TRADIPITANT
AMENDMENT NO. 9 TO VP-VLY-686-2301

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

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Document Type:	Clinical Study Protocol
Sponsor:	Vanda Pharmaceuticals Inc. 2200 Pennsylvania Ave. NW Suite 300E Washington, DC 20037 USA
Study Product:	tradipitant (VLY-686)
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[redacted]

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 Proof of Concept Study to Assess the Efficacy of Tradipitant in Relieving Symptoms of Gastroparesis	
Study center(s): approximately 30 centers in the United States	
Indication: Diabetic & Idiopathic Gastroparesis	**Phase of development:** IIa
Number of subjects (planned): Approximately 150 subjects randomized to 2 arms (75 per arm, 1:1 randomization scheme)	
[redacted]	

[redacted]

13. Indication of impaired liver function (including values for AST, ALT, or bilirubin > 1.5 times the Upper Limit of Normal, unless isolated bilirubin > 1.5 x ULN due solely to Gilbert's syndrome);
14. Has a creatinine level > 1.5x ULN;
15. Use of prohibited medication or medication with anti-nausea, antiemetic, neuromodulating, or prokinetic effect within 2 weeks of the screening visit EXCEPT when administered on a stable daily dosing schedule (stable for at least 3 months prior to the screening visit) or administered under protocol-specified rescue medication guidelines;
16. Use of the following within 2 weeks of screening: another NK-1 antagonist or a second generation 5-HT3 antagonist, phenergan more than 2 times per day, or opiods more than 2 times per week;
17. Pyloric injection of neurotoxins (e.g. botulinum type A or B) within 3 months of the Screening Visit;
18. Exposure to any investigational medication, including placebo or domperidone, within 60 days of the Baseline Visit;
19. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress; and
20. Any other reason as determined by the Investigator which may lead to an unfavorable risk-benefit of study participation, may interfere with study compliance, or may confound study results.

Investigational product, dosage and mode of administration:

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

Duration of treatment: Double Blind Evaluation Phase: 4 weeks

Open Label Extension (OLE) Phase : 8 weeks
Continued Open Label Extension (COLE) Phase: additional 52 weeks

Objectives:

Primary:

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

Secondary:

- 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. One hundred fifty (150) subjects diagnosed with gastroparesis, who satisfy the selection criteria for the study, 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.

The study is divided into four phases: the screening phase, the evaluation phase, the open label extension phase, and the continued open label extension 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 evaluation phase includes 4 weeks of randomized double-blind treatment. Daily diaries will be completed during all phases. Clinical evaluations will occur at Screening, Baseline, Week 2 and Week 4. At the end of the 28-day evaluation phase, those subjects who completed this phase will enroll into an 8-week open-label extension (OLE), where each subject will either continue (if previously on active) or be switched to (if previously on placebo) the same daily dose of tradipitant as the randomized portion of the study (85 mg bid, approximately 12 hours apart). Patients who complete the 8 week open-label extension phase will return for a 52 week continued open label extention phase (COLE).

Primary Endpoint:

Change from baseline to Day 28 in weekly average of 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)
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified Patient Assessment of Upper GI Disorders – Symptoms (mPAGI-SYM)
- Patient Global Impression – Change (PGI-C)
- Patient Assessment of Upper Gastrointestinal Disorders – QOL (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 75 subjects per arm provides 86% power to detect a mean difference of 0.8 point in the average of daily nausea severity assuming the standard deviation of 1.6 in each treatment group.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Description
AD	Atopic Dermatitis
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (also known as SGPT)
ANCOVA	Analysis of Covariance
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
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
dL	Deciliter

Abbreviation	Description
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
GCSDD	Gastroparesis Core Symptom Daily Diary
GCSI	Gastroparesis Cardinal Symptom Index
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

Abbreviation	Description
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mGCSI	Modified Gastroparesis Cardinal Symptom Index
mPAGI-SYM	Modified Patient Assessment of Upper Gastrointestinal Disorders - Symptoms
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 Upper Gastrointestinal Disorders - Quality of Life
PAGI-SYM	Patient Assessment of Upper 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

Abbreviation	Description
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
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
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

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

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 patients 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 patients, 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 patients, 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 patients suffering from gastroparesis.

3.2. Tradipitant Relevant Data Summary

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

[redacted]

3.2.2. Clinical

The clinical development of tradipitant was initiated by Eli Lilly in 2003. [redacted] 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.

4. TRIAL OBJECTIVES AND RATIONALE

4.1. Objectives

4.1.1. Primary

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

4.1.2. Secondary

- 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.

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 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.

4.2. Rationale

4.2.1. 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.

4.2.2. Rationale for Dose and Study Design

[redacted]

4.2.3. Risk and Benefit

[redacted]

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan: Description

This is a randomized, double-blind, placebo-controlled study to be conducted in the United States. Approximately one hundred fifty (150) patients diagnosed with gastroparesis of either diabetic or idiopathic origin satisfying the selection criteria for the study will be randomized 1:1 to tradipitant treatment or matching placebo (Table 2). 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.

Table 2: VP-VLY-686-2301 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

The study is divided into four phases: the screening phase, the evaluation phase, the open label extension phase, and the continued open label extension phase. The screening phase includes screening and baseline visits where eligibility for the study will be assessed. The evaluation phase includes 4 weeks of placebo-controlled, double-blind, randomized treatment. Daily diaries will be collected throughout both phases of the study. At the end of the 28-day evaluation phase, those subjects who completed this phase enroll into an 8-week open-label extension (OLE) where each subject will receive the same dose of tradipitant utilized in the randomized segment of the study (85 mg bid, approximately 12 hours apart). Subjects who complete the 8 week open label phase can return and enroll into a 52-week continued open label extension phase (COLE).

