TRADIPITANT
AMENDMENT NO. 6 TO PROTOCOL VP-VLY-686-3301

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY TO ASSESS THE EFFICACY OF TRADIPITANT IN RELIEVING SYMPTOMS OF GASTROPARESIS

Author: Jesse Carlin, Ph.D

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Sponsor: Vanda Pharmaceuticals Inc.
2200 Pennsylvania Ave. NW
Suite 300E
Washington, DC 20037
USA

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Approved by the following:

Program Lead:

[redacted]

Medical Director:

[redacted]

Name of Sponsor/Company: Vanda Pharmaceuticals Inc.
Name of Investigational Product: Tradipitant (VLY-686)
Name of Active Ingredient: {2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone
Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Assess the Efficacy of Tradipitant in Relieving Symptoms of Gastroparesis
Study center(s): Approximately 50 centers in the United States

Indication:	**Phase of development:**
Diabetic & Idiopathic Gastroparesis	III

Number of subjects (planned):

Up to 800 subjects will enroll in the study.

Group 1: Approximately 200 gastroparesis subjects will be determined eligible to enter the Evaluation Phase and be randomized to one of 2 arms (100 per arm, 1:1 randomization scheme).

Group 2: Up to 600 gastroparesis subjects that are not eligible to be randomized will enter into the 12 week Open Label Phase of the study.

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Investigational product, dosage and mode of administration:

Group 1: Oral 85 mg tradipitant and matching placebo capsules will be administered. Subjects will be randomized to one of two treatment arms to receive 85 mg tradipitant BID or placebo.

Group 2: Open label Oral 85 mg tradipitant capsules will be administered to all group 2 patients.

All subjects will be instructed to take 1 capsule in the morning and another approximately 12 hours later in the evening.

Duration of treatment: Up to 12 weeks

Objectives:

Primary:

- To evaluate the efficacy of tradipitant relative to placebo in change from baseline to Week 12 in the daily nausea severity scores.

Secondary:

- To evaluate the efficacy of tradipitant relative to placebo in change from baseline in number of days at "0" nausea.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of other individual symptoms associated with gastroparesis.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of the overall symptom burden associated with gastroparesis.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of global improvement and quality of life measures.
- To explore the safety and tolerability of multiple oral doses of tradipitant.

Overall Design:

This is a multicenter, randomized, double-blind, placebo-controlled study to be conducted in the United States. Up to eight hundred (800) subjects diagnosed with gastroparesis, who satisfy the selection criteria for the study, will be eligible for one of two groups. Group 1 will enter the Evaluation Phase of the study and Group 2 will enter the Open Label phase of the study. Patients eligible for Group 1 will be randomized to one of two treatment groups. Randomization will be stratified by disease etiology (idiopathic or diabetic), and enrollment for either of the etiologies will be capped at 60% of the total sample size. Patients eligible for Group 2 will enter the Open Label Phase of the study.

The study includes two phases: the screening phase and the evaluation phase. The screening phase includes a screening visit to evaluate subjects' preliminary eligibility for the study. During the screening phase, subjects will collect diary data for at least 4 weeks. The data collected during the screening phase must be reviewed in order to determine eligibility for enrollment into the evaluation phase. Data review will be performed prior or at Visit 2. Patients who to meet all Group 1 eligibility criteria will randomized onto double blind treatment in the evaluation phase. Patients who meet Group 2 criteria or do not meet symptom criteria for randomization but still meet all other eligibility criteria, will be offered open label treatment in the open label arm of the evaluation phase. When enrollment goal is reached for

group 1, group 1 enrollment will be closed and all subsequent patients in screening will be evaluated for group 2 eligibility only.

The Evaluation Phase includes 12 weeks of double blind randomized treatment of placebo or tradipitant (85mg bid, approximately 12 hours apart) for Group 1 or open label tradipitant (85mg bid, approximately 12 hours apart) for Group 2. Daily diaries will be completed during all phases. Clinical evaluations and safety assessments will occur at Screening, Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, and Week 12.

Following the End of Study Visit (Visit 8) patients can opt-in to a one-day optional pharmacokinetic (PK) study where one additional dose of tradipitant will be taken and blood will be drawn pre-dose and, 1, 2, 4, 6, 8-hour post dose to assess drug levels. This optional PK Visit can occur 1-14 days after Visit 8.

Primary Endpoint:

Change from baseline to Week 12 in daily individual nausea severity scores (0=none, 1=very mild, 2= mild, 3=moderate, 4=severe, 5=very severe)

Criteria for evaluation:

Efficacy:

Efficacy assessments will include:

- Gastroparesis Core Symptom Daily Diary (GCSDD)
- Patient Assessment of GI Disorders – Symptoms Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis
- Patient Rated Change in Gastroparesis Symptoms
- Patient Global Impression – Change (PGI-C)
- Patient Assessment of Gastrointestinal Disorders – Quality of Life (PAGI-QOL)
- Gastroparesis Treatment Benefit Survey (GTBS)
- Clinician Global Impression – Severity (CGI-S)

Safety:

- Safety and tolerability assessments will include the recording of adverse events (AEs), physical examinations, clinical laboratory evaluations, vital signs, and electrocardiograms.
- The Columbia-Suicide Severity Scale (C-SSRS) will be used to assess suicidal behavior and ideation.

Sample Size Discussion:

Based on a two-sided t-test with the 5% significance level, the planned sample size of 100 subjects per arm provides 95% power to detect a mean difference of 0.65 point in the average of daily nausea severity assuming the standard deviation of 1.25 in each treatment group.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 13
1. INTRODUCTION 17
1.1. Background 17
1.2. Tradipitant Relevant Data Summary 18
1.2.1. Nonclinical Pharmacology and Toxicology 18
1.2.2. Clinical 18
2. TRIAL OBJECTIVES AND RATIONALE 22
2.1. Objectives 22
2.1.1. Primary 22
2.1.2. Secondary 22
2.1.3. Exploratory 22
2.2. Rationale 23
2.2.1. Study Rationale 23
2.2.2. Rationale for Dose and Study Design 23
2.2.3. Risk and Benefit 23
3. INVESTIGATIONAL PLAN 24
3.1. Overall Study Design and Plan: Description 24
3.1.1. Screening Phase 25
3.1.2. Evaluation Phase 27
3.1.3. End of Study or Early Termination (Visit 8) 27
3.1.4. Optional Pharmacokinetic Visit (PK Visit) 28
3.2. Schedule of Evaluations 28
4. SELECTION AND WITHDRAWAL OF SUBJECTS 31
4.1. Subject Inclusion Criteria 31
4.2. Subject Exclusion Criteria 32
4.3. Subject Withdrawal Criteria 33
5. TREATMENT OF SUBJECTS 35
5.1. Study Medication 35
5.1.1. Dosing 35
5.1.2. Guidance for Taking Study Medication 35
5.2. Concomitant Medications 35

