participants are instructed to select the number that most represents the severity of their nausea symptoms [14].

Motion Sickness Assessment Questionnaire (MSAQ)

The MSAQ is a 16-statement scale to assess motion sickness, which can be sub-divided by affected body systems. Each statement is rated 1-9 with 1 representing low severity and 9 representing high severity. The overall motion sickness score is calculated by summing the total score divided by 144, and multiplied by 100 to result in a percentage. The body systems subdivided score can be calculated in a similar fashion [3].

Motion Sickness Eligibility Questionnaire (MSEQ)

The MSEQ is a questionnaire consisting of 10 items to assess a person's history of motion sickness and their eligibility to participate in this study. The questionnaire will be scored and reviewed to determine eligibility, and eligible participants will be contacted to collect more information and speak further about participating in the clinical study.

Patient Global Impression of Severity Questionnaire (PGI-S)

The PGI-S is a 1-item questionnaire to assess the disease severity as reported by the participants. The participants will rate the severity of their motion sickness symptoms on a 0-4 scale ranging from 'none' to 'very severe.'

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 participant has rested in supine position for approximately 10-15 minutes) and centrally read 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 urine for the urinalysis.

The table below, Table 3, 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 or its designee.

Values considered to be potentially clinically notable are provided in Appendix 20.1 for the Investigator's guidance. Any laboratory test result from an enrolled participant 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 3: Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count (RBC), hemoglobin, hematocrit, platelets, and white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)

Category	Parameters
Chemistry	
Electrolytes	sodium, potassium, chloride, magnesium, bicarbonate
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, eCLcr
Other	glucose, calcium, albumin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid
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, trichomonas, mucus threads, yeast

11.1.2.1. Additional Laboratory Evaluations

- Serum pregnancy test
- Urine pregnancy test
- Drugs of abuse at screening visit

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
- Sitting blood pressure (systolic and diastolic)
- Sitting pulse/ heart rate

After the participant signs the informed consent, vital sign values that the Investigator considers clinically significant will be recorded as baseline. Once randomized, all clinically significant vital sign values that the Investigator determines have changed significantly from baseline will be recorded as AEs. Vital sign values considered to be potentially clinically notable are provided in Appendix 20.1 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 3)
- Height (at Visit 1)

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 visits 1 and 3. Documentation of the PE will be included in the source documentation at the investigational site.

11.1.5. Pregnancy

Before enrolling a woman of child-bearing potential (WOCBP) in this clinical study, Investigators must review the following information with the participant:

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

All WOCBP (defined as any female unless surgically sterile or postmenopausal at least 24 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 (or designee) within 24 hours of learning of its occurrence and must be followed to determine outcome. If a participant becomes pregnant, she will be discontinued from the study.

11.1.6. Definitions Related to Safety

11.1.6.1. Adverse Event

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

11.1.6.2. 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 4.

Table 4: SAE Criteria and Definitions

SAE Criteria	Definition
Death of Subject	An event that results in the death of the subject.
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 out-patient facility.
Prolongation of Hospitalization	An event that occurs while the subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly/Birth Defect	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

SAE Criteria	Definition
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. 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	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 subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of a subject, life-threatening, subject 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.

11.1.6.3. Adverse Event Follow-up

Participants with non-serious AEs that are ongoing at the participant's last study visit must be followed until resolution or for 30 days after the participant's last study visit, whichever comes first. Non-serious AEs that are reported during the 7 days following the participant'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 participant'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 participant's last study visit should be reported as indicated in Section 11.1.6.4.

11.1.6.4. Adverse Event Reporting Period

AEs are to be recorded in the source documents from the time of the participant's randomization until the end of the participant'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 participant reports or the Investigator learns of a new AE(s) up to 7 days after the participant's last study visit or a new SAE(s) up to 30 days after the participant'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.

11.1.6.5. 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.

11.1.7. 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 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.

11.1.8. Recording Adverse Events

11.1.8.1. Adverse Events during Study Period

At each study visit following randomization, the Investigator must seek information on AEs by questioning the participant and, as appropriate, by examining the participant. Information on all AEs should be recorded immediately in the source document, and also 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.