5.1.1. Screening Phase

The screening phase includes the screening and baseline 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.

The screening phase may be extended to 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.

A full list of assessments performed at each visit are listed in Table 3 and Section 9.

5.1.1.1. 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. Collection of adverse event information will begin at the time the ICF is signed. 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 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, inclusion criteria 2d and 2e 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.

Subjects who do not meet eligibility criteria 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.

5.1.1.1.1. Visit 1 Instruction if Patient Lacks Scintigraphy or Breath Test

A potential subject without a prior scintigraphy or breath test evaluation to serve as objective evidence of delayed gastric emptying, or with a scintigraphy or breath test evaluation that demonstrates delayed gastric emptying that is outside the 10-year window can still be considered as symptomatically suffering from gastroparesis and scheduled for a Visit 1 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 criteria (including moderate to high nausea on mGCSI as determined by a score of ≥ 3), the subject may begin completing their daily diary according to the normal screening process described in Section 5.1.1.1.

The subject will also be scheduled to return for an unscheduled visit to take place within 2 weeks of their Visit 1, in order for the site to perform a breath test or scintigraphy to confirm the subject's objective evidence of delayed gastric emptying. The choice of utilizing breath test or scintigraphy will be at the investigator's discretion. 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.

5.1.1.2. 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. Subjects continuing to meet all eligibility criteria will be randomized to one of two treatment arms (Table 2), 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 Baseline Visit including diary review to determine eligibility based on symptom severity. Subjects must have at least 24 daily screening diary entries 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.

5.1.2. Evaluation Phase

5.1.2.1. Visit 3

Subjects will return to the clinic on Day 14 (± 3 days) for Visit 3 for safety and efficacy assessments. Diary and medication compliance will be reviewed. Unused study medication will be collected and subjects will be dispensed enough study medication to last until Visit 4.

5.1.2.2. End of Phase or Early Termination (Visit 4)

At the End of Study Visit (Day 28 ± 3 days) or at the time of early termination, subjects will return to the clinic for safety and efficacy assessments. Diary and medication compliance will be reviewed.

5.1.3. Open-Label Extenion Phase

All subjects who complete the short-term double-blind phase will continue treatment with tradipitant for an additional 8-weeks of treatment in the OLE phase. Subjects who have completed the trial prior to the OLE becoming available can come back and sign an additional informed consent and be evaluated for eligibility to participate in this phase during V4a. The site will record that the subject has completed the double-blind phase of the study and indicate if the subject will continue into the OLE. If the subject will continue into the OLE, enough open label medication will be dispensed to the subject to last until the next schedule visit. Patients who have previously completed this study can come back to for visit V4a to allow all original V1 screening labs and other safety assessments as well as the open label informed consent to be collected prior to OLE dosing.

A detailed description of this OLE phase can be found in Appendix 20.1

5.1.4. Continued Open-Label Extension Phase

All subjects who complete the short-term double-blind phase and the 8 week open label extension phase can continue treatment with tradipitant for an additional 52-weeks of treatment in the COLE phase. Subjects who have completed the trial prior to the COLE becoming available can come back and sign an additional informed consent and be evaluated for eligibility to participate in this phase during Visit COLE-V1-B. The site will record that the subject has completed the double-blind and open label extension phases of the study and indicate if the subject will continue into the COLE. If the subject will continue into the COLE, enough open label medication will be dispensed to the subject to last until the next schedule visit. Patients who have previously completed this study can come back to for visit COLE-V1-B to allow all

original V1 screening labs and other safety assessments as well as the continued open label informed consent to be collected prior to COLE dosing.

A detailed description of this COLE phase can be found in Appendix 20.2

Table 3: Schedule of Evaluations

Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4 EOP**
Study Day	**≥28 days prior to Day 0**	**Day 0**	**Day 14[1]**	**Day 28[1]**
Informed Consent Form (ICF) [2]	X			X
Eligibility assessment	X	X		X
Subject demography and medical history	X			
Prior/concomitant medications	X	X	X	X
Adverse Event (AE) Query[3]	X	X	X	X
Collection of menstrual cycle information	X	X	X	X
Serum β-HCG (for WOCBP)	X			X
Urine pregnancy test (for WOCBP)		X	X	
TSH, T4	X	X	X	X
Urine Drug Screen	X	X	X	X
HbA1c, hematology, chemistry, and urinalysis	X	X	X	X
Pharmacogenomic (PG) sample		X		
Pharmacokinetic (PK) sample		X	X	X
12-lead resting ECG	X	X	X	X
Vital signs and body measurements[4]	X	X	X	X
Physical Examination (PE)	X			X
C-SSRS[5]	X	X	X	X
mGCSI[6] & mPAGI-SYM	X	X	X	X
Gastroparesis Treatment Benefit Survey (GTBS)	X			
PAGI-QOL		X		X
Patient Global Impression of Change (PGI-C)			X	X
Clinical Global Impression of Severity (CGI-S)		X	X	X
Randomization		X		
Study medication dispensation		X	X	X
Study medication collection & compliance			X	X
Subject diary instruction	X			
Subject diary review		X	X	X
EOP				X
Gastroparesis Core Symptom Daily Diary (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 all visits. Height collection at V1. Body weight collection at V1, V2, and V4.
[5] The Screening/Baseline C-SSRS will occur at V1. The Since Last Visit C-SSRS will occur at all other visits.

[6] mGCSI questions on symptom changes (Part II) will only be administered at V3 and V4.

