CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220152Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993

Division of Pediatrics and Maternal Health Review

Date: 12/29/2025 **Date consulted:** 1/15/2025

From: Katherine Kratz, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: CDR Miriam Dinatale, DO, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Gastroenterology (DG)

Drug: Nereus (tradipitant)

NDA: 220152

Applicant: Vanda Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For the prevention of vomiting induced by motion in adults

Materials Reviewed:

- DPMH consult request dated 1/15/2025. DARRTS Reference ID: 5512328
- Applicant's submitted background package and proposed labeling for NDA 220152, Sequence Number (SN) 0001, dated 12/30/2024.
- Applicant's response to FDA Information Request (IR) for NDA 220152, SN 0008, dated 3/7/2025.
- [redacted] (b) (4)

Consult Request: "DG requests DPMH assistance in reviewing the USPI."

I. INTRODUCTION AND BACKGROUND

On December 30, 2024, the Applicant, Vanda Pharmaceuticals, Inc., submitted a 505(b)(1) new drug application (NDA) for tradipitant for the acute prevention of vomiting induced by motion in adults. DG consulted the DPMH MHT on January 15, 2025 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Other neurokinin-1 (NK-1) antagonists have been approved by FDA. None are approved for acute prevention of vomiting induced by motion. The other NK-1 antagonists include the following products:
    - Aprepitant (Emend for oral use and Cinvanti for intravenous use): both approved in 2003
    - Fosaprepitant (Emend for intravenous use and Focinvez for intravenous use): both approved in 2008
    - Rolapitant (Varubi): approved in 2015
    - Netupitant (Akynzeo capsules, netupitant in combination with palonosetron): approved in 2014
    - Fosnetupitant (Akynzeo solution, fosnetupitant in combination with palonosetron): approved in 2018
- The DPMH MHT was consulted to review the pregnancy and lactation labeling for all the NK-1 antagonists listed above.
    - The labelings for Emend, Focinvez and Varubi do not include a Contraindication for pregnancy or lactation or a Warning and Precaution (W&P) for embryo-fetal toxicity (EFT).
    - The labeling for Cinvanti includes a statement for Use in Specific Populations: "Pregnancy: May cause fetal harm (8.1)." This statement is based on Cinvanti containing alcohol.
    - The labeling for Akynzeo includes a statement for Use in Specific Populations: "Pregnancy: May cause fetal harm (8.1)." This statement is based on animal data for netupitant studies.
- FDA has approved other drug products indicated for motion sickness as follows:
    - Scopolamine, approved in 1979, is indicated for nausea and vomiting associated with motion sickness. The labeling for scopolamine does not include a Contraindication for pregnancy or lactation or a W&P for EFT.
    - Promethazine, approved in 1951, is indicated for active and prophylactic treatment of motion sickness. In labeling, it is categorized as a "Pregnancy category C." According to the American College of Obstetrics and Gynecology (ACOG),[1] promethazine has been shown to be safe for use during pregnancy.[2]
    - Dimenhydrinate, approved in 1972, is indicated to prevent and treat nausea, vomiting, and dizziness caused by motion sickness. It is an over-the-counter

[1] Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 189: Nausea And Vomiting Of Pregnancy. Obstet Gynecol. 2018 Jan;131(1):e15-e30. doi: 10.1097/AOG.0000000000002456. PMID: 29266076.
[2] Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol. 2002 May;186(5 Suppl Understanding):S256-61. doi: 10.1067/mob.2002.122596. PMID: 12011897.

(OTC) drug product that has been used for decades without reports of adverse pregnancy outcomes. It is listed by ACOG as a pharmacologic option for the treatment of nausea and vomiting of pregnancy.[3]

- The DPMH MHT reviewed scopolamine labeling supplements in 2010 and 2019. No DPMH MHT reviews were found for promethazine or dimenhydrinate.
- The Applicant submitted NDA 218489 for tradipitant "for the treatment of *[symptoms of]* or *[nausea in]* gastroparesis" in September 2023. A complete response (CR) was issued on September 18, 2024, because the application did not provide substantial evidence of effectiveness for the treatment of symptoms of gastroparesis or nausea in gastroparesis.

Drug Characteristics[4]

Drug class	NK-1 receptor antagonist
Mechanism of action	Binds selectively to the NK-1 receptor and inhibits emesis via central and local actions; the exact mechanism of action has not been fully established
Dosage form	Oral capsules
Dosage	85 or 170 mg; maximum dose in 24 hours is 170 mg
Active metabolites	M2, M3, M4, and M8; M2, M4 and M8 are present at disproportionally higher levels in humans compared to species used in nonclinical toxicology studies (i.e., rats and rabbits for reproductive toxicity)[5]
Molecular weight	587.9 Daltons
Half-life	34 hours
% protein bound	96.2%
Bioavailability	19.6% in dogs; not studied in humans
Adverse Events	Somnolence, headache and fatigue

II. REVIEW

PREGNANCY

Motion Sickness and Pregnancy[6]

According to UpToDate, motion sickness is a syndrome that occurs in response to real or perceived motion and may affect the gastrointestinal and central nervous systems. Pregnant patients may be particularly susceptible to motion sickness. Treatment of motion sickness in pregnancy includes dimenhydrinate or meclizine ("off label"). Scopolamine, in the absence of pre-eclampsia, and promethazine are also used to treat motion sickness in pregnancy.

[3] See ref 1.
[4] NDA 220152, Sequence number 0001. Draft labeling text. Under review by DG.
[5] NDA 220152, Integrated Review Template, Section 13.3.2.5 Metabolite Discussion by Dr. Sarah Morgan, under review by DG.
[6] Priesol, A. Motion Sickness. UpToDate. Topic 6853 Version 39.0

Nonclinical Data

No new nonclinical data related to use of tradipitant during pregnancy were submitted by the Applicant. (b) (4)

Briefly, there were no developmental toxicities identified in rats or rabbits at dose exposures 57- and 114-times the human exposure at the maximum recommended human dose of 1000 mg, respectively.

The reader is referred to the Pharmacology/Toxicology review by Dr. Sarah Morgan.

> ***Reviewer comment:***
>
> (b) (4) *DPMH stated that "the reproductive risks of tradipitant use have not been completely elucidated because human metabolism of tradipitant has not been adequately characterized by the Applicant. Specifically, in the human PK study H8R-MC-HJAK, where healthy volunteers were administered radiolabeled tradipitant, the Applicant accounted for only 26% of the drug-related radioactivity. It is not known what happened to the other 74% of drug in humans. Therefore, insufficient information was provided about metabolism in humans to directly relate the lack of reproductive findings in animals to reproductive safety in humans." More specifically, there were limitations to study H8R-MC-HJAK: 1) the low dose relative to the intended clinical dose (* (b) (4) *85 or 170 mg); 2) tradipitant and three of its major active metabolites, M2, M3, and M4, accounted for 26% of total radioactivity only, based on AUC; 3)tradipitant itself did not meet the 10% threshold; and 4) the AUC of the fourth major active metabolite, M8, was not reported.*
>
> *In this current review, additional information* (b) (4) *was identified and evaluated by the Nonclinical Team. From this additional information, the Nonclinical Team determined the following: 1) each metabolite did not meet the threshold of 10% of drug-related exposure that necessitates nonclinical qualification; 2) no idiosyncratic toxicity was expected with these metabolites based on their structural changes compared to tradipitant; and 3) the on-target safety of the metabolites was adequately covered by the nonclinical studies in rats and dogs. The Nonclinical Team concluded that this additional information may allow them to qualify the safety of the metabolites based on total drug-related exposure in animals compared to humans (i.e., exposure to all measured tradipitant-related compounds) instead of on an individual basis.*

Clinical Data

(b) (4) two pregnancies that occurred during the clinical development program were reported. Briefly, both pregnancies resulted in full-term deliveries of normal infants. Due to the limited nature of these data, they were determined to be insufficient to inform labeling related to the safety of tradipitant use

(b) (4)

during human pregnancy [redacted] (b) (4)

An IR was sent to the Applicant requesting information about additional pregnancies related to the current submission. The Applicant responded with no new reports of pregnancies in the development program for the prevention of vomiting induced by motion in adults.

> ***Reviewer comment:***
> *Clinical data from pregnancies that occurred during drug development did not provide sufficient information to inform a drug-associated risk of tradipitant use during pregnancy.*

Review of Literature

Applicant's review:

The Applicant did not provide a literature review pertaining to pregnancy in this submission [redacted] (b) (4)

DPMH review:

DPMH conducted a search of published human studies in PubMed, using the search terms "NK-1 antagonists" OR "aprepitant" OR "fosaprepitant" OR "rolapitant" AND "pregnancy," "pregnancy outcomes," "birth defects," "fetal malformations," "stillbirth," OR "spontaneous abortion." No studies or case reports were found in the published literature.

DPMH also searched Micromedex,[9] Reprotox,[10] TERIS,[11] and Shepard's[12] and no information was found.

> ***Reviewer comment:***
> *The literature search did not retrieve any data to inform a drug-associated risk of tradipitant use during pregnancy.*

LACTATION and FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

No new nonclinical data related to lactation, fertility or drug-drug interactions were provided by the Applicant in this submission. [redacted] (b) (4)

Lactation

Nonclinical studies [redacted] (b) (4) did not demonstrate adverse developmental effects in rats exposed to tradipitant via lactation. Specifically, in a pre- and post-natal development study (PPND), pregnant female rats were administered tradipitant at oral doses of 100, 300, or 1000 mg/kg from day 6 of gestation to day 20 of lactation; the study did not identify maternal or offspring toxicity at any dose up to 1000 mg/kg/day, approximately 57 times the

[8] Ibid.
[9] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 2/25/25.
[10] Reprotox Website: www.Reprotox.org. Accessed 2/25/25.
[11] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 2/25/25.
[12] Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 2/25/25.
[13] See ref. 7.

MRHD based on body surface area. In the PPND study, on lactation days 4 and 11, the Applicant measured tradipitant and the M2, M3, and M4 metabolites in the plasma of dams and rat pups. Tradipitant was measured in the plasma of nursed F1 offspring at levels up to 3.2% of the maternal level. In dams, M2 was low to absent, M3 was present at levels seen in humans and M4 was absent. In the plasma of rat pups, M2, M3 and M4 were not detected. The Applicant did not measure the other major metabolite, which is M8.

There are no clinical data from which to draw conclusions related to the safety of tradipitant use during human lactation.

> ***Reviewer comment:***
> *Tradipitant was detected in rat dam plasma and in the plasma of pups who were nursed, suggesting that tradipitant enters rat milk. When a drug is present in animal milk, it is likely to be present in human milk.*
>
> *In addition to the data from the PPND study that suggest that tradipitant may be present in rat milk, it is likely that tradipitant will enter human milk based on its molecular weight of 587.9. Per Hale's,[14] another NK-1 antagonist, aprepitant, is likely to be present in milk at minimal levels. The molecular weight of aprepitant is 534.43 Daltons, which is similar to that of tradipitant. Since tradipitant has a long half-life of 34 hours, it is possible that the drug may accumulate in human milk.*

Males and Females of Reproductive Potential
In terms of fertility, there are no nonclinical or clinical data on the drug's effects on fertility.

Since the submission of NDA 218489, the Applicant did not submit new data related to drug-drug interactions. (b) (4) the possibility of tradipitant inducing CYP3A and reducing the efficacy of hormonal contraceptives was determined to be low.

III. DISCUSSION AND CONCLUSIONS

Pregnancy
There are limited human data available from clinical trials during drug development related to pregnancy, which are insufficient to inform the risk of use during pregnancy. The Applicant did not submit new nonclinical data for this new NDA. Based on animal reproduction studies (b) (4) (b) (4) oral administration of tradipitant did not demonstrate developmental toxicity in rats or rabbits. Additional information about tradipitant's metabolites was identified and evaluated during the current review cycle, and the Nonclinical Team determined that this additional information may allow them to qualify the safety of the metabolites based on total drug-related exposure in animals compared to humans. DPMH recommends including information about the available clinical data under the Risk Summary and about the nonclinical data under the Risk Summary and Animal Data section.

[14] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

DPMH recommends issuing a pregnancy exposure registry and complementary database study as postmarketing requirements (PMRs) for tradipitant based on following rationale: 1) the drug is systemically absorbed and will likely transfer to the fetus, 2) motion sickness is common in females of reproductive potential, 3) motion sickness may be made worse during pregnancy, and 4) there are limited human pregnancy data available.

Lactation

Tradipitant is present in rat milk. DPMH recommends including a statement in labeling about the presence of tradipitant in animal milk. There are no available lactation data in humans. DPMH recommends stating in labeling that there are no available data about the presence of the proposed drug in human milk, its effects on milk product or its effects on the breastfed infant. Due to the potential for breastfed infants to experience adverse reactions due to exposure to tradipitant through breast milk, DPMH recommends including a statement in the Highlights of Prescribing Information and in subsection 8.2 that breastfed infants should be monitored for adverse reactions that occur in adults, such as somnolence.