5.2.1. Prohibited Medications 36
5.2.2. Rescue Medication 36
5.2.3. Medication Washout 37
5.3. Treatment Compliance 37
5.4. Treatment Assignment 37
5.4.1. Subject ID Assignment 37
5.4.2. Subject Replacement 38
5.4.3. Randomization 38
6. STUDY MEDICATION MATERIALS AND MANAGEMENT 39
6.1. Study Medication 39
6.2. Study Medication Packaging and Labeling 39
6.3. Study Medication Storage 39
6.4. Study Medication Accountability 39
7. STUDY ASSESSMENTS 41
7.1. Study Assessments per Visit 41
7.1.1. Screening Visit (Visit 1) 41
7.1.2. Baseline Visit (Visit 2, Study Day 0) 41
7.1.3. Evaluation Phase Visit 3, Visit 4, Visit 6 (Study Day 14, Day 28, Day 56 ± 3 days) 42
7.1.4. Evaluation Phase Visit 5 and Visit 7 (Study Day 42, Day 70 ± 3 days) 43
7.1.5. Visit 8/EOS/ET (Study Day 84 ± 3 days) 44
7.1.6. Optional Pharmacokinetic Visit (1-14 Days after EOS) 44
7.1.7. Unscheduled Visits 45
8. ASSESSMENT OF EFFICACY 46
8.1. Patient Reported Outcome (PRO) Assessments 46
8.1.1. Gastroparesis Core Symptom Daily Diary (GCSDD) 46
8.1.2. Patient Assessment of Gastrointestinal Disorders Severity Index – Symptoms (PAGI-SYM) 46
8.1.3. Global Assessment of Gastroparesis Questionnaire 47
8.1.4. Patient-Reported Change in Gastroparesis Symtpoms 47
8.1.5. Patient Global Impression-Change (PGI-C) 47
8.1.6. Patient Assessment of Gastrointestinal Disorders-Quality of Life (PAGI-QOL) 47

8.1.7. Gastroparesis Treatment Benefit Survey (GTBS) 47
8.2. Clinician Global Impression of Severity (CGI-S) 48
8.3. Gastric Emptying Breath Test (GEBT) 48
8.4. Wireless Motility Capsule 48
8.5. Gastric Emptying by Scintigraphy 48
8.6. Pharmacokinetic Assessment 49
9. ASSESSMENT OF SAFETY 50
9.1. Safety Parameters 50
9.1.1. Safety ECG 50
9.1.2. Laboratory Evaluations 50
9.1.3. Vital Signs and Body Measurements 51
9.1.4. Medical History and Physical Examinations 52
9.1.5. Pregnancy 52
9.1.6. Columbia-Suicide Severity Rating Scale (C-SSRS) 53
9.1.7. Definitions Related to Safety 53
9.1.8. Relationship to Study Medication 55
9.1.9. Recording Adverse Events 55
9.1.10. Reporting Adverse Events 56
9.1.11. Unblinding Procedures 57
10. PHARMACOGENOMICS ASSESSMENT 58
11. STATISTICS 59
11.1. Sample Size and Accrual 59
11.2. Statistical Methods and Analysis Plan 59
11.2.1. General 59
11.2.2. Subject Populations for Analysis 60
11.2.3. Subject Disposition 60
11.2.4. Demography and Other Baseline Data 60
11.2.5. Study Medication 61
11.2.6. Prior/Concomitant Therapy 61
11.3. Efficacy Data Analysis 61
11.3.1. Primary Outcome and Methodology 61
11.3.2. Secondary Efficacy Analysis 62
11.4. Safety Data Analysis 62

11.4.1. Adverse Events 62
11.4.2. Laboratory Data 63
11.4.3. Vital Signs and Body Measurements 63
11.4.4. Electrocardiogram (ECG) 63
11.4.5. C-SSRS 64
11.5. Subgroup Analysis 64
11.6. Interim Analysis 64
11.7. Deviations in Analysis from Statistical Plan and Other Issues 64
12. DIRECT ACCESS TO SOURCE DOCUMENTS 65
12.1. Definition of Source Document 65
12.2. Study Monitoring 65
12.3. Audits and Inspections 65
13. QUALITY CONTROL AND QUALITY ASSURANCE 67
13.1. Data Collection 67
13.2. Clinical Data Management 67
13.3. Database Quality Assurance 67
14. ETHICS 68
14.1. Ethics Review 68
14.2. Ethical Conduct of the Study 68
14.3. Written Informed Consent 68
15. DATA HANDLING AND RECORD KEEPING 69
15.1. Retention of Records 69
16. ADMINISTRATIVE PROCEDURES 70
16.1. Changes to the Protocol 70
16.2. Discontinuation of Study 70
16.3. Publication of Results 70
16.4. Investigator Agreement 72
17. REFERENCES 73
18. APPENDICES 75
18.1. Laboratory Ranges Used to Identify Clinically Notable Abnormal Laboratory Values 75
18.2. Vital Signs Values 76
18.3. Signals of Hepatacellular Injury 76

LIST OF TABLES

Table 1: VP-VLY-686-3301 Group 1 Treatment Arms 25
Table 2: Schedule of Evaluations 29
Table 3: Medications Allowed for Rescue Use 37
Table 4: Clinical Laboratory Tests 50
Table 5: SAE Criteria and Definitions 53
Table 6: SAE Reporting Information 57

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (also known as SGPT)
ANCOVA	Analysis of Covariance
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
CGI-S	Clinician Global Impression of Severity
CL/F	Oral Clearance
C_{max}	The highest observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DNDP	Division of Neuropharmacological Drug Products
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	Ethical Committee

Abbreviation	Description
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
GCSDD	Gastroparesis Core Symptom Daily Diary
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Empying Breath Test
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
GTBS	Gastroparesis Treatment Benefit Survey
HDL	High Density Lipoprotein
HDPE	High-Density Polyethylene
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

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
MMRM	Mixed Model Repeated Measures
ms	Milliseconds
NDA	New Drug Application
NK	Neurokinin
NKA	Neurokinin A
NKB	Neurokinin B
NOAEL	No-Observed Adverse Effect Level
OC	Observed Cases
OLE	Open-label Extension
OTC	Over the Counter
PAGI-QOL	Patient Assessment of Gastrointestinal Disorders - Quality of Life
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders - Symptom Severity Index
PD	Pharmacodynamic
PE	Physical Examination
PET	Positron Emission Tomography
PG	Pharmacogenomic
pg	Picograms
PGI-C	Patient Global Impression of Change
pH	Hydrogen ion concentration
PK	Pharmacokinetic
PONV	Post-Operative Nausea and Vomiting
PRO	Patient Reported Outcome
QD	Once a day
QT	Time Between the Start of the Q Wave and the End of the T Wave in the Heart's Electrical Cycle

Abbreviation	Description
RBC	Red blood cell
REML	Restricted Maximum Likelihood
RO	Receptor Occupancy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T4	Thyroxine
TBL	Total Bilirubin Level
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach C_{max}
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
U.S.	United States
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1. 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.

1.1. Background

Gastroparesis is a chronic disorder characterized by objective evidence of delayed gastric emptying, symptoms associated with gastric retention, and absence of mechanical obstruction [1]. The true prevalence of gastroparesis is unknown, but its US prevalence is estimated to be as high as 5 million [2]. The two primary etiologies of gastroparesis are Diabetes Mellitus and idiopathic disease together representing over 60% of all cases [3][4]. Nausea is the most commonly reported symptom of gastroparesis, and has been reported in >90% of subjects in various studies [5][6]. Vomiting is the second most commonly reported symptom with reports of incidence varying between 66 and 88 percent [5]. Other commonly reported symptoms of gastroparesis include early satiety, postprandial fullness, and abdominal pain [7].

Despite the severity of symptoms and associated distress among gastroparesis subjects, there are currently no treatments for the symptoms of gastroparesis approved for chronic use. Gastroparesis continues to represent a large unmet need. In a large cohort study of 262 gastroparesis subjects, less than one-third demonstrated clinically meaningful improvements at 48 weeks despite treatment interventions [8].

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 [9]. 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 [10].

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 [11]. 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) [12].