11.1.8.2. Post-Study Adverse Event

At the last scheduled visit, the Investigator should instruct each participant to report any subsequent event(s) that the participant or the participant'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 participant 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 participant's study participation.

11.1.8.3. 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 clinically significant laboratory values on the Adverse Events CRF using an appropriate diagnostic description.

11.1.9. Reporting Adverse Events

11.1.9.1. Study Sponsor Notification by Investigator

All SAEs should be reported on the electronic CRF within 24 hours to the Vanda Drug Safety designee using the appropriate source documents and AE electronic CRF page.

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 (or designee).

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

At the time of the initial report, the information listed in Table 5 should be provided.

Table 5: SAE Reporting Information

• Event term • Event date of onset • Brief narrative with relevant medical history	• Action taken regarding study medication administration • Seriousness criteria met • Initial PI assessment of relationship to study medication

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

Investigator or designee will submit events to the IRB/EC according to individual committee requirements. Vanda 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.

11.1.10. Unblinding Procedures

The participants and the 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 participant'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 participant received tradipitant or placebo. If possible, the Medical Monitor should be consulted prior to unblinding. If a participant's condition is so severe that time would not permit consulting with the Medical Monitor, the participant's assigned treatment can be unblinded by the Investigator using the IWRS system. In the event that it becomes necessary to unblind a participant'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. PHARMACOGENETICS ASSESSMENT

The pharmacogenetics assessment is an exploratory assessment. The DNA sample may be used for research on motion sickness and the effects of tradipitant. Participants may be asked to supply an additional blood sample only if the sample is lost or damaged.

A blood sample will be drawn at Visit 1 (screening) to obtain sufficient DNA for the pharmacogenetic assessment. The PG blood will be drawn into 1, 10-ml EDTA tube which will be gently inverted several times to prevent clotting. Detailed instructions for PG sample collection, preparation, storage, and shipment will be included in the laboratory manual. The sample will remain under control of the Sponsor and may be stored for up to 50 years.

13. STATISTICS

13.1. 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.

13.2. Statistical Methods and Analysis Plan

13.2.1. 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.

13.2.2. 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 MSSS 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.

13.2.3. 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.

13.2.4. 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.

13.2.5. Study Medication

Exposure and compliance will be tabulated by treatment groups.

13.2.6. 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.

13.3. Efficacy Data Analysis

13.3.1. Primary Outcome and Methodology

The primary endpoint is the percentage of vomiting as assessed by the MSSS 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).

13.3.2. Secondary Efficacy Analysis

The continuous secondary endpoints from MSSS 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.

13.4. Safety Data Analysis

13.4.1. 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.

13.4.2. 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).

13.4.3. 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.

13.4.4. 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).

13.5. Subgroup Analysis

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

13.6. Interim Analysis

No interim analysis planned.

13.7. 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.

14. DIRECT ACCESS TO SOURCE DOCUMENTS

14.1. 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, participants' 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, participant 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.

14.2. Study Monitoring

The Sponsor's monitor will maintain contact with the Investigator and designated staff between study visits. Monitoring or virtual 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's monitoring activities. The CRFs and participant'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 participants are protected;
- trial conduct is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

14.3. Audits and Inspections

In addition to routine monitoring procedures, Vanda 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 even after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform Vanda immediately that this request has been made, and promptly forward copies of the audit reports to Vanda.

15. 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.

15.1. 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.

15.2. 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.

15.3. 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.

16. ETHICS

16.1. 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 participants for this study will be provided a consent form describing this study and providing sufficient information for participants 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 participant by the investigative site, using the EC/IRB-approved consent form, must be obtained before that participant is submitted to any study procedure. This consent form must be signed by the participant, or participant's legally acceptable surrogate, and the Investigator-designated research professional obtaining the consent.

16.2. 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:

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).

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.