DPMH recommends issuing a PMR for a clinical lactation study because tradipitant is expected to be used by females of reproductive potential, including lactating women. Based on animal data and drug characteristics, tradipitant is likely to be transferred to human milk. A clinical lactation study is needed to assess the degree to which tradipitant is transferred to human milk and to assess the potential effects on the breastfed infant.

Females and Males of Reproductive Potential

DPMH recommends omitting subsection 8.3 as there is no information on the drug's effects on human fertility or contraception to relay to the healthcare provider.

IV. LABELING RECOMMENDATIONS

DPMH's labeling recommendations for subsections 8.1 and 8.2 and section 17 of labeling are presented below. DPMH defers to the final NDA action for final labeling.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE G KRATZ
12/29/2025 10:47:46 AM

MIRIAM C DINATALE
12/29/2025 10:51:27 AM

LYNNE P YAO
12/30/2025 09:40:41 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 30, 2025
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 220152
Product Name, Dosage Form, and Strength:	Nereus (tradipitant) capsules, 85 mg
Applicant Name:	Vanda Pharmaceuticals (Vanda)
FDA Received Dates:	December 22, 2025 and December 29, 2025
TTT ID #:	2025-12433-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, Pharm.D., FISMP

1 PURPOSE OF MEMORANDUM

Vanda Pharmaceuticals submitted revised container label and carton labeling received on December 22, 2025 and December 29, 2025 for Nereus. The Division of Gastroenterology (DG) requested that we review the revised container label and carton labeling for Nereus (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

On December 22, 2025, Vanda submitted the following revised container label and carton labeling (see figures 1 and 2).

Figure 1. Container Label

[a] Abraham S. Label and Labeling Review for Nereus (NDA 220152). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 DEC 4. TTT ID: 2025-12433.

Figure 2. Carton Labeling

During our first labeling review, we identified a potential discrepancy between the net quantity (36 capsules/bottle) and (b) (4) for the proposed product. Thus, we included the comment (b) (4) in our review. During our subsequent discussions with the review team, our clinical colleagues indicated that the net quantity may be appropriate given the recommended dose can be two 85 mg capsules daily. Further, Vanda subsequently removed the statement (b) (4) from the carton labeling, stating that the statement was included on the carton labeling in error and was inaccurate. Thus, our concerns regarding the net quantity have been alleviated at this time.

Vanda Pharmaceuticals implemented all of our previous recommendations; however, the revised container labels and carton labeling included a trademark symbol, which was not previously present. On December 23, 2025, we provided the following recommendation to Vanda via email:

The trademark symbol “TM” is too prominent. The prominence of the trademark symbol distracts from the readability of the proprietary name. Decrease the size of the trademark symbol.

3 CONCLUSION

Vanda Pharmaceuticals implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
12/30/2025 09:37:37 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	December 30, 2025
Product Name:	Tradipitant (VLY-686)
Application Type/Number:	NDA 220152
Sponsor/Applicant:	Vanda Pharmaceuticals, Inc.
NEXUS Task Tracking Tool ID #:	2025-12432
Reviewer:	Benjamin Booth, PhD, MS Division of Epidemiology I
Team Leader:	Benjamin Booth, PhD, MS Division of Epidemiology I
Acting Division Director:	Wei Hua, MD, PhD, MS, MHS Division of Epidemiology I
Sub-Office Director:	CAPT David Moeny, RPh, MPH Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD, MSPH Regulatory Science Staff Office of Surveillance and Epidemiology

1. BACKGROUND INFORMATION

1.1. Medical Product

Tradipitant is an antagonist of the human substance P/neurokinin 1 (NK1) receptor proposed for the acute prevention of vomiting induced by motion in adults. Tradipitant is formulated as 85 mg capsules with a proposed recommended dose of 85 mg or 170 mg administered orally approximately 60 minutes before anti-emetic effect is desired. Tradipitant has a half-life of 34 hours.

1.2. Describe the Safety Concern

There are limited human data available from clinical trials during drug development related to pregnancy, which are insufficient to inform the risk of use during pregnancy.[1] The Applicant did not submit new nonclinical data for this new NDA.[2] Based on animal reproduction studies (b) (4) oral administration of tradipitant did not demonstrate developmental toxicity in rats or rabbits. Additional information about tradipitant's metabolites was identified and evaluated during the current review cycle, and the Nonclinical team determined that this additional information may allow them to qualify the safety of the metabolites based on total drug-related exposure in animals compared to humans. The Division of Pediatrics and Maternal Health (DPMH) recommended including information about the available clinical data under the Risk Summary and the nonclinical data under the Risk Summary and Animal Data section.

DPMH also recommended issuing a pregnancy exposure registry and complementary database study as postmarketing requirements (PMRs) for tradipitant based on following rationale: 1) the drug is systemically absorbed and will likely transfer to the fetus, 2) motion sickness is common in females of reproductive potential, 3) motion sickness may be made worse during pregnancy, and 4) there are limited human pregnancy data available.[3]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication in pregnant women, but practitioners may use product off-label in pregnant women
- ☒ No approved indication in pregnant women, but there is the potential for inadvertent

[1] DPMH review of tradipitant, NDA 220152, by Katherine Kratz, MD, dated 12/30/2025. DARRTS Reference ID: 5719318

[2] (b) (4)

[3] (b) (4)

exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant women, but use in women of childbearing age is a general concern

2.2. Regulatory Goal[4]
- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest*.
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome*.
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a targeted or multiple safety concern(s)/health outcome(s)*.
  - ☒ Targeted evaluation of specific safety concern
  - ☐ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.
- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☒ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☐ Other, please specify:

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency
☒ Study Population	The population of interest includes both pregnant women with motion sickness and their offspring. An ICD-9 code (994.6) and ICD-10 code (T75.3) exist for motion sickness but no validated algorithms for motion sickness were found in the literature. It is unclear how well the ICD-9 or ICD-10 codes would perform in claims-based databases. ARIA is not sufficient for the study population.
☐ Exposures (and Comparators)	ARIA is sufficient for the exposure.
☒ Outcomes	The PMRs require collection of outcomes in both the pregnant women and the resultant offspring. The pregnancy

[4] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11.

	registry study and the database study under consideration require detailed clinical information from primary data collection or medical records to identify and validate outcomes. These data may also be used to assess exposure-outcome temporality and conduct causality assessments. ARIA is insufficient due to the lack of access to detailed clinical information through primary data collection or medical charts.
☐ Covariates	ARIA does not have detailed information on some potential confounders. This study is for signal identification and may not need high levels of refinement at this stage. ARIA is sufficient for covariates.
☐ Analytic Tools	ARIA is sufficient for the analytic tools.
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

PMR-1: Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to tradipitant regardless of indication during pregnancy with unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry should identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR-2: Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in individuals exposed to tradipitant during pregnancy compared to appropriate comparator population(s).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHERINE L CALLAHAN on behalf of BENJAMIN J BOOTH
12/30/2025 10:55:18 AM

WEI HUA
12/30/2025 10:55:55 AM

DAVID G MOENY
12/30/2025 11:09:37 AM

PATRICIA L BRIGHT
12/30/2025 11:10:38 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Draft Memorandum

Date: December 29, 2025

To: Mary Chung, Project Manager, DG

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEREUS (tradipitant) capsules, for oral use

NDA: 220152

In response to DG's consult request dated October 28, 2025, OPDP has reviewed the proposed product labeling (PI) for tradipitant.

Labeling: OPDP has no comments on the proposed labeling based on the draft labeling submitted by the Applicant to the electronic document room on December 29, 2025.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

11 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

QUYNH-NHU D CAPASSO on behalf of MEETA N PATEL
12/29/2025 02:29:21 PM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 29, 2025

To: Juli Tomaino, M.D., Director
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Through: Dominic Chiapperino, PhD, Director
Controlled Substance Staff

From: Chad J. Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

Subject: **NDA 220152:** Tradipitant (VLY-686) - Oral capsules
Indication: Acute prevention of vomiting induced by motion in adults
Dosage and Route: 85 or 170 mg oral administered 60 minutes before an antiemetic effect is desired
Sponsor: Vanda Pharmaceuticals, Inc.
PDUFA Goal Date: September 18, 2025

Materials Reviewed:

- Abuse Liability Justification Report
- (b) (4)

Table of Contents

I. SUMMARY

1. Background

This memorandum is in response to a consult request dated December 30, 2024 from the Division of Gastroenterology and Inborn Errors Products (DGIEP) pertaining to NDA 220152 for tradipitant (VLY-686). The Sponsor, Vanda Pharmaceuticals, Inc. is developing tradipitant for the treatment of acute prevention of vomiting induced by motion in adults (i.e., motion sickness). The Sponsor submitted an NDA for tradipitant on December 30, 2024 that included a document titled *Abuse Liability Justification Report*. DGIEP requested that the Controlled Substance Staff (CSS) review the Sponsor's NDA from an abuse potential perspective.

(b) (4) In the current review, the Sponsor has submitted an identical abuse liability assessment report for this NDA (220152) as in the previous review of NDA 218489.

Tradipitant has been evaluated for several indications (b) (4)

Vanda Pharmaceuticals acquired the development of this product from Eli Lilly in April 2012. (b) (4) tradipitant was evaluated for its primary pharmacology *in vitro* using receptor binding assays and determined to be a potent, selective, NK-1 receptor inhibitor. Tradipitant binds to the human cell membrane NK-1 receptor with high affinity: Ki = 0.062 nM in human lymphoblastoma IM-9 cells, and 0.13 nM and 0.156 nM in brain homogenates of gerbil and guinea pig, respectively. Tradipitant was also determined to have no significant activity (≥50% inhibition) in a broad panel of receptors, transporters, and ion channel receptors, enzymes and ion channels including the NK-2 and NK-3 receptors. Therefore, additional studies including non-clinical abuse potential assessments and a human abuse potential study have not been requested.

Four drug products with similar mechanism(s) of action (i.e., NK-1 antagonists) have been approved by FDA: rolapitant (Varubi), aprepitant (Emend), fosaprepitant (an intravenous form of

aprepitant, Emend Injection) and fosnetupitant (in combination with the 5HT3 antagonist, palonosetron, as Akynzeo). None of these products are controlled under the CSA. The Sponsor hypothesizes that by blocking NK-1 receptor activation, tradipitant will decrease nausea and vomiting associated with motion sickness.

2. Conclusions

- Tradipitant (VLY-686) is a new molecular entity whose primary mechanism of action is as a neurokinin-1 (NK-1) receptor inhibitor. Receptor binding studies indicated that tradipitant did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.

- Currently, there are four drug products containing NK-1 antagonists that have been approved by FDA: rolapitant (Varubi), aprepitant (Emend), fosaprepitant (an intravenous form of aprepitant, Emend Injection) and fosnetupitant (in combination with the 5-HT_3 antagonist, palonosetron, as Akynzeo).

- No neurokinin-1 (NK-1) receptor inhibitor is scheduled under the CSA, and we are unaware of any instance(s) of abuse of neurokinin-1 (NK-1) receptor inhibitors as a drug class.

- An analysis of CNS-mediated adverse events (AEs) that can be indicative of abuse liability or physical dependence was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs observed in clinical trials were somnolence, dizziness, and anxiety. CSS notes that these AEs are typically not indicative of abuse in the absence of other events such as euphoria and feeling high, among others. There were no concerning reports of AEs that suggest that tradipitant (VLY-686) has a potential for abuse or physical dependence.

- Additional studies, such as non-clinical abuse potential assessments and a human abuse potential study, were not requested.

- The proposed drug product, if approved under this NDA, will not require a Drug Abuse and Dependence section (Section 9) in its label.

3. Recommendations (to the Division)

- Tradipitant does not appear to have a potential for abuse and does not require scheduling under the Controlled Substances Act (CSA).

- Tradipitant does not require a section 9 (Drug Abuse and Dependence section) in its label.

II. DISCUSSION

1. Chemistry

1.1 Drug Substance and Product Information

Drug Substance

The IUPAC chemical name for tradipitant is: [2-[1-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-pyridin-4-yltriazol-4-yl]pyridin-3-yl]-(2-chlorophenyl) methanone. It has a molecular formula of $C_{28}H_{16}ClF_6N_5O$ and a molecular weight of 587.9 g/mol. The chemical structure of tradipitant is shown in **Figure 1**. The chemical properties and structural identifiers of tradipitant including the IUPAC Name, PubChem ID, CASRN, Molecular Formula, Molecular Weight, Canonical SMILES, InChI, and InChIKey are shown in **Table 1**.

