TRADIPITANT
AMENDMENT NO. 2 TO PROTOCOL VP-VLY-686-1301

A SINGLE CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFECTS OF TRADIPITANT ON SATIATION, GASTRIC VOLUME, GASTRIC ACCOMODATION AND GASTRIC EMPTYING IN HEALTHY VOLUNTEERS

Author: Michael Camilleri, M.D.
Jesse L. Carlin, Ph.D

Document Type: Clinical Study Protocol

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

Principle Investigator: Michael Camilleri, M.D.

Co Investigators: Dan Maselli M.D., Jessica Atieh M.D.

Study Product: tradipitant (VLY-686)

Protocol Number: VP-VLY-686-1301

Study Phase: I

IND Number: 131545

Date: 10 May, 2021
Status: Final
Number of Pages: 68

SIGNATURE PAGE FOR VANDA PHARMACEUTICALS INC.

Amendment No. 2 to VP-VLY-686-1303

Approved by the following:

Program Lead:	Jesse Carlin	5/14/2021 | 6:28 PM EDT
	Jesse L. Carlin, Ph.D. Clinical Project Lead	Date
Medical Director:		5/21/2021 | 8:59 PM BST
	Christos Polymeropoulos, M.D. Medical Director	Date

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: VP-VLY-686-1301: A Single-Center, Placebo-Controlled, Double-Blind Study to Evaluate the Effects of Tradipitant on Satiation, Gastric Volume, Gastric Accommodation and Gastric Emptying in Healthy Volunteers
Study center(s): Clinical Enteric Neuroscience Translational and Epidemiological Research, Mayo Clinic, Rochester, MN
Indication: Healthy Volunteers — **Phase of development:** I
Number of subjects (planned): Approximately 36 patients will be screened in order to fully complete the testing of 24 healthy subjects.
Inclusion Criteria: 1. Male and female subjects aged 18 – 65 years (inclusive); 2. No medical problems or chronic diseases, specifically, no type 2 diabetes mellitus. 3. Body Mass Index (BMI) of ≥18 and ≤ 35 kg/m^2 (BMI = weight (kg)/ [height (m)]^2); 4. Subjects must agree to the following study restrictions: 5. 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; 6. 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; 7. Ability and acceptance to provide written informed consent; 8. Willing to participate in the pharmacogenomics sample collection; 9. Willing and able to comply with all study requirements and restrictions 10. Willing to not participate in any other interventional trial for the duration of their participation. **Exclusion Criteria:** 11. Unable or unwilling to provide informed consent or to comply with study procedures. 12. Unwilling to agree to provide pharmacogenomics sample 13. Diagnosis of gastrointestinal diseases. 14. Structural or metabolic diseases that affect the GI system.

15. Unable to avoid the following over-the-counter medications 48 hours prior to the receipt of study medication and throughout the study:
16. Medications that alter GI transit including laxatives, magnesium and aluminum containing antacids, prokinetics, erythromycin;
17. Analgesic drugs including NSAIDs and COX-2 inhibitors

NOTE: Stable doses of thyroid replacement, estrogen replacement, low-dose aspirin for cardioprotection, and birth control are permissible.

18. History of recent surgery (within 60 days of screening).
19. Pregnant or nursing;
20. History of intolerance and/or hypersensitivity to medications similar to tradipitant and its accompanying excipients;
21. 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);
22. 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;
23. Recent history (within six months of screening) of Alcohol Use Disorder or Substance Use Disorder which may include a positive drug screen at the Screening visit;
24. Acute or chronic illness or history of illness, which in the opinion of the investigator could pose a threat or harm to the subject or obscure interpretation of laboratory test results or interpretation of study data such as frequent angina, Class III or IV congestive heart failure, any impairment of renal or hepatic function, poorly controlled diabetes, etc;
25. 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);
26. Has a creatinine level > 2x ULN;
27. Anyone affiliated as a member of the investigative team or sponsor and/or anyone who may consent under duress;
28. 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 from Mayo Research Pharmacy. Subjects will be randomized to one of two treatment arms to receive 85 mg tradipitant BID or placebo.

Duration of treatment: Up to 9 days

Objectives:

Primary:

To evaluate the effects of tradipitant *relative to placebo* in healthy volunteers in the following:

- Difference in fasting GV
- Difference in postprandial GV and in accommodation volume (that is, postprandial minus fasting gastric volumes)
- Difference in gastric emptying ($T_{1/2}$, emptying at 2h and emptying at 4h)
- Volume to fullness (sensation of usual postprandial fullness) and maximum feeling of fullness (MTV).

Secondary:

- Absolute postprandial gastric volume
- Gastric volume (GV) ratio (postprandial/fasting GV)
- Gastric emptying of solids at 2h
- Gastric emptying of solids at 4h
- Intragastric meal distribution at time zero, (IMD^0) following ingestion of test meal
- Maximum tolerated volume (MTV) during satiation test
- Aggregate symptoms score 30 min after MTV on satiation test
- Individual symptom scores (nausea, bloating, fullness, pain) on satiation test

Overall Design:

This is a randomized, double-blind, placebo-controlled, single center study during which healthy volunteers will be recruited, enrolled, and randomized to one of 2 treatment groups. Subjects meeting all inclusion/exclusion criteria will be randomized to either placebo or tradipitant, two 85mg tablet daily (b.i.d.) for 9 consecutive days. Subjects may be involved in study activity for up to five weeks from screening date to completion of all studies. The actual study related testing will be conducted on three days.

Enrollment of subjects will continue until N=24 of those that have been randomized to study medication and have completed all study testing through Day 9. Subjects who withdraw consent after being randomized will be included in an intent-to-treat analysis with missing data imputed based on data of completed subjects. Subjects that withdraw from participation before receipt of medication will be replaced. Subjects who have started their assigned study medication, but do not complete all the study testing through Day 9 will be replaced.

Primary Endpoint:

The primary objectives of this study are:

- Comparison of **fasting gastric volume** induced by tradipitant vs. placebo studied by single photon emission computed tomography (SPECT)
- Comparison of **accommodation volume** induced by tradipitant vs. placebo studied by SPECT
- Comparison of volume to fullness (VTF,mL) on **satiation test** for tradipitant vs. placebo
- Comparison of **gastric emptying** $T_{1/2}$ of solids on scintigraphy for tradipitant vs. placebo
- Comparison of gastric emptying values at 2 and 4 hours

Criteria for evaluation:

Efficacy:

- Single photon emission computed tomography (SPECT) to calculate fasting gastric volume and postprandial gastric accommodation
- Measurement of volume to fullness (mL) on satiation test
- Gastric emptying by scintigraphy

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:

Sample size is based on the results of primary endpoints in the Mayo Clinic lab. Expected (80% power, α=0.05) demonstrable differences for tradipitant compared to placebo is 23.6% in the **gastric accommodation volume** and 29.2% in **gastric emptying** T1/2, based on the coefficients of variation observed from the Mayo Clinic laboratory in prior studies.