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

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

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**Document Type:** Clinical Study Protocol

**Sponsor:** Vanda Pharmaceuticals Inc.
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**Study Product:** tradipitant (VLY-686)

**Protocol Number:** VP-VLY-686-3301

**Study Phase:** III

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# SIGNATURE PAGE FOR VANDA PHARMACEUTICALS INC.

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Approved by the following:

Program Lead: Gunther Birznieks 12/12/2022 | 5:04 PM EST

Gunther Birznieks Date

Senior Vice President, Research & Development Committee

Medical Director: 12/12/2022 | 5:02 PM EST

Christos Polymeropoulos, M.D. Date

Medical Director

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|---|---|
| **Name of Sponsor/Company:**<br>Vanda Pharmaceuticals Inc. | |
| **Name of Investigational Product:**<br>Tradipitant (VLY-686) | |
| **Name of Active Ingredient:**<br>{2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone | |
| **Title of Study:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Assess the Efficacy of Tradipitant in Relieving Symptoms of Gastroparesis | |
| **Study center(s):** Approximately 50 centers in the United States | |
| **Indication:**<br>Diabetic & Idiopathic Gastroparesis | **Phase of development:**<br>III |
| **Number of subjects (planned):**<br>Up to 800 subjects will enroll in the study.<br>Group 1: Approximately 200 gastroparesis subjects will be determined eligible to enter the Evaluation Phase and be randomized to one of 2 arms (100 per arm, 1:1 randomization scheme).<br>Group 2: Up to 600 gastroparesis subjects that are not eligible to be randomized will enter into the 12 week Open Label Phase of the study. | |
| **<u>Inclusion Criteria:</u>**<br>1. Male and female subjects aged 18 – 70 years (inclusive);<br>2. Diagnosed with gastroparesis:<br>a. Demonstrated delayed gastric emptying of a solid meal via either scintigraphy, gastric breath test, or wireless motility capsule within 10 years of screening. If solid meal is not tolerated, a liquid meal may be used instead to demonstrate delayed gastric emptying via scintigraphy<br>b. Presence of nausea symptom for at least 6 months prior to screening<br>3. Patient's gastroparesis symptoms persist despite diet and/or life-style modifications;<br>4. Body Mass Index (BMI) of ≥18 and < 40 $kg/m^2$ (BMI = weight (kg)/ [height (m)]$^2$);<br>5. Subjects must agree to the following study restrictions:<br>a. Males of procreative capacity (not surgically sterile) will use an acceptable method of contraception from randomization through 1 month following the last dose of study medication. Examples of acceptable contraception for males include abstinence, use of a barrier method, or sterilized or post-menopausal partner;<br>b. Females of child-bearing potential (not surgically sterile or post-menopausal, defined as 12 months without menses) will use an acceptable method of contraception from 1 month prior to randomization (or screening, if earlier) through 1 month following the last dose of study medication. Examples of acceptable methods of contraception for females include abstinence, double barrier method, IUD, hormonal contraception, or sterilized partner; | |

6. Ability and acceptance to provide written informed consent;
7. Willing to participate in the pharmacogenomics sample collection;
8. Willing and able to comply with all study requirements and restrictions, including but not limited to:
    a. Daily symptom diary completion,
    a. Prohibited medications,
    b. Strict control of blood glucose (T1DM and T2DM patients);
9. Willing to not participate in any other interventional trial for the duration of their participation.

**NOTE: ADDITIONAL CRITERIA ARE CONFIDENTIAL AND SHOULD NOT BE SHARED WITH SUBJECTS, POTENTIAL SUBJECTS, OR ANYONE OUTSIDE OF THE IMMEDIATE STUDY TEAM.**

**Additional Inclusion Criteria for Group 1/Evaluation Phase:**

10. Diagnosed with idiopathic or diabetic gastroparesis with moderate to severe nausea:
    a. At least 24 screening diary entries,
    b. PAGI-SYM individual nausea score ≥ 2 at Visit 1, and
    c. Average daily diary nausea severity ≥ 2.5 during the screening period,
    d. At least one episode of vomiting during the screening period.

**Additional Inclusion Criteria for Group 2/Open Label Phase:**

11. Diagnosed with diabetic, idiopathic, post-surgical or viral gastroparesis,
    a. Presence of nausea (PAGI-SYM individual nausea score ≥ 1 at Visit 1),
    b. At least 24 screening diary entries,
    c. Patients who do not qualify for Group 1/Evaluation Phase.

**Exclusion Criteria:**

1. Another active disorder or treatment which could explain or contribute to symptoms in the opinion of the Investigator (including but not limited to gastric malignancy, neurological disorder, or heavy doses of strong anticholinergics);
2. Gastric or parenteral feeding within 4 weeks of screening for Group 1;
3. Pregnancy or nursing;
4. History of intolerance and/or hypersensitivity to medications similar to tradipitant and its accompanying excipients;
5. History (including family history) or current evidence of congenital long QT syndrome or known acquired QT interval prolongation (including QTcF > 450 in males or > 470 in females at screening);

6. History of suicide attempt and/or suicidal ideation (of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS)) within 2 years of screening or subject is at risk of suicide at Screening or Baseline visits, in the opinion of the investigator;
7. History of an eating disorder within 2 years of screening for Group 1 only and within 3 months of screening for Group 2;
8. Recent history (within six months of screening) of Alcohol Use Disorder or Substance Use Disorder as defined in DSM-5 or evidence of such abuse which may include a positive drug screen at the Screening visit and does not include medical marijuana for Group 2 subjects only
9. Uncontrolled thyroid disease;
10. Unstable cardiac, respiratory, hepatic or renal disease;
11. Indication of impaired liver function (including values for AST, ALT, or bilirubin > 2 times the Upper Limit of Normal, unless isolated bilirubin > 2 x ULN due solely to Gilbert's syndrome) at screening;
12. Has a creatinine level > 2x ULN at screening;
13. Anyone affiliated with the site or sponsor and/or anyone who may consent under duress;
14. 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;
15. Evidence of uncontrolled blood glucose (including HbA1C >9 for Group 1 or HbA1C > 11 for Group 2 at screening or metabolic crisis in past 60 days);
16. Surgeries to the stomach including gastrectomy, fundoplication, vagotomy, pyloroplasty, bariatric surgery excluded in Group 1 and excluded in Group 2 if performed < 2 months from screening . Additionally, gastric stimulation device surgically implanted within the last year or if implanted more than a year ago for Group 1 subjects or withing the last 2 months for Group 2 subjects, or have changed stimulation settings within the last 3 months (ie gastric stimulation device must have a stable setting for at least 3 months) for Group 1 and withing the last 1 month for Group 2 subjects
17. 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;
18. Use of the following within 2 weeks of screening: another NK-1 antagonist or a second generation 5-HT3 antagonist for Group 1 and Group 2, phenergan more than 2 times per day for Group 1 only, or opioids more than 2 times per week for Group 1 only;
19. Pyloric injection of neurotoxins (e.g. botulinum type A or B) within 3 months of the Screening Visit for Group 1 or within 1 month of Screening for Group 2;
20. Exposure to any investigational medication, including placebo, within 60 days of the Baseline Visit;

21. Patients who previously participated in study VP-VLY-686-2301 or any other clinical study of tradipitant in the past.

**Investigational product, dosage and mode of administration:**

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

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

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

**Duration of treatment:** Up to 12 weeks

**Objectives:**

**Primary:**

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

**Secondary:**

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

**Overall Design:**

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

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

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

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

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

**Primary Endpoint:**

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

**Criteria for evaluation:**

*Efficacy*:
Efficacy assessments will include:

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

*Safety:*

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

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