Tradipitant is currently being assessed clinically to determine its efficacy in treating the symptom of nausea in subjects suffering from gastroparesis.

1.2. Tradipitant Relevant Data Summary

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

[redacted]

[redacted]

- [redacted]

- [redacted]

- [redacted]

- [redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

2. TRIAL OBJECTIVES AND RATIONALE

2.1. Objectives

2.1.1. Primary

- To evaluate the efficacy of tradipitant relative to placebo in change from baseline to Week 12 in daily nausea severity scores.

2.1.2. Secondary

- To evaluate the efficacy of tradipitant relative to placebo in change from baseline in number of days at "0" nausea score.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of other individual symptoms associated with gastroparesis.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of the overall symptom burden associated with gastroparesis.
- To evaluate the efficacy of tradipitant relative to placebo in change from baseline of global improvement and quality of life measures.
- To explore the safety and tolerability of multiple oral doses of tradipitant.

2.1.3. 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 gastroparesis and/or gastroparesis symptoms and 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 evaluate the effect tradipitant has on gastric emptying relative to placebo in change from baseline of gastric emptying rate.

2.2. Rationale

2.2.1. Study Rationale

The underlying pathophysiology of gastroparesis is complex and remains largely unknown. Prokinetic therapy has been the traditional mainstay of gastroparesis treatments, but studies continue to demonstrate a lack of correlation between reduction in gastric emptying delays and relief of gastroparesis symptoms [5].

Two case reports have documented the efficacy of open-label NK-1 antagonist therapy in severe, refractory gastroparesis cases [13][14]. Thus, NK-1 receptor antagonists, like tradipitant, are promising potential therapeutics for treating nausea associated with gastroparesis.

2.2.2. Rationale for Dose and Study Design

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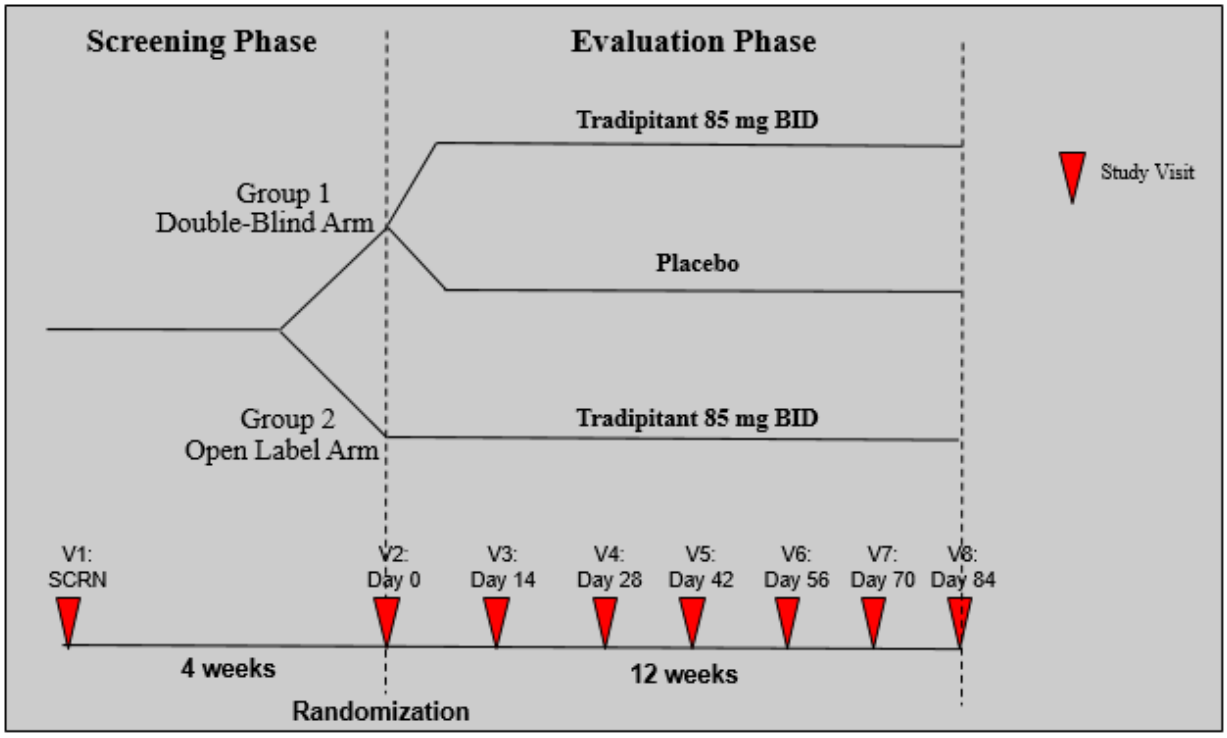
2.2.3. Risk and Benefit

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3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

Figure 1: Overall Study Design



This is a randomized, double-blind, placebo-controlled study to be conducted in the United States. Up to eight hundred (800) subjects diagnosed with gastroparesis will enter one of two treatment groups. Group 1 will include subjects of either diabetic or idiopathic origin who satisfy the Group 1 inclusion criteria for the study. Group 1 subjects will be randomized 1:1 to tradipitant treatment or matching placebo (Table 1). Randomization will be stratified by disease etiology (idiopathic or diabetic), and enrollment for each etiology will be capped at 60% of the total sample size. Group 2 subjects will enter the open label arm and will receive open label treatment with tradipitant. When enrollment goal is reached for Group 1, Group 1 enrollment will be closed and all subsequent patients in screening will be evaluated for Group 2 eligibility only.

Table 1: VP-VLY-686-3301 Group 1 Treatment Arms

Arm	Total Daily Dose	AM Dose	PM Dose
Tradipitant BID	170 mg	85 mg tradipitant	85 mg tradipitant
Placebo	0 mg	Placebo	Placebo
Open Label Tradipitant	170 mg	85 mg tradipitant	85 mg tradipitant

The Screening Phase includes Visit 1 and Visit 2 where eligibility for the study will be assessed. After the Screening Phase, all participants that qualify for Group 1 will proceed to the Evaluation Phase, which includes 12 weeks of placebo-controlled, double-blind, randomized treatment of placebo or tradipitant (85mg bid, approximately 12 hours apart). All participants that qualify for Group 2, but not Group 1 due to symptom severity or other exclusion criteria, will proceed to the Open Label Phase and will receive open label treatment of tradipitant 85 mg bid. Daily diaries will be collected throughout all phases of the study.

3.1.1. Screening Phase

The screening phase includes the Screening (Visit 1) and Baseline (Visit 2) visits. Informed consent must be obtained prior to the initiation of any study related screening procedures. The screening phase will be at least 28 days for Group 1 subjects. Throughout the Screening Phase, any subject that does not qualify for Group 1/Evaluation Phase due to symptom severity or other exclusion criteria will be evaluated for Group 2/Open Label Phase.

The screening phase may be extended up to 35 days to allow for additional screening diary data collection. The screening phase may also be extended to allow for medication washout prior to the collection of baseline diary data. Screen failures may be given the opportunity for reconsideration at a later time (re-screening) at the discretion of the Investigator and approval by the Sponsor.
A full list of assessments performed at each visit are listed in Table 2 and Section 7.

3.1.1.1. Screening Visit (Visit 1)

During the Screening Visit (Visit 1), safety and efficacy assessments will be performed to assess the subject's initial eligibility after the subject signs the informed consent form (Section 7.1.1). Collection of adverse event information will begin at the time the ICF is signed. Medical history, concomitant medications, gastric emptying study, and upper endoscopy results to demonstrate no gastric obstruction (if available) will be collected.