EOP= End of Phase;; WOCBP = Women of Child-bearing Potential; ECG = electrocardiogram; C-SSRS = Columbia Suicide Severity Rating Scale; mGCSI = modified Gastroparesis Cardinal Symptom Index; PAGI-QOL = Patient Assessment of Upper Gastrointestinal Symptoms – Quality of Life

[redacted]

[redacted]

Section 7.2.1)

[redacted]

6.3. 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 or laboratory tests are provided in Appendices Section 20.4 and Section 20.3, respectively, to guide clinical focus regarding a subject's continued participation;
- Noncompliance;

For subjects withdrawing from the study prematurely, all efforts will be made to perform the Visit 4 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.

7. TREATMENT OF SUBJECTS – EVALUATION PHASE

7.1. Study Medication

7.1.1. Dosing

Randomized subjects will be dispensed study medication under double-blind conditions. Each subject will be dispensed one bottle of study medication at Visit 2 and another bottle at Visit 3. 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.

7.1.2. 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.

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.

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]

[redacted] Section 7.2.2

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.2.2. 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.

7.2.2.1. Rescue Medication Guidelines

1. Only medications listed in Table 4 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 4: Medications Allowed for Rescue Use

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

[redacted]

7.3. Treatment Compliance

[redacted]

[redacted] Section 7.1.2)

7.4. Treatment Assignment

[redacted]

7.4.2. Subject Replacement

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

7.4.3. 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.

8. STUDY MEDICATION MATERIALS AND MANAGEMENT

8.1. Study Medication

[redacted]

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 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 2 and collected at Visit 3, a second bottle will be dispensed at Visit 3 and collected at Visit 4). 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.

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 subjects at the study site.

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 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.

9. STUDY ASSESSMENTS – EVALUATION PHASE

9.1. Study Assessments per Visit

9.1.1. 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, medical history, and prior and concurrent medications; vital sign and body measurements
- Physical examination (PE) (excluding genitourinary examination unless clinically indicated)
- ECG
- Screening/Baseline C-SSRS questionnaire
- Clinical laboratory assessments: hematology, chemistry (including estimated creatinine clearance (eCLcr; based on the Cockcroft-Gault equation), urinalysis, HbA1c, thyroid stimulating hormone (TSH), thyroxine (T4), urine drug screen,
- Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Modified Gastroparesis Cardinal Symptom Index (mGCSI) Part I
- Modified PAGI-SYM (mPAGI-SYM)
- Gastroparesis Treatment Benefit Survey (GTBS)

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 6.1).

9.1.2. 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
- Collection of concomitant medications
- vital signs and weight measurements
- Since last visit C-SSRS
- Urine pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)

- Gastroparesis Core Symptom Daily Diary (GCSDD) review: To be considered eligible for randomization, subjects must:
  - meet diary eligibility criteria (Section 6.1)
  - have at least 24 daily diary entries
  - have a daily diary completion rate ≥ 24/35 (68%)

Individuals continuing to meet eligibility criteria will be randomized, and the following assessments will also be performed during this visit:

- ECG;
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- PG sample
- Baseline Pharmacokinetic (PK) sample
- Modified Gastroparesis Cardinal Symptom Index (mGCSI) Part I
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Clinical Global Impression of Severity (CGI-S)
- Study medication instruction and dispensation (first dose will be administered on evening of Day 0)

9.1.3. Visit 3 (Study Day 14 ± 3 days)

- Urine pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Pharmacokinetic (PK) sample
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse)
- ECG
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- Adverse Event query
- Concomitant medication review
- Since last visit C-SSRS

- Diary review
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Global Impression of Change (PGI-C)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Study medication instruction and dispensation

9.1.4. Visit 4 (Study Day 28 ± 3 days)

- Full PE (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Laboratory evaluations (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Pharmacokinetic blood sample
- ECG
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse) and weight
- Adverse Event query
- Concomitant medication review
- Since last visit C-SSRS
- Review diary
- Collect diary
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Global Impression of Change (PGI-C)
- Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Records EOP
- Review of Inclusion criteria (only for subjects that are continuing to the OLE phase)

- Dispense Study Drug (only for subjects that are continuing to the OLE phase)

9.1.5. Unscheduled Visits

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

10. ASSESMENTS OF EFFICACY

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

- Gastroparesis Core Symptom Daily Diary (GCSDD)
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Global Impression – Change (PGI-C)
- Patient Assessment of Upper Gastrointestinal Disorders – QOL (PAGI-QOL)
- Gastroparesis Treatment Benefit Scale (GTBS)
- Clinician Global Impression – Severity (CGI-S)

10.1. Patient Reported Outcome (PRO) Assessments

10.1.1. 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, and abdominal pain 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.

10.1.2. Modified Gastroparesis Cardinal Symptom Index (mGCSI)

The modified Gastroparesis Cardinal Symptom Index is a patient reported outcome administered in-clinic with a 2-week recall period. Part I of the questionnaire consists of the traditional GCSI and severity rating of upper abdominal pain as well as severity of overall symptoms. The questionnaire uses the same 0-5 scale utilized in both the GCSI and the PAGI-SYM [16]. Part II of the questionnaire will be administered at post-treatment visits (Visit 3 and Visit 4), and uses a 7-point rating scale for the subject to rate their own improvement in their core gastroparesis symptoms relative to baseline. 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.

10.1.3. Modified Patient Assessment of Gastrointestinal Disorders – Symptoms (mPAGI-SYM)

The modified PAGI-SYM is a patient reported outcome administered in-clinic with a 2-week recall period. This questionnaire will include PAGI-SYM items not included in the mGCSI. The questionnaire uses the same 0-5 scale utilized in both the GCSI and the PAGI-SYM [16].

10.1.4. 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.

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

The 30-tem Patient Assessment of Upper 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 [16]. 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.

10.1.6. 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 at all 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.