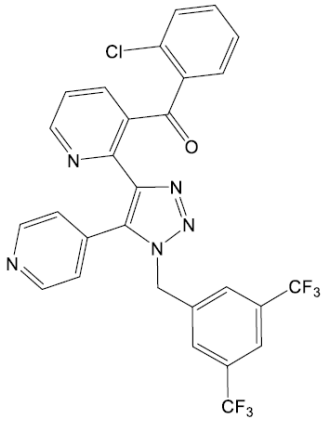


Figure 1. Chemical structure of Tradipitant

Table 1. Chemical Properties and Structural Identifiers of Tradipitant	
Property or Identifier	**Value**
Common Name	LY686017, VLY-686, 622370-35-8
IUPAC Name	[2-[1-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-pyridin-4-yltriazol-4-yl]pyridin-3-yl]-(2-chlorophenyl)methanone
PubChem ID	9916461
CASRN	622370-35-8
Molecular Formula	$C_{28}H_{16}ClF_6N_5O$
Molecular Weight	587.9 g/mol
Canonical SMILES	C1=CC=C(C(=C1)C(=O)C2=C(N=CC=C2)C3=C(N(N=N3)CC4=CC(=CC(=C4)C(F)(F)F)C(F)(F)F)C5=CC=NC=C5)Cl
InChI	InChI=1S/C28H16ClF6N5O/c29-22-6-2-1-4-20(22)26(41)21-5-3-9-37-23(21)24-25(17-7-10-36-11-8-17)40(39-38-24)15-16-12-18(27(30,31)32)14-19(13-16)28(33,34)35/h1-14H,15H2
InChIKey	CAVRKWRKTNINFF-UHFFFAOYSA-N
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number	

SMILES = Simplified Molecular-Input Line-Entry System InChI = International Chemical Identifier InChIKey = InChIKey is a hashed version of the full InChI (using the SHA-256 algorithm)

Drug Product

According to the Sponsor, tradipitant is a white to off-white (b) (4) crystalline powder. Tradipitant drug substance is practically insoluble in water, pH 1.2, pH 7.4 and pH 9.0 buffers. It is slightly soluble in isopropyl alcohol and pH 1.2. Tradipitant is supplied as a capsule dosage form for oral administration. Tradipitant capsules are hard gelatin capsules provided as 85-mg strength. The capsule formulation also contains (b) (4) lactose monohydrate, microcrystalline cellulose (b) (4) povidone, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate as excipients.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

The Sponsor conducted several *in vitro* binding studies to assess the primary and secondary pharmacology of tradipitant. The *in vitro* receptor binding profile of tradipitant was evaluated with a broad panel of receptors, ion channels, and transporters using 1μM concentrations (Study # CNS532). The *in vitro* evaluation demonstrated that tradipitant is a potent NK-1 receptor antagonist, with potencies similar to those observed with other NK-1 antagonists. Tradipitant binds to human cell membrane NK-1 receptors with high affinity: Ki = 0.062 nM in human IM-9 cells, and 0.13 nM and 0.156 nM in brain homogenates of gerbil and guinea pig, respectively. No significant activity (≥ 50% inhibition) was observed at a panel of 74 additional receptors, enzymes, and ion channels including the NK-2 and NK-3 receptors. Tradipitant did not bind to molecular targets typically associated with having a potential for abuse (e.g., GABA, opioid receptors, and NMDA receptors).

In addition, the binding affinity of tradipitant's metabolites (M2, M3, and M4) were evaluated with a panel of over 180 other receptors *in vitro* at a test concentration of 10 μM (Studies AB28300: 1190601 - 1190604). According to the Sponsor, the major circulating metabolites of tradipitant did not bind to molecular targets typically associated with having a potential for abuse.

2.2 Animal Behavioral Studies

Safety Pharmacology

(b) (4)

The Sponsor evaluated CNS/behavioral, and pulmonary effects of tradipitant in a battery of safety pharmacology studies. Behavioral and CNS properties of tradipitant were evaluated in male CD-mice. Respiratory parameters (respiratory rate, tidal volume or minute volume) were evaluated in a single-dose study following oral administration of tradipitant in male rats.

Neurological effects:

- Study # PN0318 and PN0319 - Single oral doses of 0 (vehicle), 150, 500 and 1500 mg/kg tradipitant were administered to male CD-1 mice (10/group). According to the Sponsor, there were no overt compound-related clinical signs at any dose. Tradipitant did not alter hexobarbital-induced sleep times, the number of writhes induced by acetic acid, neuromuscular functioning or convulsive thresholds evaluated by the administration of electroshock or pentylenetetrazol. Tradipitant administered at 1500 mg/kg significantly increased spontaneous ambulatory and nonambulatory activity in mice at 90- and 105-minute time points. Mean decrease in core body temperature was significantly less than the decrease for control mice, when recorded 120 minutes following administration of 1500 mg/kg tradipitant. Sensorimotor reactivity-auditory startle was significantly increased at the low dose of 15 mg/kg but significantly decreased at 150 and 500 mg/kg. Based upon this information, tradipitant may produce mild hyperactivity or mild hyperthermia at doses of 1500 mg/kg or higher. It may also alter sensitivity to auditory stimuli.

Pulmonary effects:

- Study # N103034 -The purpose of this study was to evaluate the effect of tradipitant on respiratory parameters in male rats. The following parameters were evaluated: respiratory rate, tidal volume, and minute volume. Male rats were administered vehicle, 150, 500, or 1500 mg/kg as a single oral dose. Respiratory rate, tidal volume, and minute volume were observed for 6 hours post-dose and at 24-hours post-dose. According to the Sponsor, there were no treatment-related clinical observations following dosing with tradipitant. Respiratory parameters were not significantly different from vehicle control values following dosing with tradipitant.

Animal Abuse Potential Studies

No animal studies were conducted by the Sponsor to assess the abuse potential of tradipitant.

2.3 Tolerance and Physical Dependence Studies in Animals

No animal studies were conducted by the Sponsor to assess the tolerance or physical dependence of tradipitant.

3. Clinical Studies

The Sponsor was not required to conduct a human abuse potential study to assess the abuse liability of tradipitant. According to the Sponsor, based on the in vitro and in vivo pharmacology

studies performed with tradipitant it is anticipated that tradipitant would have a negligible potential for drug abuse; therefore, no studies were conducted to formally evaluate abuse potential. Additionally, there have been no reports of drug-seeking behavior in tradipitant clinical trials and evidence points to a potential treatment to help address alcohol cravings in addicted individuals. CSS agrees with the Sponsor's assertion that tradipitant has a negligible abuse potential.

The Sponsor submitted a justification report for the abuse liability of tradipitant which relied on published literature and data submitted for study # H8R-MC-HJAP (b) (4) Study # H8R-MC-HJAP was a randomized, double-blind, phase I, multiple dose, two-period cross-over, tradipitant ethanol interaction study in healthy subjects to assess the pharmacokinetic and pharmacodynamic effects of tradipitant when administered with and without ethanol. The objective relevant to this report was to assess the pharmacodynamic interaction between tradipitant and alcohol (ethanol) using cognitive function testing. Specifically, tradipitant was studied for its ability to prevent relapse in patients with alcohol dependence who were abstinent at treatment initiation. According to the Sponsor, the results of this study showed no clear or consistent effect of tradipitant on cognition and no clear or consistent interaction effects between tradipitant and ethanol on cognitive function in healthy volunteers.

3.1 Adverse Event Profile Through all Phases of Development

(b) (4)

adverse events (AEs) from 14 clinical studies were evaluated in response to an information request submitted by CSS. After review of the information request, CSS noted the absence of abuse related AEs and concluded the AE profile was not consistent with tradipitant having an abuse potential. For the current NDA, one additional clinical studies was completed VP-VLY-686-3404) and one is in-progress (VP-VLY-686-3403). A third study (VP-VLY-686-3501) is listed as "Terminated;pending." The additional completed study was manually reviewed for abuse related AEs.

1. **VP-VLY-686-3404** was a 316-participant, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant for the prevention of motion sickness. In the study, subjects had a prior history of motion sickness and embarked on a series of 20 boat trips under varied sea conditions and received 85 or 175 mg of tradipitant or placebo. Subjects were instructed to administer tradipitant 60 minutes prior to each boat trip. The primary outcome measure was vomiting (i.e., intensity and frequency). According to the Sponsor, the overall incidence of TEAEs was similar across all treatment groups (170 mg tradipitant = 34.9%, 85 mg tradipitant = 31.7%, placebo = 26.4%). Headache was the most common AE experienced by 10 subjects (9.4%) in the tradipitant 170 mg group, 9 subjects (8.7%) in the 85 mg tradipitant group and 9 subjects (8.5%) in the placebo group. Somnolence and dizziness were also observed, but at rates that did not appear to be substantially greater than placebo. There were no reports of euphoric mood or elevated mood and the overall AE profile was not suggestive of an abuse potential in this study.

3.2 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

There were no reports of misuse, abuse, or diversion of Tradipitant in clinical trials.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHAD REISSIG
12/29/2025 05:12:43 PM

DOMINIC CHIAPPERINO
12/29/2025 05:13:38 PM

Clinical Outcome Assessment Review Memorandum

From	Ji Li, MD, PhD Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Onyeka Illoh, OD, PhD, MPH COA Team Leader, DCOA
To	Division of Gastroenterology (DG)
COA tracking number	C2025012
NDA#/Referenced IND for NDA	NDA 220152/IND 141315
Drug Sponsor	Vanda Pharmaceuticals Inc.
Meeting type	Not applicable
Proposed Indication	Prevention of vomiting induced by motion Please check all that apply: ☐ Rare Disease/Orphan Designation ☐ Pediatric
Instrument(s) reviewed	1. Vomiting Assessment (VA) 2. Nausea Assessment (NA) 3. Motion Sickness Assessment Questionnaire (MSAQ) ☒ Patient-reported outcome (PRO)

Executive Summary

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of Gastroenterology (DG) on January 15, 2025 (DARRTS Reference ID: 5512304) for NDA 220152 regarding tradipitant, a selective high affinity antagonist of human substance P/neurokinin 1 receptors, proposed for the indication of acute prevention of vomiting induced by motion. The Applicant provided data from a phase 2 trial (Study VP-VLY-686-2401) and 2 phase 3 trials (Studies VP-VLY-686-3401 and VP-VLY-686-3404) to support the efficacy and safety of tradipitant in preventing vomiting induced by motion. This COA consult response reviews the appropriateness of the selected patient-reported outcomes (PROs), including the Vomiting Assessment (VA), the nausea assessment (NA), and the Motion Sickness Assessment Questionnaire (MSAQ), for deriving the primary and secondary efficacy endpoints in the phase 3 studies.

The Applicant did not provide any associated training materials or user manuals of the PROs for review; nor did the Applicant provide an evidence dossier to support the fitness-for-purpose[1] of the selected PROs intended for this context of use. The VA and NA questionnaires are simplistic measures which appear straightforward for patients to complete and comprehend. However, there is insufficient evidence of content validity of the MSAQ in the target patient population. As such, this review concludes that the VA and NA (not the MSAQ) are deemed appropriate for assessing motion-induced vomiting presence/absence and nausea severity, respectively, in the target patient population.

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/

Regulatory Background and Materials Reviewed

(b) (4)

During the IND stage, the FDA communicated with the Applicant multiple times regarding the fitness-for-purpose of PRO instruments for use to support primary and key secondary endpoints, which were summarized as follows:

1. In the Advice/Information Request (IR) Letter dated December 19, 2018 (DARRTS Reference ID: 4365810), the FDA recommended the Applicant include well-defined and reliable COAs measuring all signs and symptoms of motion sickness that are relevant and important to patients with motion sickness in the phase 2 development, (b) (4) The FDA noted the absence of evidence that demonstrated patient input in confirming that the response options of the Motion Sickness Severity Scale (MSSS) were ranked in order of increasing severity. As such, the FDA recommended the Applicant explore existing assessments of vomiting and nausea using a 0-10 numeric rating scale (NRS), a verbal rating scale (VRS), or an open-ended count of vomiting/retching episodes. In the subsequent Advice/IR Letter dated March 12, 2019 (DARRTS Reference ID: 4402504), the FDA recommended revising the primary endpoint to "absence of vomiting or rescue medication use" in a pre-specified time period. The FDA also recommended including clear instructions to patients on how an episode of vomiting was defined.

2. In the Type B End of Phase (EOP) 2 Meeting Minutes dated May 21, 2020 (DARRTS Reference ID: 4612728), the FDA did not agree that the MSSS and the MSAQ were appropriate for use as key efficacy endpoint measures given insufficient information to demonstrate their fitness-for-purpose. During this meeting, both the FDA and the Applicant agreed on developing tradipitant for the indication of the prevention of vomiting induced by motion. The FDA acknowledged and agreed with the Applicant's proposal to not allow rescue medication use and to evaluate vomiting in the absence of rescue medication use as the primary endpoint in Study VP-VLY-686-3401. The Applicant intended to introduce a novel PRO, to be administered every 30 minutes, to document whether a subject vomited over the last 30 minutes in support of the primary efficacy endpoint. The FDA requested an exact copy of the questionnaire for review and referred the Applicant to previous advice on the use and support of COA tools. Furthermore, the FDA acknowledged the potential difficulties in incorporating a (b) (4) (b) (4) into the proposed study design. To facilitate interpretation of clinical benefit, the FDA recommended using a VRS (b) (4) for the nausea severity scale the Applicant intended to include.

3. As per the Type B Pre-NDA meeting minutes dated December 8, 2023 (DARRTS Reference ID: 5290599), the FDA identified several limitations in the design of Study VP-VLY-686-2401 that may impact the interpretability of the results, including the primary endpoints assessed with the MSSS. The FDA further recommended completing the ongoing phase 3 Study VP-VLY-686-3404 prior to NDA submission to provide additional supporting data for the proposed indication.

Document	SDN	eCTD#	Date Received
Clinical Overview	*1*	*0001*	*12/30/2024*

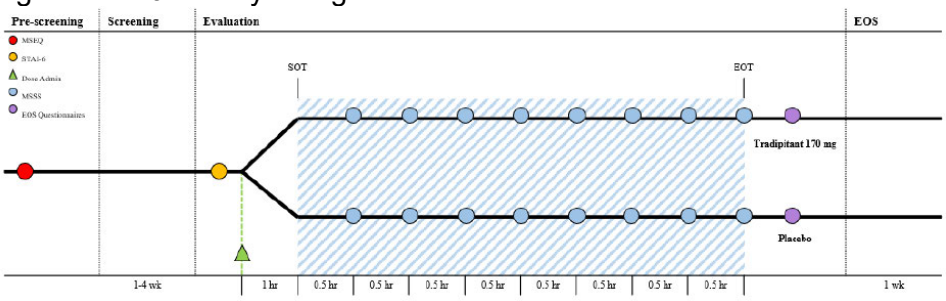
Summary of Clinical Efficacy	*1*	*0001*	*12/30/2024*
Synopses of Individual Studies	*1*	*0001*	*12/30/2024*
Study VP-VLY-686-3401 Report Body	*1*	*0001*	*12/30/2024*
Study VP-VLY-686-3404 Report Body	*1*	*0001*	*12/30/2024*
Draft Labeling Text	*1*	*0001*	*12/30/2024*
Study VP-VLY-686-3401 Protocol Amendment 2	*1*	*0001*	*12/30/2024*
Study VP-VLY-686-3404 Protocol Amendment 2	*1*	*0001*	*12/30/2024*
Communications and Reviews	**DARRTS Ref ID**		**Date**
Type B Pre-NDA Meeting Minutes	*5290599*		*12/08/2023*
Type B Pre-NDA Meeting Preliminary Comments	*5273397*		*11/06/2023*
Type B End of Phase (EOP) 2 Meeting Minutes	*4612728*		*05/21/2020*
Type B EOP 2 Meeting Preliminary Comments	*4604836*		*05/07/2020*
The Advice/Information Request Letter	*4402504*		*03/12/2019*
The Advice/Information Request Letter	*4365810*		*12/19/2018*
C2020499_IND 141315_St. Clair_COA Review	*4761650*		*03/12/2021*
C2020016-C2020125_IND 141315_St. Clair_COA Review	*4640826*		*07/31/2020*
C2018303_IND 141315_Kovacs_COA Review	*4418726*		*04/12/2019*
Publications			
Gianaros PJ, Muth ER, Mordkoff JT, Levine ME, Stern RM. A questionnaire for the assessment of the multiple dimensions of motion sickness. Aviat Space Environ Med. 2001;72(2):115-119. Available from https://www.ncbi.nlm.nih.gov/pubmed/11211039			

Trial Design and Study Endpoints

The Applicant completed 1 phase 2 study and 2 phase 3 studies. The phase 2 Study 2401 was a single center, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of a single oral dose of tradipitant 170 mg and matching placebo in 126 adults with a history of motion sickness (Figure 1). Subjects were randomly assigned to 170 mg tradipitant or placebo ~60 minutes prior to an approximately 4-hour boat trip. Throughout the trip and upon

completion of vehicle travel, subjects completed questionnaires to assess their sickness symptoms induced by motion. The study met its co-primary endpoint for vomiting incidence but not for the MSSS worst score, i.e., tradipitant significantly reduced the incidence of vomiting compared to placebo (tradipitant 170 mg=17.5%, placebo=39.7%, p=0.0039).

Figure 1. 2401 Study Design

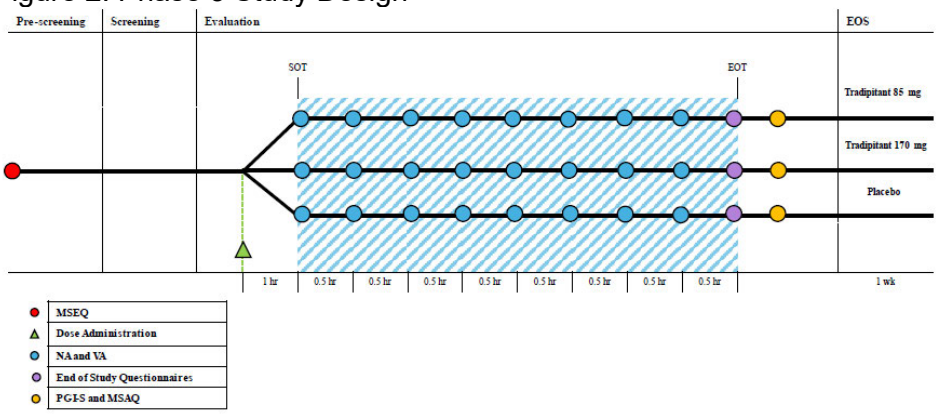


Source: Figure 3 of 2.7.3 Summary of Clinical Efficacy

Two phase 3 studies (Figure 2) were both multicenter, randomized, double-blind, placebo-controlled trials to assess the efficacy of tradipitant in adults (n=366 in Study VP-VLY-686-3401 and 361 in Study VP-VLY-686-3404) with a history of motion sickness for the acute prevention of vomiting induced by motion. Both trials consisted of administration of a single dose of study drug approximately 60 minutes prior to a boat trip lasting 120 to 300 minutes. Eligible subjects were randomized in a 1:1:1 ratio to receive tradipitant 170 mg, tradipitant 85 mg, or placebo.

The primary efficacy endpoint of both phase 3 trials was the percentage of subjects with vomiting during the trip in tradipitant 170 mg group as assessed by the VA questionnaire. The key secondary endpoints in Study VP-VLY-686-3401 included worst nausea in tradipitant 170 mg, percentage of subjects with vomiting in 85 mg, and worst nausea in tradipitant 85 mg. The key secondary endpoints in Study VP-VLY-686-3404 included percentage of subjects with vomiting in 85 mg, and percentage of subjects with vomiting and severe nausea (defined as worst nausea ≥3) in each tradipitant treatment groups. Both studies tested the key secondary efficacy endpoints in a fixed sequence, and demonstrated a statistically significant difference between tradipitant and placebo for the primary endpoint.

Figure 2. Phase 3 Study Design



Source: Figure 2 of 2.7.3 Summary of Clinical Efficacy

*[**Reviewer's comments:** In Study VP-VLY-686-3401, the percentage of subjects who vomited (assessed by the VA) was significantly lower in both the 85 mg tradipitant group (19.5%, p<0.0001) and the 170 mg tradipitant group (18.3%, p<0.0001) as compared to the placebo group (44.3%). The least squared mean of worst nausea (assessed by the NA) was 2.4 in the 170 mg tradipitant group and 2.5 in the placebo group (p=0.6110). Study VP-VLY-686-3404 demonstrated a similar pattern of results from Study VP-VLY-686-3401.*

Descriptions and Content Validity of COAs

The Vomiting Assessment (VA)
The VA (Appendix A.1) is a single-item patient-reported questionnaire that assesses the incidence of vomiting. Subjects indicated whether or not they have vomited based on the response options of Yes/No.

The Nausea Assessment (NA)
The NA (Appendix A.2) is a single-item patient-reported questionnaire that assesses nausea severity. Subjects rated their nausea symptoms in the worst severity using a 5-point Likert scale, i.e., 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.

The Motion Sickness Assessment Questionnaire (MSAQ)
The MSAQ (Appendix A.3) is a 16-statement scale to assess motion sickness. Each statement is rated on a scale of 1-9, with 1 representing low severity and 9 representing high severity. The overall score is calculated by summing the total score divided by 144 and multiplying by 100. The subscale scores can be obtained similarly by calculating the percentage of points scored within each body system, defined as gastrointestinal, central, peripheral, and sopite-related.

*[**Reviewer's comments:** In both phase 3 studies, motion-induced vomiting and nausea symptoms were assessed using the VA and NA instruments, respectively. Subjects completed the VA and NA approximately every 30 minutes throughout the boat travel. Immediately following completion of the boat travel, subjects completed the MSAQ and the Patient Global Impression of Severity (PGI-S) Questionnaire. The Applicant did not provide any associated training materials or user manuals of the selected PROs for review; nor did the Applicant provide a PRO evidence dossier to support the fitness-for-purpose of the PROs intended for this context of use. However, the VA and NA questionnaires are simplistic measures that appear straightforward for patients to complete and comprehend.*

The Applicant described the VA in Section 14 Clinical Studies of the product label as follows:

(b) (4)

Given the nature of patient self-reporting, we do not consider the VA to be an objective assessment of vomiting occurrence.

As per the Gianaros et al. article,[2] the MSAQ instrument appears to measure 4 aspects of motion sickness, defined as gastrointestinal, central, peripheral, and sopite-related. The instrument developers conducted interviews and motion sickness simulations in college students at a single university who participated for course credit. There is a lack of evidence that the study participants in the Gianaros et al. article were representative of the target trial patients.

[2] *Gianaros PJ, Muth ER, Mordkoff JT, Levine ME, Stern RM. A questionnaire for the assessment of the multiple dimensions of motion sickness. Aviat Space Environ Med. 2001;72(2):115-119. Available from https://www.ncbi.nlm.nih.gov/pubmed/11211039*

As such, we do not believe that there is sufficient evidence of content validity of the MSAQ in the target patient population.]

Measurement Properties of the COAs

The measurement properties of the VA and NA were not evaluated using data from the clinical trials.

*[**Reviewer's comments:** Based on the intrinsic construction of the instruments, the VA and NA questionnaires are deemed appropriate for assessing motion-induced vomiting presence/absence and nausea severity, respectively, in the target patient population. The primary endpoint for both phase 3 studies is constructed as an event-driven measure based on a "Yes" response on the VA instrument. It indicates the presence or absence of vomiting and inherently represents a clinically meaningful outcome for patients. In addition, the nausea component of the secondary endpoint in Study VP-VLY-686-3404, defined as worst nausea ≥3 on the NA instrument, represents severe to very severe symptoms and appears to be clinically meaningful.*

In general, the content validity of a COA needs to be established prior to establishing its quantitative psychometric properties. While existing literature[2] provides some information on psychometric properties of the MSAQ, this will not replace or rectify problems with its content validity. As such, MSAQ is not deemed fit for purpose for this context of use based on the available evidence.]

Interpretation of Responder Threshold and Meaningful Within-Patient Score Change

The Applicant did not conduct anchor-based analyses to interpret meaningful within-patient score changes in PRO endpoint scores in the phase 3 studies.

*[**Reviewer's comments**: Anchor-based analysis is not deemed necessary to interpret the meaningfulness of the primary endpoint results as this endpoint indicates the presence or absence of vomiting and is inherently clinically important to patients.]*

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JI LI
12/29/2025 01:17:27 PM

ONYEKACHUKWU A ILLOH
12/29/2025 01:46:34 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 220152
Submission Number	1
Submission Date	12/30/2024
Date Consult Received	1/23/2025
Drug Name	Tradipitant
Indication	Acute prevention of vomiting induced by motion
Therapeutic Dose	Up to 170 mg without food
Clinical Division	DG
Protocol Review	Not previously reviewed

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 1/23/2025 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Integrated assessment of cardiac safety for neurokinin-1 receptor antagonist tradipitant (NDA 220152 / SN 0001; link);
- Summary of Clinical Safety (NDA 220152 / SN 0001; link);
- (b) (4)
- Investigator's brochure (NDA 220152 / SN 0001; link);
- VP-VLY-686-2401 Study Protocol (NDA 220152 / SN 0001; link);
- VP-VLY-686-3401 Study Protocol (NDA 220152 / SN 0001; link);
- VP-VLY-686-3403 Study Protocol (NDA 220152 / SN 0001; link); and
- VP-VLY-686-3404 Study Protocol (NDA 220152 / SN 0001; link).

1 SUMMARY

Tradipitant does not cause clinically relevant QTc prolongation based on the QTc assessment of study H8REW-HJAC – see Table 1 for overall results. The data from the QTc assessment can be used as a substitute for a thorough QT study (ICH E14 Q&A 5.1) for tradipitant when administered as a 170 mg single dose without food.

The clinical study H8REW-HJAC was a single-center, subject-blind, cross-over, randomized, placebo-controlled, dose-escalating study in healthy male subjects. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that tradipitant is associated with significant QTc prolonging effect at the high exposure scenario for a single dose of 170 mg without food (section 4.5).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario is with strong CYP3A4 inhibitors or non-functional genetic variants of CYP3A4 (section 3.1).
• At higher concentrations (including the highest dose of 800 mg) the findings are inconclusive as the CI includes both 0 and 10 msec. We therefore used the median of the highest concentration quantile (125.5 ng/mL) to determine exposure margin. The exposure margin provided by the study covers the high clinical exposure scenario for a single 170 mg dose without food.
<table>
<tr><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>Single 170 mg taken orally without food</td><td>110.5 ng/mL</td><td>0.6</td><td>-1.8 to 2.9</td></tr>
<tr><td>Single 170 mg, with strong CYP3A4 inhibition or non-functional genetic variants of CYP3A4</td><td>143 ng/mL</td><td>2.5</td><td>-2.9 to 7.9</td></tr>
<tr><td>800 mg</td><td>276.6 ng/mL</td><td>6.0</td><td>-4.8 to 16.7</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated nonclinical risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 001 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At the mean maximum concentration provided by the maximum recommended single dose without food, clinically significant QTc prolongation was not observed.
Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" guidance (link). However, considering the significant increase with food, which results in mean maximum concentrations well outside the concentration range studied, we recommend explicit including "without food". *Generally, we express the exposure margin in the label based on the ratio of the Cmax of the highest dose tested (here 800 mg) and the therapeutic dose (here 170 mg). However, considering that the confidence limits at the highest dose tested include both 0 and 10 msec, we consider the QTc findings at that exposure to be inconclusive. We therefore propose to use the Cmax of the median of the highest quantile instead of the Cmax (i.e., 125.5 ng/mL) of the highest dose tested. With a dose up to 170 mg there is not a significant margin to report in the label.*

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant, Vanda Pharmaceuticals Inc, has developed tradipitant (VLY-686), a NK-1 antagonist, for the acute prevention of vomiting induced by motion in adults. The recommended dose is 85 or 170 mg under fasting conditions. The maximum dose within 24 h is 170 mg.

The Applicant has submitted an integrated assessment of cardiac safety and results from studies VP-VLY-686-2401, VP-VLY-686-3401, VP-VLY-686-3403, and VP-VLY-686-3404 to support the QTc assessment for tradipitant.

The new studies VP-VLY-686-2401 (Protocol, p340), VP-VLY-686-3401 (Protocol, p38), VP-VLY-686-3403 (Protocol, p38), and VP-VLY-686-3404 (Protocol, p35) only include ECGs collected pre-treatment and end of study or end of study / early termination. These ECGs are not adequate to support assessing the effects of tradipitant on the QTc interval.

(b) (4)

The integrated cardiac safety assessment includes four studies:

- H8REW-HJAC (Report): Randomized, subject-blind, placebo-controlled, sequential group, dose-escalating study with doses to 800 mg. See Appendix 5.1 for details.
- VP-VLY-686-1102 (Report): Open-label, single-sequence, DDI study with midazolam (n=24). Tradipitant 85 mg BID was administered on days 4 – 15, single doses on days 3 and 16. ECGs were collected at pre-dose on day 1 and pre-dose and 3 h post-dose on days 3 and 16.

- VP-VLY-686-2301 (Report): Randomized, double-blind, and placebo-controlled study with tradipitant 85 mg BID. Safety ECGs were collected at screening, pre-dose, and at weeks 2 and 4. Timing relative to dosing is unknown.
- VP-VLY-686-3301 (Report): Double-blind, placebo-controlled study with tradipitant 85 mg BID. Safety ECGs were collected at screening, pre-dose, and at days 14, 28, 42, 57, 70, and 84. Timing relative to dosing is unknown.

Study H8REW-HJAC is considered the primary study to supporting QTc assessment as it included placebo and serial time-matched ECG/PK collection. This study is therefore the focus of our review.

3.1.1 Clinical Pharmacology

Tradipitant's clinical pharmacology is summarized in investigator's brochure (link) and in the table of highlights of clinical pharmacology and cardiac safety submitted under NDA220152 (SDN12).

Tradipitant is generally rapidly absorbed with median Tmax across doses and formulations ranging between 0.5 to 3 h (Typical median Tmax = 1 h). However, it has less than dose-proportional increase in exposure.

In a food effect study utilizing the commercial formulation (85 mg hard gelatin capsules), a single dose of 85 mg provided geometric mean Cmax of 84.7 ng/mL (Tmax = 2 h), in fasted condition, while a single dose of 170 mg provided geometric mean Cmax of 110 ng/mL (Tmax = 1.5 h). High fat meal increased Cmax by 4.7- and 7.0-fold for the 85 mg, and 170 mg doses, respectively. The proposed label recommends taking tradipitant without food.

Other factors increasing tradipitant exposure are concomitant treatment with strong CYP3A4 inhibitors and dysfunctional genetic polymorphism of CYP3A4, a major metabolizing enzyme of tradipitant. Both, strong inhibition and CYP3A4 *22 resulted in about 30% increase in tradipitant Cmax.

Although peak concentrations in pivotal efficacy studies for motion sickness were not determined, they are expected to be comparable to those observed under fasting conditions in the food effect study (i.e., VP-VLY-686-1002).

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	85 mg (Oral, fasted) 170 mg (Oral, fasted)	84.7 ng/mL (Single dose Cmax) 110.5 ng/mL (Single dose Cmax)
Applicant's High clinical exposure scenario	1.3-fold increased Cmax with strong CYP3A4 inhibitors or non-functional genetic variants of CYP3A4.	85: 110 ng/mL 170: 143 ng/mL
Highest dose in QT assessment	800 mg single dose, oral capsule, without food. Median of highest exposure quantile (125.5 ng/mL) is used for exposure margin calculations.	125.5 ng/mL
C_{max} Ratio	85: 125.5 / 110 = 1.1 170: 125.5 / 143 = 0.9	

3.1.2 Nonclinical Safety Pharmacology Assessments

(b) (4)

3.2 Applicant's Results

3.2.1 By-Time Analysis

The dose-response analysis of mean vital signs and ECG data is summarised in Table HJAC.14.32 and Table HJAC.14.33 (Section 14.4), respectively. A few statistically significant changes were detected, mainly at the top dose (800 mg). However, there were no clear patterns of change over time and no clinically relevant changes for vital signs or ECG data. Furthermore, there was no evidence of a drug-related QT prolongation at any dose tested.

Reviewer's comment: *The Applicant's findings are consistent with our analysis.*

3.2.1.1 Assay Sensitivity

Not applicable as the study did not include a positive control.

3.2.1.1.1 QT Bias Assessment

Not performed.

3.2.2 Categorical Analysis

Two subjects had a maximum increase from baseline (predose) in 12-lead QTc interval (Fridericia's correction) of ≥60 ms: Subject (b) (6) received 1 mg LY686017 and changes from baseline (355 ms) were: +76 ms at 12 hours, +29 ms at 24 hours, +39 ms at 48 hours, and +88 ms at 72 hours. Subject (b) (6) received 400 mg LY686017 and changes from baseline (402 ms) were +74 ms at 2 hours, before returning to +14 ms at 3 hours with no other high increases.

Reviewer's comment: *The Applicant only presented outlier analysis for ≥60 msec, which are consistent with our analysis.*

3.2.3 Exposure-Response Analysis

The Applicant did not perform concentration-QTc analysis.

3.2.4 Safety Analysis

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 Evaluation of the QT/RR Correction Method

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG Assessments

4.2.1 Overall

Digital ECG waveforms were not submitted.

In the checklist the Applicant did not clarify how ECGs were analyzed in this study. We therefore submitted an IR, and the Applicant stated that this is a legacy study and that information beyond the CSR is not available. The Applicant has no additional information about how ECGs were read. (NDA 220152, SN 0014) The CSR notes that the ECGs were interpreted by the ECG vendor cardiologist for "*data analysis and reporting writing purposes*". (CSR, p28) The protocol further notes the following: "*With respect to the QT interval, ECGs will be recorded and stored electronically and may be over read at a later date*." (CSR, p295) The ECGs appeared to have been collected digitally and analyzed automatically. Submitted datasets include individual-level data.

4.2.2 QT Bias Assessment

Not performed as no alternative QT measurements are available.

4.3 By-Time Analysis

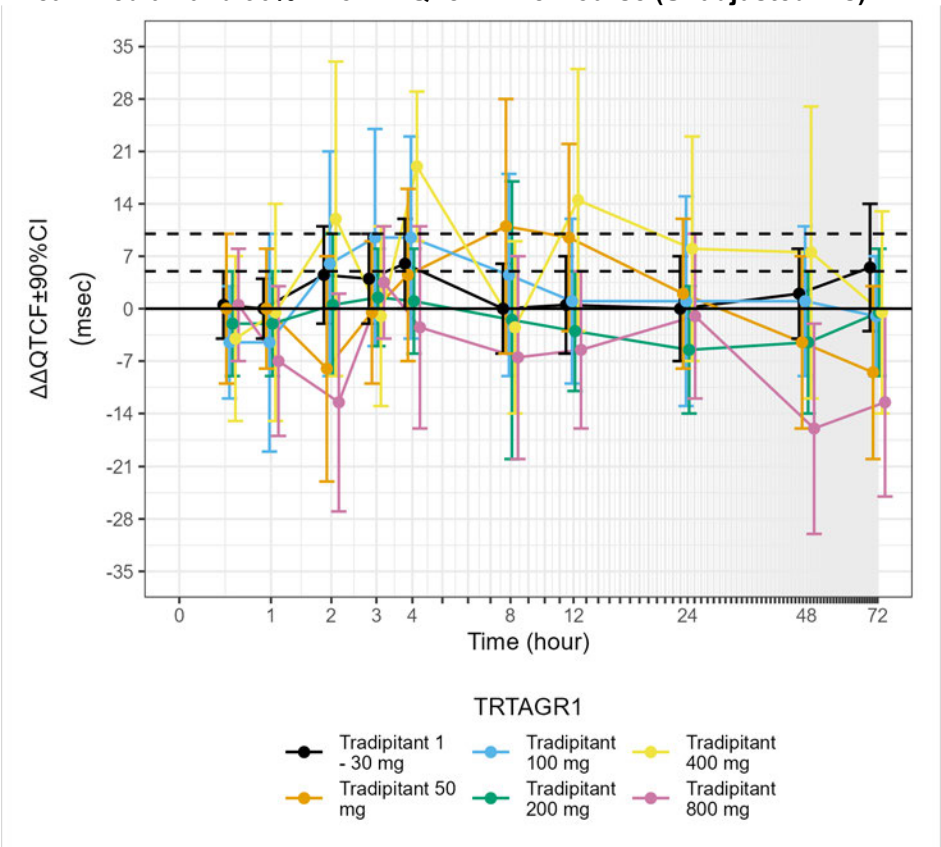
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics because of the small sample size per dose group.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. No dose-dependent changes in QTc were observed.

Figure 1. Mean/Median and 90% CI of ΔΔQTcF Time-Course (Unadjusted CIs)



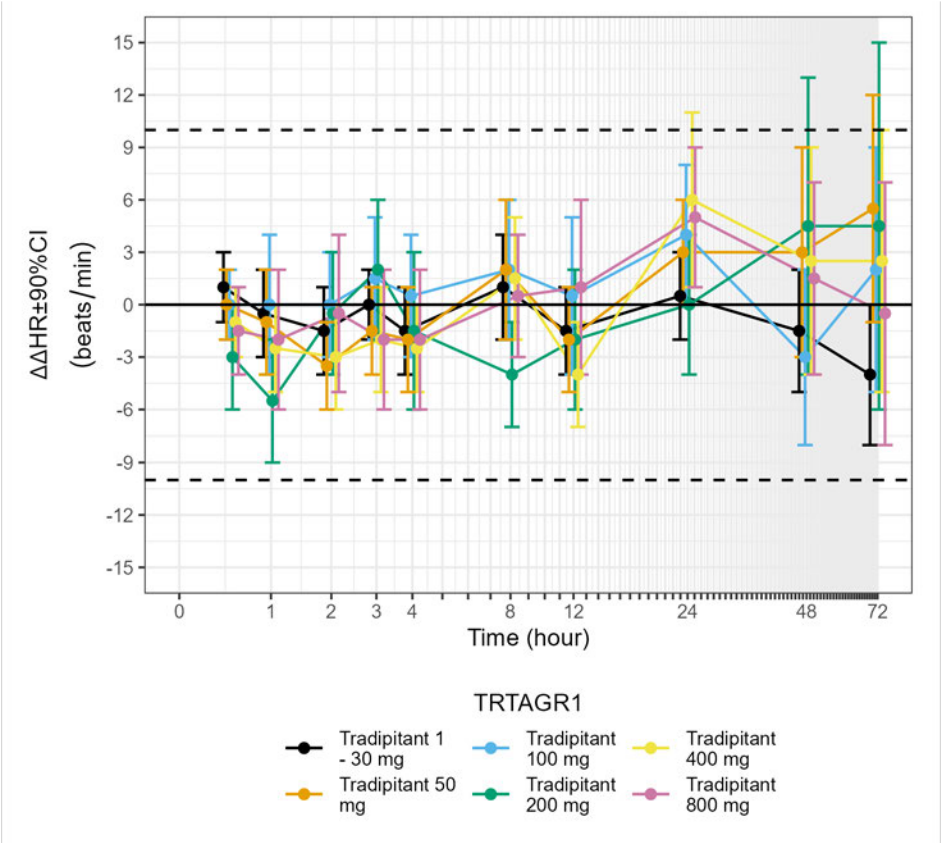
4.3.1.1 Assay Sensitivity

Not applicable – no positive control was included.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups. No dose-dependent changes in HR were observed.

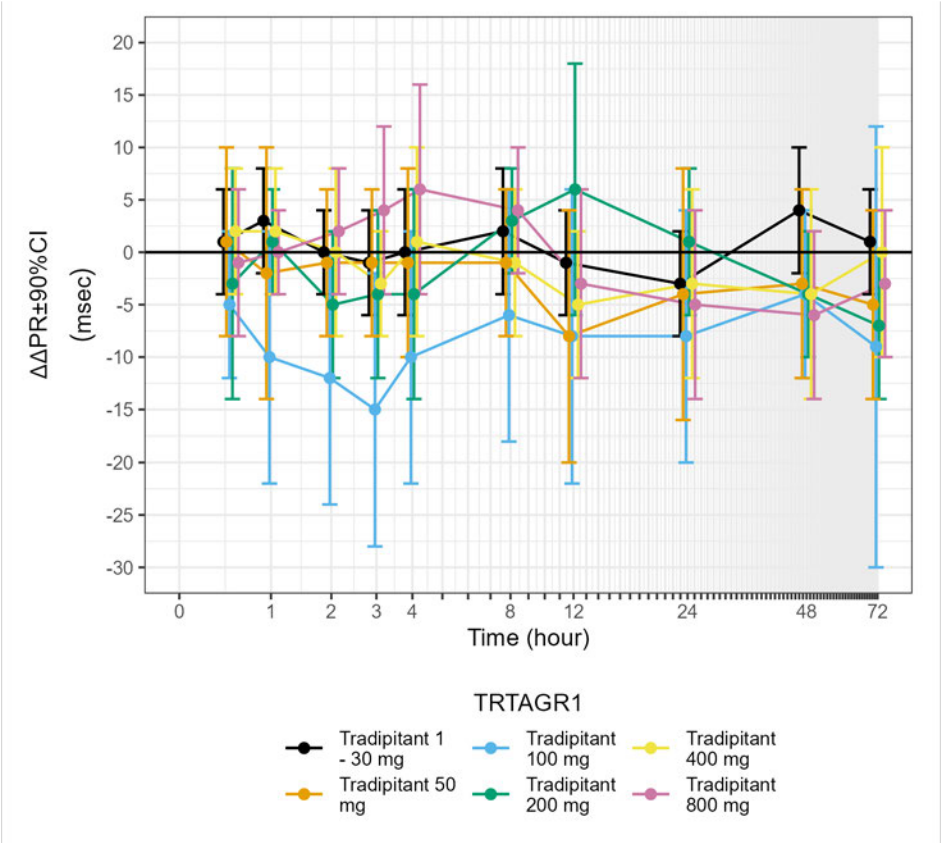
Figure 2. Mean/Median and 90% CI of ΔΔHR Time-Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups. No dose-dependent changes in PR were observed.

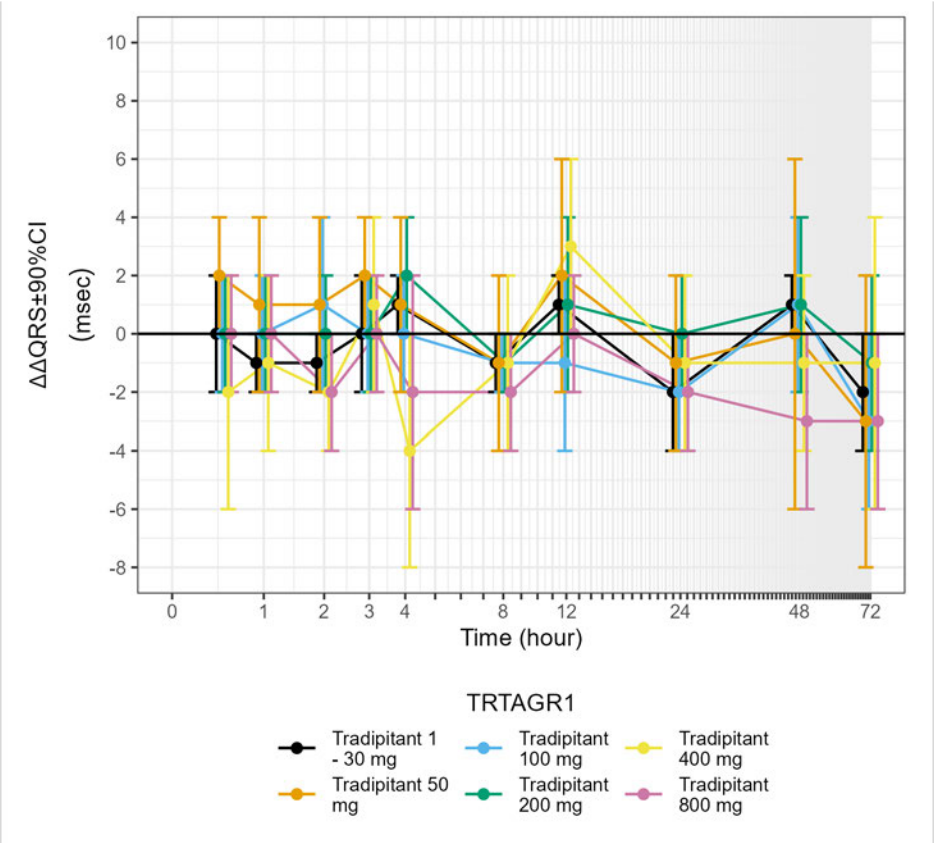
Figure 3. Mean/Median and 90% CI of ΔΔPR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups. No dose dependent changes in QRS were observed.

Figure 4. Mean/Median and 90% CI of ΔΔQRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no QTcF measurements >480 msec. Three observations of ΔQTcF > 60 msec (Placebo, Tradipitant 1 – 30 mg, and Tradipitant 400 mg).

4.4.2 HR

Maximum HR > 100 beats/min was observed for one participant receiving tradipitant 200 mg. Minimum HR beats/min was observed across dose groups, and placebo, except for tradipitant 800 mg.

4.4.3 PR

No PR values > 220 msec were observed.

4.4.4 QRS

There was a single participant (tradipitant 100 mg) that observed QRS > 120 msec but <25% at a single time-point.

4.5 EXPOSURE-RESPONSE ANALYSIS

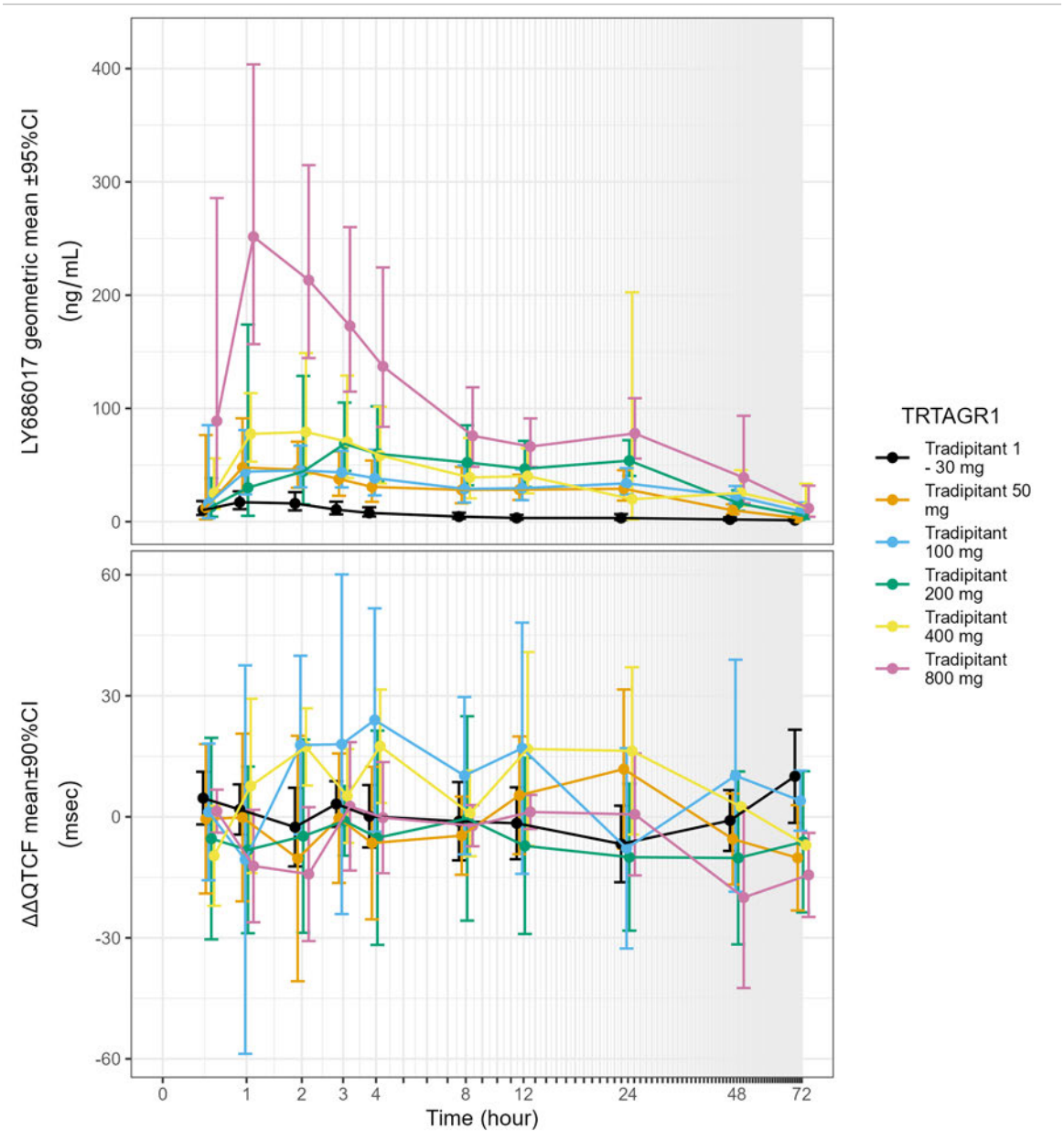
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

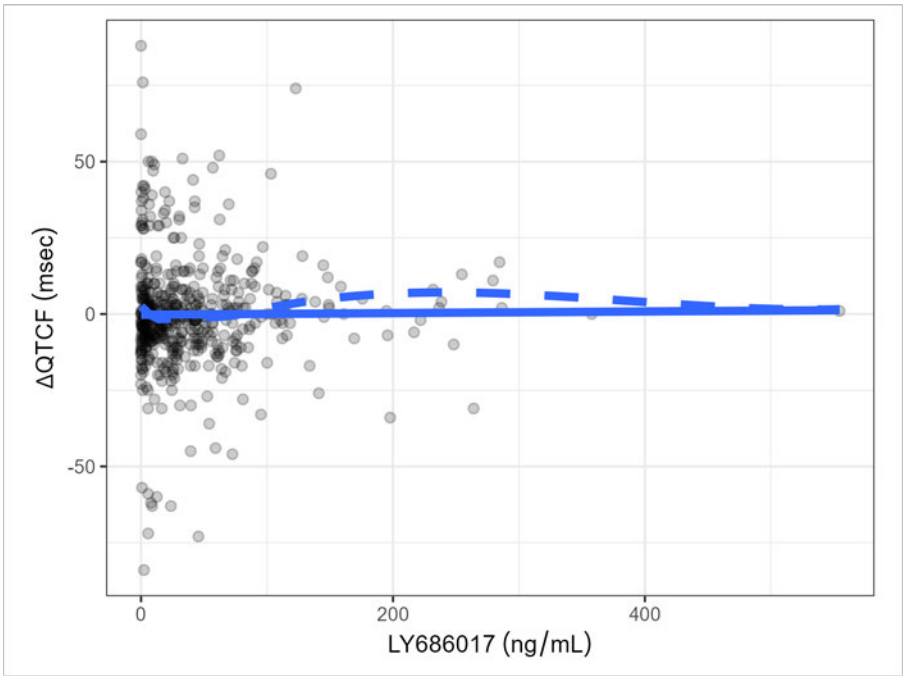
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF, and supports the use of a linear model.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 15.

Figure 7. Goodness-of-Fit Plot for QTcF

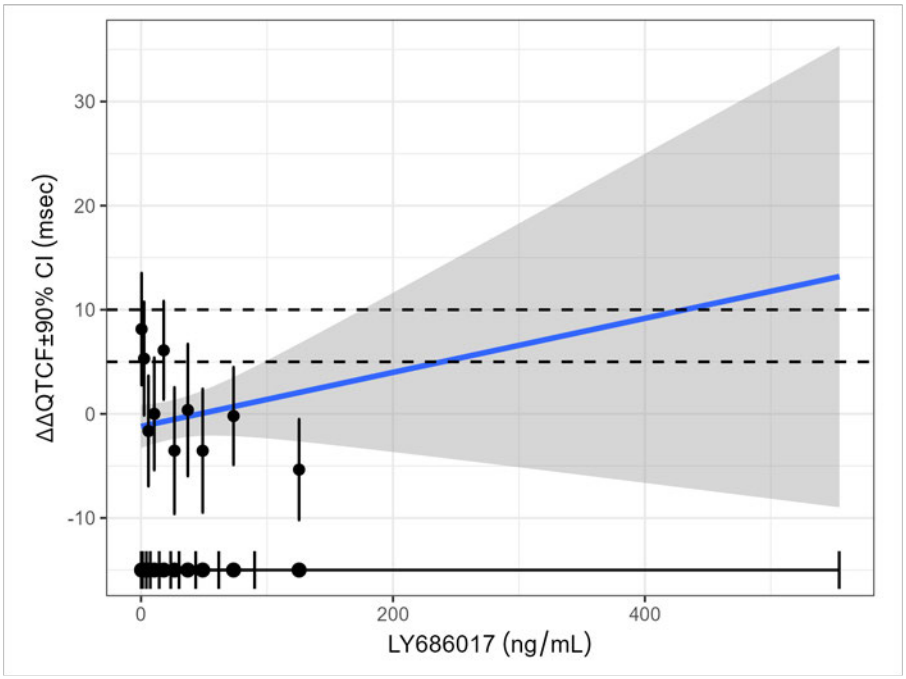


Table 3. Predictions From Concentration-QTcF Model

Actual Treatment	LY686017 (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Tradipitant 170 mg	110.5	0.6	(-1.8 to 2.9)
Single 170 mg, with strong CYP3A4 inhibition or non-functional genetic variants of CYP3A4	143	2.5	(-2.9 to 7.9)
Tradipitant 800 mg	276.6	6.0	(-4.8 to 16.7)

4.5.1.1 Assay Sensitivity

Not applicable as the study did not include a positive control.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	**ECG Quality**	**Treatments**		**Sample Size**	**ECG & PK Assessments**
		Arms	**Dose Coverage**		
Protocol Number: H8R-EW-HJAC Population: Healthy volunteers Design: Crossover	Digital: Yes Central Read? No Blinded? No Replicates? No	Highest Dose: 800 mg Placebo: Yes Positive Control: No	Above therapeutic	28	Baseline: Pre-dose baseline Timing: 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72.
Reviewer's comments: The study included 3 groups with staggered dosing (see below): - *Group 1: 1, 30, and 200 mg* - *Group 2: 3, 50, and 400 mg* - *Group 3: 10, 100, and 800 mg*					

	Period 1	Period 2	Period 3
Group 1	Placebo (n=3)	Dose 4 (n=3)	Dose 7 (n=3)
	Dose 1 (n=3)	Placebo (n=3)	Dose 7 (n=3)
	Dose 1 (n=3)	Dose 4 (n=3)	Placebo (n=3)
Group 2	Placebo (n=3)	Dose 5 (n=3)	Dose 8 (n=3)
	Dose 2 (n=3)	Placebo (n=3)	Dose 8 (n=3)
	Dose 2 (n=3)	Dose 5 (n=3)	Placebo (n=3)
Group 3	Placebo (n=3)	Dose 6 (n=3)	Dose 9 (n=3)
	Dose 3 (n=3)	Placebo (n=3)	Dose 9 (n=3)
	Dose 3 (n=3)	Dose 6 (n=3)	Placebo (n=3)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LARS JOHANNESEN
12/18/2025 02:01:26 PM

ELIFORD N KITABI
12/18/2025 02:04:59 PM

CHRISTINE E GARNETT
12/18/2025 02:29:20 PM

Clinical Inspection Summary

Date	December 16, 2025
From	Courtney McGuire, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Joshua Eisenberg, MD, Clinical Reviewer Matthew Kowalik, MD, Clinical Team Leader Mary Chung, Regulatory Project Manager Division of Gastroenterology (DG)
NDA #	220152
Applicant	Vanda Pharmaceuticals, Inc.
Drug	Tradipitant (VLY-686)
NME (Yes/No)	Yes
Therapeutic Classification	Neurokinin-1 (NK-1) receptor antagonist
Proposed Indication	Acute prevention of vomiting induced by motion in adults
Consultation Request Date	February 19, 2025
Summary Goal Date	December 22, 2025 (extended)
Action Goal Date	December 30, 2025
PDUFA Date	December 30, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Vanda Pharmaceuticals, Inc., submitted clinical data from Studies VP-VLY-686-3401 (Study 3401, NCT04327661) and VP-VLY-686-3404 (Study 3404, NCT05903924) to the Agency in support of a New Drug Application (NDA 220152) for tradipitant. The proposed indication is acute prevention of vomiting induced by motion in adults.

Three clinical investigators were inspected: Drs. Jed Kaminetsky (Studies 3401 and 3404), Sarbani Maitra (Study 3404), and Stephen Thein (Study 3401 and 3404).

The inspections of Drs. Kaminetsky and Maitra did not find significant concerns regarding the study conduct, data integrity, Good Clinical Practice (GCP), or regulatory compliance. The inspection of Dr. Thein determined that the self-reported vomiting response for Subject (b) (6) (Study 3401, tradipitant 85 mg arm) was unreliable. OSI recommends conducting a sensitivity analysis that excludes this subject to investigate the potential impact on the dose response or efficacy.

Apart from this finding, based on the results of these inspections, data generated by the inspected CIs and submitted by the Applicant, Vanda, appear verifiable in support of the proposed indication.

II. BACKGROUND

On December 30, 2024, Vanda Pharmaceuticals submitted NDA 220152 seeking approval of tradipitant for the acute prevention of vomiting induced by motion in adults. Tradipitant is an orally bioavailable neurokinin-1 (NK-1) receptor antagonist.

For this NDA, the primary evidence of safety and efficacy for tradipitant for the proposed indication was from two similarly designed phase 3 trials, Studies 3401 and 3404, and these were the focus of the BIMO GCP inspections.

Design

Studies 3401 and 3404 were phase 3, multicenter, randomized, double-blind, placebo-controlled trials. These studies investigated the efficacy and safety of a single oral dose of tradipitant (85 mg or 170 mg) for motion sickness during vehicle travel. The studies consisted of two phases: Screening (Visit 1) and Evaluation (Visits 2 and 3).

After completing screening assessments, eligible participants were randomized in a 1:1:1 ratio to receive a single dose of tradipitant 85 mg, tradipitant 170 mg, or placebo. The study drug was administered approximately 60 minutes prior to a boat trip lasting 120 to 300 minutes (Visit 2). During the boat trip and upon returning to port, subjects completed two questionnaires at 30-minute intervals: Vomiting Assessment (VA) and Nausea Assessment (NA). An assessment of sea conditions, including wave height, was required 24 to 48 hours before Visit 2. Within 7 days of travel assessment, an end of study visit (Visit 3) was conducted.

Endpoints

- *Primary Endpoint (compared to placebo):* Percentage of subjects with vomiting in tradipitant 170 mg group as assessed by the VA questionnaire*
  *Same for both Studies 3401 and 3404
- *Key secondary (*compared to placebo*):*
  Study 3401
  - Worst nausea in tradipitant 170 mg group
  - Percentage of vomiting in tradipitant 85 mg group
  - Worst nausea in tradipitant 85 mg group

Study 3404

- Percentage of subjects with vomiting in tradipitant 85 mg group
- Percentage of subjects with vomiting and severe nausea defined as worst nausea ≥ 3 on the NA in tradipitant treatment groups

Study Status
Study 3401 enrolled the following subjects across 7 study centers in US.

- Safety population: N =365
- Efficacy population: N =365

Study 3404 enrolled the following subjects across 5 study centers in US.

- Safety population: N =316
- Efficacy population: N =316

III. RESULTS

1. Dr. Jed Kaminetsky (Site 106, Study 3401; Site 103, Study 3404)
   Integrated Medical Professionals PLLC (IMP)
   145 East 32nd street, 10th floor
   New York, NY, 10016

Inspection Dates: March 26, 2025, to March 28, 2025; March 31, 2025, to April 3, 2025

This investigator was inspected as a review-based, comprehensive inspection for Studies 3401 and 3404. The last FDA inspection in December 2022 issued an Inspectional Observation for protocol non-compliance.

For Study 3401, the site screened a total of 121 subjects, of which 98 were enrolled and randomized. For Study 3404, the site screened a total of 108 subjects, of which 87 were enrolled and randomized. No subjects discontinued from either study.

The inspection reviewed subject-related paper and electronic source documents for all 185 randomized subjects in both studies consisting of informed consent forms (ICFs), eligibility worksheets, paper medical records, physician's notes, questionnaires, vital signs, IP administration records, concomitant medications, and laboratory reports.

Study-related documents reviewed for each study included: study protocols and amendments, Institutional Review Board (IRB) approvals, curriculum vitae (CV), Organizational Chart, site training records, Site Signature and Delegation Log, regulatory documents, laboratory certifications, enrollment / screening logs, investigational product (IP) receipt and accountability records, sponsor communications, monitoring records, ICFs, adverse event (AE) logs, protocol deviation logs, financial disclosures, recruitment documents, and eSystem 21 CFR 11 compliance documentation.

For verification of the primary and secondary endpoints, the inspection compared source data with data line listings (DLL) for the individual vomiting and nausea assessment responses at Baseline and at each protocol-specified timepoint. No discrepancies were found.

The inspection identified no unreported AEs. There was one minor unreported protocol deviation for an out of window visit (Study 3401, Subject (b) (6) Visit 3-End of Study Visit).

Based on the results of the inspection, data generated at Dr. Kaminetsky's site from Studies 3401 and 3404 appear to be verifiable in support of the proposed indication in the NDA.

2. Dr. Sarbani Maitra (Site 104, Study 3404)
   2516 Samaritan Drive, Suite B
   San Jose, CA 95124
   USA

Inspection Dates: April 21, 2025, to April 28, 2025

This investigator was inspected as a review-based, comprehensive inspection for Study 3404. This was the first FDA inspection for this investigator.

The site screened 116 subjects. Eighty-five subjects were randomized, dosed with IP, and completed the study. One subject was lost to follow-up and 7 withdrew from the study.

Reviewed subject-related records included ICFs for the 116 screened subjects and the following for the 85 randomized subjects: electronic medical records, laboratory reports, AEs, eligibility checklists, electrocardiogram analyses, boat trip records, patient reported outcome (PRO) questionnaires, concomitant medications, and IP administration records.

Study-related records reviewed included: the protocol and amendments, CV, Form FDA 1572s, IRB approval letters and correspondence, monitoring reports, ICFs, electronic case report forms (eCRFs), financial disclosure forms, Delegation of Authority logs, Screening and Enrollment Log, protocol deviation log, IP accountability log, laboratory certifications, and site training documentation.

For verification of the primary and secondary endpoints, the inspection compared source data with DLL for the individual vomiting and nausea assessment responses at Baseline and at each protocol-specified timepoint. No discrepancies were found.

The inspection identified no evidence of unblinding or underreporting of AEs.

There were two minor unreported protocol deviations:

1. End of Study (EOS) pregnancy serum for two subjects were administered outside of the protocol-defined window.

   Reviewer comment. The pregnancy tests were completed and negative. There was no impact on the subject safety.

2. Six subjects screened positive for cannabinoids, but the CI did not document prior recreational marijuana use as a concomitant medication (CM):

Table 1. Subjects with Positive Cannabinoid Screen and Unreported Marijuana CM

Subject ID (arm)	Protocol Version	Screening	IP Administration
(b) (6) (Tradipitant 85 mg)	Amendment 2, (11/14/2023) [1]	(b) (6)	(b) (6)
(b) (6) (placebo)	Amendment 2, (11/14/2023) [1]		
(b) (6) (tradipitant 170 mg)	Amendment 2, (11/14/2023) [1]		
(b) (6) (tradipitant 170 mg)	Amendment 2, (11/14/2023) [1]		
(b) (6) (placebo)	Amendment 2, (11/14/2023) [1]		
(b) (6) (tradipitant 170 mg)	Amendment 2, (11/14/2023) [1]		

[1]Protocol, Section 6.1, added the following language to Inclusion Criterion #10 "Note: positive test results are permitted if determined by the investigator and the medication is prescribed by a physician and used as directed."

Reviewer comment. The protocols did not include a list of the "selected" substances of abuse for Inclusion Criterion #10 and only specified marijuana as prohibited from 1 week before randomization until End of Study Visit 2. The CI documented that the subjects were willing to stop marijuana use 7 days before the trip. Overall, the lack of CM reporting appears unlikely to impact the interpretation of safety or efficacy as the subjects agreed to abstain from use 7 days prior to the boat trip.

Based on the results of the inspection, data generated at Dr. Maitra's site from Studies 3404 appear to be verifiable in support of the proposed indication in the NDA.

3. Dr. Stephen Thein (Site 109, Study 3401; Site 102, Study 3404)
   3003 Fourth Avenue
   San Diego, CA 92103
   USA

Inspection Dates: April 14, 2025, to April 25, 2025

This investigator was inspected as a review-based, comprehensive inspection for Studies 3401 and 3404. The most recent FDA inspection, conducted in June 2021, yielded no significant findings.

For Study 3401:
- The site screened a total of 135 subjects.
- 79 subjects were enrolled and randomized at the site.
- 77 subjects completed the study.

For Study 3404:
- The site screened a total of 66 subjects.
- 35 subjects were enrolled and randomized at the site.
- 34 subjects completed the study.

The inspection reviewed the following subject-related source documents for all 114 randomized subjects in both studies: source visit records (ICFs, procedures, IP administration, eligibility assessments), concomitant medications, interactive response technology confirmations, laboratory result reports, adverse events, and nausea / vomiting questionnaires.

Study-related documents reviewed for each study included: study protocols and amendments, ICFs, CV, signed investigator agreements, Institutional Review Board (IRB) approvals, Delegation and Responsibility Logs, training records, Screening and Enrollment logs, Case Report forms (eCRFs), financial disclosures, monitoring reports, and IP handling and accountability.

There was no evidence of unblinding or underreporting of AEs.

Two unreported protocol deviations were identified: subjects screened positive for cannabinoids, but the CI did not document prior recreational marijuana use as a CM (Table 2).

Table 2. Subjects with Positive Cannabinoid Screen and Unreported Marijuana CM

Subject ID (arm)	Protocol Version	Screening	IP Administration
(b) (6) (tradipitant 85 mg)	Study 3401, Amendment 2,[1] 11/7/22	(b) (6)	(b) (6)
(b) (6) (tradipitant 170 mg)	Study 3404, Original Protocol,[1] 2/14/23		

[1]Subjects screened and enrolled under protocol versions included the following pertinent language:
(1) Section 6.1, Inclusion Criterion 10 "Has negative test result for selected substances of abuse at screening."
(2) Section 7.2.1.2, Prohibited Medications from 1 Week before randomization until End of V2: Marijuana (illicit or medical).

Reviewer comment. The protocols did not include a list of the "selected" substances of abuse for Inclusion Criterion #10 and only specified marijuana as prohibited from 1 week before randomization until End of Study Visit 2. The CI documented that the subjects were willing to stop marijuana use 7 days before the trip (see Final FDA 483 Response dated 5/13/2025). Overall, the lack of CM reporting appears unlikely to impact the interpretation of safety or efficacy as the subjects agreed to abstain from use 7 days prior to the boat trip.

For verification of the primary and secondary endpoints, the inspection compared source data with DLL for the individual vomiting and nausea assessment responses at Baseline and at each protocol-specified timepoint. No discrepancies were found. However, the inspection identified one inconsistency with Subject (b) (6) questionnaire response (tradipitant 85 mg arm, Study 3401, non-responder):

- Subject (b) (6) marked "yes" on the 120-minute vomiting assessment and then withdrew consent.
- At the EOS visit, source records note the subject self-reported lying about vomiting in an effort to end the boat ride early.

Reviewer comment. The PRO response for Subject (b) (6) was unreliable. While the submitted DLL maintained the subject (from the low dose tradipitant arm) as a non-responder, OSI recommends conducting a sensitivity analysis that excludes this subject from the efficacy analysis to investigate the potential impact on the dose response or efficacy results.

The inspection identified missing documentation for several protocol-required conditions of the vehicle travel assessment. These included, but were not limited to:

- Individual participant trip information, such as assigned seat numbers and participant movement around the boat.
- Identity of personnel responsible for reminding subjects to complete questionnaires.

- Additional boat trip conditions, including boat route, boat motion parameters (e.g., heave, pitch, etc.), and degree of vertical displacement.

  Reviewer comment. The travel assessment worksheet was completed for each boat trip (i.e., rather than per individual subject) and documented trip date, travel time, peak wave height, peak wave period, average wind speed, and wind direction. The CI provided the FDA investigator with a list of subjects on each trip, derived from their trip date, allowing verification of the critical trip data for each subject. While it appears that the key efficacy data were collected, OSI defers to the Review Division regarding the potential impact of the missing trip information on the primary efficacy analysis.

With the exception of discrepancies identified in Subject (b) (6) questionnaire response, based on the results of the inspection, data generated at Dr. Thein's site from Studies 3401 and 3404 overall appear to be verifiable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division/Office Director/Nikolay Nikolov
Review Division/Division Director/Juli Tomaino
Review Division/Project Manager/Mary Chung
Review Division/Cross Discipline Team Lead/Matthew Kowalik
Review Division/Clinical Reviewer/Joshua Eisenberg
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY S MCGUIRE
12/16/2025 11:47:41 AM

MICHELE B FEDOWITZ
12/16/2025 11:49:48 AM

JENN W SELLERS
12/16/2025 11:55:15 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 4, 2025
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 220152
Product Name, Dosage Form, and Strength:	Nereus (tradipitant) capsule, 85 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Vanda Pharmaceuticals (Vanda)
FDA Received Date:	December 30, 2024 and November 7, 2025
TTT ID #:	2025-12433
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP
DMEPA 1 Associate Director for Nomenclature & Labeling:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the review process for NDA 220152 for Nereus capsule, the Division of Gastroenterology (DG) requested that we review the proposed Nereus prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Labels and Labeling	B

3 CONCLUSION AND RECOMMENDATIONS

We recommend revisions to the proposed PI, container label, and carton labeling to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Vanda Pharmaceuticals.

4 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

A. Prescribing Information

1. Prescribing Information – General issues

   a. The statement, (b) (4) lacks clarity. We defer to the review team to provide more clarity surrounding the appropriate spacing interval relative to food.

   b. As currently stated, the strength statement lacks adequate spacing between the numerical dose and unit of measure throughout the PI. Lack of adequate spacing may impact readability and might result in wrong strength errors. For example (e.g., the "m" in mg can sometimes be mistaken as a zero or two zeros). We recommend placing adequate space between the numerical dose and unit of measure (e.g., 85 mg instead of 85mg), to improve readability.

2. Highlights (HL) of Prescribing Information

   a. Recommendations to increase the readability of important product information for Highlights are noted in track changes below:

(b) (4)

3. Full Prescribing Information: Section 2 Dosage and Administration

   a. Recommendations to increase the readability and prominence of important dosage and administration within Section 2 are noted in track changes below:

(b) (4)

4. Full Prescribing Information: Section 16 How supplied/Storage and Handling

   a. Recommendations for Section 16 are noted in track changes below:

5. Full Prescribing Information: Section 17 Patient Counseling Section

   a. Recommendations for Section 17 are noted in track changes below:

5 RECOMMENDATIONS FOR VANDA PHARMACEUTICALS

Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	We note that you are proposing to market tradipitant for the acute prevention of vomiting induced by motion in adults. Additionally, we note that the container label and carton labeling contain the instructions to (b) (4) Additionally, we note you are proposing a 36 count bottle.	(b) (4)	
Container Label and Carton Labeling			
1.	The established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states *"the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features."*	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

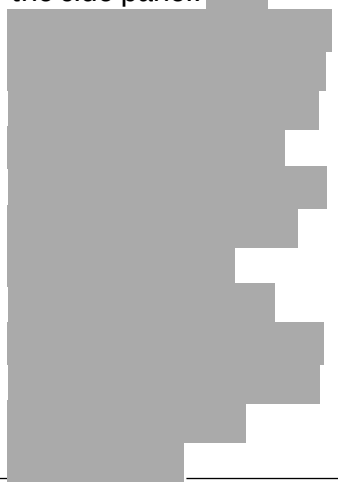
Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The strength statement lacks prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21 CFR 201.15(a)(6) which states *"a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter."*	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement).
3.	The following statements of dosage are found on the side panel: (b) (4) 	 (b) (4)	Delete the statements, (b) (4)  We recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information."

Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		may not be understood by lay users.	
4.	The placeholder for the lot number is missing.	Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1)(iii).	Add the placeholder for the lot number in accordance with 21 CFR 201.10(i)(1)(iii).
5.	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only

Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.
6.	As currently presented, the symbol "-" is used in the storage statement to represent the word "to". Additionally, each numeric value presented in the storage statement is not immediately followed by its intended units of measurement, °C or °F.	The presentation of the storage statement should be clearly stated to avoid errors.	Revise the storage statement to read, "Store at controlled room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."
7.	(b) (4)		
Container Label			
1.	The net quantity statement is overly prominent and takes the reader's attention away from critical product	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when	We recommend ensuring that the net quantity statement does not compete in size or prominence with critical

Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	information, such as the product strength.	the net quantity statement is more prominent.	information on the principal display panel. *See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[a]
2.	As currently presented, the Rx Only statement on the principal display panel (PDP) compete for prominence with important information such as the medication strength.	The Rx Only statement should not compete in size and prominence with critical information on the PDP.	We recommend ensuring that the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. *See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*[b]
3.	The intended meaning of the undefined code (b) (4) located at the bottom right-hand side of the Principal Display Panel (PDP) is not clear.	The PDP is reserved for the most important information such as the proprietary name, established name, dosage form, and strength.	Define the meaning of the undefined code (b) (4) If it is an internal code, relocate to the side panel away from lot number/expiration date and decrease its prominence.
Carton Labeling			
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product*

[a] https://www.fda.gov/media/158522/download.

[b] https://www.fda.gov/media/158522/download.

Table 2. Identified Issues and Recommendations for Vanda Pharmaceuticals (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	*Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*[c] If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

[c] https://www.fda.gov/media/116304/download.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Nereus that Vanda Pharmaceuticals submitted on December 30, 2024.

Table 3. Relevant Product Information for Nereus	
Initial Approval Date	N/A
Active Ingredient	tradipitant
Indication	acute prevention of vomiting induced by motion in adults
Route of Administration	oral
Dosage Form	capsule
Strength	85 mg
Dose and Frequency	The recommended dose is 85 mg or 170 mg. The maximum dose in a 24-hour period is 170 mg.
How Supplied	Bottle of 36
Storage	Store at controlled room temperature, 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Nereus 85 mg capsules are packaged in HDPE bottles with child-resistant closures containing aluminum foil-lined induction seals.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects analysis,[d] along with postmarket medication error experiences with similar products, we reviewed the following Nereus labels and labeling submitted by Vanda Pharmaceuticals.

- Container label received on November 7, 2025
- Carton labeling received on November 7, 2025
- Prescribing Information (Image not shown) received on December 30, 2024, available from \\CDSESUB1\EVSPROD\nda220152\0001\m1\us\draft-labeling-text.doc

B.2 Label and Labeling Images

Container label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
12/04/2025 04:35:43 PM

DAMON A BIRKEMEIER
12/05/2025 08:44:39 AM

IDALIA E RYCHLIK
12/05/2025 11:56:26 AM