Subjects will be trained and provided access to diary, which will be used to collect daily symptoms. Subjects will complete their first diary entry at the Visit 1 (V1) as part of the training process. Subjects will be instructed to complete the diary once daily for at least 28 days prior to the baseline visit. **In order to avoid subject reporting bias which could negatively impact the results of the study, additional inclusion criteria for Group 1 should NEVER be shared with subjects or potential subjects.**

The Screening Visit may be repeated following medication washout and prior to baseline diary collection at the discretion of the Investigator and/or Medical Monitor. The Screening Visit can be split up into multiple days if necessary.

Patients who do not qualify for the study will be considered screen failures. Screen failures may be given the opportunity for reconsideration at a later time (re-screening) at the discretion of the Investigator and approval by the Sponsor.

3.1.1.1.1. Visit 1 Instruction If Patient Lacks a Historical Gastric Emptying Test

Potential subjects without a prior scintigraphy, breath test, or wireless motility capsule evaluation to serve as evidence of delayed gastric emptying within the 10-year window can still be considered as symptomatically suffering from gastroparesis. To confirm a gastroparesis diagnosis, subjects can undergo a gastric empting breath test (GEBT), scintigraphy, or wireless motility capsule test provided they meet all other Visit 1 criteria, including:

-history of nausea for the past 6 months
-at least one other symptom of gastroparesis, such as vomiting, postprandial fullness, or abdominal pain

If evaluation at Visit 1 confirms the subject meets all other, the subject may begin completing their daily diary according to the normal screening process described in Section 3.1.1.1. The subject then has the option to:

1. Be scheduled to return for an unscheduled visit to perform a GEBT or scintigraphy test
2. or given a wireless motility capsule system for the subject to perform at home (where available).

The gastric emptying test is to take place within 2 weeks of their Visit 1 to confirm the subject's objective evidence of delayed gastric emptying. Which test the subject receives will depend on what is available at site and/or the subject's preference. If this test confirms delayed gastric emptying, the subject will continue participation in the study according to the normal screening procedures. Subjects whose test does not confirm delayed gastric emptying will be considered screen failures.

Subjects who undergo the GEBT in screening will be asked to undergo an additional GEBT at EOS/Visit 8.

3.1.1.2. Baseline Visit (Visit 2)

On Day 0 (Visit 2/Baseline), assessments will be performed and diary data will be reviewed to assess the subject's continued eligibility for Group 1 or Group 2 (Section 7.1.2).

Group 1

Subjects continuing to meet all eligibility criteria for Group 1 will be randomized to one of two treatment arms (Table 1), and will be given enough study medication to last until the next visit. Study staff should be careful to review eligibility criteria that is specific to the Group 1 Baseline Visit including diary review to determine eligibility based on symptom severity. Subjects in Group 1 must have at least 24 daily screening diary entries and sufficient study compliance prior to randomization. The screening may be extended for a total of up to 35 days to accommodate this. Subjects who are randomized will be instructed to begin taking study medication in the evening of Day 0 (Baseline/Visit 2). Twice daily dosing will begin the day following the baseline visit.

Group 2

Subjects who do not meet criteria for Group 1,or when Group 1 enrollment is complete, or meet criteria for Group 2, will enter the Open Label Phase of the study and will be given enough open label medication to last until the next visit. Study staff should be careful to review eligibility criteria that is specific to the Group 2 Baseline Visit including diary review to determine eligibility based on symptom severity. Subjects in Group 2 must have at least 24 daily screening diary entries and sufficient study compliance prior to placement in the Open Label Phase. The screening may be extended for a total of up to 35 days to accommodate this. All Visit 2 procedures will be performed and patient will receive open label study medication and will be instructed to begin taking study medication in the evening of Day 0 (Baseline/Visit 2). Twice daily dosing will begin the day following the baseline visit.

3.1.2. Evaluation Phase

3.1.2.1. Group 1/Double Blind Arm Visit 3-Visit 7

Subjects will return to the clinic on Day 14 (± 3 days), Day 28 (± 3 days), Day 42 (± 3 days), Day 56 (± 3 days), and Day 70 (± 3 days) for safety and efficacy assessments (Section 7.1.3, Section 7.1.4). Diary and medication compliance will be reviewed. Unused study medication will be collected and subjects will be dispensed enough study medication to last until next visit

3.1.2.2. Group 2/Open Label Arm Visit 3-Visit 7

Subjects who are not randomized, but enter the Open Label Phase, will return to the clinic on Day 14 (± 3 days), Day 28 (± 3 days), Day 42 (± 3 days), Day 56 (± 3 days) and Day 70 (± 3 days) for safety and efficacy assessments (Section 7.1.3, Section 7.1.4). Diary and medication compliance will be reviewed. Unused study medication will be collected and subjects will be dispensed enough open label medication to last until next visit.

3.1.3. End of Study or Early Termination (Visit 8)

At the End of Study Visit (Day 84 ± 3 days) or at the time of Early Termination, subjects will return to the clinic for safety and efficacy assessments (Section 7.1.5). Diary and medication compliance will be reviewed.

3.1.4. Optional Pharmacokinetic Visit (PK Visit)

Patients who complete the study can volunteer to participate in a pharmacokinetic sampling visit. This visit can occur 1-14 days after the EOS and patients will be asked to return to the clinic to receive one additional dose of tradipitant (85mg). Blood samples to assess drug levels will be taken pre-dose, and 1, 2, 4, 6, 8-hours post dose.

3.2. Schedule of Evaluations

Below is the schedule of evaluations for VP-VLY-686-3301:

Table 2: Schedule of Evaluations

Phase	Screening	Baseline	Evaluation Phase					EOS	
Visit	V1	V2	V3	V4	V5	V6	V7	V8 EOS/ET	PK Visit
Study Day	≥28 days prior to Day 0	Day 0	Day 14[1]	Day 28[1]	Day 42[1]	Day 56[1]	Day 70[1]	Day 84[1] or ET	1-14 days post EOS
ICF [2]	X								
Review of Inclusion / Exclusion Criteria	X	X							
Demography and Medical History	X								
AE Query[3]	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	
Weight and Vital Signs[4]	X	X	X	X		X		X	
Physical Examination (PE)	X							X	
12-lead resting ECG	X	X	X	X		X		X	
Hematology, Chemistry, Urinalysis, HbA1c, TSH, T4, and exploratory tests	X	X	X	X		X		X	
Blood coagulation testing[5]	X								
Urine Drug Screen	X	X	X	X		X		X	
Serum β-HCG (for WOCBP)	X							X	
Urine Pregnancy Test (for WOCBP)		X	X	X		X			
Pharmacogenomic (PG) sample	X								
Pharmacokinetic (PK) pre-dose sample									X
In-clinic dose									X
Pharmacokinetic (PK) sample(s)		X	X	X		X		X	X
C-SSRS[6]		X	X	X	X	X	X	X	
PAGI-SYM	X	X	X	X	X	X	X	X	
Global Assessment of Gastroparesis Questionnaire	X	X	X	X	X	X	X	X	
Patient-Rated Change in Gastroparesis Symptoms			X	X	X	X	X	X	
GTBS		X							
PAGI-QOL		X						X	
PGI-C			X	X	X	X	X	X	
CGI-S		X	X	X	X	X	X	X	
Gastric Emptying Test[7]	X							X[8]	