10.2. 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.

10.3. Pharmacokinetic Assessment

A single blood sample will be collected at each visit as a secondary measure of overall study medication compliance. Samples will be tested for plasma concentrations of tradipitant and major metabolites. Pharmacokinetic analyses may be provided in a separate report.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety assessments should be conducted as specified in the Schedule of Evaluations (Table 3). 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 subject has rested in supine position for approximately 10-15 minutes) and centrally read at as specified in Table 3.

11.1.2. Laboratory Evaluations

The Schedule of Evaluations (Table 3) shows the days at which blood will be collected for clinical laboratory tests and urine for the urinalysis.

The table below, Table 5, 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 20.3 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 5: 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)
Chemistry	

Category	Parameters
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, 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

11.1.2.1. Additional Laboratory Evaluations

- Serum pregnancy test at Visits 1, 4/4a,6, COLE-V1, and COLE-V7
- Urine pregnancy test at Visits 2 , 3, 5, 6, and COLE V2-V6.
- Drugs of abuse at all visits
- Thyroid stimulating hormone (TSH) at all visits
- Thyroxine (T4) at all visits
- HbA1c measurement at all visits

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 3). 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 20.4 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 2, and Visit 4)
- Height (at Visit 1 only)

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 Visit 1 (Screening), Visit 4/a, and Visit 6. 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 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.

11.1.6. 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 3). The Screening/Baseline version of the C-SSRS will be completed at Visit 1 and the Since Last Visit version of the C-SSRS will be completed at Visits 2-4. 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.

11.1.7. Definitions Related to Safety

11.1.7.1. 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.

11.1.7.2. 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 6.

Table 6: 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.

SAE Criteria	Definition
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.
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.

11.1.7.3. 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 11.1.10.

11.1.7.4. 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.

11.1.7.5. 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.

11.1.8. 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.

11.1.9. Recording Adverse Events

11.1.9.1. 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]

11.1.10. Reporting Adverse Events

11.1.10.1. 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]

[redacted]

[redacted] Table 7

[redacted]

[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. PHARMACOGENOMICS ASSESSMENT

The pharmacogenomic assessment is an exploratory assessment. [redacted]

[redacted]

13. STATISTICS

13.1. Sample Size and Accrual

Based on a two-sided t-test with the 5% signicance level, the planned sample size of 75 subjects per arm (a total of 150 subjects) provides around 86% power to detect a mean difference of 0.8 point in the average of nausea severity score assuming the standard deviation of 1.6 in each treatment group.

13.2. 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.

13.2.1. 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.

13.2.2. 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.

13.2.3. 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.

13.2.4. 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.

13.2.5. 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.

13.2.6. 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.

13.3. Efficacy Data Analysis

13.3.1. Primary Outcome and Methodology

The primary efficacy outcome measure will be change from baseline to Day 28 in the weekly average of 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.

13.3.2. Secondary Efficacy Analysis

The secondary efficacy outcomes include:

- Other Gastroparesis Core Symptoms: vomiting, early satiety, post-prandial fullness, and upper abdominal pain;
- mGCSI
- mPAGI-SYM
- 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.

13.4. 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.

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 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.

13.4.2. 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 20).

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.

13.4.3. Vital Signs and Body Measurements

Data from vital signs and body measurements will be listed, clinically notable values (Appendix 20.2) 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.

13.4.4. 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.

13.4.5. 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.

13.5. 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.

13.6. Interim Analysis

No interim analyses are 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

[redacted]

[redacted]

15. QUALITY CONTROL AND QUALITY ASSURANCE

[redacted]

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 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.

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, 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.

17. DATA HANDLING AND RECORD KEEPING

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17.1. Retention of Records

18. ADMINISTRATIVE PROCEDURES

18.1. Changes to the Protocol

[redacted]

18.2. Discontinuation of Study

[redacted]

18.3. Publication of Results

[redacted]

18.4. Investigator Agreement

[redacted]

Investigator

Name: _____

Signature: _____

Date: _____

Protocol Number: VP-VLY-686-2301

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20. APPENDICES

20.1. Open-Label Extension Phase

20.1.1. Phase Objective

The objective of the open-label extension (OLE) phase is to explore the long-term safety of daily dosing with tradipitant over an additional 8 weeks of treatment.

20.1.2. Phase Rationale

[redacted]

20.1.3. Study Design for OLE Phase

The OLE phase consists of an additional 8-weeks of treatment where all subjects will receive the same daily dose of tradipitant in an open-label fashion. Subjects who received tradipitant during the evaluation phase will continue to receive tradipitant. Subjects who received placebo during the evaluation phase will also receive tradipitant.

Subjects will go to the clinic during the OLE on the days specified in the Schedule of Evaluations for OLE (Table 8) for routine safety assessments which may include a urine pregnancy test for women of child-bearing potential (WOCBP), urine drug screen, vital signs measurements, safety labs, physical exam, an ECG and collection of adverse event including suicidality ideation and behavior and concomitant medication information. Refer to Table 8 and Section 20.1.10 for details of which assessments are done per Study Visit. Study medication will be dispensed at some of these visits and compliance will also be assessed. End-of-study (EOS) assessments and an additional gastric emptying breath test will be performed at Visit 6 (Study Day 84 ± 3 days) or at the time of early discontinuation. EOS assessments include safety evaluations such as serum pregnancy test for females, physical examination (PE), vital signs, ECG, collection of adverse event including suicidality ideation and behavior and clinical laboratory assessments (Table 8).