16.3. Written Informed Consent

Prior to any study procedures being performed, participants and persons conducting the consent process will be required to sign and date the IRB/EC approved informed consent, and each participant will be given a copy. In addition, this information should be recorded in the participant'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 participant. The Investigator or designee will give the participant adequate opportunity to read the consent form and to discuss any questions.

17. DATA HANDLING AND RECORD KEEPING

Throughout this study, all data will be linked to the electronic CRF via the unique participant identification number. However, participants' 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. This data will be blinded in corresponding analyses. Medical records of consented participants will be reviewed by Sponsor or designee including, but not limited to, laboratory test results, ECG reports, hospital admission and discharge summaries for admissions occurring during a participant'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 participant 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 participant before the participant is entered into the study.

Samples collected for pharmacogenetic analysis will be labeled with a coded identification number. 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 the participants.

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, participants will not have access to their genetic data. Families, relatives or study personnel will also not have access to the participant's genetic data.

Participants 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 participant'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 participant 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 participant's request, Vanda Pharmaceuticals Inc. will destroy the participant'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 destroyed, 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.

17.1. 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.

18. ADMINISTRATIVE PROCEDURES

18.1. Changes to the Protocol

Except for a change that is intended to eliminate an immediate hazard to participants, 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 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 participants, 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 in the interests of preserving the safety of all participants 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 monitor and the IRB/EC at the center 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.

18.2. Discontinuation of Study

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

18.3. Publication of Results

Manuscript(s) for publication, texts of presentations, abstracts of papers, and similar material should be submitted to Vanda 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, the site shall remove any confidential information (other than study results) prior to submitting or presenting the materials. Vanda 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 owns an interest. In the latter case, Vanda 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 site(s). 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's name, in connection with any advertising, publication, or promotion without prior written permission.

18.4. Investigator Agreement

This protocol is being provided to me for conducting a clinical trial for Vanda. The information contained in the protocol is confidential and proprietary to Vanda. Study documents provided by Vanda (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 to me may not be disclosed to others without direct written authorization from Vanda, except to the extent necessary to obtain informed consent from participants 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 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.

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: _____

Protocol Number: VP-VLY-686-3401

19. REFERENCES

[1] A. Brainard and C. Gresham, “Prevention and Treatment of Motion Sickness,” *Am. Fam. Physician*, vol. 90, no. 1, pp. 41–48, 2014.

[2] J.F. Golding, “Chapter 27: Motion sickness” in *Handbook of Clinical Neurology*, vol. 137, pp. 371-390, 2016.

[3] P. J. Gianaros, E. R. Muth, J. T. Mordkoff, M. E. Levine, and R. M. Stern, “A Questionnaire for the Assessment of the Multiple Dimensions of Motion Sickness.,” *Aviat. Space. Environ. Med.*, vol. 72, no. 2, pp. 115–9, 2001.

[4] R. P. Simon, M. J. Aminoff and D. A. Greenberg, "Chapter 8: Disorders of Equlibrium" in *Clinical Neurology*, 10th ed., New York: McGraw-Hill, 2017.

[5] M. Turner, "Motion sickness in public road transport: passenger behaviour and susceptibility," *Ergonomics*, vol. 42, no. 3, pp. 444-461, 1999.

[6] L.-L. Zhang, J.-Q. Wang, R.-R. Qi, M. Li, Y.-L. Cai and L.-L. Pan, "Motion Sickness: Current Knowledge and Recent Advances," *CNS Neuroscience and Therapeutics*, vol. 22, no. 1, pp. 15-24, 2016.

[7] M. Otsuka and K. Yoshioka, “Neurotransmitter functions of mammalian tachykinins,” *Physiol Rev.*, vol. 73, no. 0031–9333 (Print), pp. 229–308, Apr. 1993.

[8] L. Quartara and C. A. Maggi, “The tachykinin NK1 receptor. Part II: Distribution and pathophysiological roles,” *Neuropeptides*, vol. 32, no. 0143–4179 (Print), pp. 1–49, Feb. 1998.