Phase	Screening	Baseline	Evaluation Phase					EOS	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 EOS/ET**	**PK Visit**
Study Day	**≥28 days prior to Day 0**	**Day 0**	**Day 14[1]**	**Day 28[1]**	**Day 42[1]**	**Day 56[1]**	**Day 70[1]**	**Day 84[1] or ET**	**1-14 days post EOS**
Randomization		X							
Study Medication Dispensation		X	X	X	X	X	X		
Study Medication Collection & Compliance			X	X	X	X	X	X	
Subject Diary Instruction	X								
Subject Diary Review		X						X	
GCSDD	→								

[1] Within +/- 3 days
[2] Informed consent will be obtained prior to the performance of any study procedure(s)
[3] Adverse event collection will begin at the time the ICF is signed.
[4] Vital sign collection at Visits 3,4, 6 and 8. Height collection at V1. Body weight collection at Visits 3,4, 6 and 8.
[5] Blood coagulation will be measured at Screening and at Unscheduled Visits
[6] The Screening/Baseline C-SSRS will occur at V2. The Since Last Visit C-SSRS will occur at visits V3-V8.
[7] Only in subset of patients who do not have breath test, scintigraphy, or wireless motility capsule demonstrating delayed gastric emptying within 10 years of screening. Type of test will depend what is available at site and/or patient's preference.
[8]Patients who receive the GEBT in screening only will be asked to repeat at EOS.

AE = Adverse Event, CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; GCSDD = Gastroparesis Core Symptom Daily Diary; GCSI = Gastroparesis Cardinal Symptom Index; GEBT = Gastric Emptying Breath Test; GTBS = Gastroparesis Treatment Benefit Survey; ICF = Informed Consent Form; PAGI-QOL = Patient Assessment of Gastrointestinal Symptoms – Quality of Life; PAGI-SYM = Patient Assessment of Gastrointestinal Disorders Symptoms Severity Index; PGI-C = Patient Global Impression of Change; PK= Pharmacokinetic; WOCBP = Women of Child-Bearing Potential

4. SELECTION AND WITHDRAWAL OF SUBJECTS

[redacted]

[redacted]

4.3. Subject Withdrawal Criteria

The term “discontinuation” refers to the randomized subject’s premature withdrawal from the study before completing all scheduled evaluations.

Subjects may voluntarily withdraw from the study at any time for any reason. Subjects 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 subject. 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 subject's continued participation in the trial. Clinically notable abnormalities in vital signs, laboratory tests, or liver enzymes are provided in Appendices 18.2,Section 18.1, and Section 18.3 respectively, to guide clinical focus regarding a subject's continued participation. Please refer to FDA Guidance [16] recommendations for discontinuing treatment. Investigators may utilize unscheduled visits to repeat safety labs to provide adequate information to make an informed decision based on the totality of the evidence at the time.
- Noncompliance;

For subjects withdrawing from the study prematurely, all efforts will be made to perform the Visit 8 Early Termination procedures.

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

Subjects 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.

5. TREATMENT OF SUBJECTS

5.1. Study Medication

5.1.1. Dosing

Group 1 subjects will be dispensed study medication under double-blind conditions. Each subject will be dispensed one bottle of study medication at Visit 2 through Visit 8. Subjects will be instructed to take one capsule of study medication every day in the morning, and one capsule of study medication every day in the evening approximately 12 hours later. Each capsule will contain either 85 mg of tradipitant or matching placebo.

Open Label Group 2 subjects will be dispensed open label tradipitant at Visit 2 through Visit 8. Subjects will be instructed to take one capsule of study medication every day in the morning, and one capsule of study medication every day in the evening approximately 12 hours later. Each capsule will contain either 85 mg of tradipitant.

Patients who opt-in to the pharmacokinetic (PK) visit 1-14 days after Visit 8 will receive 1 additional dose (85mg) of open label tradipitant in clinic.

5.1.2. Guidance for Taking Study Medication

Subjects should be instructed to take study medication approximately every 12 hours at the same times each day. The morning dose of study medication should be taken at least 30 minutes before breakfast and the evening dose of study medication should be taken at least 30 minutes prior to dinner or bedtime. Study medication should be taken on an empty stomach whenever possible.

In the event that a patient vomits within 15 minutes of taking study medication and an intact capsule can be identified in the emesis, a second capsule should be administered.

5.2. 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.

Prohibited medications and treatments are prohibited from the screening visit (or 4 weeks prior to the Randomization Visit when a washout is required) through the end of study participation. Questions regarding the use of concomitant medications not listed should be directed to the Medical Monitor.

[redacted]

5.2.2. Rescue Medication

Anti-nausea or antiemetic medication that is not administered on a stable daily dosing regimen is considered rescue medication. Patients may use rescue medication per the Rescue Medication Guidelines.

5.2.2.1. Rescue Medication Guidelines

1. Only medications listed in Table 3 can be used as rescue medication.
2. Patients should have previous experience with use of the medication.
3. Rescue medication administration should be documented in the patient diary
4. Patient use of rescue medication will be reviewed at study visits

Table 3: Medications Allowed for Rescue Use

The following medications are allowed for rescue use
ondansetron, prochlorperazine, promethazine

[redacted]

5.4. Treatment Assignment

[redacted]

5.4.2. Subject Replacement

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

5.4.3. Randomization

Randomization will be performed through a centralized, web-based, validated system that automates the assignment of subjects 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 subject will be assigned.

6. STUDY MEDICATION MATERIALS AND MANAGEMENT

6.1. Study Medication

[redacted]

6.2. Study Medication Packaging and Labeling

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

Study medication capsules will be provided in high-density polyethylene (HDPE) bottles with a child-resistant cap containing desiccant. Each bottle will contain 36 capsules. At each visit, subjects will be given enough study medication to last until the next visit (one bottle will be dispensed at Visit and collected next Visit). Subjects should be instructed to bring the study medication bottle along with any unused capsules to the site at his/her next visit. Each bottle will have a two-part label. The second part of the label will be attached to the subject's source documents before the bottle is dispensed to the subject.

6.3. 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 subjects at the study site.

6.4. 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 subjects 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 subject's CRF and source documents.

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 subject'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.

7. STUDY ASSESSMENTS

7.1. Study Assessments per Visit

7.1.1. Screening Visit (Visit 1)

The following will be performed after the subject signs the informed consent form:

- Review of Inclusion/Exclusion Criteria
- Collection of demographic information, and medical history (including gastric emptying study, and upper endoscopy results if available)
- Adverse Event Query
- Prior and Concomitant Medications
- Weight and Semi-supine routine vital signs collection (body temperature, respiratory rate, blood pressure, and pulse)
- Physical examination (PE) (excluding genitourinary examination unless clinically indicated)
- ECG
- Clinical laboratory assessments: hematology, chemistry (including estimated creatinine clearance (eCLcr; based on the Cockcroft-Gault equation), urinalysis, HbA1c, thyroid stimulating hormone (TSH), thyroxine (T4), blood coagulation, and exploratory tests
- Urine Drug Screen
- Serum β-HCG pregnancy test (for females of child-bearing potential)
- PG sample collection
- Patient Assessment of Gastrointestinal (PAGI-SYM) Questionnaire Packet
- Global Assessment of Gastroparesis Questionnaire
- Gastric Emptying Breath Test (GEBT), scintigraphy, or wireless motility capsule test for patients who do not have gastric emptying test within 10 years
- Instruct Subject on Daily Diary

Collection of adverse event information will begin at the time the ICF is signed. Subjects will be given a diary and instructed to begin completing the screening portion of their diary for at least 4 weeks prior to the baseline visit. Diary data will be assessed at Visit 2 to confirm patient eligibility for randomization (see Section 4.1).