Table 8: Schedule of Evaluations for OLE

Visit	**V4a**[1]	**V5**	**V6** EOP
Study Day		**Day 56**[2]	**Day 84**[2]
Informed Consent	X		
Prior/concomitant medications	X	X	X
Adverse Event (AE) Query[3]	X	X	X
Collection of menstrual cycle information	X	X	X
Serum β-HCG (for WOCBP)	X		X
Urine pregnancy test (for WOCBP)		X	
TSH, T4	X	X	X
Urine Drug Screen	X	X	X
HbA1c, hematology, chemistry, and urinalysis	X	X	X
12-lead resting ECG	X	X	X
Vital signs and body measurements[4]	X	X	X
Physical Examination (PE)	X		X
Gastric Emptying Breath Test (GEBT)			X
C-SSRS[5]	X	X	X
Clinical Global Impression of Severity (CGI-S)	X	X	X
PGI-C		X	X
mGCSI & mPAGI-SYM	X	X	X
PAGI-QOL	X		X
Gastroparesis Core Symptom Daily Diary (GCSDD)	⟷		
Subject diary review		X	X
Study medication dispensation	X	X	

Visit	**V4a**[1]	**V5**	**V6** EOP
Study Day		**Day 56**[2]	**Day 84**[2]
Study medication collection & compliance		X	X
EOP			X

[1] Only for subjects that completed the Double-Blind Phase prior to the OLE being available.
[2] within +/- 3 days
[3] Adverse event collection will begin at the time the ICF is signed.
[4] Vital sign collection at all visits. Height collection at V1 only.
[5] The Screening/Baseline C-SSRS will occur at V1. The Since Last Visit C-SSRS will occur at all other visits.
EOS = End of Study; ET = Early Termination; WOCBP = Women of Child-bearing Potential; ECG = electrocardiogram; C-SSRS = Columbia Suicide Severity Rating Scale

20.1.4. Selection and Withdrawal Criteria of Subjects for the OLE Phase

20.1.4.1. Inclusion Criteria

A subject is eligible for enrollment into the OLE phase of this study if he/she meets the following criteria:

- Has completed the randomization phase through Visit 4 (Study Day 28);
- Is willing to provide an additional written informed consent for the OLE phase if enrolled in study prior to OLE becoming available.

20.1.4.2. Early Withdrawal of Subjects

T

Appendices 20.4 20.3

[redacted]

20.1.5. Study Medication

20.1.5.1. Dosing

Subjects will be dispensed study medication under open-label conditions at the study visits indicated in the Schedule of Evaluations for OLE (Table 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.

20.1.5.2. Guidance for Taking Study Medication

[redacted]

20.1.6. Concomitant Medication During the OLE Phase

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.

20.1.6.1. Prohibited Medication

[redacted]

Section 7.2.1

[redacted]

20.1.6.2. 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 (Section 7.2.2.1).

20.1.7. Treatment Compliance

Compliance in this study will be assessed by the Investigator. The Investigator will consider patient interviews as well as returned capsules when assessing compliance. Subjects who were not fully compliant will be re-educated by the Investigator or study staff on the importance of taking the study medication daily at the scheduled time.

Any overdose that occurs during study participation must be recorded on the overdose CRF. An overdose (intentional or accidental) is defined as the following: >3 capsules of open label study medication taken within a 24-hour period (except when re-administered within the guidance of Section 7.1.2).

20.1.8. Treatment Assignment

At study Visits 4/4a, and 5, (Table 3 and Table 8), study personnel will dispense enough OLE medication to the subject to last until the next scheduled visit.

20.1.9. Study Drug, Packaging, and Labeling

[redacted]

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. 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.

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.

20.1.10. Assessments Performed During the OLE

20.1.10.1. Visit 4a (Only for subjects that completed the Double-Blind Phase prior to the OLE being available)

- Signing of the Informed Consent
- Review of concomitant medication
- Adverse event query

- Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Clinical laboratory assessments (HbA1C, hematology, chemistry, thyroid stimulating hormone (TSH), thyroxine (T4), urinalysis, and urine drug screen)
- ECG
- Semi-supine routine vital signs (weight, body temperature, respiratory rate, blood pressure, and pulse)
- Full PE (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Since last visit C-SSRS
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Clinical Global Impression of Severity (CGI-S)
- Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Study medication dispensation

20.1.10.2. Visit 5 (Study Day 56 +/- 3 days)

- Adverse event query
- Review of concomitant medication
- Urine pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Clinical laboratory assessments (HbA1C, hematology, chemistry, thyroid stimulating hormone (TSH), thyroxine (T4), urinalysis, and urine drug screen)
- ECG
- Semi-supine routine vital signs (weight, body temperature, respiratory rate, blood pressure, and pulse)
- Since last visit C-SSRS
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Clinical Global Impression of Severity (CGI-S)
- Patient Global Impression of Change (PGI-C)
- Diary review
- Study medication collection and review
- Study medication dispensation

20.1.10.3. Visit 6 (Day 84/EOS ± 3 days or ET)

- Adverse event query
- Review of concomitant medication
- Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- ECG
- Semi-supine routine vital signs (weight, body temperature, respiratory rate, blood pressure, and pulse)
- Full PE (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Gastric Emptying Breath Test (GEBT)
- Since last visit C-SSRS
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Clinical Global Impression of Severity (CGI-S)
- Patient Global Impression of Change (PGI-C)
- Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Diary review
- Study medication collection and review

20.1.11. Efficacy Assessments

The efficacy assessments should be conducted as specified in the Schedule of Evaluations for OLE (Table 8). These assessments include: the Gastroparesis Core Symptom Daily Diary (GCSDD), Modified Gastroparesis Cardinal Symptom Index (mGCSI), Modified PAGI-SYM (mPAGI-SYM), Patient Global Impression of Change (PGI-C), and the Patient Assessment of Upper Gastrointestinal Disorders-QOL (PAGI-QOL) (see Section 10.1.1 for a description of the patient reported outcomes) and the Clinician Global Impression – Severity (CGI-S) (see Section 10.2 for a description of the assessment).