[9] S. M. Stahl, “The ups and downs of novel antiemetic drugs, part 2: An illustration,” *J. Clin. Psychiatry*, vol. 64, no. 6, pp. 626–627, 2003.

[10] M. Bergstrom, R. J. Hargreaves, H. D. Burns, M. R. Goldberg, D. Sciberras, S. A. Reines, K. J. Petty, M. Ogren, G. Antoni, B. Langstrom, O. Eskola, M. Scheinin, O. Solin, A. K. Majumdar, M. L. Constanzer, W. P. Battisti, T. E. Bradstreet, C. Gargano, and J. Hietala, “Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant,” *Biol.Psychiatry*, vol. 55, no. 0006–3223 (Print), pp. 1007–1012, May 2004.

[11] Cerenia (maropitant citrate) [Prescribing Information]. Kalamazoo, MI: Zoetis Inc.; 2015.

[12] Emend (aprepritant) [Prescribing Information]. Whitehouse Station, NJ: MERCK & CO., INC.; 2017

[13] J. Fahler, G. C. Wall, and B. I. Leman, “Gastroparesis-associated refractory nausea treated with aprepitant,” *Annals of Pharmacotherapy*, vol. 46, no. 12. 2012.

[14] N. M. Price, L. G. Schmitt, J. McGuire, J. E. Shaw, and G. Trobough, “Transdermal scopolamine in the prevention of motion sickness at sea,” *Clin. Pharmacol. Ther.*, vol. 29, no. 3, pp. 414–419, 1981.

20. APPENDICES

20.1. 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	

20.2. 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 ^{o}C	and a	change of ≥ 1.1 ^{o}C
	≥ 101 ^{o}F	and a	change of ≥ 2 ^{o}F
Weight	--		change of ≥ 7% body weight

20.3. Questionnaires

20.3.1. Motion Sickness Eligibility Questionnaire – MSEQ

Sponsor code VP-VLY-686-3401
VP-VLY/Tradipitant

Subject ID |__|__|__|- |__|__|__|__|

Screening

MSEQ – Motion Sickness Eligibility Questionnaire

1. Have you experienced symptoms of motion sickness in the past year?
a. Yes
b. No

2. Which of the following symptoms of motions sickness do you experience? (Select all that apply)
a. Nausea
b. Vomiting
c. Dizziness
d. Headache
e. Anxiety
f. Queasiness
g. Irritability

3. In which vehicle(s) do you experience motion sickness? (Select all that apply)
a. Car
b. Bus
c. Boat
d. Plane
e. Train

4. How often do you experience motion sickness in the vehicle(s) selected above?
a. Always
b. Sometimes
c. Rarely

5. How do you cope with your motion sickness? (Select all that apply)
a. Medication
b. Avoiding the travel
c. Seating strategies
d. Dietary supplements
e. Other

Subject ID |__|__|__|- |__|__|__|__|

6. Do any of your relatives experience motion sickness?
a. Yes
b. No

7. How much does motion sickness affect your life?
a. Severely
b. Moderately
c. Minimally

8. Have you spoken with your doctor about your motion sickness?
a. Yes
b. No

9. Are you pregnant or breastfeeding?
a. Yes
b. No

10. Congratulations! You may qualify to participate in a clinical study on motion sickness. Please enter your contact information and we will be contacting you shortly to speak further!
a. Name (First and Last)
b. Sex
    i. Male
    ii. Female
c. Ethnicity
    i. Hispanic
    ii. Non-Hispanic
d. Race
    i. American Indian or Alaska Native
    ii. Asian
    iii. Black or African American
    iv. Native Hawaiian or Pacific Islander
    v. White
    vi. Other
e. Age
f. Phone Number
g. Email
h. Zip Code
i. When is the best time to reach you?
    i. Morning
    ii. Afternoon
    iii. Evening
    iv. Anytime

20.3.2. Motion Sickness Eligibility Questionnaire Inclusion Criteria

Subject ID |__|__|__|- |__|__|__|__|

Screening

MSEQ – Motion Sickness Eligibility Questionnaire

Questions	Inclusion Criteria
1. Have you experienced symptoms of motion sickness in the past year? a. Yes b. No	Yes
2. Which of the following symptoms of motions sickness do you experience? (Select all that apply) a. Nausea b. Vomiting c. Dizziness d. Headache e. Anxiety f. Queasiness g. Irritability	Need to select at least 2, with one answer being nausea or vomiting
3. In which vehicle(s) do you experience motion sickness? (Select all that apply) a. Car b. Bus c. Boat d. Plane e. Train	Need to select at least one of car, bus or boat
4. How often do you experience motion sickness in the vehicle(s) selected above? a. Always b. Sometimes c. Rarely	Need to select either Always or Sometimes for at least one vehicle
5. How do you cope with your motion sickness? (Select all that apply) a. Medication b. Avoiding the travel c. Seating strategies d. Dietary supplements e. Other	Need to select one

Subject ID |__|__|__|- |__|__|__|__|

6. Do any of your relatives experience motion sickness? a. Yes b. No	Not a selection criterion
7. How much does motion sickness affect your life? a. Severely b. Moderately c. Minimally	Not a selection criterion
8. Have you spoken with your doctor about your motion sickness? a. Yes b. No	Not a selection criterion
9. Are you pregnant or breastfeeding? a. Yes b. No	No
10. Congratulations! You may qualify to participate in a clinical study on motion sickness. Please enter your contact information and we will be contacting you shortly to speak further! a. Name (First and Last) b. Sex i. Male ii. Female c. Ethnicity i. Hispanic ii. Non-Hispanic d. Race i. American Indian or Alaska Native ii. Asian iii. Black or African American iv. Native Hawaiian or Pacific Islander v. White vi. Other e. Age f. Phone Number g. Email h. Zip Code i. When is the best time to reach you? i. Morning ii. Afternoon iii. Evening iv. Anytime	Collecting this contact and demographic information for contacting patients to speak about the study and confirm their information from this questionnaire, and collect further information.

20.3.3. Motion Sickness Severity Scale – MSSS

Sponsor code VP-VLY-686-3401
VP-VLY/Tradipitant

Subject ID |__|__|__|- |__|__|__|__|

Travel Assessment – 30 minutes

MSSS – Motion Sickness Severity Scale

In the **last 30 minutes**, how severe is your motion sickness?

Please circle the number below that best represents your response:

Please select only one response.

0	1	2	3	4	5	6
No symptoms	Stomach awareness or discomfort	Mild nausea	Moderate nausea	Severe nausea	Retching	Vomiting

20.3.4. Motion Sickness Assessment Questionnaire - MSAQ

Sponsor code VP-VLY-686-3401
VP-VLY/Tradipitant

Subject ID |__|__|__|- |__|__|__|__|

End of Travel Assessment

MSAQ – Motion Sickness Assessment Questionnaire

Using the scale below, please rate how accurately the following statements describe your experience:

1 2 3 4 5 6 7 8 9

Not at all — Severely

1. I felt sick to my stomach	☐	9. I felt disoriented	☐
2. I felt faint-like	☐	10. I felt tired/fatigued	☐
3. I felt annoyed/irritated	☐	11. I felt nauseated	☐
4. I felt sweaty	☐	12. I felt hot/warm	☐
5. I felt queasy	☐	13. I felt dizzy	☐
6. I felt lightheaded	☐	14. I felt like I was spinning	☐
7. I felt drowsy	☐	15. I felt as if I may vomit	☐
8. I felt clammy/cold sweat	☐	16. I felt uneasy	☐

20.3.5. Patient Global Impression of Severity Questionnaire – PGI-S

Sponsor code VP-VLY-686-3401
VP-VLY/Tradipitant

Subject ID |__|__|__|- |__|__|__|__|

End of Travel Assessment

PGI-S – Patient Global Impression of Severity Questionnaire

Use the following scale to rate the severity of your motion sickness symptoms during the travel:

0	1	2	3	4
None	Mild	Moderate	Severe	Very Severe