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

On Day 0 (Visit 2/Baseline), the following assessments will be performed to assess the subject's continued eligibility:

- Review of Inclusion/Exclusion Criteria

- Adverse Event Query
- Prior and Concomitant Medications
- Weight and Semi-supine routine vital signs collection (body temperature, respiratory rate, blood pressure, and pulse)
- Urine pregnancy test (for females of child-bearing potential)
- Gastroparesis Core Symptom Daily Diary (GCSDD) review
- ECG
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), exploratory tests
- Urine Drug Screen
- Baseline Pharmacokinetic (PK) sample
- Screening/Baseline C-SSRS questionaire
- Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis Questionnaire
- Gastroparesis Treatment Benefit Survey (GTBS)
- Patient Assessment of Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Clinical Global Impression of Severity (CGI-S)
- Individuals continuing to meet eligibility criteria for Group 1 will be randomized

To be considered eligible for Evaluation Phase randomization, subjects must:

- meet symptom diary eligibility criteria (Section 4.1)
- have delayed gastric emptying
- have at least 24 daily diary entries

- Other subjects continuing to meet eligibility criteria for Group 2, but not Group 1, will continue into the Open Label Phase of the Study.
- Study medication instruction and dispensation (first dose will be administered on evening of Day 0)

7.1.3. Evaluation Phase Visit 3, Visit 4, Visit 6 (Study Day 14, Day 28, Day 56 ± 3 days)

- Adverse Event Query

- Prior and Concomitant Medications
- Weight and Semi-supine routine vital signs collection (body temperature, respiratory rate, blood pressure, and pulse)
- Urine pregnancy test (for females of child-bearing potential)
- Pharmacokinetic (PK) sample
- ECG
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), exploratory tests
- Urine Drug Screen
- Since last visit C-SSRS
- Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis Questionnaire
- Patient-Rated Change in Gastroparesis Symptoms
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Study medication instruction and dispensation

7.1.4. Evaluation Phase Visit 5 and Visit 7 (Study Day 42, Day 70 ± 3 days)

- Adverse Event Query
- Prior and Concomitant Medications
- Since last visit C-SSRS
- Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis Questionnaire
- Patient-Rated Change in Gastroparesis Symptoms
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Study medication instruction and dispensation

7.1.5. Visit 8/EOS/ET (Study Day 84 ± 3 days)

- Adverse Event Query
- Prior and Concomitant Medications
- Physical examination (PE) (excluding genitourinary examination unless clinically indicated)
- Weight and Semi-supine routine vital signs collection (body temperature, respiratory rate, blood pressure, and pulse)
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), exploratory tests
- Serum pregnancy test (for females of child-bearing potential)
- Urine Drug Screen
- Pharmacokinetic blood sample
- ECG
- Since last visit C-SSRS
- Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis Questionnaire
- Patient-Reported Change in Gastroparesis Symptoms
- Patient Global Impression of Change (PGI-C)
- Patient Assessment of Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Gastric Emptying Breath Test (GEBT, for patients who had a GEBT at screening only)
- Mark EOS
- Mark participation in PK Visit portion of the study

7.1.6. Optional Pharmacokinetic Visit (1-14 Days after EOS)

- Adverse Event Query
- Pharmacokinetic pre-dose sample
- Take 1 capsule in-clinic
- Pharmacokinetic samples 1,2,4,6,8-hour post dose

7.1.7. Unscheduled Visits

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

If ALT or AST > 3X ULN is observed in safety labs, a repeated evaluation at minimum within 3 days from observation should be performed.

8. ASSESSMENT OF EFFICACY

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

- Gastroparesis Core Symptom Daily Diary (GCSDD)
- Patient Assessment of Gastrointestinal Disorder Symptom Severity Index (PAGI-SYM)
- Global Assessment of Gastroparesis Questionnaire
- Patient-Reported Change in Gastroparesis Symptoms
- Patient Global Impression – Change (PGI-C)
- Patient Assessment of Gastrointestinal Disorders – Quality of Life (PAGI-QOL)
- Gastroparesis Treatment Benefit Scale (GTBS)
- Clinician Global Impression – Severity (CGI-S)

8.1. Patient Reported Outcome (PRO) Assessments

8.1.1. Gastroparesis Core Symptom Daily Diary (GCSDD)

Subjects will complete a daily symptom questionnaire at least 28 days prior to randomization through the end of study. The diary questionnaire will include questions related to the experience of gastroparesis core symptoms over the previous 24 hours. The severity of nausea, early satiety, post-prandial fullness, bloating, abdominal pain, retching, and loss of appetite will be rated by severity on a Likert scale from 0 = none to 5 = very severe. The frequency of vomiting, duration of nausea, and the use of rescue medication will also be collected.

8.1.2. Patient Assessment of Gastrointestinal Disorders Severity Index – Symptoms (PAGI-SYM)

The PAGI-SYM is a patient reported outcome which asks patients to describe the severity of their symptoms over the last two weeks. The PAGI-SYM was developed to measure symptom severity for gastroparesis, functional dyspepsia, and gastroesophageal reflux disease. The measure consists of 20 symptom severity items, which cover the following domains: nausea/vomiting, fullness/early satiety, bloating, upper abdominal pain, heartburn/regurgitation, and lower abdominal pain. This questionnaire includes the Gastroparesis Cardinal Symptom Index. Research has demonstrated the reliability and validity of the PAGI-SYM . The questionnaire uses a 0-5 Likert scale from 0 = none to 5 = very severe [17].

8.1.3. Global Assessment of Gastroparesis Questionnaire

This question will be administered at every visit. This question asks patients to rate their overall gastroparesis symptoms on a 0-5 scale; the same utilized in the PAGI-SYM. Symptoms are rated as: 0, none; 1, very mild; 2, mild; 3, moderate; 4, severe; 5, very severe.

8.1.4. Patient-Reported Change in Gastroparesis Symtpoms

This questionnaire will be administered at post-treatment visits (Visit 3 through Visit 8), and uses a 7-point rating scale for the subject to rate their own improvement in their core gastroparesis symptoms relative to baseline. The questions asks patients whther their gastroparesis symptoms have improved, remained the same, or worsened since they began treatment. Symptoms are rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

8.1.5. Patient Global Impression-Change (PGI-C)

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

8.1.6. Patient Assessment of Gastrointestinal Disorders-Quality of Life (PAGI-QOL)

The 30-tem Patient Assessment of Gastrointestinal Disorders-Quality of Life (PAGI-QOL©) questionnaire is a valid and reliable instrument assessing quality of life in patients with gastroparesis. The questionnaire covers five domains: Daily Activities, Clothing, Diet and Food Habits, Relationship, and Psychological Well-Being and Distress [17]. Affect to overall quality of life and well-being over the past two weeks is rated on a scale of 0 = “None of the time” to 5 = “All of the time” for each item.

8.1.7. Gastroparesis Treatment Benefit Survey (GTBS)

The Gastroparesis Treatment Benefit Survey (GTBS) is administered prior to the initiation of therapy. The GTBS requires the subject to rate the relative importance of the relief of each of the core symptoms from 0 = ‘not important’ to 4 = ‘very important’. The GTBS is designed to be used in conjunction with Gastroparesis Core Symptom Daily Diary (GCSDD) data to provide symptom-specific and overall benefit scores which place higher weight on the relief of symptoms most important to the individual patient.