20.1.12. Safety Assessments

The safety assessments should be conducted as specified in the Schedule of Evaluations for OLE (Table 8). These assessments include: the regular monitoring and recording of all adverse events and serious adverse events (SAEs); the regular monitoring of hematology, blood biochemistry and urinalysis values; the regular monitoring of vital signs; the regular monitoring of suicidal ideation

and behavior, and the performance of physical examinations, and electrocardiograms. Refer to Section 11 for additional details relating to the collection of safety assessments.

20.1.13. Statistical Methods

Statistical analysis for the OLE phase will be based on data summaries, using similar layouts as for the randomization phase, and will be exploratory in nature.

20.2. Continued Open Label Extension Phase

20.2.1. Phase Objectives

20.2.1.1. Primary

- To evaluate long term dosing of tradipitant on standard measures of subject safety by assessing adverse events (AEs) including suicidal ideation or behavior, changes in vital signs, clinical laboratory evaluations, electrocardiograms (ECGs) and physical exam findings during treatment

20.2.1.2. Secondary

- To evaluate the efficacy of tradipitant in reducing individual symptoms associated with gastroparesis
- To evaluate the efficacy of tradipitant in global improvement and quality of life measures

20.2.2. Phase Rationale

20.2.2.1. 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].

[redacted]

20.2.2.2. Rationale for Dose and Study Design

[redacted]

[redacted]

[redacted]

20.2.2.3. Risk Benefit

[redacted]

20.2.3. Investigational Plan

20.2.3.1. Overall Phase Design and Plan: Description

This is a continued open label extension phase. Approximately one hundred fifty (150) patients diagnosed with gastroparesis of either diabetic or idiopathic origin that have previously enrolled in VLY-VP-686-2301 randomized and open label phases will be asked to take 85mg tradipitant twice daily at 12 hour intervals for 12 months in an open-label fashion. Patient participation will include:

- Day 0, COLE Screening Visit 1 (A/B)
- Week 4, COLE Visit 2

- Week 8, Health Assessment Call 1
- Week 12, COLE Visit 3
- Week 16, Health Assessment Call 2
- Week 20, COLE Visit 4
- Week 24, Health Assessment Call 3
- Week 28, COLE Visit 5
- Week 32, Health Assessment Call 4
- Week 36, Health Assessment Call 5
- Week 40, COLE Visit 6
- Week 44, Health Assessment Call 6
- Week 48, Health Assessment Call 7
- Week 52, COLE Visit 7

20.2.3.2. Screening Visit COLE-Visit 1-A (Day 0)

For patients currently enrolled in VP-VLY-686-2301, this visit should correspond to the Visit 6 visit such that there is no interruption of participation between phases if possible.

During this visit, patients will sign the informed consent. Eligibility will be assessed based on their current medication use, physical examination (PE), vital signs, ECG, C-SSRS result, urine drug screen, urine and serum pregnancy test, if applicable, and clinical laboratory results from VP-VLY-686-2301 Visit 6.

Patients that meet all of the study requirements will be enrolled into the phase. The study staff will provide instructions to patients detailing the instructions on how to take tradipitant. Study drug will be dispensed to the patient.

20.2.3.3. Screening Visit COLE-Visit 1-B (Day 0)

For patients who completed VP-VLY-686-2301 through Visit 6 and would like to enroll in the continued open label phase (COLE) after being off study drug for a period of time.

During this visit, patients will sign the informed consent. Eligibility will be assessed based on their gastroparesis diagnosis, their current medication use, medical history, a physical examination (PE), vital signs, ECG, C-SSRS, urine drug screen, urine and serum pregnancy test, if applicable, and clinical laboratory results. Patients will complete the since last visit C-SSRS, Modified Gastroparesis Cardinal Symptom Index (mGCSI), Modified PAGI-SYM (mPAGI-SYM), Clinical Global Impression of Severity (CGI-S), Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL).

Patients that meet all of the study requirements will be enrolled into the COLE. The study staff will confirm the patient's demographic information and provide instructions to patients detailing the instructions on how to take tradipitant. Study drug will be dispensed to the patient.

20.2.3.4. COLE Visit 2-Visit 6 (Day 28, Day 84, Day 140, Day 196, Day 280 ± 5 days)

On COLE Visit 2, COLE Visit 3, COLE Visit 4, COLE Visit 5 and COLE Visit 6, patients will return to the site to be queried for any adverse events and updates to their current medication use. Patients will undergo a physical examination (PE), vital signs, ECG, C-SSRS, urine drug screen, urine and serum pregnancy test, if applicable, and clinical laboratory results. Patients will complete the since last visit C-SSRS, Modified Gastroparesis Cardinal Symptom Index (mGCSI), Modified PAGI-SYM (mPAGI-SYM), Clinical Global Impression of Severity (CGI-S), Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL). Daily diary compliance will be reviewed, study medication will be collected and reviewed, and new study drug will be dispensed.

20.2.3.5. Monthly Call to Subjects to Assess Health (Day 56, Day 112, Day 224, Day 252, Day 308, Day 336, ± 3 days)

A member of the study team will call patients to assess overall health and query for any adverse events or updates to their current medication. Note: An unscheduled visit will be performed if medically warranted in the opinion of the Investigator.

20.2.3.6. End of Study or Early Termination COLE Visit 7 (Day 364 ± 7 days)

At the End of Study COLE Visit 7 Day 364 ± 7 days or at the time of early termination, subjects will return to the clinic for safety and efficacy assessments. Diary and medication compliance will be reviewed. Patients will undergo a physical examination (PE), vital signs, ECG, urine drug screen, urine and serum pregnancy test, if applicable, and clinical laboratory results. Patients will complete the since last visit C-SSRS, Modified Gastroparesis Cardinal Symptom Index (mGCSI), Modified PAGI-SYM (mPAGI-SYM), Clinical Global Impression of Severity (CGI-S), Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL). Daily diary compliance will be reviewed, study medication will be collected and reviewed.

Table 9: Schedule of Evaluations for COLE

COLE Visits	**V1-A Screening**	**V1-B Screening**	**V2**	**V3-V6**	**V7 EOS/ET**
COLE Study Day	**Day 0**	**Day 0**	**Day 28**[1]	**Day 84, 140, 196, 280**[1]	**Day 365**[2]
VP-VLY-686-2301 EOS Procedures	X				
Informed Consent Form (ICF)[3]	X	X			

COLE Visits	**V1-A Screening**	**V1-B Screening**	**V2**	**V3-V6**	**V7 EOS/ET**
COLE Study Day	**Day 0**	**Day 0**	**Day 28**[1]	**Day 84, 140, 196, 280**[1]	**Day 365**[2]
VP-VLY-686-2301 EOS Procedures	X				
Eligibility assessment	X	X			
Subject demography and medical history	X	X			
Prior/concomitant medications	X	X	X	X	X
Adverse Event (AE) Query[4]	X	X	X	X	X
Serum β-HCG (for WOCBP)		X			X
Urine pregnancy test (for WOCBP)			X	X	
TSH, T4		X	X	X	X
Urine Drug Screen		X	X	X	X
HbA1c, hematology, chemistry, and urinalysis		X	X	X	X
12-lead resting ECG		X	X	X	X
Vital Signs and Body Measurements[5]		X	X	X	X
Physical Examination (PE)		X	X	X	X
C-SSRS[6]		X	X	X	X
mGCSI [7]		X	X	X	X
mPAGI-SYM		X	X	X	X
PAGI-QOL		X	X	X	X
Patient Global Impression of Change (PGI-C)			X	X	X
Clinical Global Impression of Severity (CGI-S)		X	X	X	X
Study medication dispensation	X	X	X	X	
Study medication collection & compliance			X	X	X
Subject diary instruction	X	X			
Subject diary review			X	X	X
Schedule Monthly Call			X	X	
EOS					X
Gastroparesis Core Symptom Daily Diary (GCSDD)	→	→	→	→	→

COLE Visits	V1-A Screening	V1-B Screening	V2	V3-V6	V7 EOS/ET
COLE Study Day	**Day 0**	**Day 0**	**Day 28[1]**	**Day 84, 140, 196, 280[1]**	**Day 365[2]**
VP-VLY-686-2301 EOS Procedures	X				
Health Assessment Call between Visits (every 4 weeks)			X	X	

EOS= End of Study; WOCBP = Women of Child-bearing Potential; ECG = electrocardiogram; C-SSRS = Columbia Suicide Severity Rating Scale; mGCSI = modified Gastroparesis Cardinal Symptom Index; PAGI-QOL = Patient Assessment of Upper Gastrointestinal Symptoms – Quality of Life
[1] within ± 5 days
[2] within ± 7 days
[3] Informed consent will be obtained prior to the performance of any study procedure(s)
[4] Adverse event collection will begin at the time the ICF is signed.
[5] Vital sign collection at all visits. Height collection at V1. Body weight collection at V1-V7.
[6] The Screening/Baseline C-SSRS will occur at V1-B. The Since Last Visit C-SSRS will occur at all other visits.
[7] mGCSI questions on symptom changes (Part II) will only be administered at V2- V7.

20.2.4. Selection and Withdrawal Criteria of Subjects for the OLE Phase

20.2.4.1. Inclusion Criteria

A subject is eligible for enrollment into the COLE phase of this study if he/she meets the following criteria:

- Has completed the randomization phase and open label phase through Visit 6 (Study Day 84);
- Is willing to provide an additional written informed consent for the COLE phase if enrolled in study prior to COLE becoming available.

See Section 6.1 for complete study Inclusion Criteria and Section 6.2 for complete study Exclusion Criteria.

20.2.4.2. Early Withdrawal of Subjects

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

Subjects may voluntarily withdraw from the COLE 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 or laboratory tests are provided in Appendices 20.4 and 20.3, respectively, to guide clinical focus regarding a subject's continued participation;
- Noncompliance;

For subjects withdrawing from the study prematurely, all efforts will be made to perform the COLEVisit 7 Early Termination procedures.

Documented reason:

It will be documented whether or not each subject completed the clinical study. If, for any subject, study treatment or observations were discontinued, the reason will be recorded (only 1 choice is acceptable) on the electronic case report form (electronic CRF). Acceptable reasons for a subject discontinuing participation in this clinical study are as follows:

9. Protocol deviation (including noncompliance to study requirements)
10. Adverse event(s) (including abnormal laboratory values, and abnormal test procedures)
11. Pregnancy
12. Lost to follow-up
13. Death
14. Subject withdrew consent
15. Unsatisfactory therapeutic effect
16. Other (specify).

20.2.5. Treatment of Subjects

20.2.5.1. Dosing

Subjects will be dispensed study medication under open-label conditions at the study visits indicated in the Schedule of Evaluations for COLE (Table 9). 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.

20.2.5.2. 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.

20.2.6. Concomitant Medication During the COLE Phase

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.

20.2.6.1. Prohibited Medication

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.

All medications prohibited during the randomization phases (Section 7.2.1) will also be prohibited during this phase.

20.2.6.2. 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 (Section 7.2.2.1).

20.2.7. Treatment Compliance

Compliance in this study will be assessed by the Investigator. The Investigator will consider patient interviews as well as returned capsules when assessing compliance. Subjects who were not fully compliant will be re-educated by the Investigator or study staff on the importance of taking the study medication daily at the scheduled time.

Any overdose that occurs during study participation must be recorded on the overdose CRF. An overdose (intentional or accidental) is defined as the following: >3 capsules of open label study medication taken within a 24-hour period (except when re-administered within the guidance of Section 7.1.2).

20.2.8. Treatment Assignment

At COLE Visits 1-6, (Table 9), study personnel will dispense enough COLE medication to the subject to last until the next scheduled visit.

20.2.9. Study Drug, Packaging, and Labeling

[redacted]

[redacted]

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.

20.2.10. Study Medication Materials and Management

See Section 8 for information on study medication packaging, storage and accountability.

20.2.11. Study Assessments per Visit

20.2.11.1. COLE Screening Visit A or B (Visit 1, COLE Day 0)

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

- Review of inclusion/exclusion criteria
- Collection of demographic information, medical history, and prior and concurrent medications;
- Vital sign and body measurements
- Patients who are coming directly from VP-VLY-686-2301 Visit 6 can coordinate this visit with VP-VLY-686-2301 Visit 6.
- Patients who are returning after a gap (Vist 1-B) will perform the following additional procedures:
  - Physical examination (PE) (excluding pelvic, rectal and breast examinations unless clinically indicated)

  - ECG
  - Screening C-SSRS questionnaire
  - Clinical laboratory assessments: hematology, chemistry (including estimated creatinine clearance (eCLcr; based on the Cockcroft-Gault equation), urinalysis, HbA1c, thyroid stimulating hormone (TSH), thyroxine (T4), urine drug screen,
  - Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
  - Modified Gastroparesis Cardinal Symptom Index (mGCSI) Part I
  - Modified PAGI-SYM (mPAGI-SYM)
  - Gastroparesis Treatment Benefit Survey (GTBS)
- Study medication instruction and dispensation

Collection of adverse event information will begin at the time the ICF is signed. Subjects will be set up on phone diary and instructed to begin completing their diary daily (Section 10.1.1).

20.2.11.2. COLE Visit 2-Visit 6 (COLE Day 28, Day 84, Day 140, Day 196, Day 280, ± 5 days)

On COLE Visit 2 through Visit 6, the following assessments will be performed to assess the subject's continued eligibility:

- Adverse Event query
- Concomitant medication review
- Urine pregnancy test (for females of child-bearing potential)
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse)
- ECG
- Physical examination (PE) (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Clinical laboratory assessments (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- Since last visit C-SSRS
- Diary review
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Global Impression of Change (PGI-C)

- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Study medication dispensation
- Schedule Monthly Calls

20.2.11.3. COLE Visit 7/End of Study/Early Termination (COLE Day 365, ± 7 days)

- Adverse Event query
- Concomitant medication review
- Full PE (excluding pelvic, rectal and breast examinations unless clinically indicated)
- Laboratory evaluations (HbA1C, hematology, chemistry (including eCLcr; based on the Cockcroft-Gault equation), urinalysis, thyroid stimulating hormone (TSH), thyroxine (T4), and urine drug screen)
- Serum pregnancy test and collection of menstrual cycle information (for females of child-bearing potential)
- ECG
- Semi-supine routine vital signs (body temperature, respiratory rate, blood pressure, and pulse) and weight
- Since last visit C-SSRS
- Diary review
- Modified Gastroparesis Cardinal Symptom Index (mGCSI)
- Modified PAGI-SYM (mPAGI-SYM)
- Patient Global Impression of Change (PGI-C)
- Patient Assessment of Upper Gastrointestinal Disorder Quality of Life (PAGI-QOL)
- Clinical Global Impression of Severity (CGI-S)
- Study medication collection and review
- Record EOS

20.2.11.4. Unscheduled Visits

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

20.2.11.5. Monthly Calls to Patients (COLE Day 56, Day 112, Day 224, Day 252, Day 308, Day 336, ± 3 days)

Members of the study team will call patients between visits to assess overall health and query for any adverse events or updates to their current medication. An unscheduled visit will be performed if medically warranted in the opinion of the Investigator.

20.2.12. Efficacy Assessments

The efficacy assessments should be conducted as specified in the Schedule of Evaluations for COLE (Table 9). These assessments include: the Gastroparesis Core Symptom Daily Diary (GCSDD), Modified Gastroparesis Cardinal Symptom Index (mGCSI), Modified PAGI-SYM (mPAGI-SYM), Patient Global Impression of Change (PGI-C), and the Patient Assessment of Upper Gastrointestinal Disorders-QOL (PAGI-QOL) (see Section 10.1.1 for a description of the patient reported outcomes) and the Clinician Global Impression – Severity (CGI-S) (see Section 10 for complete descriptions of the assessments).

20.2.13. Safety Assessments

The safety assessments should be conducted as specified in the Schedule of Evaluations for COLE (Table 9). These assessments include: the regular monitoring and recording of all adverse events and serious adverse events (SAEs); the regular monitoring of hematology, blood biochemistry and urinalysis values; the regular monitoring of vital signs; the regular monitoring of suicidal ideation and behavior, and the performance of physical examinations, and electrocardiograms.

Refer to Section 11 for additional details relating to the collection of safety assessments and adverse event reporting.

20.2.14. Statistical Methods

Statistical analysis for the COLE phase will be based on data summaries, using similar layouts as for the randomization phase, and will be exploratory in nature (See Section 13 for further details).

20.3. 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	

20.4. 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