8.2. Clinician Global Impression of Severity (CGI-S)

The CGI-S is a 7-point scale in which the clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating 1: normal, not at all ill; 2: borderline ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; or 7: extremely ill.

8.3. Gastric Emptying Breath Test (GEBT)

The Gastric Emptying Breath Test (GEBT) is a non-radioactive test that utilizes carbon-13 (13C). The test measures the rate of gastric emptying of a standardized radio-labled meal and can aid in the diagnosis of gastroparesis. The GEBT is measured over a 4-hour time cycle and should be performed subsequent to an 8-hour fast. The test utilizes a gas isotope ratio mass spectrometer for the measurement of the ratio of $13CO_2$ to $12CO_2$ in breath samples. By measuring the change in this ratio over time, the patient's gastric-emptying rate determined.

8.4. Wireless Motility Capsule

The wireless motility capsule is a disposable capsule that is swallowed and measures the acid level, the pressure level, the temperature, and time of the subject's GI tract. The wireless motility capsule measures motility and movement of the gut by wirelessly transmitting data to a recorder that is worn on the subject (such as on a belt clip or lanyard around the neck). The patient takes the capsule after eating a standardized meal and wears a small monitor that allows the telemetry recordings to be made. Gastric emptying time is assessed from ingestion of the capsule, a point at which there is a low pH reading, to an abrupt rise in pH after it moves into the small bowel. After 2-3 days, the subject will return the recorder to a centralized site to analyze data on the testing system.

The testing system calculates gastric emptying time, colonic transit time, whole gut transit time and pressure patterns from the antrum and duodenum from data stored on the recorder. A cutoff point for gastric emptying time has been established to be 300 minutes in a tandem scintigraphic study of the capsule alone in comparison to a radiolabeled meal [18].

8.5. Gastric Emptying by Scintigraphy

Scintigraphy is a nuclear medicine scan which provides an assessment of the stomach's ability to empty. Radio-labeled solid food will be ingested and movement of food out of the stomach will be captured by external gamma cameras to form a two-dimensional images. 99mTc-sulfur colloid (0.5 mCi) will be added to food and ingested by subject within 10 minutes.

An example of a validated is 2 scrambled eggs with 99mTc-sulfur colloid (0.5 mCi) added during the cooking process. The eggs are served on 1 slice of bread and with 240 mL of skim

milk (296 kcal, 32% protein, 35% fat, 33% carbohydrate). The meal can vary from testing site to testing site. The Gamma camera scans will be taken at intervals from 0-4 hours with the patient standing up or sitting up in front of the camera.

Geometric means of decay-corrected counts in anterior and posterior gastric regions of interest will be used to estimate the proportion of 99mTc emptied at each time point. Gastric half-emptying time (GE T1/2) can also be calculated from these scans.

Grading for severity of delayed gastric emptying is based on the 4-h percent of retention of food in stomach: grade 1 (mild): 11–20% retention at 4 h; grade 2 (moderate): 21–35% retention at 4 h; grade 3 (severe): 36–50% retention at 4 h; and grade 4 (very severe): >50% retention at 4 h. [19]

8.6. Pharmacokinetic Assessment

A single blood sample will be collected at Visit 2,3,4,6, and 8 as a secondary measure of overall study medication compliance. At the optional pharmacokinetic visit, a blood sample will be collected pre-dose and 1, 2, 4, 6, 8-hours post dose. Samples will be tested for plasma concentrations of tradipitant and major metabolites. Pharmacokinetic analyses may be provided in a separate report.

9. ASSESSMENT OF SAFETY

9.1. 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.

9.1.1. Safety ECG

A full standard 12-lead ECG will be performed (after the subject has rested in supine position for approximately 10-15 minutes) and centrally read at as specified in Table 2.

9.1.2. 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 4, presents the clinical laboratory tests to be performed.

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

Values considered to be potentially clinically notable are provided in Appendix 18.1 for the Investigator's guidance. Any laboratory test result from an enrolled subject that the Investigator considers clinically significant may be repeated once to rule out laboratory error. For tests where a persistent abnormality is considered to be drug related, repeat analyses will be performed until the cause is determined and either a return to normality occurs or the Investigator deems the abnormality to be of no clinical significance. Any laboratory test result that the Investigator considers clinically significant must also be recorded as an adverse event.

Table 4: Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count (RBC), hemoglobin, hematocrit, platelets, and white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), blood coagulation
Chemistry	
Electrolytes	sodium, potassium, chloride, magnesium, bicarbonate

Category	Parameters
Liver function test	alkaline phosphatase, aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), total bilirubin, gamma-glutamyltransferase (GGT)
Renal function parameters	blood urea/blood urea nitrogen (BUN), creatinine, eCLcr
Other	glucose, calcium, albumin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine kinase
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

9.1.2.1. Additional Laboratory Evaluations

Laboratory Evaluations will be specified in the Schedule of Evaluations (Table 2). Measurements will include the following

- Serum pregnancy test at Visits 1, and 8
- Urine pregnancy test at Visits 2 , 3, 4, and 6
- Drugs of abuse at Visits 1, 2 , 3, 4, 6 and 8
- Thyroid stimlulating hormone (TSH) at Visits 1, 2 , 3, 4, 6 and 8
- Thyroxine (T4) at Visits 1, 2 , 3, 4, 6 and 8
- HbA1c measurement at Visits 1, 2 , 3, 4, 6 and 8

9.1.3. Vital Signs and Body Measurements

Vital Signs

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

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

After the subject signs the informed consent, vital sign values that the Investigator considers clinically significant will be recorded as AEs. Vital sign values considered to be potentially clinically notable are provided in Appendix 18.2 for the Investigator's guidance. The recording must be in the form of a clinical sign, symptom, or diagnosis, and not a mere description of the vital sign abnormality. Measurements will be repeated at medically appropriate intervals until they return to acceptable levels.

Body Measurements

Body measurements include the following assessments:

- Body weight (at Visit 1,2,3,4,6,8)
- Height (at Visit 1 only)

9.1.4. Medical History and Physical Examinations

A medical history will be taken at Visit 1 (Screening). A full PE (excluding pelvic, rectal and breast examinations unless clinically indicated) will be performed at Visit 1 (Screening), and Visit 8 (EOS). Documentation of the PE will be included in the source documentation at the investigational site.

9.1.5. Pregnancy

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

- 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 12 months) should be instructed to contact the Investigator immediately if they suspect they might be pregnant while participating in this study. Any pregnancy that occurs during study participation must be reported to Vanda (or designee) within 24 hours of learning of its occurrence and must be followed to determine outcome. If a subject becomes pregnant, she will be discontinued from the study.

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

The C-SSRS is a semi-structured clinical interview designed to systematically assess and track suicidal adverse events (behavior and ideation) throughout different settings including clinical trials. This scale was developed by researchers at Columbia University and will be administered in this study as specified in the Schedule of Evaluations (Table 2). The Screening/Baseline version of the C-SSRS will be completed at Visit 2 and the Since Last Visit version of the C-SSRS will be completed at Visits 3-8. Results from the C-SSRS will be listed for each subject. These data will also be summarized for each treatment group and for suicidal ideation events, suicidal behaviors and completed suicides.

9.1.7. Definitions Related to Safety

9.1.7.1. Adverse Event

An ***adverse event*** (AE) is defined as any untoward medical occurrence in a clinical investigation subject 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.

9.1.7.2. Serious Adverse Event

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

Table 5: SAE Criteria and Definitions

SAE Criteria	Definition
Death of 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.

SAE Criteria	Definition
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.
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[1]	An important medical event that, based on medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the 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.

9.1.7.3. Adverse Event Follow-up

Subjects with non-serious AEs that are ongoing at the subject's last study visit must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. Non-serious AE that are reported during the 7 days following the subject'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 subject'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 subject's last study visit should be reported as indicated in Section 9.1.10.

9.1.7.4. Adverse Event Reporting Period

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

9.1.7.5. Pre-Existing Condition

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

9.1.8. Relationship to Study Medication

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

- **Certain**: occurs in a reasonable time after study drug administration and cannot be explained by concurrent disease or drugs. The event should respond to withdrawal of study drug (de-challenge) and recur with re-challenge when clinically plausible.
- **Probable:** occurs in a reasonable time after study drug administration and it is unlikely to be to be attributed to concurrent disease or drugs, and it has a response to de-challenge. Re-challenge information is not required to fulfill this definition.
- **Possible:** occurs in a reasonable time after study drug administration, but could be related to concurrent disease or drugs. De-challenge information may be lacking or unclear.
- **Unrelated:** the event has an improbable temporal relationship (too soon, or too late after study drug, or study drug is not taken) and is plausibly related to other drugs or underlying disease.
- **Unassessable:** available information is insufficient, contradictory, and cannot be supplemented or verified at the time of the report. **This assessment will be considered as "related" for all expedited reports until an alternative assessment is made.**

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

9.1.9. Recording Adverse Events

9.1.9.1. Adverse Events during Study Period

At each study visit, the Investigator must seek information on AEs by questioning the subject and, as appropriate, by examining the subject. 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.

[redacted]

[redacted]

9.1.10. Reporting Adverse Events

9.1.10.1. 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 AE electronic CRF page.

[redacted]

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[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. PHARMACOGENOMICS ASSESSMENT

The pharmacogenomic assessment is an exploratory assessment. [redacted]

[redacted]

11. STATISTICS

11.1. Sample Size and Accrual

Based on a two-sided t-test with the 5% significance level, the planned sample size of 100 subjects per arm (a total of 200 subjects) provides approximately 98% power to detect a mean difference of 0.65 point in the average of nausea severity score assuming the standard deviation of 1.15 in each treatment group. Assuming an equal enrollment for each of diabetic and idiopathic etiology groups, a total of 100 subjects (50 per arm) per etiology will also provide approximately 80% power for each of these groups.

11.2. Statistical Methods and Analysis Plan

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

11.2.1. General

Statistical analyses will be performed using two-sided tests.

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

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

Continuous efficacy variables will be analyzed using a mixed-effect model for repeated measures (MMRM) and/or an analysis of covariance (ANCOVA) model. The models will be described in the SAP.

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

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

Categorical variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test blocking on sites, and Fisher's exact test will be used when site is not adjusted (mainly for safety assessment).

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

11.2.2. Subject Populations for Analysis

The following analysis populations will be defined for this study:

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

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

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

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

11.2.3. Subject Disposition

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

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

11.2.4. Demography and Other Baseline Data

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

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

Past medical conditions will be defined as an onset date prior to randomization (Visit 2) and resolved (not on-going) as of Visit 2. Current medical conditions, defined as an onset date on or after the date of randomization (Visit 2) or an onset date prior to randomization (Visit 2) and

unresolved (on-going) as of Visit 2, will be reported separately, but similarly to the past medical conditions. If both a past and a current (on-going) medical condition record are indicated for a condition, the condition will be presented under current medical conditions only.

11.2.5. Study Medication

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

The compliance to study medication, as recorded in the CRF, will also be summarized by treatment group. The proportion of subjects who are significantly noncompliant in the double-blind phasewill be summarized by treatment groups.

11.2.6. Prior/Concomitant Therapy

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

11.3. Efficacy Data Analysis

11.3.1. Primary Outcome and Methodology

The primary efficacy outcome measure will be change from baseline to Week 12 (Visit 8) in daily nausea severity score. A repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) will be used to analyze the primary efficacy outcome. The MMRM model will include the fixed, categorical effects of treatment group assignment, visit, treatment group-by-visit interaction and pooled site as well as the fixed, continuous covariates of baseline symptom score and the baseline symptom score-by-visit interaction. A detailed description of the MMRM model will be included in the SAP.

In addition to the MMRM model, an analysis of covariance (ANCOVA) model will also be applied. The last-observation-carried-forward (LOCF) will be used to impute any subsequent missing data. The model will have baseline as a covariate, and the fixed, categorical effects of treatment group assignment, pooled site. An observed cases (OC) analysis will also be performed.

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

11.3.2. Secondary Efficacy Analysis

The secondary efficacy outcomes include:

- -
- Other Gastroparesis Core Symptoms: vomiting, early satiety, post-prandial fullness, and upper abdominal pain;
- Gastroparesis Cardinal Symptom Index (GCSI, calculated out of PAGI-SYM)
- PAGI-SYM
- Global Assessment of Gastroparesis
- Patient Rated Change in Gastroparesis Symptoms
- PGI-C
- PAGI-QOL
- GTBS
- CGI-S

Continuous endpoints will be summarized and analyzed in a manner similar to the primary endpoint. Details of the analysis will be described in the SAP.

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

11.4. Safety Data Analysis

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

11.4.1. Adverse Events

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

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

Adverse events will further be categorized by severity, relationship to study medication, and action taken. Other information collected will be listed, as appropriate. Any event starting more than 3 days after the final dose of study medication will be excluded from the above tables and only listed, unless the event caused discontinuation.
The proportions of subjects experiencing SAEs and AEs resulting in discontinuation from the study will be summarized by treatment groups.

11.4.2. Laboratory Data

Clinical Laboratory Data

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

Clinical laboratory data will be summarized for each treatment group by presenting the proportions of subjects with clinically notable abnormalities (Appendix 18).

Clinically notable values will be identified according to the criteria identified in the FDA's "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates" (Revised 2-APR-87) provided by the FDA Division of Neuropharmacological Drug Products (DNDP). Differences in incidence rates between the treatment groups will be tested as described in the SAP.

11.4.3. Vital Signs and Body Measurements

Data from vital signs and body measurements will be listed, clinically notable values (Appendix 18.2) will be flagged, and any other information collected will be listed. Data will also be summarized by treatment group using mean change from baseline and proportions of subjects with values outside the normal range, and values that were clinically notable.

11.4.4. Electrocardiogram (ECG)

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

11.4.5. C-SSRS

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

11.5. Subgroup Analysis

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

11.6. Interim Analysis

No interim analyses are planned.

11.7. 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.

12. DIRECT ACCESS TO SOURCE DOCUMENTS

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13. QUALITY CONTROL AND QUALITY ASSURANCE

[redacted]

14. ETHICS

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

14.2. 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.

14.3. Written Informed Consent

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

15. DATA HANDLING AND RECORD KEEPING

[redacted]

15.1. Retention of Records

[redacted]

16. ADMINISTRATIVE PROCEDURES

16.1. Changes to the Protocol

[redacted]

16.2. Discontinuation of Study

[redacted]

16.3. Publication of Results

[redacted]

[redacted]

16.4. Investigator Agreement

[redacted]

Investigator

Name: _____

Signature: _____

Date: _____

Protocol Number: VP-VLY-686-3301 Amendment No 6.

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18. APPENDICES

18.1. 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	

18.2. 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

18.3. Signals of Hepatacellular Injury

According to the FDA Guidance on Drug-Induced Liver Injury [16] a signal of potential drug-induced liver injury (DILI) can be considered to be:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury