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RESEARCH**

APPLICATION NUMBER:

220152Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	220152
Priority or standard	STANDARD
Submit date(s)	12/30/2024
Received date(s)	12/30/2024
PDUFA goal date	12/30/2025
Division/office	Division of Gastroenterology (DG)
Review completion date	12/30/2025
Established/proper name	Tradipitant
(Proposed) proprietary name	NEREUS
Pharmacologic class	Substance P/neurokinin-1 (NK-1) receptor antagonist
Other product name(s)	Tradipitant
Applicant	Vanda Pharmaceuticals Inc.
Dosage form(s)/formulation(s)	Capsule
Dosing regimen	85 mg or 170 mg as a single oral dose approximately 60 minutes before an event expected to cause vomiting induced by motion. The safety of NEREUS for the prevention of vomiting induced by motion in adults for more than 90 doses has not been established in clinical trials. The maximum dosage in a 24-hour period is 85 mg or 170 mg. Administer on an empty stomach, at least 1 hour prior to or 2 hours after a full meal.
Applicant-proposed indication(s)/population(s)	Acute prevention of vomiting induced by motion
SNOMED CT code for proposed indication disease term(s)¹	37031009 [Motion sickness (finding)]
Regulatory action	Approval
Approved dosage (if applicable)	85 mg or 170 mg as a single oral dose approximately 60 minutes before an event expected to cause vomiting induced by motion. The safety of NEREUS for the prevention of vomiting induced by motion in adults for more than 90 doses has not been established in clinical trials. The maximum dosage in a 24-hour period is a single dose of 85 mg or 170 mg. Administer on an empty stomach, at least 1 hour prior to or 2 hours after a full meal.
Approved indication(s)/population(s) (if applicable)	The prevention of vomiting induced by motion in adults.
SNOMED CT code for approved indication disease term(s)¹	No SNOMED CT exists for vomiting induced by motion

¹ For internal tracking purposes only. The existing SNOMED CT code for "motion sickness" is not appropriate to describe the indication recommended for approval.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADSL	ADaM Subject-Level Analysis
AE	adverse event
AI	acceptable intake
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CL/F	apparent clearance
C _{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CSS	Controlled Substance Staff
CT	computed tomography
CU	CASE Ultra
CTCS	Computational Toxicology Consultation Service
CYP	cytochrome P450
DDI	drug-drug interaction
DPMH	Division of Pediatrics and Maternal Health
ECG	electrocardiogram
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GABA _A	gamma-aminobutyric acid type A receptor
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HED	human equivalent dose
HEK	human embryonic kidney
hERG	human ether-a-go-go-related gene
IC ₅₀	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IND	investigational new drug
IRT/IWRS	Interactive Response Technology/Interactive Web Response System
ITT	intent-to-treat
IV	intravenous
IVIVE	in vitro to in vivo extrapolation
K _i	inhibitory constant
KIM	kidney injury molecule-1
LC-MS/MS	liquid chromatographic separation with tandem mass spectrometry
LMA	Leadscope Model Applier
LS	least squares
MPS	microphysiological system

NDA 220152
NEREUS (tradipitant)

MSAQ	Motion Sickness Assessment Questionnaire
MSEQ	Motion Sickness Eligibility Questionnaire
MSSS	Motion Sickness Severity Scale
NA	nausea assessment
NAM	new approach methodology
NDA	new drug application
NK-1	neurokinin-1
NMT	not more than
NOAEL	no-observed-adverse-effect level
OPQ	Office of Pharmaceutical Quality
PET	positron emission tomography
PGI-S	Patient Global Impression of Severity Questionnaire
PI	Prescribing Information
PK	pharmacokinetic
PMC	postmarketing commitment
PP	per-protocol
PPND	pre- and postnatal development
Q12H	every 12 hours
QT	time from the start of the Q wave to the end of the T wave
QTc	QT interval adjusted for heart rate
QTcB	QT interval adjusted for heart rate using Bazett's formula
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
t _{1/2}	elimination half-life
TBOB	t-butyl bicycloorthobenzoate
TEAE	treatment-emergent adverse event
(b) (4)	(b) (4)
T _{max}	time to maximum concentration
TQT	thorough QT
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
VA	vomiting assessment
WoE	Weight of Evidence

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On December 30, 2024, Vanda Pharmaceuticals (“the Applicant”) submitted a new drug application (NDA) 220152 for tradipitant 85-mg oral capsules under the 505(b)(1) regulatory pathway. The Applicant’s proposed indication is the “acute prevention of vomiting induced by motion in adults.” At the time of this review, tradipitant was not approved for marketing in any country.

The Applicant conducted two phase 3 randomized, double-blind, placebo-controlled trials, VP-VLY-686-3401 (Trial 3401) and VP-3404 (Trial 3404). The submission also contained data from a phase 2 randomized, double-blind, placebo-controlled trial, VP-VLY-686-2401 (Trial 2401), and interim data from an ongoing phase 3 open-label, uncontrolled trial, VP-VLY-686-3403 (Trial 3403). Trials 3401 and 3404 evaluated the safety and efficacy of a single dose of tradipitant for the prevention of vomiting induced by motion. Trial 3403 evaluated as needed administration of tradipitant for the prevention of vomiting induced by motion. The data from Trial 3403, the only repeat-dosage trial, was limited to a maximum of 90 dosing days over the course of the 12-month trial. The Applicant did not have adequate nonclinical safety data to support more than 90 dosing days in a clinical trial. As a result, at the time of submission of the NDA, Trial 3403 was on partial clinical hold as there was insufficient information to assess risks to humans beyond 90 dosing days.

The primary endpoint of Trials 3401 and 3404 was the percentage of subjects who vomited during the vehicle travel event in the tradipitant 170-mg treatment arm as compared to placebo. In Trial 3401, there was a statistically significantly lower percentage of subjects who vomited in the tradipitant 170-mg treatment arm compared to placebo (risk difference [95% CI], -25.9% [-37.1, -14.7], $p < 0.0001$). The percentage of subjects who vomited during the vehicle travel event in the tradipitant 85-mg treatment arm was a secondary endpoint and was nominally significant (risk difference [95% CI], -24.9 [-36.0, -13.9], $p < 0.0001$).¹ Additional secondary endpoints for other symptoms of motion sickness (e.g., worst nausea severity, Motion Sickness Assessment Questionnaire [MSAQ], Motion Sickness Severity Scale [MSSS]) were not statistically significant. In Trial 3404, there was a statistically significantly lower percentage of subjects who vomited in the tradipitant 170-mg treatment arm compared to placebo (risk difference [95% CI], -27.4% [-38.3, -16.5], $p < 0.0001$). The percentage of subjects who vomited during the vehicle travel event in the tradipitant 85-mg treatment arm was a secondary endpoint and was also statistically significant (risk difference [95% CI], -19.5 [-31.3, -7.6], $p = 0.0025$). Similar to

¹ In the prespecified multiple-testing procedure, the Applicant tested the secondary endpoint of worst nausea severity during the vehicle travel event in the 170-mg tradipitant arm, after the primary endpoint. For this endpoint, the 170-mg tradipitant arm was not statistically significantly different than placebo. Thus, according to the multiple-testing procedure, other endpoints tested after this endpoint are not considered statistically significant due to a lack of type I error control.

Trial 3401, additional secondary endpoints for other symptoms of motion sickness (e.g., worst nausea severity, MSAQ, MSSS) were not statistically significant.

Safety data from the single-dose, placebo-controlled Trials 3401 and 3404 adequately characterized the safety of a single dose of tradipitant for the prevention of vomiting induced by motion. There were no serious adverse events (SAEs) or adverse events (AEs) that led to discontinuation reported for Trials 3401 and 3404. The most common AEs were somnolence, fatigue, and headache for both 170-mg tradipitant and 85-mg tradipitant treatment arms in a dose-dependent manner. The only source of repeat-dose safety information for the proposed intended use was from Trial 3403; however, the data for Trial 3403 submitted to the NDA were limited to a maximum of 90 dosing days over the course of the 12-month trial. Additionally, although subjects were eligible to use tradipitant for up to 90 dosing days, the majority of subjects used tradipitant for 30 dosing days or fewer (170-mg tradipitant 67.2% [123/183], 85-mg tradipitant 67.8% [135/199]). Overall, the most common adverse events in Trial 3403 were similar to those in the single-dose trials; however, limitations in the design of Trial 3403 (e.g., variability in the timing and frequency of tradipitant administration, infrequent follow-up visits [i.e., every 4 months], subject e-diaries lacking questions about adverse events, lack of a comparator arm) resulted in uncertainty attributing the causality of adverse events to tradipitant versus other factors, as well as an increased likelihood that adverse events were under-reported.

The Applicant also submitted safety data from trials conducted in subjects with gastroparesis; however, the dosage used (i.e., 85 mg twice daily [BID]) and the patient population differ from the proposed dosage and intended use population for the prevention of vomiting induced by motion. Notably, clinical trials in gastroparesis have been limited to 12 weeks in duration. Additionally, these trials include placebo-controlled data from a phase 2 trial over a 4-week period in 64 subjects and from a phase 3 trial over a 12-week period in 74 subjects, while the remaining data are uncontrolled and from either open-label studies² or individual patient expanded access protocols. Therefore, although the safety data from subjects with gastroparesis were considered, these data do not provide information that characterizes safety of tradipitant for use beyond 90 days, and do not address the limitations of the available safety information for the prevention of vomiting induced by motion.

To support the marketing of tradipitant for the prevention of vomiting induced by motion, the Applicant conducted a battery of nonclinical tests with tradipitant, including pharmacology, safety pharmacology, pharmacokinetic (PK), general toxicology, reproductive toxicology, and carcinogenicity studies. In addition, the Applicant conducted five human cell-based in vitro safety pharmacology studies and two special toxicology studies using alternative assays, also referred to as new approach methodologies (NAMs). At the time of the NDA submission, general toxicity studies with tradipitant included studies of up to 6 months in rats and up to 3 months in dogs. Because vomiting induced by motion is a condition that is expected to recur repeatedly each time the motion stimulus is present, the Division had previously recommended that the Applicant conduct a chronic (e.g., ≥ 6 -month) toxicity study in a nonrodent species to adequately assess the risk of cumulative toxicity following repeated short-term exposures to tradipitant and, thus, support the safety of unrestricted use of tradipitant over a lifetime, for the

² The phase 2 trial had an 8-week open-label treatment period for a total treatment duration of 12 weeks. The phase 3 trial had a separate open-label treatment single arm with a treatment duration of 12 weeks.

indication of the prevention of vomiting induced by motion.³ Based on the review team's experience as well as the team's understanding of the scientific literature regarding the utility of toxicology studies to support the safety of human drug products, the recommended nonclinical data (i.e., a 6-month toxicity study in rodents and a ≥ 6 -month toxicity study in a nonrodent species) are the most appropriate to support the safety of drug products used over a person's lifetime, such as tradipitant for the prevention of vomiting induced by motion. However, the Applicant did not submit a ≥ 6 -month toxicity study in a nonrodent species and did not provide sufficient scientific justification for why such a study was not warranted to support the safety of unrestricted use of tradipitant over a lifetime for this indication. Importantly, the relatively long half-life of tradipitant and its major human metabolites (i.e., ≥ 28 hours) supports that even single doses spaced days apart could lead to sustained exposure to and even accumulation of tradipitant. Moreover, the unrestricted use of tradipitant over a lifetime for the prevention of vomiting induced by motion could expose some individuals to levels of tradipitant over a duration of use that do not have adequate nonclinical assessment of the toxicological risks (see Section 7.7). Thus, there is insufficient nonclinical information to adequately characterize the safety of unrestricted use of tradipitant over a lifetime in human subjects, and, therefore, the available nonclinical data do not support that tradipitant should be considered safe for unrestricted use. The review team identified that the limitations of the nonclinical data were an approvability issue.⁴

The review team considered the nature of vomiting induced by motion (i.e., generally a self-limited condition characterized by acute episodes that are predictable, infrequent, and in many cases avoidable) and that clinical use would likely mirror the infrequent use observed in Trial 3403 (e.g., the majority of patients did not use more than 2 consecutive doses, the median exposure was 15 and 18 doses over 12 months for the 85-mg arm and 170-mg arm, respectively, the vast majority of subjects did not approach the 90 dose maximum over the 12 month trial duration).⁵ Given that vomiting induced by motion is expected to recur and may result in repeat administrations of tradipitant on multiple occasions over a lifetime of an individual, the team also considered the limitations and the uncertainties of the available safety information that could inform unrestricted use of tradipitant. Based on these considerations, the review team determined that a favorable risk-benefit assessment may be supported for the prevention of vomiting induced by motion in adults provided the limitations of the safety data could be adequately communicated in the label to ensure the safe use of the product. The originally proposed product labeling was modified to describe the upper limit beyond which safety has not been established (i.e., more than 90 doses). The clinical review team expects that stating that safety has not been established for more than 90 total doses will adequately inform prescribers of the safe use of the drug according to the recommended dosage and administration described in the label. This

³ IND 141315: Advice Letter dated February 28, 2023.

⁴ The review team had extensive discussions regarding whether the application should be filed, based on the concern that the submitted nonclinical information was incomplete for the proposed indication due to the lack of a nonrodent toxicity study of ≥ 6 months duration. Although the absence of the nonrodent toxicity study of ≥ 6 months duration could be considered a deficiency that results in refusing to file an application, the review team determined that the proposed indication (i.e., prevention of vomiting induced by motion, a condition that is induced by an external stimulus with no symptoms in the absence of the stimulus) warranted review of the application to determine whether the available data are adequate to characterize the safety of tradipitant for the proposed indication and to inform potential labeling recommendations.

⁵ See Section [7.6.2.1](#) for additional details.

description of the limitations of the available safety data for more than 90 total doses was supported by the safety data from tradipitant clinical trials in the intended use population and other populations, which were limited to 90 dosing days or daily dosing for up to 12 weeks. Therefore, the benefits of tradipitant for this indication outweigh the risks when used according to the recommended dosage and administration.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

- VP-VLY-686-3401 (Trial 3401): A multicenter, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of a single dose of tradipitant 85 mg or 170 mg in subjects with a history of motion sickness. Subjects (N=365) were randomized 1:1:1 to tradipitant 85 mg (n=123), tradipitant 170 mg (n=120), or placebo (n=122). Subjects were administered the investigational product approximately 60 minutes before a planned vehicle travel event via a boat. During the vehicle travel event, subjects completed nausea and vomiting questionnaires every 30 minutes, and additional assessments were performed at the end of the travel event. The primary endpoint was the percentage of subjects with vomiting during the vehicle travel event in the tradipitant 170-mg treatment arm. The percentage of subjects with vomiting during the vehicle travel event in the tradipitant 85-mg treatment arm was a secondary endpoint. The results showed a statistically significant reduction in the percentage of subjects with vomiting in the 170 mg treatment arm (18.3% vs. 44.3%; risk difference [95% CI] -25.9% [-37.1%, -14.7%], $p < 0.0001$) and a nominally significant reduction in the 85 mg treatment arm (19.5% vs. 44.3%; risk difference [95% CI] -24.9% [-36.0%, -13.9%], $p < 0.0001$). These results support the efficacy of tradipitant for the proposed indication.
- VP-VLY-686-3404 (Trial 3404): Trial 3404 was nearly identical to Trial 3401. Trial 3404 was a multicenter, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of a single dose of tradipitant 85 mg or 170 mg in subjects with a history of motion sickness. Subjects (N=316) were randomized 1:1:1 to tradipitant 85 mg (n=104), tradipitant 170 mg (n=106), or placebo (n=106). Subjects were administered the investigational product approximately 60 minutes before a planned vehicle travel event via a boat. During the vehicle travel event, subjects completed nausea and vomiting questionnaires every 30 minutes, and additional assessments were performed at the end of the travel event. The primary endpoint was the percentage of subjects with vomiting during the vehicle travel event in the tradipitant 170-mg treatment arm. The percentage of subjects with vomiting during the vehicle travel event in the tradipitant 85-mg treatment arm was a secondary endpoint. The results showed a statistically significant reduction in the percentage of subjects with vomiting in the 170 mg treatment arm (10.4% vs. 37.7%; risk difference [95% CI] 27.4% [-38.3%, -16.5%], $p < 0.0001$) and in the 85 mg treatment arm (18.3% vs. 37.7%; risk difference [95% CI] -19.5% [-31.3%, -7.6%], $p = 0.0025$). These results support the efficacy of tradipitant for the proposed indication.

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Trials 3401 and 3404 were two adequate and well-controlled clinical investigations assessing a single dose of tradipitant prior to a travel event that provide SEE to support the approval of tradipitant for the proposed indication of prevention of vomiting induced by motion in adults.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Some individuals are at risk for developing vomiting induced by motion. - In affected individuals, symptoms are typically triggered by lateral and vertical motion (e.g., travel by sea, virtual simulator motion), which signal afferents from the vestibular apparatus, visual system, and proprioceptive systems to trigger the vestibular nuclei of the brainstem. In response, efferent projections to multiple brain and brainstem regions trigger autonomic reactions and the “vomiting center,” leading to vomiting. - Vomiting induced by motion is one manifestation of the complex and multisystem disorder commonly referred to as “motion sickness.” Other signs and symptoms may include nausea, confusion, fatigue, dizziness, malaise, headache, pallor, and diaphoresis. - Vomiting induced by motion is expected to recur in susceptible individuals upon reintroduction of the triggering motion stimulus. - Vomiting induced by motion may have significant impacts on quality of life and the ability to perform tasks during or following the motion event. - Previously affected or susceptible individuals often seek treatment to prevent the occurrence of these symptoms prior to onset or prior to encountering an inducing event.	Vomiting induced by motion is one of several heterogenous symptoms of motion sickness. The underlying etiology and pathophysiology of vomiting induced by motion is multifactorial and not well understood. Vomiting induced by motion is expected to recur with repeat exposure to a triggering motion stimulus.
Current treatment options	- Behavioral modifications may be used to manage symptoms of nausea and vomiting induced by motion, including avoidance of triggering travel events, positional changes (e.g., sitting in the front seat of a car), avoiding conflicts between vestibular and visual cues (e.g., reading), habituation, and distraction techniques. - There are several prescription products (i.e., Phenergan and Transderm Scop) and therapies available over-the-counter for the prevention and treatment of the nausea, vomiting, or dizziness associated with motion sickness, including cyclizine hydrochloride,	There are several behavioral modifications and medications available for the prevention of vomiting induced by motion. Medications are commonly associated with adverse reactions that include drowsiness, fatigue, and dizziness.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dimenhydrinate, diphenhydramine hydrochloride, and meclizine hydrochloride. Available medical therapies are commonly associated with a risk of drowsiness, fatigue, and dizziness, which is attributed to their anticholinergic and/or antihistaminergic mechanisms of action.	
Benefit	- Trials 3401 and 3404 demonstrated substantial evidence of effectiveness for a single dose of tradipitant for the prevention of vomiting induced by motion. - In Trial 3401, a statistically significantly lower percentage of subjects who vomited in the tradipitant 170-mg arm versus placebo (risk difference [95% CI], -25.9% [-37.1, -14.7], $p < 0.0001$). A nominally significantly lower percentage of subjects who vomited in the tradipitant 85-mg arm versus placebo (risk difference [95% CI], -24.9 [-36.0, -13.9], $p < 0.0001$).¹ - In Trial 3404, a statistically significantly lower percentage of subjects who vomited in the tradipitant 170-mg arm versus placebo (risk difference [95% CI], -27.4% [-38.3, -16.5], $p < 0.0001$), and in the tradipitant 85-mg arm versus placebo (risk difference [95% CI], -19.5 [-31.3, -7.6], $p = 0.0025$). - Trials 3401 and 3404 did not demonstrate substantial evidence of effectiveness for tradipitant for prevention of nausea induced by motion. - In Trial 3401, there was no nominally statistically significant difference between subjects' worst nausea scores in either tradipitant arm versus placebo. The worst nausea scores were similar among the treatment arms (difference in LS means [95% CI], tradipitant 85 mg: 0.04 [-0.27, 0.36], $p = 0.7913$; tradipitant 170 mg: -0.08 [-0.40, 0.24], $p = 0.6110$). - In Trial 3404, there was no nominally statistically significant difference between subjects' worst nausea scores in either tradipitant arm versus placebo. The worst nausea scores were similar among the treatment arms (difference in LS means [95% CI], tradipitant 85 mg: 0.13 [-0.21, 0.47], $p = 0.4568$, tradipitant 170 mg -0.23 [-0.57, 0.10], $p = 0.1755$).	In Trials 3401 and 3404, in which subjects received a single dose of tradipitant 85 mg or 170 mg, there was a statistically significant reduction in the proportion of subjects who vomited in the tradipitant 170-mg arms compared to the placebo arms. There was a nominally significant reduction in the proportion of subjects who vomited in the tradipitant 85-mg arm compared to placebo in Trial 3401 and a statistically significant reduction in the proportion of subjects who vomited in the tradipitant 85-mg arm compared to placebo in Trial 3404. There were no statistically significant differences between the tradipitant treatment arms and placebo for endpoints related to the prevention of nausea. There were no prespecified statistical comparisons between the 170-mg treatment arm and the 85-mg treatment arm; however, the treatment effect of each dose arm versus placebo was generally similar with a small numerical decrease in the percentage of subjects with vomiting in the 170-mg arm. The following postmarketing requirements will be issued under PREA: - A pharmacokinetic study of an age-appropriate formulation of tradipitant - A randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of tradipitant in pediatric patients 2 to <18 years of age with a history of motion sickness

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There are no data in pediatric subjects. Tradipitant is a new molecular entity and the requirements under the Pediatric Research Equity Act (PREA) are applicable. The Applicant's request for a partial waiver for pediatric patients 0 to less than 2 years of age and a deferral for pediatric patients 2 to less than 18 years of age is granted.	
Risk and risk management	- The clinical safety database included: - Single-dose placebo-controlled data from Trials 2401, 3401, and 3404 - Repeat-dose open-label data from Trial 3403 for up to 90 doses per subject over the trial duration - Additional data from trials for other indications, including gastroparesis, (b) (4), and atopic dermatitis. - Safety data from trials conducted in the intended use population (i.e., otherwise healthy individuals with a history of motion sickness) were considered most relevant, as they specifically assessed prevention of vomiting induced by motion in a cohort with few underlying comorbidities and concomitant medications that could confound the interpretation of safety data. - There were no deaths, serious treatment-emergent adverse events, or adverse events that led to study discontinuation in the single-dose placebo-controlled trials. - Adverse events occurring in ≥5% of subjects who received tradipitant 85 mg or 170 mg and greater than placebo in the single-dosage trials (Trials 2401, 3401, and 3404) were somnolence, headache, and fatigue. - In the pooled tradipitant 85-mg arms compared to placebo (Trials 3401 and 3404), there were higher rates of somnolence (6.2% vs. 3.9%; risk difference 2.3%), headache (7.0% vs. 5.3%; risk difference 1.7%), and fatigue (6.2% vs. 2.6%; risk difference 3.6%). - In the pooled tradipitant 170-mg arms compared to placebo (Trials 2401, 3401, and 3404), there were higher rates of somnolence (12.5% vs. 5.8%; risk difference 6.7%), headache (9.7% vs. 5.8%; risk difference 3.9%), and fatigue (8.3% vs. 2.1%; risk difference 6.2%).	The clinical safety database included clinical trial data from three single-dose placebo-controlled trials (i.e., one phase 2 trial [Trial 2401] and two phase 3 trials [Trials 3401 and 3404]), one phase 3 open-label repeat-dose trial (Trial 3403), and trials for indications other than vomiting induced by motion. There are no clinical trials that exceed 12 weeks of daily dosing or a total of 90 dosing days in duration to inform the safety of use beyond 90 dosing days. - Among subjects in single-dose placebo-controlled trials assessing the prevention of vomiting induced by motion, there were no deaths or serious treatment-emergent adverse events. The adverse events that occurred most commonly and at higher rates in tradipitant arms than in placebo arms were somnolence, headache, and fatigue. These occurred at higher rates in the tradipitant 170 mg arms compared to the 85-mg arms. - There are no controlled safety assessments of repeated doses of tradipitant for this indication. There was one open-label, uncontrolled repeat-dose trial, wherein subjects were permitted no more than 90 dosing days. The safety results were similar to the single-dose, placebo-controlled trials. However, the results of this trial are challenging to interpret due to multiple factors including but not limited to infrequent safety assessments, lack of a comparator, and variability of the timing of drug administration. Additionally, the majority of subjects did not receive more than 30 doses during the trial and consecutive use was rare.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- These adverse events overlap with symptoms of motion sickness, which may present with a variety of symptoms (e.g., belching, diaphoresis, dizziness, headache, fatigue, and somnolence); however, these adverse events were reasonably likely to be related to tradipitant, as they occurred more frequently in the tradipitant arms than in the placebo arms consistently across trials. - The clinical safety results from Trial 3403 are limited by several factors, including but not limited to, infrequent exposure that was limited to a maximum of 90 doses over 12 months, variability in the timing of tradipitant administration, type and duration of travel event, infrequent safety assessments, and lack of a comparator. Overall, the adverse events reported in Trial 3403 were similar to the placebo-controlled trials and no new safety signals were identified. - Notwithstanding the limitations of Trial 3403, subjects appeared to use tradipitant infrequently, as greater than two-thirds of subjects used tradipitant for 30 days or fewer (69.6% in the 85 mg arm; 68.0% in the 170 mg arm), and greater than three-quarters of subjects reported a maximum consecutive days of use of 1 to 2 days (80.9% in the 85-mg arm; 76.0% in the 170-mg arm). - While vomiting induced by motion is an intermittent condition, it is expected to recur with repeated exposures to triggering stimuli in individuals who are susceptible to motion sickness. This underscores the importance of characterizing the safety related to repeated exposures for this indication. - The Applicant did not submit a ≥6-month toxicity study in a nonrodent species and did not provide sufficient scientific justification for why such a study is not warranted to support the safety of unrestricted use of tradipitant over a lifetime for this indication. The relatively long half-life of tradipitant and its major human metabolites (28+ hours) supports that even single doses spaced days apart could lead to sustained exposure to and even accumulation of tradipitant. Moreover, the unrestricted use of tradipitant over a lifetime for the prevention of vomiting due to motion would expose some individuals to physiological levels of tradipitant over a duration of use that do not have adequate nonclinical assessment of the toxicological risks. Thus, the	Taken together, the safety of more than 90 doses of tradipitant has not been established in clinical trials. In addition to the limitations of the clinical safety data described above, the nonclinical data are insufficient to support the safety of unrestricted use of tradipitant. Based on the available safety data, the label will communicate the upper limit beyond which safety has not been established to adequately inform prescribers of the safe use of tradipitant. The clinical review team expects that stating that safety has not been established for more than 90 total doses will adequately inform prescribers of the safe use of the drug according to the recommended dosage and administration described in the label. Therefore, the benefits of tradipitant for the indication of the prevention of vomiting induced by motion outweigh the risks when used according to the recommended dosage and administration. The overall benefit-risk assessment supports approval of both 85 mg and 170 mg doses. The labeling will recommend that patients receive the lowest effective dose (i.e., 85 mg) as a dose-dependent increase in adverse events was observed in subjects who received the 170 mg dose. Since somnolence and fatigue occurred at higher rates in subjects who received tradipitant compared to placebo, a warning and precaution will be included in labeling regarding the potential affect on a patient's ability to drive or operate machinery. The potential risk of QT prolongation has not been adequately assessed in the fed state, which is associated with a higher tradipitant exposure; therefore, tradipitant should be taken without food. The Applicant has agreed to conduct a thorough QT study to evaluate the effect of tradipitant on QT prolongation in the fed state.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nonclinical data submitted are insufficient to adequately characterize the safety of tradipitant for the originally proposed conditions of use and, therefore, do not support that tradipitant should be considered safe for unrestricted use over a lifetime. • In lieu of a TQT study to characterize the potential risk of QT prolongation due to tradipitant, the Applicant submitted an integrated summary of cardiac safety that included data from studies conducted in healthy subjects (Trials H8R-EW-HJAC and VP-VLY-686-1102) and subjects with gastroparesis (Trials 2301 and 3301). The data provided did not cover the high-exposure scenario (i.e., a 4.7-fold increase in C_{max} for the 85 mg dose and 7.0-fold increase in C_{max} for the 170 mg dose due to the effect of food). However, the data supported that tradipitant did not cause clinically relevant QTc prolongation when administered without food. The proposed labeling will specify tradipitant should be administered without food. • The available data are insufficient to inform tradipitant-associated risk during pregnancy and lactation. • The available data are insufficient to inform tradipitant-associated risk in patients with hepatic impairment, severe renal impairment, and potential drug-drug interactions.	The following postmarketing requirements will be issued under 505(o): • A lactation study • Pregnancy registry, both prospective and retrospective studies. The following postmarketing commitments will be issued: • A clinical pharmacology study to evaluate the effects of hepatic impairment on the PK of tradipitant and its major metabolites • A clinical pharmacology study to evaluate the effects of severe renal impairment on the PK of tradipitant and its major metabolites • An in vitro assessment(s) to evaluate the contribution of all major CYP enzymes to the overall metabolism of tradipitant and its active metabolites, and to assess the relative contribution of specific CYP enzymes to tradipitant metabolism. The in vitro study results will determine the need for a subsequent clinical drug-drug interaction study(ies).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; C_{max} , maximum plasma concentration; DILI, drug-induced liver injury; LS, least squares; n, number; QT, time from the start of the Q wave to the end of the T wave; TQT, thorough QT

2.2. Conclusions Regarding Benefit-Risk

The data submitted in the NDA demonstrated a favorable benefit-risk profile for the indication of the prevention of vomiting induced by motion in adults with a description that the safety of more than 90 total doses has not been established. Vomiting induced by motion is one of several heterogeneous symptoms of motion sickness. Motion sickness is a generally self-limited condition characterized by episodes of symptoms associated with motion, which are generally predictable, and in many cases, avoidable. Vomiting induced by motion is expected to recur in susceptible individuals upon repeat exposure to motion; however, in most individuals, travel events that are anticipated to cause vomiting induced by motion that require preventative treatment are infrequent, as supported by the tradipitant use data from the repeat-dose trial, Trial 3403, in which tradipitant was administered on an as-needed basis.

Two adequate and well-controlled single-dose trials (Trials 3401 and 3404) provided substantial evidence of effectiveness, showing statistically significant reductions in the proportion of subjects with vomiting compared to placebo for the tradipitant 170-mg arms, a nominally significant reduction in the proportion of subjects who vomited in the tradipitant 85-mg arm compared to placebo in Trial 3401, and a statistically significant reduction in the proportion of subjects who vomited in the tradipitant 85-mg arm compared to placebo in Trial 3404. Notably, while tradipitant was effective in preventing vomiting induced by motion, it did not demonstrate efficacy for the prevention of nausea induced by motion. Thus, the indication of “prevention of vomiting induced by motion” is appropriate based on the trial results. In addition, the results of the worst nausea score secondary endpoint are included in the label to inform prescribers of the lack of efficacy for the prevention of nausea induced by motion as nausea is a common symptom of motion sickness.

The safety of tradipitant for the prevention of vomiting induced by motion was primarily informed by the results of the randomized, double-blind, placebo-controlled, single-dose trials (Trials 2401, 2401, and 3404). The most common adverse reactions in these trials were somnolence, headache, and fatigue. There were no notable serious adverse events, adverse events that led to discontinuation, laboratory abnormalities, or vital sign changes; however, the trials evaluated only a single dose of tradipitant. Safety information for repeated administration of tradipitant in the intended use population was provided by the open-label, repeat-dose, as needed trial, Trial 3403. Overall, the adverse events reported during Trial 3403 were similar to those of Trials 3401 and 3404; however, the interpretation of the safety information from the trial was limited by several factors (e.g., infrequent safety assessments, variability in timing/frequency of tradipitant administration, lack of a comparator arm). The Applicant also submitted safety data from trials conducted in unapproved populations, which included up to 85 mg twice daily for 12 weeks. The available clinical safety data submitted to the application were limited to 90 dosing days or 12 weeks because, at the time of the NDA submission, clinical trials with a longer duration were on partial clinical hold. The nonclinical data remained insufficient in this NDA submission. The Applicant did not submit sufficient nonclinical data to support unrestricted use of tradipitant over a lifetime. Additionally, the relatively long half-life of tradipitant and its major human metabolites (i.e., ≥ 28 hours) supports that even single doses spaced days apart could lead to sustained exposure to and even accumulation of tradipitant. Furthermore, the unrestricted use of tradipitant over a lifetime for the prevention of vomiting due to motion would expose some individuals to levels of tradipitant over a duration of use that does not have adequate nonclinical

assessment of the toxicological risks (see Section 7.7). Therefore, the available nonclinical data do not support that tradipitant is safe for unrestricted use over a lifetime.

Based on the available safety data, tradipitant is recommended for approval with a description in the label that the safety of tradipitant has not been established for more than 90 total doses to adequately inform prescribers of the safe use of tradipitant.

The following postmarketing requirements will be issued:

- Tradipitant is anticipated to be used by women of childbearing potential and it is not known whether tradipitant may affect maternal, fetal, and infant outcomes. Therefore, postmarketing requirements (PMRs) will be issued under 505(o) to collect data from a 1) prospective pregnancy registry, 2) a retrospective pregnancy cohort study, and 3) a lactation study in lactating women.
- Tradipitant is a new molecular entity and vomiting induced by motion is experienced by pediatric subjects. Therefore, PMRs will be issued under PREA to 1) evaluate the PK of an age-appropriate liquid formulation of tradipitant and 2) conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of tradipitant in pediatric patients 2 to <18 years of age.

The Applicant agreed to the following postmarketing commitments:

- A clinical pharmacology study to evaluate the effects of hepatic impairment on the PK of tradipitant and its major metabolites.
- A clinical pharmacology study to evaluate the effects of severe renal impairment on the PK of tradipitant and its major metabolites.
- An in vitro assessment to evaluate the contribution of all major CYP enzymes to the metabolism of tradipitant and its active metabolites, and to assess the relative contribution of specific CYP enzymes to tradipitant metabolism. The results of the in vitro study will determine the need for a subsequent drug-drug interaction study(ies).
- A thorough QT study to evaluate the effects of tradipitant on QT intervals in the fed state.

II. Interdisciplinary Assessment

3. Introduction

Vanda Pharmaceuticals submitted NDA 220152 for tradipitant 85-mg oral capsules. Tradipitant is a neurokinin-1 (NK-1) receptor antagonist, which has a proposed mechanism of action of blocking substance P from binding to NK-1 receptors in the brain and gastrointestinal tract, and subsequently produces anti-emetic effects.

Tradipitant is currently not approved for marketing in any country. The Applicant proposes to market tradipitant 85 mg or 170 mg, administered orally without food approximately 60 minutes prior to the desired antiemetic effect, for the following indication: “[TRADENAME] is a (b) (4) substance P/neurokinin 1 (NK1) receptor antagonist indicated for the acute prevention of vomiting induced by motion in adults.” Reviews of three proposed proprietary names were conducted during the course of the review of this application. The first proposed proprietary name, (b) (4) was determined to be unacceptable on April 14, 2025.⁶ The second proposed proprietary name, (b) (4) was determined to be unacceptable on September 24, 2025.⁷ The third proposed proprietary name, NEREUS, was determined to be acceptable on December 5, 2025.⁸

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Benefit-Risk Assessment of Tradipitant 85-mg and 170-mg Doses

3.1.1.2. Impact of Variable Travel Duration on Efficacy

3.1.2. Key Safety Review Issues

3.1.2.1. Adequacy of Nonclinical Information To Assess the Toxicological Effects of Tradipitant

3.1.2.2. Adequacy of Nonclinical Information To Assess the Toxicological Effects of Metabolites M2, M4, and M8

3.1.2.3. Adequacy of the Clinical Safety Database To Characterize Safety of Tradipitant for Vomiting Induced by Motion

⁶ See DMEPA Proprietary Name Review dated April 14, 2025, DARRTS ID #5571787.

⁷ See DMEPA Proprietary Name Review dated September 24, 2025, DARRTS ID #5665244.

⁸ See DMEPA Proprietary Name Review dated December 5, 2025, DARRTS ID #5706914.

3.2. Approach to the Clinical Review

As described in Section [6.2](#), the efficacy review focused on controlled data from the phase 3 randomized placebo-controlled trials, Trials 3401 and 3404. As described in Section [7.4](#), the safety review focused on data from the phase 2 and phase 3 randomized, double-blind, placebo-controlled trials, Trials 2401, 3401, and 3404. In addition, data from the phase 3 open-label uncontrolled phase 3 trial, Trial 3403, were considered.

[Table 3](#) provides an overview of the trials evaluated as a part of this review.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

[TRADENAME] is indicated for the prevention of vomiting induced by motion in adults.

2. SEE was established with:

a. Adequate and well-controlled clinical investigation(s):

- i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
- ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{9,10,11}

OR

c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)

3. Complete response, if applicable

- a. ☐ SEE was established
- b. ☐ SEE was not established (*if checked, omit item 2*)

⁹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#))

¹⁰ FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([May 1998](#))

¹¹ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#))

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Tradipitant

Trial Identifier	Trial Population	Trial Design	Regimen	Primary Endpoints	Number of Subjects	Number of Centers and Countries
<i>Randomized, Double-Blind, Placebo-Controlled Trials</i>						
VP-VLY-686-2401	Adults with history of motion sickness	Single-dose, single center, randomized, placebo-controlled	Tradipitant 170 mg (N=63) Duration: Single dose	Primary: Incidence of vomiting and worst score on the Motion Sickness Severity Scale (MSSS)	Planned: 150 Randomized: 126	1 site in the United States
VP-VLY-686-3401	Adults with history of motion sickness	Single-dose, multicenter, randomized, placebo-controlled	Tradipitant 85 mg (N=123) Tradipitant 170 mg (N=120) Duration: Single dose	Primary: Incidence of vomiting	Planned: 300 Randomized: 365	17 sites in the United States
VP-VLY-686-3404	Adults with history of motion sickness	Single-dose, multicenter, randomized, placebo-controlled	Tradipitant 85 mg (N=104) Tradipitant 170 mg (N=106) Duration: Single dose	Primary: Incidence of vomiting	Planned: 300 Randomized: 316	5 sites in the United States
<i>Open-Label Data Sources</i>						
VP-VLY-686-3403	Adults with history of motion sickness	12-month, uncontrolled, open-label	Tradipitant 85 mg (N=199) ² Tradipitant 170 mg (N=183) ² Duration: As-needed use, 90-dose maximum over 12 months.	Primary: Safety and tolerability	Planned: 500 Randomized: 382 (ongoing) ²	22 sites in the United States

Source: Reviewer.

¹ Includes all submitted clinical trials for indications that include motion sickness

² Number of subjects as reflected in the Applicant's interim analysis, as of October 2024. The Applicant submitted a 120-Day Safety Update report on April 30, 2025, which included N=268 in the tradipitant 85-mg arm, N=257 in the tradipitant 170-mg arm, and a total N=525.

Abbreviations: N, number of subjects

4. Patient Experience Data

Patient-reported outcome (PRO) data were collected in Trials 3401 and 3404 to support efficacy analyses. In both trials, subjects completed questionnaires during the travel assessment and upon concluding the travel assessment.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		1 , 2 , 6 , 21.1
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Tradipitant is a selective, competitive inhibitor of the human cell membrane NK-1 receptor in vitro. Tradipitant completely inhibited ligand binding to the human NK-1 receptor in vitro at a concentration of 10 μ M (5.9 μ g/mL). The half-maximal inhibitory concentrations (IC₅₀ values) of tradipitant for binding at the NK-1 receptor were 0.40 and 3.3nM (0.24 and 1.9 μ g/mL, respectively) in two separate studies. Tradipitant was also shown to inhibit substance P-mediated

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calcium release in human embryonic kidney (HEK) 293 cells with an IC₅₀ value of 0.63nM (0.37 µg/mL).

The four major human metabolites of tradipitant, M2, M3, M4, and M8, have been shown or are presumed to be pharmacologically active based on available data. All four metabolites inhibited ligand binding to the NK-1 receptor in vitro by ≥99.0% at a concentration of 10µM. M8 was shown to inhibit binding at the receptor with an IC₅₀ of 0.49nM and to inhibit substance P-mediated calcium release in vitro with an IC₅₀ of 6.3nM. M2, M3, and M4 were reported by the Applicant¹² to inhibit binding to the NK-1 receptor with IC₅₀ values of 1.55, 0.38, and 2.23nM, respectively; the functional activity of these metabolites was not tested.

In a study in male Beagle dogs, a single oral dose of tradipitant at 0.3, 1.0, or 3.0 mg/kg (less than the clinical dose of tradipitant of 170 mg/day, based on human equivalent dose [HED]) administered 2 hours prior to challenge with the pro-emetogenic drug, apomorphine, resulted in significantly decreased incidence of emesis compared to no treatment.

¹² These values were reported by the Applicant in Module 2.6.2 Pharmacology Written Summary (based on Studies AB28300-1190601, AB28300-1190602, AB28300-1190603, and AB28300-1190604). However, IC₅₀ values for M2, M3, and M4 were not stated in these study reports.

5.2. Clinical Pharmacology/Pharmacokinetics

This submission consists of 11 phase 1 trials in healthy subjects, one phase 2 trial, and two completed phase 3 trials in subjects with history of a motion sickness.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Substance P/ NK-1 receptor antagonist.
Mechanism of action	Tradipitant is a competitive inhibitor of the NK-1 receptor.
Active moieties	Tradipitant is the active moiety. Its metabolites M2, M3, M4, and M8 are also pharmacologically active as NK-1 inhibitors, the IC ₅₀ of M8 was 6.7-fold lower than tradipitant but the IC ₅₀ values of other metabolites were not determined. In the mass balance study, based on AUC _{inf} , tradipitant, M2, M3, and M4 accounted for approximately 9%, 4%, 5%, and 8% of plasma radioactivity, respectively (Study H8R-MC-HJAK). Following a single dose of 85 mg in healthy subjects under fasted condition, the AUC _{inf} ratio between M2, M3, M4, and M8 to tradipitant was 40%, 33%, 43%, and 42%, respectively (Trial VP-VLY-686-1002).
QT prolongation	No thorough QT (TQT) study was conducted. The Applicant submitted an integrated assessment of cardiac safety. The integrated assessment included Trial H8REW-HJAC, which was considered the primary study supporting QTc assessment, as it included placebo and serial time-matched ECG/PK collection. The results of the trial support that tradipitant did not cause clinically relevant QTc prolongation. However, the risk of QTc prolongation has not been characterized for tradipitant when administered with food, which results in a 4.7-fold increase in C _{max} for the 85 mg dose and 7.0-fold increase in C _{max} for the 170 mg dose. The Applicant agreed to conduct a thorough QT study as a postmarketing commitment to address the potential for QTc prolongation when administered with food. Refer to Section 24 .
	General Information
Bioanalysis	Concentrations of tradipitant and its metabolites (M3, M4, M6, and M8) in human plasma samples have been measured using adequately validated LC-MS/MS assays in clinical studies. All clinical samples were analyzed within the established stability period. Overall, the bioanalytical method validation and performance is acceptable.
Healthy subjects versus patients	The general population of patients experiencing motion sickness is not expected to have significantly different systemic exposure compared to healthy subjects.

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Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	While population PK analysis was unable to adequately predict the exposure of tradipitant and its metabolites due to limitations in the dataset and analysis methodology, disease condition was not identified as a covariate affecting pharmacokinetics in subjects with motion sickness. Refer to Section 14.5 for additional details. In healthy subjects, following single oral doses of 85 mg and 170 mg under fasting conditions, geometric mean C_{max} values were 84.7 ng/mL and 112 ng/mL, and geometric mean $AUC_{0-\infty}$ values were 1839 ng·hr/mL and 3526 ng·hr/mL, respectively (Trial 1002).
Range of effective dose(s) or exposure	In the randomized, placebo-controlled phase 3 trials (Trials 3401 and 3404), a single dose of 85-mg and 170-mg tradipitant was evaluated in subjects with a history of motion sickness during vehicle travel. In Trial 3401, the percentage of subjects who vomited was significantly lower in both the 85-mg tradipitant arm (19.5%, $p<0.0001$) and the 170-mg tradipitant arm (18.3%, $p<0.0001$) as compared to the placebo arm (44.3%). In Trial 3404, the percentage of subjects who vomited was significantly lower in both the 170-mg tradipitant arm, (10.4%, $p<0.0001$) and the 85-mg tradipitant arm (18.3%, $p=0.0014$) as compared to the placebo arm (37.7%).
Maximally tolerated dose or exposure	In healthy subjects, single dose up to 800 mg given under fasted condition was well tolerated. The 800 mg single dose administered in Trial H8R-EW-HJAC was a different formulation than the proposed TBM formulation. The mean C_{max} and AUC_{0-inf} of tradipitant are 277 ng/mL and 4620 ng·h/mL, respectively (Trial H8R-EW-HJAC). While no relative bioavailability study was conducted, cross-study comparison showed that tradipitant C_{max} and AUC_{0-inf} after single dose of 800 mg are 3.3-fold and 2.5-fold of those with the proposed to-be-marketed (TBM) formulation at 85 mg single dose, respectively, and 2.5-fold and 1.3-fold higher than those at 170 mg, respectively (Trial 1002). The PK parameters for total drug-related concentrations (tradipitant and its metabolites M2, M3, M4, and M8) are not available.
Dose proportionality	In healthy subjects, following a single dose of 85 mg and 170 mg under fasted condition, tradipitant C_{max} increased less than dose proportionally (1.3-fold), and AUC_{inf} increased approximately dose-proportionally (1.9-fold) (Trial 1002).
Accumulation	The Applicant has not provided the accumulation ratio following repeated dosing in subjects with a history of motion sickness.
Time to achieve steady state	Time to reach steady state was not determined in the intended population.
Bridge between to-be-marketed and clinical trial/study formulations	The proposed TBM formulation was used in phase 2 and phase 3 trials conducted in subjects with history of motion sickness (Trials 3401 and 3404). No formulation bridging is needed.
Absorption	
Bioavailability	The bioavailability of tradipitant is not determined.
T_{max}	Following a single-dose administration of 85-mg tradipitant in healthy subjects, the median T_{max} of tradipitant was 2 hours (range 1 to 8 hours) under fasted condition (Trial 1002).

Characteristic	Drug Information
Food effect (fed/fasted) Geometric least-squares mean and 90% CI	Concomitant high-fat meal significantly increased the systemic exposure to tradipitant and its metabolites and delayed T_{max}. The median T_{max} of tradipitant was 4 hours (range 1.5 to 6 hours) under fed condition. A single dose of 85 mg and 170 mg of tradipitant was administered in healthy subjects comparing the pharmacokinetics of tradipitant and its metabolites under fasted and fed (high-fat high-calorie meal) conditions (Trial 1002).

Table 6. Summary of Food Effect on Tradipitant and Its Metabolites, Trial 1002

Analytes	85 mg Single Dose		170 mg Single Dose	
	C_{max}	AUC_{0-inf}	C_{max}	AUC_{0-inf}
	LSGMR Fed/Fast (90% CI)			
Tradipitant	4.74 (4.08, 5.50)	2.63 (2.01, 3.44)	7.03 (5.46 - 9.05)	3.81 (2.38 - 6.11)
M2	4.08 (3.39, 4.91)	2.39 (1.76, 3.25)	6.54 (5.11 - 8.37)	3.51 (1.78 - 6.91)
M3	3.70 (3.17, 4.33)	2.64 (2.13, 3.27)	5.26 (4.17 - 6.64)	3.56 (3.03 - 4.18) ¹
M4	3.4 (2.85, 4.04)	2.39 (2.04, 2.82)	5.47 (4.39 - 6.82)	3.2 (2.30 - 4.46)
M8	4.29 (3.46, 5.31)	2.73 (2.05, 2.63)	5.59 (4.64 - 6.73)	3.53 (2.24 - 5.56)

Source: Table 11-13, 11-15, 11-17, 11-19, 11-21, 11-23, 11-25, 11-27, 11-29, and 11-31 from the clinical study report for Trial VP-VLY-686-1002

¹ AUC_{0-t} is used for M3 170-mg dose, as AUC_{0-inf} could not be estimated due to missing values.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time zero to time t; CI, confidence interval; C_{max} , maximum plasma concentration; LSGMR, least-squares geometric mean ratio for fed and fasted treatment arm; M, metabolite

For the fed condition, a high-calorie, high-fat meal was given 30 minutes or less prior to administration of study medication and finished prior to dosing. The high-calorie, high-fat meal contained two eggs cooked in butter, two pieces of buttered toast, two strips of bacon, 4 oz. of hash browns, and a cup of whole milk.

Distribution	
Volume of distribution	The apparent volume of distribution (V_d/F) of tradipitant was 1956 L in healthy subjects (Trial VP-VLY-686-1102).
Plasma protein binding	The protein binding of tradipitant in human plasma ranged from 96.2% to >99%.
Drug as substrate of transporters	Tradipitant is a P-gp substrate and is not a substrate of BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K.

Characteristic	Drug Information
	Elimination
Mass balance results	In the mass balance study, following a single 25 mg (100 µCi) oral dose administration of ¹⁴C-radiolabelled tradipitant, about 88% of the administered radioactivity was recovered mainly as metabolites over 312 hours postdose, in which 80% and 7% was in feces and urine, respectively. The administered radioactivity was mostly (85%) recovered within 168 hours postdose. In feces, tradipitant and 10 metabolites were detected, in which unchanged tradipitant was minimal and 4 metabolites (M17, M35, M58, and M59) were the major components, accounting for 9%, 9%, 9%, and 6% of the dose, respectively. In urine, tradipitant was not detected and 10 metabolites were detected with M60 as the major urinary metabolite, accounting for <2% of the dose (Trial H8R-MC-HJAK). In plasma, within 24 hours postdose, tradipitant, M2, M3, M4, and M8 were the main circulating entities identified. At 4 hours postdose, tradipitant, M2, M3, M4, and M8 accounted for 24%, 11%, 13%, 16%, and 13% of the radioactivity in the plasma sample, respectively. Based on AUC_{0-inf}, tradipitant, M2, M3, and M4 each accounted for approximately 9%, 4%, 5%, and 8% of radioactivity in plasma, respectively while AUC_{0-inf} for M8 was not assessed in the mass balance study. The mean t_{1/2} of total radioactivity was 113 hours compared to mean t_{1/2} of 20 to 30 hours of tradipitant, M2, M3, or M4, indicating that additional metabolites with longer t_{1/2} may be circulating in plasma. The clinical relevance of unaccounted radioactivity in human plasma is unknown.
Clearance	The apparent oral clearance of tradipitant was 41.7 L/hr in healthy subjects (Trial 1102).
Half-life	In healthy subjects, following a single dose of 85-mg tradipitant under fasted condition, the mean elimination half-life of tradipitant was 31.6 hours, and the mean elimination half-lives of M2, M3, M4, and M8 were 43.7, 30.2, 32.4, and 36.3 hours, respectively (Trial 1002).
Metabolic pathway(s)	Tradipitant is extensively metabolized; however, the metabolism pathway and the contribution of a specific metabolizing enzyme to tradipitant elimination was not fully characterized. Based on in vitro studies, the formation of M3 is mainly by CYP3A4, CYP2C19, and to a lesser extent CYP2C8 while the formation of M2 appears to be by non-CYP450-mediated processes (unspecified). Tradipitant is also glucuronidated by UGT1A4 and UGT2B7 to form M8. Tradipitant and metabolites M2, M3, and M4 only account for 26% of radioactivity in plasma based on AUC _{0-inf} , and additional metabolites may not have been identified. Refer to Section 8.2.
Primary excretion pathways (% dose)	Hepatobiliary excretion is the main elimination pathway of tradipitant. In the mass balance study, about 80% of the radioactivity was recovered in feces, mainly as metabolite forms following oral administration. In Beagle dogs, after intravenous dosing, 77% of the administered radioactive dose was recovered in feces suggesting biliary excretion as the primary excretion pathway (Report 008D04).

Characteristic	Drug Information
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	The population PK model failed to incorporate body weight as a significant covariate
Age	The population PK model failed to incorporate age as a significant covariate
Renal impairment	Renal excretion is not a major elimination pathway for tradipitant and its metabolites. No dedicated renal impairment study was conducted. Based on population PK analysis, EBE of CL/F were similar in subjects with mild renal impairment (n=79) and normal renal function (n=366). A 23% lower EBE of CL/F were observed in subjects with moderate renal impairment (n=11) compared to subjects with normal renal function; however, the difference is not considered clinically significant. Tradipitant was not studied in subjects with severe renal impairment.
Hepatic impairment	While hepatobiliary excretion is the main elimination pathway of tradipitant and its metabolites, the effect of hepatic impairment on tradipitant pharmacokinetics has not been studied and is unknown.
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	In vitro, tradipitant inhibits and induces CYP3A4. Oral midazolam exposure was increased 16% when coadministered with tradipitant 85 mg BID. Tradipitant did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, nor induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19.
Inhibition/induction of transporter systems	In vitro, tradipitant did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2-K at clinically relevant concentrations.

Source: FDA reviewer's summary

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; BCRP, breast cancer resistance protein; BID, twice daily; BMI, body mass index; C₁₂, concentration 12 hours postdose; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; EBE, Empirical Bayes estimate; IC₅₀, half-maximal inhibitory concentration; LC-MS/MS, liquid chromatographic separation with tandem mass spectrometry; M, metabolite; MATE, multidrug and toxin extrusion transporter; N, number of subjects; NK-1, neurokinin; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PK, pharmacokinetic; SD, standard deviation; t_{1/2}, elimination half-life; TBM, to-be-marketed; T_{max}, time to maximum concentration; UGT, uridine glucuronosyltransferase

6. Efficacy (Evaluation of Benefit)

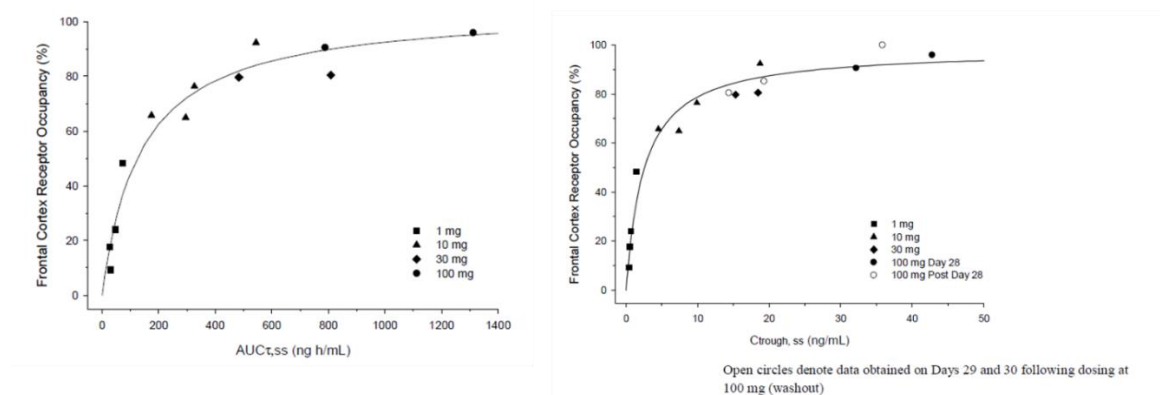
6.1. Assessment of Dose and Potential Effectiveness

Dose Rationale for Phase 3 Studies

The doses for the two phase 3 trials were selected initially based on the data obtained from a phase 1 trial (Trial H8R-EW-HJAD) in healthy subjects, and subsequently, a phase 2 trial (Trial 2401) in subjects with history of motion sickness.

Trial H8R-EW-HJAD assessed frontal cortex NK-1 receptor occupancy following multiple ascending doses in healthy subjects using positron emission tomography (PET). In this trial, healthy subjects received oral once-daily administration of tradipitant for 7 days at escalating doses (1, 10, 30, and 100 mg), with maximum frontal cortex NK-1 receptor occupancy of 93% $\pm$ 4% observed 24 hours after the final 100 mg dose (Figure 1). The Applicant estimated that approximately 85 mg daily would achieve 90% brain NK-1 receptor occupancy at steady state. However, the clinical relevance of this receptor occupancy assessment in proposed indication is unclear.

Figure 1. Relationship of Plasma Tradipitant $AUC_{T,ss}$ (Left Panel) or $C_{trough,ss}$ (Right Panel) and % Receptor Occupancy in the Frontal Cortex



Source: Adapted from Figures HJAD.11.2 and HJAD.11.3 of Study H8R-EW-HJAD CSR

Dose was escalated every 7 days within subjects from 1 mg to 100 mg.

Abbreviations: $AUC_{T,ss}$, area under the concentration-time curve for a dosing interval at steady state; CSR, clinical study report; $C_{trough,ss}$, trough concentration at steady state

Trial 2401, the phase 2 trial, evaluated a single 170-mg dose of tradipitant in subjects with a history of motion sickness during a 4-hour boat trip. The percentage of subjects who vomited was lower in the tradipitant arm compared to placebo (17.5% versus 39.7%, respectively).

Dose Response in Phase 3 Trials

The efficacy of tradipitant 85 mg and 170 mg for the prevention of motion-induced vomiting in adults was evaluated in two randomized, placebo-controlled phase 3 trials (Trial 3401 and Trial 3404). In Trial 3401 (N=365), both tradipitant doses demonstrated similar treatment effect, with

vomiting rates of 18.3% for the 170-mg dose and 19.5% for the 85-mg dose compared to 44.3% for placebo. In Trial 3404 (N=316), tradipitant 170 mg appeared to demonstrate lower vomiting rate compared to the 85-mg dose, with vomiting rates of 10.4% and 18.3%, respectively, compared to 37.7% for placebo.

In Trial 3401, the percentage of subjects who vomited was lower in both the tradipitant 170-mg arm (18.3%, $p < 0.0001$) and the tradipitant 85-mg arm (19.5%) compared to the placebo arm (44.3%) ([Table 9](#)). However, due to the hierarchical testing procedure, the tradipitant 85 mg result is considered nominally significant since the preceding secondary endpoint (worst nausea score for tradipitant 170 mg) did not achieve statistical significance. No apparent dose-response relationship was observed between the two doses, as both demonstrated similar vomiting rates. Neither dose demonstrated efficacy for the worst nausea score secondary endpoint, with results numerically similar across all treatment arms ([Table 9](#)). Additionally, neither dose showed superiority to placebo for MSAQ subscales or Patient Global Impression of Severity Questionnaire (PGI-S) scores, with the tradipitant 85-mg arm performing nominally worse than placebo on the sopite-related MSAQ subscale ([Table 10](#)).

In Trial 3404, the percentage of subjects who vomited was lower in both the tradipitant 170-mg arm (10.4%, $p < 0.0001$) and the tradipitant 85-mg arm (18.3%, $p = 0.0025$) compared to the placebo arm (37.7%) ([Table 13](#)). While the 170-mg dose demonstrated a lower vomiting rate than the 85-mg dose, the applicant did not conduct a formal comparison, and this trend was not observed in the other trial. Neither dose demonstrated efficacy for nausea-specific endpoints such as worst or average nausea scores ([Table 14](#)), MSAQ subscales ([Table 15](#)), or PGI-S scores ([Table 15](#)), with results numerically similar across all treatment arms.

Refer to Section [6.2](#) and Section [6.3](#) for more details.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The Applicant submitted two randomized, double-blind, placebo-controlled phase 3 trials to support the efficacy of tradipitant: Trial 3401 and Trial 3404. In both trials, the Applicant reported a statistically significant difference between tradipitant and placebo for the primary endpoint of percentage of vomiting during the trip in the tradipitant 170-mg arm compared to placebo as assessed by the vomiting assessment questionnaire.

6.2.1. Trial 3401

6.2.1.1. Design, Trial 3401

Trial 3401 was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial to assess the efficacy of tradipitant for the prevention of vomiting induced by motion. The trial included subjects with a history of motion sickness and consisted of administration of a single dose of trial drug approximately 60 minutes prior to a travel assessment (i.e., a boat trip) lasting 120 to 300 minutes. Eligible subjects were randomized in a 1:1:1 ratio to receive tradipitant 85 mg, tradipitant 170 mg, or placebo.

At the screening visit, potential subject eligibility for the trial was assessed based on the Motion Sickness Eligibility Questionnaire (MSEQ), interview, physical examination, vital signs, electrocardiogram (ECG), clinical laboratory tests, drug and alcohol screen, and medical history. Subjects who fulfilled all of the inclusion-exclusion criteria continued into the evaluation phase of the trial (travel assessment, Visit 2).

For each travel assessment visit, an assessment was made 24 to 48 hours in advance of the visit based on National Oceanic and Atmospheric Administration sea conditions to determine if the travel assessment visit would take place. This was determined based on the wave height: if the wave height was predicted to be above 1 meter, then the travel assessment would proceed. If the wave height was predicted to be below 1 meter, the travel assessment would be rescheduled and subjects who were not able to proceed with a rescheduled visit would have the option to withdraw consent and be documented as having failed the subject screening. During Visit 2, subjects were randomly assigned to 1 of 3 treatment arms stratified by port: 85-mg tradipitant, 170-mg tradipitant, or placebo. Subjects were assigned to take 85-mg tradipitant, 170-mg tradipitant, or placebo approximately 60 minutes prior to entering the boat. Throughout the duration of boat travel, the vomiting assessment (VA) and nausea assessment (NA) would be completed approximately every 30 minutes. Immediately following completion of the boat travel, subjects were instructed to complete several questionnaires to assess their travel: the MSAQ to assess the symptoms associated with motion sickness, and the PGI-S.

6.2.1.2. Eligibility Criteria, Trial 3401

Key eligibility criteria for Trial 3401 included:

- History of symptoms consistent with motion sickness
- Men or women between 18 to 75 years, inclusive
- Body mass index (BMI) of ≥ 18 and < 40 kg/m²
- Males, non-fecund females (i.e., surgically sterilized, if procedure was done 6 months before screening or participant is postmenopausal for at least 2 years), or females of child-bearing potential using an acceptable method of birth control (i.e., condoms, diaphragm, spermicidal agents, cervical cap, Copper intrauterine device) for a period of 35 days before the first dosing, during the study and for one month after the last dose and must have a negative pregnancy test at the screening visit

6.2.1.3. Statistical Analysis Plan, Trial 3401

Analysis Populations

Intent-to-Treat Population

The intent-to-treat (ITT) population included any subject randomized that received a dose of trial drug and had at least one post baseline vomiting assessment. The ITT population analyzed subjects as they were randomized, regardless of which treatment a subject received. The primary efficacy analyses were performed in the ITT population.

In general, the Agency recommends against defining the primary efficacy analysis population based on post-randomization outcomes. As post-randomization, such as requiring a postbaseline assessment, could be related to treatment assignment, the inclusion of subjects in the efficacy analysis based on post-randomization outcomes could bias efficacy results. Excluding subjects who did not receive any trial drug is generally reasonable in a double-blind trial, as treatment administration should be independent of treatment assignment. In Trial 3401, all randomized subjects who received trial drug had at least one postbaseline vomiting assessment; therefore, the criterion for inclusion in the ITT population did not impact efficacy conclusions.

Safety Population

The safety population included any subject randomized that received a dose of trial drug. The safety population was analyzed based on the actual treatment received. Safety summaries were based on the safety population.

Per-Protocol Population

The per-protocol (PP) population included any subject who was randomized and received the protocol-required trial drug exposure and required protocol processing. Blinded clinical data were reviewed prior to data lock to finalize the list of the PP population.

Sample Size

A sample size of 100 subjects per arm (300 in total) was planned to provide around 96% power to detect a 26% difference in vomiting between tradipitant and placebo assuming 50% of subjects on placebo would vomit and 24% of subjects on tradipitant would vomit, given a two-sided significance level of 0.05.

Efficacy Assessments

Vomiting Assessment

The VA was a 1-item questionnaire to objectively measure the incidence of emesis. Subjects would indicate whether or not they had vomited.

Nausea Assessment

The NA was a 1-item questionnaire to assess nausea severity as reported by the subjects. The subjects would rate the worst severity of their nausea on a 5-point scale in which 0 – none, 1 – mild, 2 – moderate, 3 – severe, and 4 – very severe. Subjects were instructed to select the number that most represents the severity of their nausea symptoms every 30 minutes.

Motion Sickness Assessment Questionnaire

The MSAQ was a 16-statement scale to assess motion sickness, which could be sub-divided by affected body systems (gastrointestinal: sick to stomach, queasy, nauseated, vomit; central: faint-like, lightheaded, dizzy, spinning, disoriented; peripheral: sweaty, clammy/cold sweat, hot/warm; sopite-related: annoyed/irritated, drowsy, tired/fatigued, uneasy). Each response was rated 1 to 9 with 1 representing low severity and 9 representing high severity. The overall motion sickness score was obtained by calculating the percentage of total points scored: (sum of points from all

items/144) $\times 100$. Subscale scores were obtained by calculating the percentage of points scored within each factor: (sum of gastrointestinal items/36) $\times 100$; (sum of central items/45) $\times 100$; (sum of peripheral items/27) $\times 100$; (sum of sopite-related items/36) $\times 100$.

Patient Global Impression of Severity Questionnaire

The PGI-S is a general assessment tool used by subjects to rate the overall severity of their disease or condition at a specific point in time. In Trial 3401, the PGI-S assessed motion sickness severity at the end of the travel. The subjects rated the severity of their motion sickness symptoms on a 0 to 4 scale in which 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.

Efficacy Endpoints

The primary efficacy endpoint was the percentage of subjects with vomiting during the trip in the tradipitant 170-mg arm as assessed by the VA questionnaire.

The secondary endpoints included:

- Worst nausea score in the tradipitant 170-mg arm
- Percentage of subjects with vomiting in the tradipitant 85-mg arm
- Worst nausea score in the tradipitant 85-mg arm

The secondary efficacy endpoints were tested in a fixed sequence as specified above.

Other secondary efficacy endpoints that were not under multiplicity control for each tradipitant treatment arm included:

- Total score of MSAQ
- Subscale scores of MSAQ
- PGI-S

Pooling Port

According to the statistical analysis plan (SAP), low enrollment ports were pooled for analysis. If a port had <3 subjects in any treatment arm or <9 in a total of subjects, the port (herein known as a small port) was pooled with another small port until the resulting pooled port has reached the threshold. The pooling process was as the following: the largest small port was pooled with the smaller port starting with the smallest until a non-small port was formed. If at the end one pooled port still did not meet the threshold, it would be pooled to the smallest port which has met the threshold.

Analysis of Efficacy Endpoints

The percentage of vomiting was assessed in the ITT population by the Cochran-Mantel-Haenszel (CMH) test adjusting for the pooled port. The proportion of subjects vomiting and the p-values for the CMH test were reported.

The worst nausea was analyzed in the ITT population, using an analysis of covariance (ANCOVA) model with the main effects of pooled port, peak wave height and treatment arm. A

summary of each endpoint, by treatment arm, was presented together with the least squares (LS) mean and standard error in each treatment arm, the difference in LS means between treatment arm and placebo and its 95% CI, and the p-value for the difference in LS means.

Based on the datasets submitted by the Applicant, it appeared that pooled site rather than pooled port was used as the covariate in both the CMH test and the ANCOVA model. On March 14, 2025, an information request was issued to clarify the rationale for using pooled site instead of pooled port. In a response dated March 25, 2025, the Applicant stated that each site corresponded to a unique port; however, the review team identified that both sites 113 and 117 in the dataset were listed as having the same port, “Port 07 – Fort Myer.” A follow-up information request for clarification was sent on March 25, 2025, and on April 4, 2025, the Applicant explained that each site number represented a unique physical location in Trials 3401 and 3404. Specifically, sites 113 and 117 in Trial 3401 corresponded to Tampa, FL and Fort Myers, FL, respectively. In the response received on April 4, 2025 (SDN 10), the Applicant stated,

participants’ randomization was stratified by port in this study. Based on the enrollment plan and timeline, a maximum of ten ports were originally designed in the IRT/IWRS system. However, due to enrollment difficulties, more than ten ports were explored to be open during the study. Adding more ports to the IRT/IWRS system would take a couple of weeks. To avoid delaying some scheduled boat trips, we assigned sites 113 and 117 to the same port in the IRT/IWRS system. The ADSL dataset directly used this information from the unblinded randomization list.

The review team conducted sensitivity analyses using the prespecified port pooling algorithm (based on the listed port in the Subject-Level Analysis Dataset [ADSL]) and found that efficacy conclusions were not impacted.¹³ Therefore, the choice of pooling by port versus site, as reflected in the ADSL dataset, does not appear to impact the efficacy results. Unless specified otherwise, all analyses in the review adjusting for location used pooled site as the covariate, consistent with the Applicant’s implementation.

The continuous secondary endpoints, the total score and subscale scores of MSAQ, and PGI-S, were analyzed in the ITT population, using an ANCOVA model with the main effects of pooled port, wave high and treatment arm. A summary of each endpoint, by treatment arm, was presented together with the least-squared mean and standard error in each treatment arm, the difference in LS means between treatment arm and placebo and its 95% CI, and the p-value for the difference in LS means.

Estimands and Intercurrent Events

The protocol and SAP did not specify an estimand of interest; however, based on the analyses, the impact of potential intercurrent events appears minimal. Treatment discontinuation was not applicable due to the single-dose design for efficacy assessment. The protocol listed medications prohibited from 1 week before randomization until the end of the treatment period. On March 14, 2025, an information request was issued asking for a list of subjects who used prohibited medications between 1 week prior to randomization and the end of treatment period. On March 25, 2025, the Applicant responded, indicating only three subjects used prohibited

¹³ Data not shown.

medications during this period, which the review team confirmed. A sensitivity analysis was performed using nonresponder imputation for subjects who used prohibited medication.¹⁴ These subjects were considered to have experienced vomiting during the travel for this analysis. The results of the sensitivity analysis were consistent with the primary analysis, indicating that intercurrent events appear to have minimal impact on the efficacy conclusions.

Handling of Missing Data

No imputation was performed for primary or secondary endpoints. In the Applicant's primary analysis, vomiting assessments with missing values were excluded from the calculation of the primary endpoint. Refer to Section [6.2.1.4](#) for a discussion of the amount of missing data and its impact.

6.2.1.4. Results of Analyses, Trial 3401

Demographic characteristics are summarized by treatment arm in [Table 7](#) for Trial 3401, within the ITT population. Overall, the baseline demographic characteristics were balanced between treatment arms and were representative of the population anticipated in motion sickness. Most subjects were White (85%), female (67%), and not Hispanic or Latino (84%). The mean age was approximately 49 years with a range from 19 to 75 years, and the majority (86%) of subjects were younger than 65 years of age.

Table 7. Baseline Demographics, ITT Population, Trial 3401

Demographic	Tradipitant 85 mg N=123	Tradipitant 170 mg N=120	Placebo N=122	Total N=365
Sex, n (%)				
Female	82 (67)	87 (72)	75 (61)	244 (67)
Male	41 (33)	33 (28)	47 (39)	121 (33)
Age, years				
Mean (SD)	50 (14)	48 (15)	49 (13)	49 (14)
Median	51	49	51	51
Min, max	21, 75	21, 75	19, 75	19, 75
Age categories, n (%)				
<65	100 (81)	101 (84)	112 (92)	313 (86)
≥65	23 (19)	19 (16)	10 (8)	52 (14)
Race, n (%)				
American Indian or Alaska Native	0	1 (1)	2 (2)	3 (1)
Asian	9 (7)	7 (6)	11 (9)	27 (7)
Black or African American	5 (4)	10 (8)	5 (4)	20 (5)
Native Hawaiian or Other Pacific Islander	1 (1)	0	0	1 (<1)
White	105 (85)	102 (85)	102 (84)	309 (85)
Other ¹	3 (2)	0	2 (2)	5 (1)

¹⁴ Data not shown.

Demographic	Tradipitant 85 mg N=123	Tradipitant 170 mg N=120	Placebo N=122	Total N=365
Ethnicity (%)				
Hispanic or Latino	12 (10)	13 (11)	14 (11)	39 (11)
Not Hispanic or Latino	102 (83)	99 (82)	105 (86)	306 (84)
Not reported	8 (7)	8 (7)	3 (2)	19 (5)
Unknown	1 (1)	0	0	1 (<1)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1

¹ There is no description provided regarding specific classifications included under "Other" racial categories.

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the treatment arm; n, number of subjects with given characteristic; SD, standard deviation

A summary of the analysis populations for Trial 3401 is presented in [Table 8](#). Of the 366 randomized subjects, only one subject, although randomized to tradipitant 170-mg arm, did not receive the trial drug, and was excluded from the ITT population. No subjects received the incorrect trial drug according to their assigned randomization arm and all subjects who took trial drug had a postbaseline vomiting assessment. Therefore, the ITT population and the safety population were consistent with no discrepancies.

Table 8. Population of Analysis, Trial 3401

Population	Number of Subjects			Total
	Tradipitant 85 mg	Tradipitant 170 mg	Placebo	
Randomized population	123	121	122	366
Intent-to-treat population	123	120	122	365
Safety population	123	120	122	365
Per-protocol population	123	118	122	363

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1

For subject disposition in Trial 3401, only one subject in the tradipitant 170-mg arm discontinued the trial due to withdrawal of consent. The data indicated that this subject withdrew from the trial after 60 minutes of the boat trip. There was no dropout in the other arms. Treatment discontinuation was not applicable to the ITT population as the ITT population included subjects who received the treatment, and the trial only had a single dose for efficacy.

The Applicant's primary efficacy results were confirmed by the statistical review team, and the results demonstrate superiority of the tradipitant 170-mg dose compared to placebo in percentage of subjects with vomiting during the boat travel. The percentages of subjects with vomiting during the travel were 18.3%, 19.5%, and 44.3% in the tradipitant 170 mg, tradipitant 85 mg, and placebo arms, respectively, as shown in [Table 9](#), which also presents the results for the secondary endpoint of the worst nausea score during travel.

Table 9. Results for the Primary Endpoint and Key Secondary Endpoint, ITT Population, Trial 3401

Parameter	Tradipitant 85 mg N=123	Tradipitant 170 mg N=120	Placebo N=122
Subjects with vomiting during the boat travel			
n (%)	24 (19.5 ¹)	22 (18.3)	54 (44.3)
Unadjusted treatment difference (95% CI) ²	-24.9 (-36.0, -13.9)	-25.9 (-37.1, -14.7)	
Adjusted treatment difference (95% CI) ³	-24.8 (-36.0, -13.5)	-25.8 (-37.0, -14.6)	
P-value ⁴	<0.0001 ⁵	<0.0001	
Subjects with missing VA, n (%)	3 (2.4)	4 (3.3)	3 (2.5)
Worst nausea score during the boat travel			
Mean (SD)	2.40 (1.32)	2.32 (1.28)	2.37 (1.33)
LS means (SE) ⁶	2.56 (0.13)	2.44 (0.13)	2.52 (0.13)
Difference in LS means (95% CI) ⁶	0.04 (-0.27, 0.36)	-0.08 (-0.40, 0.24)	
P-value ⁴	0.7913	0.6110	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ The percentage is 19.51% and is rounded as 20% in labeling.

² Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

³ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated common risk difference using the Mantel-Haenszel weights, adjusted for pooled site.

⁴ The 2-sided p-value is based on the Cochran-Mantel-Haenszel test for the common odds ratio.

⁵ Per the multiple testing hierarchy, the tradipitant 85 mg versus placebo comparison for vomiting was contingent upon demonstrating statistical significance for tradipitant 170 mg versus placebo on worst nausea score. Since the latter comparison was not statistically significant, the tradipitant 85-mg vomiting result is considered nominally significant.

⁶ LS means, SEs, treatment differences, CIs, and p-values were obtained from the linear model with treatment arm as factor and peak wave height and pooled site as covariates.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; N, number of subjects in treatment arm; n, number of subjects in specified population or arm; SE, standard error; SD, standard deviation; VA, vomiting assessment

Per the multiple testing hierarchy, the comparison of tradipitant 85 mg versus placebo for the percentage of subjects with vomiting was to be conducted only after the comparison of tradipitant 170 mg versus placebo on worst nausea score. Since the testing did not demonstrate statistical significance for the latter comparison, the result for tradipitant 85 mg on the vomiting endpoint is considered nominally significant.

For the primary endpoint, the SAP did not specify which summary statistics would be reported. In the clinical study report, the Applicant presented the unadjusted treatment difference along with its 95% CI. However, since sites were used as a stratification factor at randomization, and the p-value was based on the CMH test, the review team also examined the adjusted treatment difference that accounts for the stratification factor. The unadjusted treatment differences between each tradipitant arm and placebo were consistent with the adjusted treatment differences, indicating the use of pooled site in the primary analysis did not have an impact on efficacy conclusions.

The proportion of subjects with missing vomiting assessments was balanced across treatment arms. A sensitivity analysis considering subjects with missing assessments as treatment failures (i.e., as having experienced vomiting) resulted in only two subjects in the tradipitant 170-mg arm and one subject in the placebo arm changing their status from no vomiting to vomiting. This small amount of missing data did not impact the efficacy conclusion.¹⁵

For the secondary endpoint of worst nausea score during the boat travel, neither the tradipitant 170-mg nor the 85-mg arm demonstrated a statistically significant difference compared to placebo and the average of the worst nausea score was similar across arms, indicating

¹⁵ Data not shown.

insufficient evidence to support the effectiveness of tradipitant in reducing nausea for this patient population.

The results for other secondary endpoints by treatment arm are summarized in [Table 10](#). Neither the tradipitant 170-mg arm nor the tradipitant 85-mg arm demonstrated nominal superiority to placebo for any of the endpoints listed in [Table 10](#). Some endpoints were numerically worse in the tradipitant arms compared to placebo. In fact, for the “sopite-related” score of the MSAQ, the tradipitant 85 mg performed nominally worse than placebo (p-value=0.0155). This indicates that despite the reduction in vomiting observed with tradipitant, there is no evidence of prevention of symptoms other than vomiting, and tradipitant may even worsen some motion-sickness symptoms (i.e., sopite-related symptoms showed a nominally significant difference in favor of placebo compared to tradipitant 85-mg dose). Furthermore, for the PGI-S, the results were nearly numerically identical across treatment arms, indicating that when subjects were asked to rate their overall motion sickness severity, they provided similar ratings across different treatment arms.

Table 10. Results for Other Secondary Endpoints, ITT Population, Trial 3401

Parameter	Tradipitant 85 mg N=123	Tradipitant 170 mg N=120	Placebo N=122
Total score of MSAQ	N'=122	N'=118	N'=122
LS means (SE) ¹	49.2 (2.5)	46.0 (2.5)	45.1 (2.5)
Difference in LS means (95% CI) ¹	4.1 (-2.1, 10.3)	0.9 (-5.3, 7.2)	
P-value ¹	0.1899	0.7746	
Gastrointestinal score of MSAQ	N'=122	N'=118	N'=122
LS means (SE) ¹	59.9 (3.5)	57.6 (3.5)	61.2 (3.5)
Difference in LS means (95% CI) ¹	-1.4 (-9.9, 7.2)	-3.7 (-12.3, 5.0)	
P-value ¹	0.7540	0.4058	
Central score of MSAQ	N'=122	N'=118	N'=122
LS means (SE) ¹	37.0 (2.5)	34.0 (2.5)	32.1 (2.5)
Difference in LS means (95% CI) ¹	4.9 (-1.2, 11.0)	2.0 (-4.2, 8.1)	
P-value ¹	0.1121	0.5318	
Peripheral score of MSAQ	N'=122	N'=118	N'=122
LS means (SE) ¹	50.8 (3.3)	45.5 (3.3)	45.6 (3.3)
Difference in LS means (95% CI) ¹	5.2 (-2.9, 13.3)	-0.2 (-8.3, 8.0)	
P-value ¹	0.2079	0.9691	
Sopite-related score of MSAQ ²	N'=122	N'=118	N'=122
LS means (SE) ¹	52.7 (2.6)	49.8 (2.6)	44.9 (2.6)
Difference in LS means (95% CI) ¹	7.9 (1.5, 14.2)	5.0 (-1.4, 11.4)	
P-value ¹	0.0155	0.1281	
PGI-S	N'=123	N'=119	N'=122
LS means (SE) ¹	2.0 (0.1)	2.1 (0.1)	2.2 (0.1)
Difference in LS means (95% CI) ¹	-0.2 (-0.5, 0.2)	-0.1 (-0.4, 0.2)	
P-value ¹	0.3025	0.5542	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ LS means, SEs, treatment differences, CIs, and p-values were obtained from the linear model with treatment arm as factor and peak wave height and pooled site as covariates.

² Sopite-related scores of MSAQ were obtained by calculating the percentage of points scored on a scale of 1 to 9 for each of the following four symptoms: annoyed/irritated, drowsy, tired/fatigued, uneasy (see Section 6.2.1.3).

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; N, number of subjects in treatment arm; N', number of subjects without missing data; MSAQ, Motion Sickness Assessment Questionnaire; SE, standard error; PGI-S, Patient Global Impression Scale

6.2.2. Trial 3404

6.2.2.1. Design, Trial 3404

Trial 3404 was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial to assess the efficacy of tradipitant in the prevention of vomiting induced by motion. The trial included subjects with a history of motion sickness and consisted of administration of a single dose of trial drug approximately 60 minutes prior to a travel assessment (i.e., 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. Subjects received an offer to participate in an optional PK assessment at the end-of-trial visit. Trial 3404 used the same trial design as Trial 3401. Refer to Section [6.2.1.1](#) for details.

6.2.2.2. Eligibility Criteria, Trial 3404

The key eligibility criteria for Trial 3404 were the same as those for Trial 3401. Refer to Section [6.2.1.2](#) for details.

6.2.2.3. Statistical Analysis Plan, Trial 3404

Analysis Populations

The analysis populations and corresponding definitions for Trial 3404 were the same as those described for Trial 3401. Refer to Section [6.2.1.3](#).

Sample Size

The sample size determination was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Efficacy Assessments

Vomiting Assessment

The VA was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Nausea Assessment

The NA was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Motion Sickness Assessment Questionnaire

The MSAQ was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Patient Global Impression of Severity Questionnaire

The PGI-S was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Efficacy Endpoints

The primary efficacy endpoint was the percentage of subjects with vomiting during the trip in tradipitant 170-mg arm as assessed by the VA questionnaire.

The secondary endpoints included:

- Percentage of subjects with vomiting in the tradipitant 85-mg arm
- Percentage of subjects with vomiting and severe nausea defined as worst nausea ≥ 3 in each tradipitant treatment arms

The secondary efficacy endpoints were tested in a fixed sequence as specified above. However, for the percentage of subjects with vomiting and severe nausea, it was not explicitly specified whether the tradipitant 170-mg arm was tested prior to the 85-mg arm.

Other secondary efficacy endpoints that were not under multiplicity control for each tradipitant treatment arm included:

- Worst nausea score
- Average nausea score
- Total score of MSAQ
- Subscale scores of MSAQ
- PGI-S

Pooling Port

Subjects were enrolled from five ports. The algorithm for pooling port was the same in Trial 3404 as described for Trial 3401. Refer to Section [6.2.1.3](#).

Analysis of Efficacy Endpoints

The percentage of vomiting was assessed in the ITT population by the CMH test adjusting for the pooling port. The proportion of subjects with vomiting and the p-values for the CMH test were reported. The secondary endpoints were assessed in the same way as the primary endpoint.

Based on the datasets submitted by the Applicant, it appeared that pooled site rather than pooled port was used as the covariate in both the CMH test and the ANCOVA model. However, since each site in Trial 3404 corresponded to a unique port, pooling by site or port yields the same result.

The continuous secondary endpoints, including worst nausea score, average nausea score, the total score and subscale scores of MSAQ, and PGI-S, were analyzed in the ITT population, using an ANCOVA model with the main effects of pooled port, wave height and treatment arm. A summary of each endpoint, by treatment arm, was presented together with the least-squared mean and standard error in each treatment arm, the difference in LS means between treatment arm and placebo and its 95% CI, and the p-value for the difference in LS means.

Estimands and Intercurrent Events

The protocol and SAP did not specify an estimand of interest; however, based on the analyses, the impact of potential intercurrent events appears minimal. Treatment discontinuation was not applicable due to the single-dose design for efficacy assessment. The protocol listed medications prohibited from 1 week before randomization until the end of the treatment period. On March 14, 2025, an information request was issued asking for a list of subjects who used prohibited medications between 1 week prior to randomization and the end of treatment period. On March 25, 2025, the Applicant responded, indicating no subjects used prohibited medications during this period, which the review team confirmed.

Handling of Missing Data

No imputation was performed for primary or key secondary endpoints. Refer to Section [6.2.2.4](#) for a discussion of the amount of missing data and its impact.

6.2.2.4. Results of Analyses, Trial 3404

Demographic characteristics are summarized by treatment arm in [Table 11](#) for Trial 3404. Overall, the baseline demographic characteristics were balanced across treatment arms and considered representative of the motion sickness population. The mean age was 46 years with a range from 18 to 75 years, and the majority (88%) of subjects were younger than 65 years of age. Most subjects were White (78%), female (56%), and not Hispanic or Latino (81%).

Table 11. Baseline Demographics, ITT Population, Trial 3404

Demographic	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106	Total N=316
Sex, n (%)				
Female	62 (60)	56 (53)	60 (57)	178 (56)
Male	42 (40)	50 (47)	46 (43)	138 (44)
Age, years				
Mean (SD)	47 (14)	46 (15)	45 (15)	46 (15)
Median	48	46	46	47
Min, max	18, 73	18, 75	18, 72	18, 75
Age categories, n (%)				
<65	92 (88)	93 (88)	93 (88)	278 (88)
≥65	12 (12)	13 (12)	13 (12)	38 (12)
Race, n (%)				
American Indian or Alaska Native	0	0	1 (1)	1 (<1)
Asian	9 (9)	15 (14)	12 (11)	36 (11)
Black or African American	4 (4)	5 (5)	6 (6)	15 (5)
Multiple	2 (2)	3 (3)	4 (4)	9 (3)
Native Hawaiian or Other Pacific Islander	0	2 (2)	0	2 (1)
White	88 (85)	80 (75)	78 (74)	246 (78)
Other ¹	1 (1)	1 (1)	5 (5)	7 (2)

Demographic	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106	Total N=316
Ethnicity (%)				
Hispanic or Latino	16 (15)	11 (10)	16 (15)	43 (14)
Not Hispanic or Latino	84 (81)	91 (86)	82 (77)	257 (81)
Not reported	4 (4)	4 (4)	8 (8)	16 (5)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1

¹ There is no description provided regarding specific classifications included under "Other" racial categories.

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the treatment arm; n, number of subjects with given characteristic; SD, standard deviation

A summary of the analysis populations is presented in [Table 12](#). All randomized subjects received the trial drug according to their assigned randomization arm and all randomized subjects had a post baseline vomiting assessment. Therefore, the randomized population, the ITT population, and the safety population were the same.

Table 12. Population of Analysis, Trial 3404

Population	Number of Subjects			Total
	Tradipitant 85 mg	Tradipitant 170 mg	Placebo	
Randomized population	104	106	106	316
Intent-to-treat population	104	106	106	316
Safety population	104	106	106	316
Per-protocol population	104	106	106	316

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1.

Regarding subject disposition for Trial 3404, only one subject in the tradipitant 170-mg arm discontinued the trial due to loss to follow-up. This subject completed all vomiting and nausea assessments during the boat trip. The loss to follow-up occurred after travel had ended, and thus did not affect the efficacy evaluation for this subject.

The review team verified the Applicant's primary efficacy results, which demonstrated that both tradipitant 170-mg and 85-mg doses were superior to placebo in reducing the percentage of subjects who experienced vomiting during the travel event, as presented in [Table 13](#). The observed percentages of subjects with vomiting were 10.4% for tradipitant 170 mg, 18.3% for tradipitant 85 mg, and 37.7% for placebo.

Table 13. Results for the Primary Endpoint and Key Secondary Endpoints, ITT Population, Trial 3404

Parameter	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106
Subjects with vomiting during the boat travel			
n (%)	19 (18.3)	11 (10.4)	40 (37.7)
Unadjusted treatment difference (95% CI) ¹	-19.5 ² (-31.3, -7.6)	-27.4 (-38.3, -16.5 ³)	
Adjusted treatment difference (95% CI) ⁴	-19.4 (-30.9, -7.8)	-27.1 (-37.8, -16.5)	
P-value ⁵	0.0025 ⁶	<0.0001	
Subjects with missing VA, n (%)	2 (1.9)	0	1 (0.9)

Parameter	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106
Subjects with vomiting and severe nausea			
n (%)	18 (17.3)	10 (9.4)	35 (33.0)
Unadjusted treatment difference (95% CI) ¹	-15.7 (-27.2, -4.2)	-23.6 (-34.1, -13.0)	
Adjusted treatment difference (95% CI) ⁴	-15.6 (-26.9, -4.2)	-23.4 (-33.8, -13.0)	
P-value ⁵	0.0136 ⁷	<0.0001	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

² The percentage is -19.47% and is rounded as -19% in labeling.

³ The upper bound of the 95% CI for the unadjusted treatment difference is -16.46%, which is rounded to -16% in labeling.

⁴ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated common risk difference using the Mantel-Haenszel weights, adjusted for pooled site.

⁵ The 2-sided p-value is based on the Cochran-Mantel-Haenszel test for the common odds ratio.

⁶ The value listed in this table is different from the value of 0.0014 reported in the clinical study report submitted by the Applicant. The p-value provided by the Applicant in the clinical study report were based on the Mantel-Haenszel test for the relative risk. The SAP indicates testing would be based on the Cochran-Mantel-Haenszel test, which, while related to the Mantel-Haenszel test for the relative risk, provides a test of the common odds ratio. Regardless of the p-value calculation method, the statistical significance remains unchanged.

⁷ The value listed in this table is different from the value of 0.0086 reported in the clinical study report submitted by the Applicant. The p-value provided by the Applicant in the clinical study report were based on the Mantel-Haenszel test for the relative risk. The SAP indicates testing would be based on the Cochran-Mantel-Haenszel test, which, while related to the Mantel-Haenszel test for the relative risk, provides a test of the common odds ratio. Regardless of the p-value calculation method, the statistical significance remains unchanged.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or arm; VA, vomiting assessment

The SAP did not specify the summary statistics to be reported for the binary endpoints. In the clinical study report, the Applicant presented unadjusted treatment differences with corresponding 95% CIs. However, because ports were used as the stratification factor at randomization and the p-values were derived from a CMH test, the review team also examined the adjusted treatment differences. The adjusted and unadjusted treatment differences between each tradipitant arm and placebo were consistent, indicating that the inclusion of pooled site/port in the primary efficacy analysis did not have an impact of efficacy conclusions.

The number of subjects with missing vomiting assessments was balanced across treatment arms, with two in the tradipitant 85-mg arm, one in the placebo arm, and none in the tradipitant 170-mg arm. Given the minimal amount of missing data, there was no impact on the overall efficacy conclusions.

For the endpoint assessing the percentage of subjects with vomiting and severe nausea, both tradipitant arms demonstrated a statistically significant difference compared to placebo. However, the treatment difference for this endpoint was driven by vomiting, and there was no distinct difference for nausea. Specifically, the percentage of subjects with a worst nausea score ≥ 3 was 52.9%, 35.8%, and 45.3% for tradipitant 85 mg, tradipitant 170 mg, and placebo, respectively, which was similar across treatment arms. None of the unadjusted risk differences for the percentage of subjects with worst nausea score ≥ 3 compared to placebo achieved nominal significance. Thus, the significance observed in the multi-component endpoint was driven by the vomiting component. Therefore, this endpoint analysis does not provide additional information to characterize the effect of treatment beyond the information provided by the primary endpoint analysis. See [Table 14](#) for a summary of the secondary endpoints related to nausea assessments.

[Table 14](#) presents the results for secondary endpoints related to nausea assessments, which were not subject to multiplicity control. Neither the tradipitant 170-mg nor the tradipitant 85-mg treatment arms demonstrated a nominally statistically significant difference from placebo for either the worst nausea score or the average nausea score. In fact, the endpoint results were

similar between tradipitant and placebo. These results do not support the efficacy of tradipitant in preventing nausea in this patient population.

Table 14. Results for the Secondary Endpoints for Nausea Assessments, ITT Population, Trial 3404

Parameter	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106
Worst nausea score during the boat travel			
Mean (SD)	2.55 ¹ (1.27)	2.19 (1.20)	2.42 (1.29)
LS means (SE) ²	2.54 (0.13)	2.18 (0.13)	2.41 (0.13)
Difference in LS means (95% CI) ²	0.13 (-0.21, 0.47)	-0.23 (-0.57, 0.10)	
P-value ²	0.4568	0.1755	
Average nausea score during the boat travel			
LS means (SE) ²	1.69 (0.11)	1.45 (0.11)	1.58 (0.11)
Difference in LS means (95% CI) ²	0.11 (-0.17, 0.40)	-0.13 (-0.41, 0.15)	
P-value ²	0.4408	0.3737	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ The value is 2.548, which is rounded to 2.5 in labeling.

² LS means, SEs, treatment differences, CIs, and p-values were obtained from the linear model with treatment arm as factor and peak wave height and pooled site as covariates.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; N, number of subjects in treatment arm; SE, standard error; SD, standard deviation

The results for other secondary endpoints by treatment arm are presented in [Table 15](#). Neither the tradipitant 170 mg nor the tradipitant 85 mg treatment arms demonstrated nominal superiority to placebo across any of the other secondary endpoints. Some endpoints were numerically worse in the tradipitant arms compared to placebo. Additionally, PGI-S results were numerically similar across all treatment arms. Despite the observed reduction in vomiting in the tradipitant arms compared to placebo, subjects' assessments of overall motion sickness severity remained similar across treatment arms. The results do not provide evidence that tradipitant improves any symptoms other than vomiting.

Table 15. Results for Other Secondary Endpoints, ITT Population, Trial 3404

Parameter	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106
Total score of MSAQ	N=104	N=105	N=106
LS means (SE) ¹	44.9 (2.6)	39.5 (2.6)	41.2 (2.6)
Difference in LS means (95% CI) ¹	3.7 (-3.0, 10.5)	-1.7 (-8.4, 5.1)	
P-value ¹	0.2797	0.6254	
Gastrointestinal score of MSAQ	N=104	N=105	N=106
LS means (SE) ¹	58.2 (3.6)	47.2 (3.5)	54.8 (3.5)
Difference in LS means (95% CI) ¹	3.4 (-5.8, 12.6)	-7.7 (-16.8, 1.5)	
P-value ¹	0.4689	0.1002	
Central score of MSAQ	N=104	N=105	N=106
LS means (SE) ¹	33.6 (2.6)	31.4 (2.6)	31.0 (2.6)
Difference in LS means (95% CI) ¹	2.6 (-4.2, 9.4)	0.3 (-6.4, 7.1)	
P-value ¹	0.4524	0.9207	
Peripheral score of MSAQ	N=104	N=105	N=106
LS means (SE) ¹	41.0 (3.2)	34.8 (3.2)	36.6 (3.2)
Difference in LS means (95% CI) ¹	4.3 (-3.9, 12.6)	-1.8 (-10.1, 6.4)	
P-value ¹	0.3019	0.6620	

Parameter	Tradipitant 85 mg N=104	Tradipitant 170 mg N=106	Placebo N=106
Sopite-related score of MSAQ	N'=104	N'=105	N'=106
LS means (SE) ¹	48.6 (2.7)	45.5 (2.7)	43.6 (2.7)
Difference in LS means (95% CI) ¹	5.0 (-2.0, 12.0)	1.9 (-5.1, 8.9)	
P-value ¹	0.1616	0.5910	
PGI-S	N'=104	N'=105	N'=106
LS means (SE) ¹	2.1 (0.1)	1.8 (0.1)	1.9 (0.1)
Difference in LS means (95% CI) ¹	0.1 (-0.2, 0.5)	-0.2 (-0.5, 0.2)	
P-value ¹	0.4106	0.3176	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1
¹ LS means, SEs, treatment differences, CIs, and p-values were obtained from the linear model with treatment arm as factor and peak wave height and pooled site as covariates.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; N, number of subjects in treatment arm; N', number of subjects without missing data; MSAQ, Motion Sickness Assessment Questionnaire; SE, standard error; PGI-S, Patient Global Impression Scale

6.2.3. Pooled Results, Trials 3401 and 3404

Demographic characteristics are summarized by treatment arm in [Table 16](#) for the pooled data of Trials 3401 and 3404. Trials 3401 and 3404 had identical trial designs, eligibility criteria, and statistical analysis plans. Overall, baseline demographic characteristics were balanced across treatment arms and are considered representative of the motion sickness population. There were 365 subjects in Trial 3401 and 316 subjects in Trial 3404, with a mean age of 48 years (range from 18 to 75 years), 62% were female, 12% identified as Hispanic or Latino, 81% identified as White, 9% as Asian, 5% as Black or African American, and 4% identified as another racial arm.

Table 16. Baseline Demographics, ITT Population, Pooled Trials 3401 and 3404

Demographic	Tradipitant 85 mg N=227	Tradipitant 170 mg N=226	Placebo N=228	Total N=681
Sex, n (%)				
Female	144 (63)	143 (63)	135 (59)	422 (62)
Male	83 (37)	83 (37)	93 (41)	259 (38)
Age, years				
Mean (SD)	49 (14)	47 (15)	47 (14)	48 (14)
Median	49	48	49	49
Min, max	18, 75	18, 75	18, 75	18, 75
Age categories, n (%)				
<65	192 (85)	194 (86)	205 (90)	591 (87)
≥65	35 (15)	32 (14)	23 (10)	90 (13)
Race, n (%)				
American Indian or Alaska Native	0	1 (<1)	3 (1)	4 (1)
Asian	18 (8)	22 (10)	23 (10)	63 (9)
Black or African American	9 (4)	15 (7)	11 (5)	35 (5)
Multiple	2 (1)	3 (1)	4 (2)	9 (1)
Native Hawaiian or Other Pacific Islander	1 (<1)	2 (1)	0	3 (<1)
White	193 (85)	182 (81)	180 (79)	555 (81)
Other ¹	4 (2)	1 (<1)	7 (3)	12 (2)

Demographic	Tradipitant 85 mg N=227	Tradipitant 170 mg N=226	Placebo N=228	Total N=681
Ethnicity (%)				
Hispanic or Latino	28 (12)	24 (11)	30 (13)	82 (12)
Not Hispanic or Latino	186 (82)	190 (84)	187 (82)	563 (83)
Not reported	12 (5)	12 (5)	11 (5)	35 (5)
Unknown	1 (<1)	0	0	1 (<1)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1

¹ There is no description provided regarding specific classifications included under "Other" racial categories.

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the treatment arm; n, number of subjects with given characteristic; SD, standard deviation

A supplementary analysis was performed on the percentage of subjects with vomiting during the travel event, using pooled data from Trials 3401 and 3404. The results, presented in [Table 17](#), further support the statistical conclusion from the individual trials, Trials 3401 and 3404, that both tradipitant arms demonstrate superiority over placebo in the prevention of vomiting induced by motion. The tradipitant 170-mg arm had a numerically lower percentage of vomiting than the 85-mg arm, though the difference between the two tradipitant arms was small.

Table 17. Pooled Analysis for the Percentage of Subjects With Vomiting During the Boat Travel Event, ITT Population, Trials 3401 and 3404

Parameter	Tradipitant 85 mg N=227	Tradipitant 170 mg N=226	Placebo N=228
n (%)	43 (18.9)	33 (14.6)	94 (41.2)
Unadjusted treatment difference (95% CI) ¹	-22.3 (-30.5, -14.1)	-26.6 (-34.5, -18.8)	
Adjusted treatment difference (95% CI) ²	-22.4 (-30.4, -14.4)	-26.4 (-34.2, -18.6)	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

² Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated common risk difference using the Mantel-Haenszel weights, adjusted for pooled site.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or arm

6.3. Key Efficacy Review Issues

6.3.1. Benefit-Risk Assessment of Tradipitant 85-mg and 170-mg Doses

Issue

The primary sources of efficacy data submitted were obtained from two phase 3 randomized, placebo-controlled clinical trials, Trials 3401 and 3404, conducted in subjects with a history of motion sickness. Due to the lack of statistical significance for a preceding secondary endpoint in the testing hierarchy (i.e., worst nausea score in the tradipitant 170-mg arm), Trial 3401 did not demonstrate statistical significance for the percentage of subjects with vomiting in the tradipitant 85-mg arm compared to placebo under the prespecified fixed-sequence multiple testing procedure for secondary endpoints. However, the tradipitant 85-mg arm achieved nominal statistical significance for the prespecified analysis of the percentage of subjects with vomiting in Trial 3401 and the nominal p-value was well below the 0.05 threshold used to evaluate statistical significance in the trial (i.e., $p < 0.0001$). Additionally, the results were robust against missing

data and intercurrent events, demonstrating the consistency of the treatment effect across different statistical analyses. Trial 3404 provided confirmation that the tradipitant 85-mg dose was effective in reducing the percentage of subjects who vomited compared to placebo by demonstrating statistical significance on the prespecified analysis.

The overall evidence supports the efficacy of both the tradipitant 85-mg and 170-mg arms on vomiting. While the tradipitant 170-mg arm had a numerically lower percentage of subjects experiencing vomiting during travel, the overall efficacy appears similar between the two doses. Further exploratory analyses were performed to evaluate the benefit-risk profile of both doses.

Background

During the pre-NDA meeting held on November 8, 2023, the Applicant asked whether the Agency would consider Trials 2401 and 3401 sufficient to support NDA filing and review of tradipitant for the prevention of vomiting induced by motion, while Trial 3404 was still ongoing. The clinical study report and statistical analysis plan were submitted after the meeting request. The Agency expressed concern that in Trial 3401, the worst nausea score in the tradipitant 170-mg arm was not statistically significantly different from placebo. As a result, per the fixed-sequence testing procedure, subsequent hypotheses including the percentage of vomiting in the tradipitant 85-mg arm were not controlled for type I error. Additionally, since Trial 2401 only evaluated the 170-mg dose, data supporting the 85-mg dose appeared insufficient without results from Trial 3404. When the Applicant asked whether the results from the analyses of the tradipitant 85-mg dose arm on the percentage of vomiting would not be considered by the Agency. The Agency indicated that any efficacy data submitted as part of a future NDA would be considered but that the type I error control was an important aspect of the assessment of efficacy.

In the NDA submission, the primary sources of efficacy data were from two phase 3 trials, Trials 3401 and 3404. Although the percentage of vomiting in the tradipitant 85-mg arm reached only nominal statistical significance in Trial 3401, it achieved statistical significance in Trial 3404. The efficacy results were robust with respect to the handling of missing data and intercurrent events, demonstrating SEE for the tradipitant 85-mg dose. Given both treatment arms demonstrated SEE and there appeared to be some dose-related safety outcomes, the review team conducted additional analysis to assess the benefit-risk profile of the two dose arms to determine whether there was sufficient evidence to recommend the use of one dose over the other.

Assessment

To further evaluate the benefit-risk profile between the two doses, the review team conducted an exploratory responder analysis evaluating the percentage of subjects with vomiting during travel or one of the following treatment-emergent adverse events (TEAEs): headache, somnolence, or fatigue. This responder analysis was conducted for both Trials 3401 and 3404, as well as a pooled analysis of both trials. This analysis was designed to assess both efficacy and safety endpoints simultaneously to better characterize the overall benefit-risk profile of each dose. The safety signals included in the responder analysis were TEAEs with a frequency $\geq 5\%$ that occurred with greater frequency in the tradipitant arms compared to placebo. Therefore, the selected TEAEs are likely related to tradipitant. Furthermore, these TEAEs represent unfavorable treatment outcomes for subjects, and subjects who experienced these TEAEs would likely have

experienced limited, if any, benefit from treatment. The results of the responder analysis are shown in [Table 18](#).

Table 18. Results for the Percentage of Subjects With Vomiting During the Travel or Treatment-Emergent Adverse Events (Headache, Somnolence, or Fatigue), ITT Population, Trials 3401 and 3404

Parameter	Tradipitant 85 mg	Tradipitant 170 mg	Placebo
Trial 3401			
n/N (%)	41/123 (33.3)	47/120 (39.2)	57/122 (46.7)
Unadjusted treatment difference (95% CI) ¹	-13.4 (-25.5, -1.2)	-7.6 (-20.0, 4.9)	
Adjusted treatment difference (95% CI) ²	-13.5 (-25.7, -1.2)	-7.4 (-20.2, 5.4)	
Trial 3404			
n/N (%)	40/104 (38.5)	37/106 (34.9)	55/106 (51.9)
Unadjusted treatment difference (95% CI) ¹	-13.4 (-26.8, -0.1)	-17.0 (-30.1, -3.8)	
Adjusted treatment difference (95% CI) ²	-13.6 (-26.8, -0.5)	-16.9 (-29.5, -4.3)	
Pooled Trials 3401 and 3404			
n/N (%)	81/227 (35.7)	84/226 (37.2)	112/228 (49.1)
Unadjusted treatment difference (95% CI) ¹	-13.4 (-22.4, -4.4)	-12.0 (-21.0, -2.9)	
Adjusted treatment difference (95% CI) ²	-13.5 (-22.5, -4.6)	-12.0 (-21.0, -2.9)	

Source: Review team's analysis using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

² Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated common risk difference using the Mantel-Haenszel weights, adjusted for pooled site.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or arm

Results from the pooled analysis of Trials 3401 and 3404 showed that 35.7% of subjects in the 85-mg arm experienced vomiting or one of the specified TEAEs compared to 37.2% in the 170-mg arm and 49.1% in the placebo arm. Overall, the response rates for this analysis were numerically better, though similar, for the tradipitant 85-mg arm compared to the tradipitant 170-mg arm. While the percentage of subjects who vomited was slightly lower for the tradipitant 170-mg arm compared to the 85-mg arm, this responder analysis suggests that the 85-mg dose may have a slightly more favorable benefit-risk profile after accounting for TEAEs that appear to be related to tradipitant. It should be noted that these data exclusively represent the effects of a single administration of tradipitant and there are no clinical trials with a treatment duration of more than 90 doses. Furthermore, there are no randomized controlled data to support repeated doses of tradipitant for this indication, and there are substantial limitations to the data provided to support the safety of repeated use of both proposed doses (see Section [7.6.2](#)).

Conclusion

While the percentage of vomiting in the tradipitant 85-mg arm reached only nominal statistical significance in Trial 3401, it achieved statistical significance in Trial 3404. The consistently lower percentage of vomiting observed in analyses for Trials 3401 and 3404 supports that the superiority of tradipitant 85 mg over placebo is robust and persuasive. The tradipitant 170-mg arm had a slightly lower percentage of subjects who vomited compared to the 85-mg arm; however, a responder analysis evaluating the percentage of subjects who either vomited or experienced the TEAEs of headache, somnolence, or fatigue numerically favored the 85-mg dose, though the results were generally similar for the two arms. Despite some AEs occurring at a higher rate in the 170-mg arm, there was a numerically lower rate of vomiting in the 170-mg

arm and some patients may benefit from the higher dose. The review team recommends the approval of both doses given the data support a favorable risk-benefit profile for both doses. It should be noted that the results of this analysis were based on TEAEs from a single dose. The safety profile of repeated intermittent dosing over a lifetime has not been established. It is possible there are additional unknown safety risks from unrestricted, repeated dosing over a lifetime that will occur more frequently when using the 170-mg dose compared to the 85-mg dose. Therefore, the review team recommends use of the lowest effective dose (i.e., the tradipitant 85-mg dose).

6.3.2. Impact of Variable Travel Duration on Efficacy

Issue

As outlined in the protocols for Trials 3401 and 3404, the expected duration of the boat travel ranged from approximately 120 to 300 minutes. This wide variability in travel time could affect the efficacy assessment if, for example, a longer travel event increases the likelihood of vomiting. Imbalanced travel duration across treatment arms could impact the symptoms and severity of motion sickness experienced by subjects, potentially complicating the results.

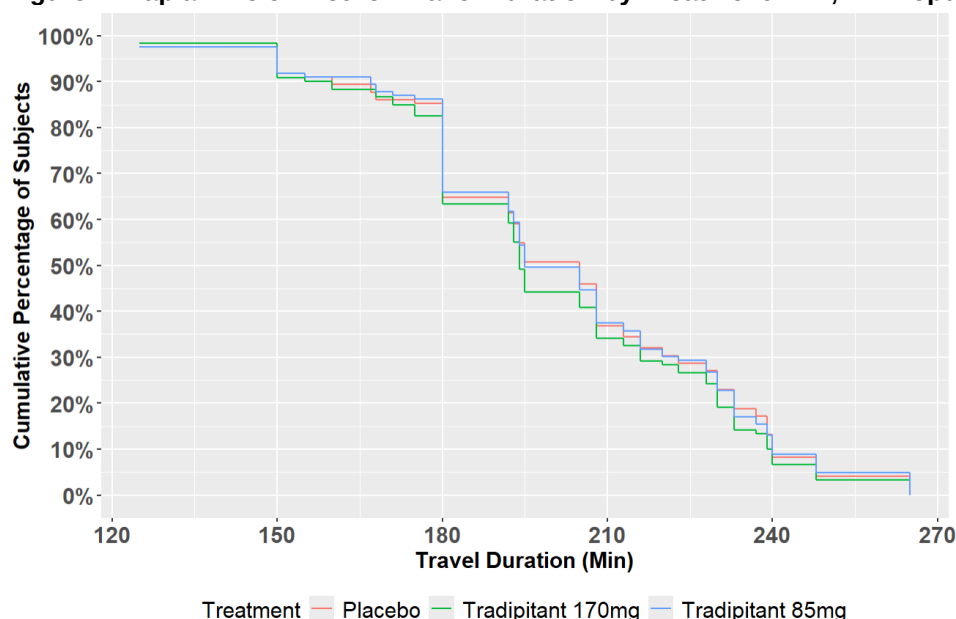
Background

According to the protocols for Trials 3401 and 3404, travel durations ranged from 120 to 300 minutes. Vomiting was assessed every 30 minutes during the trip to evaluate the percentage of subjects with vomiting. Longer exposure to motion could increase the chance of vomiting. There may also be unidentified potential confounders associated with a longer travel duration (e.g., a travel event takes longer due to rough seas). Although site was the randomization stratification factor for both trials, boat trips from the same site could still differ in duration. As a result, potential imbalances in travel time across treatment arms may complicate the interpretation of the percentage of subjects with vomiting. The review team conducted analyses to assess the potential impact of variable travel duration on efficacy results.

Assessment

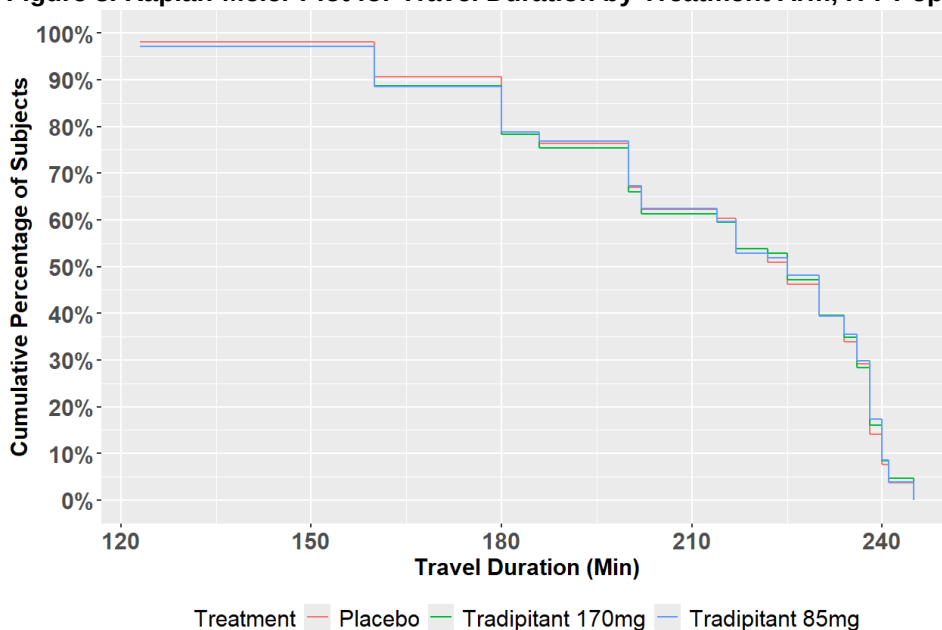
Based on the datasets submitted by the Applicant, the actual travel durations ranged from 125 to 265 minutes in Trial 3401 and from 123 to 245 minutes in Trial 3404. Kaplan-Meier plots of travel duration by treatment arms for Trials 3401 and 3404 are presented in [Figure 2](#) and [Figure 3](#), respectively. Around 85% and 90% of subjects in each treatment arm had a travel duration of at least 180 minutes in Trials 3401 and 3404, respectively. The majority of subjects had a travel duration between 180 minutes and 240 minutes. Overall, travel durations were comparable across treatment arms in both trials.

Figure 2. Kaplan-Meier Plot for Travel Duration by Treatment Arm, ITT Population, Trial 3401



Source: Reviewer-generated figure using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1
Abbreviations: ITT, intent-to-treat

Figure 3. Kaplan-Meier Plot for Travel Duration by Treatment Arm, ITT Population, Trial 3404



Source: Reviewer-generated figure using data submitted by the Applicant in NDA 220152, SDN 1, dataset adsl.xpt, module 5.3.5.1
Abbreviations: ITT, intent-to-treat

The review team conducted supplementary analyses where the endpoint was defined as the percentage of subjects with vomiting by specific timepoints during the travel, ranging from 30 to 270 minutes in 30-minute increments. The results are presented in [Table 19](#) and [Table 20](#) for Trials 3401 and 3404, respectively. The percentages at 210, 240, and 270 minutes were identical within each treatment arm for both trials. The treatment differences began to stabilize when censoring the data at 120 minutes for Trial 3401 and at 180 minutes for Trial 3404.

Table 19. Percentage of Subjects With Vomiting During the Boat Travel by a Certain Timepoint, ITT Population, Trial 3401

Percentage of Subjects With Vomiting by	Tradipitant	Tradipitant	Placebo N=122 n (%)	Treatment Difference (Tradipitant 85 mg–Placebo) (95% CI) ¹	Treatment Difference (Tradipitant 170 mg–Placebo) (95% CI) ¹
	85 mg N=123 n (%)	170 mg N=120 n (%)			
30 minutes	1 (0.8)	1 (0.8)	1 (0.8)	0.0 (-2.3, 2.3)	0.0 (-2.3, 2.3)
60 minutes	5 (4.1)	6 (5.0)	18 (14.8)	-10.7 (-17.9, -3.5)	-9.8 (-17.2, -2.4)
90 minutes	14 (11.4)	13 (10.8)	34 (27.9)	-16.5 (-26.2, -6.8)	-17.0 (-26.7, -7.3)
120 minutes	19 (15.4)	18 (15.0)	47 (38.5)	-23.1 (-33.8, -12.3)	-23.5 (-34.3, -12.8)
150 minutes	22 (17.9)	21 (18.0)	50 (41.0)	-23.1 (-34.1, -12.1)	-23.5 (-34.5, -12.4)
180 minutes	23 (18.7)	21 (18.0)	53 (43.4)	-24.7 (-35.9, -13.6)	-25.9 (-37.1, -14.8)
210 minutes	24 (19.5)	21 (18.0)	54 (44.3)	-24.8 (-36.0, -13.5)	-25.9 (-37.1, -14.7)
240 minutes	24 (19.5)	21 (18.0)	54 (44.3)	-24.8 (-36.0, -13.5)	-25.9 (-37.1, -14.7)
270 minutes	24 (19.5)	21 (18.0)	54 (44.3)	-24.8 (-36.0, -13.5)	-25.9 (-37.1, -14.7)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1.

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval. Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the corresponding arm; n, number of subjects in specified population or arm

Table 20. Percentage of Subjects With Vomiting During the Boat Travel by a Certain Timepoint, ITT Population, Trial 3404

Percentage of Subjects With Vomiting by	Tradipitant	Tradipitant	Placebo N=106 n (%)	Treatment Difference (Tradipitant 85 mg–Placebo) (95% CI) ¹	Treatment Difference (Tradipitant 170 mg–Placebo) (95% CI) ¹
	85 mg N=104 n (%)	170 mg N=106 n (%)			
30 minutes	0	1 (0.9)	4 (3.8)	-3.8 (-7.4, -0.1)	-2.8 (-6.9, 1.2)
60 minutes	2 (1.9)	3 (2.8)	16 (15.1)	-13.2 (-20.5, -5.9)	-12.3 (-19.8, -4.8)
90 minutes	8 (7.7)	5 (4.7)	26 (24.5)	-16.8 (-26.5, -7.2)	-19.8 (-28.9, -10.7)
120 minutes	15 (14.4)	7 (6.6)	33 (31.1)	-16.7 (-27.8, -5.6)	-24.5 (-34.5, -14.5)
150 minutes	17 (16.3)	11 (10.4)	35 (33.0)	-16.7 (-28.1, -5.2)	-22.6 (-33.3, -12.0)
180 minutes	18 (17.3)	11 (10.4)	39 (36.8)	-19.5 (-31.2, -7.8)	-26.4 (-37.3, -15.6)
210 minutes	19 (18.3)	11 (10.4)	40 (37.7)	-19.5 (-31.3, -7.6)	-27.4 (-38.3, -16.5)
240 minutes	19 (18.3)	11 (10.4)	40 (37.7)	-19.5 (-31.3, -7.6)	-27.4 (-38.3, -16.5)
270 minutes	19 (18.3)	11 (10.4)	40 (37.7)	-19.5 (-31.3, -7.6)	-27.4 (-38.3, -16.5)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1.

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval. Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the corresponding arm; n, number of subjects in specified population or arm

Conclusion

The distribution of travel duration was balanced across treatment arms in both Trials 3401 and 3404, supporting that the observed superiority of tradipitant over placebo in prevention of vomiting was not driven by differences in travel duration. Additionally, the supplementary analyses censoring data at specific timepoints suggest that the impact of variable travel duration on efficacy was minimal.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

7.1.1. Overall Risks and Safety Concerns

Notable risks and safety concerns based on completed nonclinical studies include the following:

- The submitted nonclinical information is insufficient to adequately characterize the safety profile of tradipitant for unrestricted use over a lifetime.
 - The Applicant has not conducted a chronic (e.g., ≥ 6 months in duration) toxicity study in a nonrodent species.
 - Although the Applicant conducted additional in vitro nonclinical tests intended to support the safety of tradipitant, this information does not substantially contribute to assessing the safety of unrestricted use over a lifetime (see Section [13.2.5](#)).
 - As such, the safety of unrestricted use of tradipitant over a lifetime has not been adequately addressed by nonclinical data (see further discussion in Section [7.7.1](#)).
- A risk of hepatotoxicity was identified in a subchronic toxicity study¹⁶ in Han Wistar rats (see Section [13.1.5](#)) and was further explored in short-duration in vitro safety pharmacology studies with tradipitant and its major human metabolites (see Section [13.2.3](#)). Based on the available nonclinical data, a risk for liver injury with tradipitant and its major metabolites has been identified. This safety concern was not identified in clinical trials with tradipitant up to 90 doses.

Completed nonclinical studies with tradipitant include an in vitro human ether-a-go-go-related gene (hERG) assay, an in vitro study in dog Purkinje fibers, four in vitro safety pharmacology studies using cultured 3D human hepatocyte spheroids, one in vitro safety pharmacology study using a human liver co-culture microphysiological system (MPS), and single-dose in vivo cardiovascular (dog), respiratory (rat), and central nervous system (mouse) safety pharmacology studies; repeat-dose toxicity studies in mice (13 weeks), Fisher rats (1, 3, and 6 months), Han Wistar rats (3 months), and dogs (1 and 3 months); a complete battery of genetic toxicity studies including an Ames assay, an in vitro chromosomal aberration assay in human lymphocytes, and an in vivo micronucleus assay in mice; a complete battery of reproductive toxicity studies including a combined fertility, early embryonic development, and embryo-fetal development study in rats, an embryo-fetal development study in rabbits, and a pre- and postnatal development study in rats; a juvenile toxicity study in Han Wistar rats; carcinogenicity studies of 26 weeks in transgenic mice and 104 weeks in Han Wistar rats; two special toxicology studies

¹⁶ Although a 13-week study is not generally considered pivotal to support the safety of a drug for chronic or repeated intermittent use, the 13-week Han Wistar rat study is considered pivotal in this NDA. This study demonstrated new and adverse toxicities with tradipitant administration that were not observed in the 26-week Fisher rat study. In alignment with the principles of 3R's to reduce animal use when possible, an additional 26-week study in Han Wistar rats was not requested. Therefore, both rat studies are considered integral in determining the safety of tradipitant for the prevention of vomiting induced by motion.

using a four-organ MPS comprised of human liver, cardiac, renal, and neuronal cells; and an assessment of phototoxic potential. As previously stated, a chronic toxicity study in a nonrodent species has not been conducted.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Tradipitant is a substance P/NK-1 receptor antagonist. Other substance P/NK-1 receptor antagonists have been approved, including aprepitant (oral), fosaprepitant (intravenous [IV]), and rolapitant (oral or IV). Some substance P/NK-1 receptor antagonists have been approved as fixed-combination products, such as netupitant and palonosetron (oral) and fosnetupitant and palonosetron (IV). The approved indications for these substance P/NK-1 receptor antagonists are prevention of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). These substance P/NK-1 receptor antagonists are approved for patients who are either undergoing chemotherapy treatment for an oncologic diagnosis or undergoing a surgical procedure. The currently approved substance P/NK-1 receptor antagonists also have a limited administration schedule with at least some of the exposure occurring in a healthcare setting. For example, the recommended dosage regimen for the fixed-dose combination aprepitant/palonosetron is a 3-day course of oral capsules prior to highly emetogenic chemotherapy or moderately emetogenic chemotherapy. The clinical trials that supported the use of the currently approved substance P/NK-1 receptor antagonists were in alignment with the intended use of the products. Additionally, marketing applications for approved substance P/NK-1 receptor antagonists have included data from 6-month rodent and 9-month nonrodent toxicity studies.

Due to differences in the intended use population between tradipitant and the approved substance P/NK-1 receptor antagonists, the known safety concerns for the drug class may not be directly relevant to tradipitant, and the benefit-risk assessment for tradipitant differs from other drugs in its class. As described above, the approved in-class medications are indicated for specific populations undergoing treatments (i.e., chemotherapy and surgery) for underlying and often life-threatening disease. This contrasts with the proposed population with a history of motion sickness, a non-life-threatening physiologic response to stimuli that is self-limited and often avoidable. The proposed population includes generally healthy individuals, which may lower the acceptability of risk compared to other in-class drugs. In addition, due to the physiologic nature of motion sickness, the proposed population may experience motion sickness in response to a variety of stimuli (e.g., sea travel, car travel, air travel), under no healthcare supervision, and repeatedly over a prolonged period.

The currently approved substance P/NK-1 receptor antagonists have several associated safety concerns addressed in their approved labels. Aprepitant (Cinvanti, NDA 209296 and Emend, NDAs 021549, 022023, and 207865) labeling includes Warnings and Precautions for hypersensitivity reactions including anaphylaxis, and drug-drug interactions (DDIs) due to aprepitant's properties as a substrate, weak-to-moderate inhibitor, and inducer of cytochrome P450 (CYP)3A4. Rolapitant (Varubi, NDA 206500 and 208399) labeling includes Warnings and Precautions for DDIs due to rolapitant's properties as a moderate inhibitor of CYP2D6. These medications' labels describe adverse events that occurred in CINV clinical trials including but not limited to fatigue, dizziness, dehydration, abdominal pain, nausea, diarrhea, dyspepsia,

gastritis, stomatitis, anemia, neutropenia, decreased appetite, hiccups, and urinary tract infection. Adverse events described in the labeling that occurred in PONV clinical trials include (but are not limited to) bradycardia, hypotension, and constipation. Some of these adverse events also occurred in the tradipitant safety database; however, the patient population and intended use of tradipitant differ from the approved substance P/NK-1 receptor antagonists.

There are potential safety concerns for substance P/NK-1 receptor antagonists that are not marketed in the United States. Casopitant mesylate (Rezonic, NDA 022336) is a drug with this mechanism of action for which a marketing authorization application was filed with FDA in May 2008, that received a complete response in June 2009, due to safety concerns and was subsequently withdrawn by the Applicant. A similar marketing authorization application was filed with the European Medicines Agency in 2008, and it was withdrawn by the Applicant in 2009. Repeat-dose toxicity studies in rats (6 months) and in dogs (9 months) showed evidence of cardiomyopathy. These changes occurred with increased levels of biomarkers for cardiomyocyte injury (i.e., troponin I and creatine kinase muscle and brain mass isoenzyme). There were also ultrastructural changes in the hearts of both preclinical species detected on transmission electron microscopy, suggestive of accumulation of phospholipids ([Pagliarusco et al. 2011](#)). In shorter-duration nonclinical studies, these findings were not observed. These long-term nonclinical studies of casopitant were important in identifying safety concerns that differed from other drugs of the same class and highlight the importance of obtaining appropriate and complete toxicology data for each unique drug candidate.¹⁷

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. Tradipitant is not commercially available in any country.

7.4. FDA Approach to the Safety Review

The clinical safety review primarily focused on data from the two randomized, double-blind, placebo-controlled phase 3 trials, Trial 3401 and Trial 3404, and the randomized, double-blind, placebo-controlled phase 2 trial, Trial 2401. All three trials were conducted in subjects who had a history of motion sickness who were otherwise healthy.¹⁸ In each trial, subjects received a single dose of tradipitant approximately 60 minutes prior to a vehicle travel assessment consisting of a boat trip lasting 123 to 265 minutes, during which safety data were collected. In Trials 3401 and 3404, subjects were randomized to receive a single dose of either tradipitant 85 mg, tradipitant 170 mg, or placebo before the travel event. In Trial 2401, subjects were randomized to receive a single dose of either tradipitant 170 mg or placebo before the travel

¹⁷ See Remand Response from Dr. Julie G. Beitz, FDA, to Mr. Birznieks, Vanda Pharmaceuticals, Inc. (April 26, 2019). Also see Memorandum to File from Dr. David Joseph, FDA, under NDA 022336 (June 15, 2009).

¹⁸ Trials 2401, 3401, and 3404 included the following exclusion criterion: “current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal, gastrointestinal or metabolic dysfunction unless currently controlled and stable.”

event. The review team determined that pooling of safety data from Trials 2401, 3401, and 3404 was appropriate as the patient population and trial design for each trial were sufficiently similar.

The Applicant also submitted an interim report and 120 Day Safety Update for Trial 3403, which was an ongoing open-label trial wherein subjects received either tradipitant 85 mg or 170 mg approximately 60 to 120 minutes prior to a travel event anticipated to induce motion sickness¹⁹ for up to 90 dosing days over the course of 12 months. Trial 3403 was the only source of clinical safety data for repeat dosing of tradipitant in the intended use population. The Division had previously recommended that the Applicant include a concurrent comparator arm to increase the likelihood of Trial 3403 resulting in interpretable data; however, the Applicant did not alter the trial design.

The Applicant's safety database also included all trials in which tradipitant was administered, including trials with indications other than vomiting induced by motion (i.e., gastroparesis, social anxiety disorder, irritable bowel syndrome, alcohol use disorder, atopic dermatitis). The generalizability of these data is limited due to differences in pathophysiology, chronicity, and associated symptoms of these conditions as compared to the intended use population (i.e., vomiting induced by motion).

The Applicant defined TEAEs as adverse events that were "newly occurring or worsening from treatment dosing until 3 days after the final dose of study medication." Tradipitant has a reported half-life of approximately 34 hours (2 half-lives are approximately 3 days, and 5 half-lives are approximately 7 days). Therefore, within the Applicant's selected 3-day timeframe, it is anticipated that 25% of tradipitant is expected to remain in the body. The review team considered TEAE definitions that included a duration of up to 7 days after the last dose (i.e., 5 half-lives), but these definitions did not meaningfully change the safety analyses. Therefore, the safety analyses described in this review use the TEAE definition described in the trial protocols.

7.5. Adequacy of the Clinical Safety Database

The Applicant provided safety data from a total of 516 subjects (including 227 who received 85 mg and 289 who received 170 mg) with a history of motion sickness who were exposed to a single dose of tradipitant in Trials 2401, 3401, and 3404. In addition, in their original submission, the Applicant provided interim safety data for 382 subjects (including 199 who received 85 mg and 183 who received 170 mg) with a history of motion sickness who received repeated dosing of tradipitant in the ongoing Trial 3403. Additional safety data from Trial 3403 were provided for 143 subjects (525 subjects total) in the 120-Day Safety Update report. [Table 21](#) shows the total number of subjects exposed to each dose of tradipitant in trials for the proposed intended use.

¹⁹ Travel events anticipated to induce motion sickness were defined as "any vehicle travel (car, plane, train, boat, etc.) historically known to induce motion sickness in the participant."

Table 21. Overall Exposure, Safety Population

Parameter	Tradipitant 85 mg N=426	Tradipitant 170 mg N=472
Exposure in single-dose trials, ¹ n (%)	227 (53.3)	289 (61.2)
Exposure in multiple-dose trial, ² n (%)	199 (46.7)	183 (38.8)

Source: adsl.xpt; Software: JMP

¹ Single-dose trials include Trials 2401, 3401, and 3404.

² Multiple-dose trial includes Trial 3403, conducted over the course of 12 months, with a maximum of 90 doses of tradipitant to be used as needed.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects in each trial design

The submitted clinical safety database in the intended use population along with the available nonclinical data support the safety of tradipitant for up to 90 doses. However, the available safety data are inadequate to support the safety of unrestricted use. The single-dose clinical trials (i.e., Trials 2401, 3401, 3404) support the safety of a single dose of tradipitant, while the multiple-dose trial (i.e., Trial 3403) provides additional safety data with several limitations that limit the interpretability of the results (e.g., limited to 90 doses, infrequent safety assessments). These limitations of the data from Trial 3403 are discussed in detail in Section [7.6.2](#).

The Applicant also submitted data from clinical trials of tradipitant in other conditions (e.g., gastroparesis). Notably, no clinical trials have had a duration of more than 12 weeks (or 90 dosing days). Additionally, in many of the clinical trials, the dosage of tradipitant differed from the dosages assessed for vomiting induced by motion and there may be differences in disease-specific risks for these other indications. Thus, the safety data from other indications does not address the lack of data for the prevention of vomiting induced by motion.

To address the limitations of the clinical and nonclinical safety data, the review team determined that the label should include a description that the safety of tradipitant beyond 90 doses has not been established, to ensure the safe and effective use of tradipitant for the prevention of vomiting induced by motion. Refer to Section [7.7.3](#) for additional discussion.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Trials 3401, 3404, and 2401

Pooled analyses of the double-blind, placebo-controlled data from the single-dose Trials 3401, 3404, and 2401 were conducted. The main limitation to pooling data from these trials is that Trial 2401 only compared tradipitant 170 mg to placebo, whereas Trials 3401 and 3404 included an additional tradipitant 85-mg arm. In order to preserve randomized comparisons and guard against potential bias, pooled data were assessed separately for the 85-mg arm versus placebo and the 170-mg arm versus placebo.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials 3401, 3404, and 2401

[Table 22](#) below provides a summary of TEAEs reported in the pooled single-dose trials for tradipitant 85 mg versus placebo (i.e., Trials 3401 and 3404), and [Table 23](#) provides a summary of TEAEs for tradipitant 170 mg versus placebo (i.e., Trials 2401, 3401, and 3404). No SAEs were reported in the tradipitant or placebo arms. No subjects withdrew due to TEAEs, and there

were no deaths reported. Overall, TEAEs were reported in a greater proportion of subjects in the tradipitant arms compared to placebo (see Tables 22 and 23 below). The majority of TEAEs were of mild severity. The higher rates of TEAEs in the pooled analysis for tradipitant 170 mg versus placebo were in part driven by the reporting of “motion sickness” as a TEAE in Trial 2401.

Table 22. Overview of Adverse Events,¹ Safety Population, Pooled Analyses for Tradipitant 85 mg vs. Placebo, Trials 3401 and 3404

Event Category	Tradipitant 85 mg N=227 n (%)	Placebo N=228 n (%)
Any TEAE ²	66 (29.1)	39 (17.1)
Severe	0	0
Moderate	13 (5.7)	13 (5.7)
Mild	53 (23.3)	26 (11.4)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 23.0 and 26.0.

² Severity as assessed by the investigator. For subjects who experienced more than one TEAE, the severity of the most severe TEAE is represented.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

Table 23. Overview of Adverse Events,¹ Safety Population, Pooled Analyses for Tradipitant 170 mg vs. Placebo, Trials 3401, 3404, and 2401

Event Category	Tradipitant 170 mg N=289 n (%)	Placebo N=291 n (%)
Any TEAE ²	113 (39.1)	85 (29.2)
Severe	1 (0.3)	0
Moderate	19 (6.6)	21 (7.2)
Mild	93 (32.2)	64 (22.0)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 21.0, 23.0, and 26.0.

² Severity as assessed by the investigator. For subjects who experienced more than one TEAE, the severity of the most severe TEAE is represented.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

7.6.1.2. Treatment-Emergent Adverse Events, Pooled Analyses, Trials 3401, 3404, and 2401

[Table 24](#) and [Table 25](#) below describe TEAEs occurring in $\geq 5\%$ of subjects and higher in those receiving tradipitant compared to placebo in the single-dose trials (Trials 3401, 3404, and 2401). The TEAEs that occurred at a higher rate in the tradipitant 85-mg arm compared to the placebo arm included headache (7.0% versus 5.3%), fatigue (6.2% versus 2.6%), and somnolence (6.2% versus 3.9%).

Table 24. Treatment-Emergent Adverse Events¹ Occurring at ≥5% Frequency, Safety Population, Pooled Analyses for Tradipitant 85 mg vs. Placebo, Trials 3401 and 3404

	Tradipitant 85 mg N=227 n (%)	Placebo N=228 n (%)
Preferred Term²		
Any TEAE	66 (29.1)	39 (17.1)
Headache	16 (7.0)	12 (5.3)
Somnolence	14 (6.2)	9 (3.9)
Fatigue	14 (6.2)	6 (2.6)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, versions 23.0 and 26.0.

² Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

The TEAEs that occurred at a higher rate in the tradipitant 170-mg arm compared to the placebo arm included somnolence (12.5% versus 5.8%), headache (9.7% versus 5.8%), and fatigue (8.3% versus 2.1%).

Table 25. Treatment-Emergent Adverse Events¹ Occurring at ≥2% Frequency, Safety Population, Pooled Analyses for Tradipitant 170 mg vs. Placebo, Trials 3401, 3404, and 2401

	Tradipitant 170 mg N=289 n (%)	Placebo N=291 n (%)
Preferred Term²		
Any TEAE	113 (39.1)	85 (29.2)
Somnolence	36 (12.5)	17 (5.8)
Headache	28 (9.7)	17 (5.8)
Fatigue	24 (8.3)	6 (2.1)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, versions 21.0, 23.0, and 26.0.

² Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

The TEAEs of headache, somnolence, and fatigue occurred more commonly in both tradipitant arms compared to placebo. Among the trials that assessed 170 mg (Trials 2401, 3401, and 3404), and trials that assessed 85 mg (Trials 3401 and 3404), somnolence occurred at a higher rate for the pooled 170-mg arms versus pooled placebo arms (12.5% versus 5.8%, risk difference 6.7%) compared to the pooled 85-mg arms versus pooled placebo arms (6.2% versus 3.9%; risk difference 2.3%). There were also greater risk differences in the 170-mg arms versus placebo for headache (9.7% versus 5.8%; risk difference 3.9%) and fatigue (8.3% vs. 2.1%; risk difference 6.2%) compared to the 85-mg arms for headache (7.0% vs. 5.3%; risk difference 1.7%) and fatigue (6.2% versus 2.6%; risk difference 3.6%). Of note, the TEAEs reported by subjects may be a result of motion sickness, as motion sickness may present with a variety of symptoms (e.g., nausea, vomiting, headache, somnolence, fatigue, dizziness, belching, diaphoresis). However, the review team determined that the TEAEs described above were likely related to tradipitant, as they occurred more frequently in at least one of the tradipitant arms than in the placebo arm and are consistent with the mechanism of action of tradipitant (i.e., centrally-acting NK-1 receptor antagonist).

7.6.1.3. Laboratory Findings, Pooled Analyses, Trials 3401, 3404, and 2401

During the single-dose trials, no notable trends in changes from baseline were observed on routine clinical laboratory parameters (e.g., chemistry, hematology, urinalysis).

7.6.1.4. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials 3401, 3404, and 2401

No potential cases were identified for cholestasis or Hy's Law (i.e., AST or ALT $>3\times$ ULN, total bilirubin $>2\times$ ULN and ALP $<2\times$ ULN), or Temple's Corollary (i.e., AST or ALT $>3\times$ ULN) among subjects receiving tradipitant. There was one subject who met criteria for Temple's Corollary in the placebo arm (1/291, 0.3%).

In the pooled tradipitant 85-mg arms, there were few subjects (4/227, 1.8%) whose AST or ALT rose to $\geq 2\times$ ULN at a postbaseline trial visit. There was one subject in the placebo arm (1/228, 0.4%) with such an elevation. In the pooled tradipitant 170-mg arms, there were two subjects (0.7%) whose AST or ALT rose to $\geq 2\times$ ULN at a postbaseline trial visit. There were three subjects in the placebo arm (3/291, 1.0%) with such an elevation. Overall, there were no clear trends for elevated liver enzymes among the generally healthy individuals enrolled in these single-dose trials.

7.6.1.5. Vital Sign Analyses, Pooled Analyses, Trials 3401, 3404, and 2401

No notable trends were observed during this trial for vital sign parameters, including blood pressure, pulse rate, respiratory rate, and body temperature.

7.6.1.6. Electrocardiogram Analyses, Pooled Analyses, Trials 3401, 3404, and 2401

Subjects underwent 12-lead ECGs at the screening visit and at the end-of-trial visit. One subject who received tradipitant 85 mg (1/227, 0.4%) experienced a QTc interval >500 ms, as well as an increase in QTc interval of ≥ 60 ms. No other subjects among the three trials experienced such prolongation of the QTc interval. There were no other notable trends in ECG abnormalities.

7.6.1.7. Demographic Subgroup Analyses, Pooled Analyses, Trials 3401, 3404, and 2401

[Table 26](#) and [Table 27](#) below describe TEAEs by demographic subgroups (sex, age group, race) in those receiving tradipitant compared to placebo in the single-dose trials (Trials 2401, 3401, 3404). For subjects who received tradipitant 85 mg, rates of adverse events were at least 5% higher than placebo for those who were female (27.1% versus 17.8%), male (32.5% versus 16.1%), <65 years of age (28.6% versus 17.1%), ≥ 65 years of age (31.4% versus 17.4%), whose race was White (29.5% versus 16.1%) or Asian (33.3% versus 13.0%), and whose ethnicity was Hispanic or Latino (39.3% versus 20.0%) or not Hispanic or Latino (28.0% versus 16.0%). The numbers of subjects whose race was other than White or Asian, and whose ethnicities were not

reported or unknown were small, precluding a clear determination regarding whether there is an increased risk of adverse events in these demographic subgroups.

Table 26. Overview of Treatment-Emergent Adverse Events by Demographic Subgroup, Safety Population, Pooled Analyses for Tradipitant 85 mg, Trials 3401 and 3404

Characteristic	Tradipitant 85 mg N=227 n/N _s (%)	Placebo N=228 n/N _s (%)
Sex		
Female	39/144 (27.1)	24/135 (17.8)
Male	27/83 (32.5)	15/93 (16.1)
Age group, years		
<65	55/192 (28.6)	35/205 (17.1)
≥65	11/35 (31.4)	4/23 (17.4)
Race		
American Indian or Alaska Native	0/0 (NA)	0/3 (0.0)
Asian	6/18 (33.3)	3/23 (13.0)
Black or African American	1/9 (11.1)	1/11 (9.1)
Native Hawaiian or Other Pacific Islander	0/1 (0.0)	0/0 (NA)
White	57/193 (29.5)	29/180 (16.1)
Other	2/6 (33.3)	6/11 (54.5)
Ethnicity		
Hispanic or Latino	11/28 (39.3)	6/30 (20.0)
Not Hispanic or Latino	52/186 (28.0)	30/187 (16.0)
Not reported or unknown	3/13 (23.1)	0/11 (0.0)

Source: adae.xpt, adsl.xpt; Software: JMP

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

For subjects who received tradipitant 170 mg, rates of adverse events (i.e., excluding *motion sickness*) were at least 5% higher than placebo for those who were female (35.8 % versus 24.2%), male (33.3% versus 18.3%), <65 years of age (34.9% versus 22.6%), ≥65 years of age (35.3% versus 15.4%), whose race was Black or African American (28.6% versus 20.0%), White (32.7% versus 21.8%), or Asian (42.9% versus 12.9%), and whose ethnicity was Not Hispanic or Latino (35.1% versus 27.9%). The numbers of subjects whose race was other than Black or African American, White, or Asian, and whose ethnicities were not reported or unknown were small, precluding a clear determination regarding whether there is an increased risk of adverse events in these demographic subgroups.

Table 27. Overview of Treatment-Emergent Adverse Events Excluding *Motion Sickness* by Demographic Subgroup, Safety Population, Pooled Analyses for Tradipitant 170 mg, Trials 2401, 3401, and 3404

Characteristic	Tradipitant 170 mg N=289 n/N_s (%)	Placebo N=291 n/N_s (%)
Sex		
Female	69/193 (35.8)	44/182 (24.2)
Male	32/96 (33.3)	20/109 (18.3)
Age group, years		
<65	89/255 (34.9)	60/265 (22.6)
≥65	12/34 (35.3)	4/26 (15.4)
Race		
American Indian or Alaska Native	1/1 (100.0)	0/4 (0.0)
Black or African American	6/21 (28.6)	3/15 (20.0)
White	74/226 (32.7)	50/229 (21.8)
Asian	12/28 (42.9)	4/31 (12.9)
Native Hawaiian or Other Pacific Islander	2/4 (50.0)	0/0 (NA)
Other	6/9 (66.7)	7/12 (58.3)
Ethnicity		
Hispanic or Latino	19/46 (41.3)	19/51 (37.3)
Not Hispanic or Latino	81/231 (35.1)	64/229 (27.9)
Not reported or unknown	1/12 (8.3)	0/11 (0.0)

Source: adae.xpt, adsl.xpt; Software: JMP

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.2. Safety Results, Open-Label Trial, Trial 3403

Subjects in Trial 3403 were randomized to either tradipitant 85 mg or tradipitant 170 mg to be taken as needed 60 to 120 minutes prior to a travel event anticipated to induce motion sickness symptoms during the 12-month evaluation period.

Trial 3403 was the only trial that assessed multiple doses of tradipitant for the indication of prevention of vomiting induced by motion. The trial duration was limited to 90 dosing days, which does not allow for an assessment of clinical safety of tradipitant beyond 90 doses for the proposed indication. Thus, adverse effects arising from long-term usage of tradipitant cannot be assessed.

The design of this trial included several limitations that affect the interpretability of the results:

- The trial included infrequent safety assessments, occurring every 4 months. Between the clinical site visits, subjects were expected to report adverse events to the Investigator, but neither the travel event e-diary nor the weekly e-diary used in the trial queried subjects about adverse events, which may have results in underreporting of adverse events. The potential of an underreporting of adverse events is further suggested by the fact that there was a similar rate of TEAEs reported for Trial 3403 (32.7% for tradipitant 85 mg; 34.4% for tradipitant 170 mg), as compared to the rate of TEAEs in the single dose Trials 3401 (26.8% for tradipitant 85 mg; 28.3% for tradipitant 170 mg) and 3404 (31.7% for tradipitant 85 mg; 34.9% for tradipitant 170 mg). It would generally be assumed that the rate of TEAEs in Trial 3403 would be greater than in the single-dose trials, due to the subjects' mean exposure of approximately 24 doses of tradipitant over the course of 12 months in Trial 3403, and due to

the Applicant's definition of TEAE that includes adverse events that are newly occurring or worsening from baseline until 3 days after the last dose of trial medication (i.e., rather than the *most recent* dose of trial medication). Thus, any adverse event occurring between the first dose and 3 days following the final dose (e.g., occurring during Month 12) would be considered a TEAE. While the Applicant states that this definition was selected as a conservative approach, the rates of TEAEs reported in single-dose trials were similar to rates of TEAEs in Trial 3403. Therefore, due to the infrequent safety assessments, there may have been underreporting of adverse events.

- Subjects were permitted to use tradipitant prior to a variety of travel events, which could differ in durations and intensities. Approximately half of reported travel events were travel by car (1142 out of 2302 events in the 85-mg arm, 1107 out of 2198 events in the 170-mg arm), with the remainder of events distributed among boat, bus, plane, train, and other modes of travel with similar proportions between the two treatment arms. The variety of travel conditions permitted in the trial may have introduced additional variability in the effects of motion among different subjects and among travel events for each subject. Additionally, subjects may have chosen alternative types of travel to reduce the likelihood of anticipated motion sickness, or used methods to alleviate symptoms that are specific to the mode of travel (e.g., sitting in the front seat of a car, sitting in a forward-facing seat on a train). Without standardization of the travel conditions and without a placebo control, it is challenging to assess whether reported AEs were due to tradipitant or due to motion sickness.
- The two methods utilized by the Applicant to determine the number of doses of tradipitant used by each subject were found by the review team to have some discrepancies. One method was to subtract the number of capsules returned from the number of capsules dispensed. The second method was based on subjects self-reporting when they used tradipitant in an e-diary. When determining the total number of doses with the first method (counting returned capsules), a majority of subjects (272 out of 382 [71.2%]) used more doses of tradipitant than using the second method (subject self-reporting). Conversely, there were some subjects who used more doses according to their self-reporting than the total calculated based on the number of capsules dispensed and returned (66 out of 382 [17.3%]). This discrepancy in the methods for determining exposure limits the interpretation of use patterns observed in this trial. Specifically, subjects' overall use of tradipitant may be over-estimated as these data were calculated based on the number of capsules returned compared to those dispensed, and capsules/bottles of medication that were "missing" were presumed to be utilized by subjects. Additionally, the number of doses determined to be used during time periods shorter than the full duration of the trial (i.e., maximum use in any 30-day period, maximum consecutive dosing days) may be under-estimated, as these exposure data are determined based on subjects' e-diary records, which may be incomplete depending on subjects' utilization of the e-diary.
- Subjects did not strictly adhere to their assigned dosing regimens. Among the trips taken by subjects in the 85-mg arm, a different dose was used (i.e., a subject self-administered 170 mg rather than 85 mg) in approximately 9% of trips. Among trips taken by subjects in the 170-mg arm, a different dose was used (i.e., a subjects self-administered 85 mg rather than 170 mg) in approximately 5% of trips. These deviations in dosing from the assigned treatment arms limits the interpretability of the data for each treatment arm.

- The trial did not include a placebo arm or concurrent comparator; therefore, it is challenging to determine which adverse events were attributable to tradipitant rather than other factors (e.g., symptoms of motion sickness, concomitant medications) in the intended use population. This is particularly relevant for tradipitant, as the most common adverse events in the single-dose trials (i.e., somnolence, headache, and fatigue) overlap with symptoms of motion sickness.

7.6.2.1. Overall Exposure, Trial 3403

[Table 28](#) below summarizes exposure durations from the evaluation period of Trial 3403. Overall cumulative exposure was calculated as the difference between capsules dispensed and capsules returned.

Table 28. Duration of Exposure,¹ Safety Population, Trial 3403

Parameter	Tradipitant 85 mg N=194 ² n (%)	Tradipitant 170 mg N=181 ² n (%)
Duration of treatment, days		
Mean (SD)	23.8 (22.5)	23.9 (20.9)
Median (Q1, Q3)	15 (7, 36)	18 (8.75, 36)
Min, max	1, 108	0, 108
Subjects treated by duration in days, n (%)		
≤30 days	135 (69.6)	123 (68.0)
0 days ³	0	4 (2.2)
>0 to ≤5 days	40 (20.6)	25 (13.8)
>5 to ≤10 days	25 (12.9)	25 (13.8)
>10 to ≤20 days	46 (23.7)	43 (23.8)
>20 to ≤30 days	24 (12.4)	26 (14.4)
>30 days	59 (30.4)	58 (32.0)
>30 to ≤60 days	46 (23.7)	48 (26.5)
>60 to ≤90 days	8 (4.1)	6 (3.3)
>90 days	5 (2.6)	4 (2.2)

Source: adex.xpt; Software: JMP, R

¹ Exposure determined by cumulative dosing days, excluding days between doses, calculated as the difference between capsules dispensed and capsules returned, except for capsules reported as lost.

² Differences in N for exposure duration compared to the safety population (tradipitant 85 mg, N=199; tradipitant 170 mg, N=183) are due to 7 subjects who were lost to follow-up, making their total exposure unknown.

³ Four subjects in the tradipitant 170 mg arm were documented as having 0 days of exposure despite having received a dose of tradipitant at the time of randomization, and were thus included in the safety population. In a July 30, 2025, response to an information request sent on June 27, 2025, the Applicant stated that they had identified study coordinators who misunderstood the number of lost capsules as being the number of un-retained capsules. They sent queries to sites regarding such data issues, and stated that only 10 of these “bottle record” issues were unresolved at the time of the interim data cut for Trial 3403. Because few subjects in the safety population were impacted (10 of 382, 2.6%), they were not excluded from this table.

Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects who were exposed to the drug for the indicated number of dosing days; Q, quartile; SD, standard deviation

It is notable that a majority of subjects (69.6% in the tradipitant 85-mg arm, and 68.0% in the tradipitant 170-mg arm) used tradipitant for 30 or fewer days throughout the duration of the 12-month trial. This indicates that most subjects used the drug infrequently, consistent with the typical sporadic occurrence of motion sickness symptoms. However, the remaining subjects, which amount to nearly one-third of the trial population, used the drug for greater than 30 days,

and some (2.6% in the tradipitant 85-mg arm and 2.2% in the tradipitant 170-mg arm) used it beyond the 90-day maximum permitted in the protocol.²⁰

[Table 29](#) below summarizes the maximum number of doses in a 30-day period for all subjects who completed the trial. For each subject, the 30 consecutive days during the trial with the highest reported usage of tradipitant based on travel e-diary entries were identified, and the number of doses used in those 30 days was determined. The most common maximum dosage in a 30-day period was 3 to 4 doses (36.2% in the tradipitant 85-mg arm; 31.7% in the tradipitant 170-mg arm), and few subjects used a maximum of 9 or more doses in a 30-day period (4.5% in the tradipitant 85-mg arm; 6.6% in the tradipitant 170-mg arm).

Table 29. Maximum Number of Doses in Any 30-Day Period, Safety Population, Trial 3403

	Tradipitant 85 mg	Tradipitant 170 mg
	N=199	N=183
Maximum Doses Per 30-Day Period ¹	n (%)	n (%)
0	13 (6.5)	14 (7.7)
1 to 2	64 (32.2)	44 (24.0)
3 to 4	72 (36.2)	58 (31.7)
5 to 6	27 (13.6)	40 (21.9)
7 to 8	14 (7.0)	15 (8.2)
≥9	9 (4.5)	12 (6.6)

Source: adqs.xpt; Software: R

¹ Data for this table are based on the ADQS dataset, which relies on subjects reporting their use of tradipitant via an e-diary, rather than relying on numbers of capsules dispensed and returned at study visits. In a communication from the Applicant received May 19, 2025, in response to an information request sent on May 12, 2025, the Applicant stated that “patients may forget to report a given event,” and that a limitation of this dataset is that “it relies on patient reporting which is only as accurate as the patient’s compliance on reporting the information about motion sickness inducing events timely and accurately.” These data are therefore derived from a different dataset compared to the overall exposure data, and may underestimate subjects’ use of tradipitant. See Section [7.6.2](#).

Abbreviations: N, number of subjects in treatment arm; n, number of subjects who used a maximum dose per 30 days in each listed range; NA, not applicable

[Table 30](#) below summarizes the maximum consecutive days that subjects were exposed to tradipitant throughout the course of the 12-month trial, based on subjects’ entries into a travel e-diary during the trial. In both treatment arms, subjects most commonly used tradipitant for a maximum 1 to 2 consecutive days (80.9% in the tradipitant 85-mg arm; 76.0% in the tradipitant 170-mg arm), and subjects rarely used tradipitant for 5 or greater consecutive days (3.0% in the tradipitant 85-mg arm; 4.9% in the tradipitant 170-mg arm).

²⁰ Subjects in Trial 3403 were dispensed tradipitant in either one or two 36-count bottles every four months during the 12-month trial. Despite the protocol specifying that tradipitant capsules should be dispensed such that subjects do not exceed 90 doses, there were 9 total cases of subjects receiving greater than the permitted duration of use.

Table 30. Maximum Consecutive Dosing Days, Safety Population, Trial 3403

	Tradipitant 85 mg N=199 n (%)	Tradipitant 170 mg N=183 n (%)
Maximum Consecutive Doses¹		
0	13 (6.5)	14 (7.7)
1 to 2	161 (80.9)	139 (76.0)
3 to 4	19 (9.5)	21 (11.5)
5 to 6	3 (1.5)	6 (3.3)
7 to 8	3 (1.5)	2 (1.1)
9 to 10	0 (0.0)	1 (0.5)

Source: adqs.xpt; Software: R

¹ Data for this table are based on the ADQS dataset, which relies on subjects reporting their use of tradipitant via an e-diary. In a communication from the Applicant received May 19, 2025, in response to an information request sent on May 12, 2025, the Applicant stated that “patients may forget to report a given event,” and that a limitation of this dataset is that “it relies on patient reporting which is only as accurate as the patient’s compliance on reporting the information about motion sickness inducing events timely and accurately.” These data are therefore derived from a different dataset compared to the overall exposure data, and may underestimate subjects’ use of tradipitant. See Section 7.6.2.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects whose maximum number of consecutive days of using tradipitant was in each listed range; NA, not applicable

7.6.2.2. Overview of Treatment-Emergent Adverse Events, Summary, Trial 3403

Table 31 below provides a summary of TEAEs reported in Trial 3403. Overall, TEAEs were reported by a similar proportion of subjects in the tradipitant 85-mg (32.7%) and tradipitant 170-mg (34.4%) arms. A higher proportion of subjects had TEAEs leading to permanent discontinuation of trial drug in the tradipitant 170-mg arm than the tradipitant 85-mg arm (4.4% versus 2.5%, respectively), as described in Section 7.6.2.5 below.

Table 31. Overview of Adverse Events,¹ Safety Population, Trial 3403

	Tradipitant 85 mg N=199 n (%)	Tradipitant 170 mg N=183 n (%)
Event Category		
SAE	1 (0.5)	3 (1.6)
SAEs with fatal outcome	0	0
TEAE leading to permanent discontinuation of trial drug	5 (2.5) ³	8 (4.4)
TEAE leading to interruption of trial drug	1 (0.5)	0
Any TEAE ²	65 (32.7)	63 (34.4)
Severe	3 (1.5)	3 (1.6)
Moderate	19 (9.5)	19 (10.4)
Mild	43 (21.6)	41 (22.4)

Source: адае.xpt; Software: R

¹ Treatment-emergent adverse events defined as an adverse event that is newly occurring or worsening from baseline until 3 days after the last dose of trial medication.

² Severity as assessed by the investigator.

³ One subject in the tradipitant 85-mg arm (Subject (b) (6)) withdrew consent voluntarily after experiencing an adverse event. The Investigator considered their action taken with trial treatment to be “none,” and that the reason for trial discontinuation was withdrawal of consent. The review team considers this subject to have withdrawn as a result of a TEAE, and is thus included in this table.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2.3. Deaths, Trial 3403

There was one death that occurred among subjects in Trial 3403. Subject (b) (6) a 39-year-old male subject with history of motion sickness as well as depression and anxiety, was

randomized to receive tradipitant 170 mg as needed. He experienced a self-inflicted gunshot wound resulting in death 17 days after the subject's last dose of tradipitant. The death was not considered a treatment-emergent event or related to trial medication.

7.6.2.4. Serious Treatment-Emergent Adverse Events, Trial 3403

There was one subject in the tradipitant 85-mg arm who experienced an SAE (1/199, 0.5%), and three subjects in the tradipitant 170-mg arm who experienced an SAE (3/183, 1.6%). Eleven SAEs occurred in one subject in the tradipitant 170-mg arm, and an additional 2 SAEs (i.e., femur fracture and sinus node dysfunction) each occurred in different subjects. No SAE occurred in more than one subject.

The narratives for the SAEs in the tradipitant 85-mg arm and tradipitant 170-mg arm are described below:

- Anemia: Subject (b) (6), a 72-year-old female with history of motion sickness as well as left hip osteoarthritis was randomized to receive tradipitant 85 mg as needed. On trial Day 164, 87 days following her most recent dose of tradipitant, the subject experienced symptomatic anemia and was hospitalized for 5 days. She presented to an emergency department immediately following an outpatient left hip total arthroplasty, due to symptomatic anemia associated with hypotension as a result of surgical bleeding. She received intravenous normal saline, albumin, and a unit of packed red blood cells. Her symptomatic anemia and hypotension resolved. The event was determined by the investigator to be unrelated to the trial medication, and she remained enrolled in the trial, in which she used a total of 7 doses of tradipitant. The clinical context suggests that the TEAE of anemia was secondary to a complication of the surgery that the subject underwent for a pre-existing condition.
- Femur fracture: Subject (b) (6), a 62-year-old female with history of motion sickness was randomized to receive tradipitant 170 mg as needed. On trial Day 106, 57 days following her most recent dose of tradipitant, the subject experienced an accidental slip and fall while at home, which resulted in a left proximal femur fracture. She was hospitalized for 5 days and underwent surgery for a rod implantation. The event was determined by the investigator to be unrelated to the trial medication, and she remained enrolled in the trial, in which she used a total of 30.5 doses of tradipitant.²¹
- Sinus node dysfunction: Subject (b) (6), a 63-year-old male with history of motion sickness was randomized to receive tradipitant 170 mg as needed. On trial Day 73, 3 days following a dose of tradipitant, the subject visited an emergency department for syncope and stayed overnight for diagnostic tests and observation. Tests that were performed included computerized tomography scan of the head without contrast, and a chest radiograph. He was diagnosed with sick sinus syndrome as the etiology for his syncopal event. He underwent placement of a pacemaker and was discharged from the hospital in stable condition 2 days after his initial presentation. The event was determined by the investigator to be unrelated to

²¹ Subjects who were assigned to the 170-mg arm and returned an odd number of capsules resulted in the reporting of half-doses.

the trial medication, as it occurred greater than 72 hours following his previous dose and he remained enrolled in the trial, in which he used a total of 24 doses of tradipitant.

- Cerebrovascular accident, cerebral arteriosclerosis, cerebral artery occlusion, cerebral artery stenosis, dysarthria, and essential hypertension: Subject (b) (6), a 69-year-old female with history of motion sickness was randomized to receive tradipitant 170 mg as needed. On trial Day 256, 41 days following her most recent dose of tradipitant, the subject experienced an initial cerebrovascular accident prompting hospitalization, and diagnosis was performed via magnetic resonance imaging of the brain. The investigator was made aware of these events 87 days after the onset of the SAEs, when trying to schedule an interim trial visit. The investigator considered all of these events to be unrelated to tradipitant and were instead attributed to obesity as the primary precipitating factor. She remained enrolled in the trial, in which she used a total of 29 doses of tradipitant. The constellation of TEAEs suggests that the subject experienced multiple sequelae of a cerebrovascular accident, which may have been precipitated by underlying obesity and hypertension.
- Asthenia, glucose tolerance impaired, influenza-like symptoms, myalgia, urinary tract infection: Subject (b) (6), a 69-year-old female with history of motion sickness as well as a recent cerebrovascular accident (see above), was randomized to receive tradipitant 170 mg as needed. On trial Day 303, 6 weeks after her hospitalization for cerebrovascular accident (see above), and 3 days following her most recent dose of tradipitant, she presented with nausea and chills upon returning home from a cruise. She was hospitalized for 2 days and underwent a diagnostic evaluation that included a chest radiograph, transthoracic echocardiogram, computed tomography (CT) scan of the head, magnetic resonance imaging of the head, electrocardiogram, and laboratory evaluations, all of which did not reveal evidence of a new stroke or a specific unifying etiology for her symptoms. She underwent CT angiography of the head and neck, which showed chronic left vertebral artery stenosis. She was diagnosed with generalized weakness and myalgia, flu-like symptoms, and possible urinary tract infection with secondary diagnoses of hypertension and prediabetes. She received anticoagulants, antihypertensive medication, and statins. She reported ongoing symptoms of shaking hands, difficulties with problem solving, generalized weakness, and dizziness. The investigator considered this event to be unrelated to tradipitant, and more likely a result of underlying disease and pre-existing conditions, including obesity. She remained enrolled in the trial and ultimately received a total of 29 doses of tradipitant. The constellation of TEAEs suggests that the subject experienced a likely infectious illness in the context of multiple pre-existing conditions.

7.6.2.5. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Trial 3403

[Table 32](#) below shows TEAEs leading to discontinuation from Trial 3403. The most common TEAE leading to discontinuation in the tradipitant 85-mg arm was somnolence, which occurred in two subjects and was the only TEAE that led to discontinuation in more than one subject in that treatment arm. There was one TEAE leading to interruption of the trial drug in the tradipitant 85-mg arm, which was a rise in serum transaminase levels. In the tradipitant 170-mg arm, the most common TEAEs that led to trial discontinuation were somnolence, dizziness, and fatigue, which each occurred in two subjects.

Table 32. Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Safety Population, Trial 3403

Preferred Term	Tradipitant 85 mg	Tradipitant 170 mg
	N=199 n (%)	N=183 n (%)
Any TEAE leading to discontinuation ¹	5 (2.5)	8 (4.4)
Somnolence	2 (1.0)	2 (1.1)
Dizziness	1 (0.5)	2 (1.1)
Fatigue	0	2 (1.1)
Arteriosclerosis coronary artery	0	1 (0.5)
Disturbance in attention	0	1 (0.5)
Dry mouth	0	1 (0.5)
Feeling abnormal	0	1 (0.5)
Headache	0	1 (0.5)
Malaise	0	1 (0.5)
Nausea	0	1 (0.5)
Dysphagia	1 (0.5)	0
Fractured sacrum	1 (0.5)	0
Hyperhidrosis	1 (0.5)	0
Paranoia	1 (0.5)	0
Syncope	1 (0.5)	0

Source: Trial 3403 adae.xpt

¹ Number of subjects with at least one TEAE leading to discontinuation.

Treatment-emergent adverse events defined as an adverse event that is newly occurring or worsening from baseline until 3 days after the last dose of trial medication.

Severity as assessed by the investigator.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

Narratives for TEAEs leading to treatment discontinuation or interruption that the review team considered as likely related to tradipitant are summarized as follows:

- **Somnolence and dry mouth:** Subject (b) (6), a 52-year-old male with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had a pertinent past medical history of hearing loss in the left ear and benign premature ventricular contractions. Concomitant medications and supplements included naproxen, B complex vitamins, vitamin C, Vitamin D3, omega complex, magnesium, glucosamine chondroitin, and a multivitamin. On Day 1, the subject experienced mild dry mouth and mild somnolence, which improved on Day 30. The last dose of tradipitant prior to the event was earlier on Day 1. The subject was discontinued due to TEAEs on Day 56 of the trial at which time he had used a total of 6.5 doses of tradipitant. The Investigator determined that the TEAEs were certainly related to the trial drug and not serious. The Investigator coded the AE outcomes as *resolved* for dry mouth, and *unknown* for somnolence, both without treatment. The constellation and timing of TEAEs suggests that the subject's symptoms were related to tradipitant.
- **Dizziness, malaise, and nausea:** Subject (b) (6), a 40-year-old woman with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had a pertinent past medical history of attention-deficit/hyperactivity disorder, depression, anxiety disorder, migraine with aura, and seasonal allergies. Concomitant medications included immunotherapy injections, diphenhydramine, cetirizine, dextroamphetamine, and ibuprofen. On Day 1, the subject experienced dizziness, malaise, and nausea. The TEAEs resolved later the same day. The last dose of tradipitant prior to the event was earlier on Day 1. The subject

was discontinued due to TEAEs on Day 112 of the trial, at which time she had used a total of one dose of tradipitant. The Investigator determined that the TEAEs were possibly related to the trial drug and not serious. The Investigator coded the AE outcomes as resolved with no specific treatment. The constellation and timing of TEAEs suggests that the subject's symptoms were related to tradipitant.

- Fatigue, dizziness, disturbance in attention: Subject (b) (6), a 59-year-old female with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had no reported pertinent past medical history or concomitant medications. On Day 1, the subject experienced mild fatigue, dizziness, and disturbance in attention, and recovered within one day. The subject experienced mild dizziness again on Day 35, which resolved within one day. The last dose of tradipitant prior to the event on Day 1 was earlier on Day 1, and the last dose prior to the event on Day 35 was on Day 4. The TEAEs resolved without treatment. The subject was discontinued due to TEAEs on Day 93 of the trial, at which time she had used a total of 4 doses of tradipitant. The Investigator determined that the TEAEs were probably related to the trial drug and not serious. The Investigator coded the AE outcomes as resolved with no specific treatment. The constellation and timing of TEAEs suggests that the subject's symptoms were related to tradipitant.
- Somnolence: Subject (b) (6), a 46-year-old male with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had no other pertinent past medical history or concomitant medications. On Day 1, following the initial dose of the trial drug, the subject experienced somnolence, and continued to experience intermittent mild somnolence until Day 14. The TEAE resolved without treatment. The subject was discontinued due to TEAEs on Day 15 of the trial, at which time he had used a total of 1 dose of tradipitant. The Investigator determined that the TEAE was certainly related to the trial drug and not serious. The Investigator coded the AE outcome as resolved with no specific treatment. The timing of the TEAE suggests that the subject's symptoms were related to tradipitant.
- Headache: Subject (b) (6), a 39-year-old female with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had a pertinent past medical history of goiter status-post thyroidectomy, elevated diastolic blood pressure, and dengue fever. She reported no concomitant medication use. On Day 3 and Day 8, the subject experienced headaches, which each resolved within the same day. The last doses of tradipitant prior to the event on Day 3 was on Day 1; the last dose prior to the event on Day 8 was earlier on Day 8. The TEAEs resolved without treatment. The subject did not take any subsequent doses prior to trial discontinuation due to TEAEs on Day 78, at which time she had used a total of 4 doses of tradipitant. The Investigator determined that the TEAEs were possibly related to the trial drug and not serious. The Investigator coded the AE outcomes as resolved with no specific treatment. The timing of the TEAEs suggests that the subject's symptoms were related to tradipitant.
- Fatigue: Subject (b) (6), a 48-year-old female with history of motion sickness was randomized to receive tradipitant 170 mg as needed. The subject had a pertinent past medical history of insomnia, allergic rhinitis, and atopic dermatitis. Concomitant medications included dupilumab and lorazepam. On Day 1, following the initial dose of the trial drug, the subject experienced fatigue, which resolved within one day. The TEAE resolved without

treatment. The subject did not take any subsequent doses prior to trial discontinuation due to TEAEs on Day 124, at which time she had used a total of 1 dose of tradipitant. The Investigator determined that the TEAE was possibly related to tradipitant and not serious. The Investigator coded the AE outcome as resolved with no specific treatment. The timing of the TEAE suggests that the subject's symptom was related to tradipitant.

- Feeling abnormal: Subject (b) (6), a 37-year-old female with history of motion sickness was assigned to receive tradipitant 170 mg as needed. The subject had a pertinent past medical history of headaches, atopic dermatitis, and menstrual cramps. Concomitant medications included Dupixent, Excedrin, Pamprin, ibuprofen, and Opzelura cream. On Days 1 to 3, the subject reported a TEAE of feeling abnormal (verbatim "foggy feeling in head") after receiving the initial dose of tradipitant on Day 1. She again reported a TEAE of feeling abnormal on Days 13 to 15 following a dose of tradipitant on Day 12. The subject's last dose of tradipitant was on Day 13, and she later discontinued the trial due to TEAEs on Day 127, at which time she had used a total of 3 doses of tradipitant. The Investigator determined that the TEAE was probably related to tradipitant and not serious. The Investigator coded the AE outcome as resolved with no specific treatment. The timing of the TEAEs suggests that the subject's symptoms were related to tradipitant.
- Syncope, hyperhidrosis, and fractured sacrum: Subject (b) (6), a 40-year-old male with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of prediabetes, gout, myopia, and eczema. Concomitant medications included allopurinol, metformin, and ibuprofen. On Day 2, the subject experienced hyperhidrosis, syncope, and sacral fracture. He experienced two sweating events, occurring for 2 hours after drug administration, and again 13 hours afterward, which was associated with a syncopal event. The last dose of tradipitant prior to the event was earlier on Day 2. The TEAE was treated with no specific medication. The subject was discontinued due to TEAEs on Day 12 of the trial, at which time she had used a total of 2 doses of tradipitant. The Investigator determined that the syncopal event was likely related to dehydration, rather than a vasovagal event. The Investigator and Applicant considered hyperhidrosis to be moderate and possibly related to tradipitant, and syncope was considered to be severe and possibly related to tradipitant. The sacral fracture was considered severe and unrelated to tradipitant. The Investigator coded the AE outcome of hyperhidrosis and syncope as resolved, and fractured sacrum as not resolved, with continuing use of concomitant medication. The constellation and timing of TEAEs suggests that the subject possibly experienced hyperhidrosis and syncope related to tradipitant.
- Somnolence and paranoia: Subject (b) (6), a 54-year-old female with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of hyperparathyroidism status-post partial parathyroidectomy and seasonal allergies. Concomitant medications and supplements included loratadine, vitamin C, vitamin B, and a multivitamin. On Day 15, the subject experienced somnolence, and on Day 16, the subject experienced paranoia. The last dose of tradipitant prior to these events was on Day 15. The TEAEs were treated with no medication. The subject's last dose of tradipitant was on Day 15, and she was discontinued due to TEAEs on Day 105 of the trial, at which time she had used 5 doses of tradipitant. The Investigator determined that the TEAEs were certainly related to the trial drug and not serious. The Investigator coded the AE outcomes as

resolved without use of concomitant medication. The constellation and timing of TEAEs suggests that the subject's adverse events were related to use of tradipitant.

- Elevated liver tests: Subject (b) (6), a 43-year-old male with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of nonalcoholic steatohepatitis, and he used no concomitant medications. At Visit 4 on Day 230, the subject experienced elevated ALT of 132 U/L (ULN =40 U/L), elevated from a baseline value of 56 U/L. The most recent dose prior to the start of the TEAE was on Day 228, by which time he had e-diary entries reporting that he had used 9 doses of tradipitant. He underwent an unscheduled visit on Day 246 showing reduced ALT to 109 U/L. Although AST was elevated from 23 U/L at baseline to 51 U/L at Visit 4 (ULN =43 U/L), this improved to 37 U/L at the unscheduled visit. He did not experience elevated alkaline phosphatase or total bilirubin levels. The TEAE resolved without treatment, and the TEAE was documented as having ended on Day 246, despite the ALT remaining elevated as it declined to 92 U/L at Visit 5 on Day 336. The subject's treatment was documented as *interrupted* due to this TEAE, despite e-diary documentation of the subject taking tradipitant 2 times during the period between TEAE onset and resolution. He documented using tradipitant another 13 times after resolution of the TEAE. By the end of the trial, he had used 58 doses of tradipitant.²² The case narrative indicates that the site reported that the subject could continue the trial without interruption due to the potential for the subject's underlying nonalcoholic steatohepatitis serving as an alternative explanation for the laboratory abnormalities. The constellation and timing of TEAEs indicates that the subject's adverse events were possibly related to tradipitant.
- Dysphagia: Subject (b) (6), a 53-year-old female with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of temporomandibular joint dysfunction, allergy to sulfonamides, and transient insomnia. Concomitant medications and supplements included cyclobenzaprine, diphenhydramine, melatonin, and a multivitamin. On Day 17, the subject experienced difficulty coordinating swallowing when eating food, and needed to drink water to assist with swallowing food. There was no reported swelling, food impaction, shortness of breath, dry mouth, coughing, or aspiration. The last dose of tradipitant prior to this event was on Day 16. The subject experienced similar symptoms after she used an additional dose of tradipitant on Day 18. The TEAE was treated with no medication. The subject's last dose of tradipitant was on Day 18, and she was discontinued due to TEAEs on Day 113, at which time she had used 3 doses of tradipitant. The Investigator determined that the TEAE was possibly related to the trial drug and not serious, despite assigning it a grade 3 severity. The Investigator coded the AE outcomes as resolved without use of concomitant medication. The timing of this TEAE suggests that the subject's adverse events were related to use of tradipitant.
- Dizziness: Subject (b) (6), a 48-year-old female with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), vertigo, hay fever, and herpes zoster. There were no reported concomitant medications. On Day 1, the

²² In determining total doses by subtracting doses returned from doses dispensed, and excluding capsules indicated as "lost," this subject received 58 total doses. However, the e-diary reporting accounts for 24 doses. The discrepancy between the two methods of determining tradipitant use is discussed above (see Section [II.7.6.2](#)).

subject experienced an episode of dizziness following the initial dose of tradipitant. The TEAE was treated with no medication. The subject was discontinued due to TEAEs on Day 1 after receiving a single dose of tradipitant. The Investigator determined that the relationship of the TEAE to tradipitant was not assessable. The Investigator coded the AE outcome as resolved without use of concomitant medication. The timing of this TEAE suggests that the subject's adverse event was possibly related to tradipitant.

- **Somnolence:** Subject (b) (6) a 60-year-old female with history of motion sickness was randomized to receive tradipitant 85 mg as needed. The subject had a pertinent past medical history of hypothyroidism, hyperlipidemia, seasonal allergies, allergy to sulfa drugs and papaya. Concomitant medications and supplements included levothyroxine, azelastine, omega-3 fatty acids, and a multivitamin. On Day 29 through Day 30, the subject experienced somnolence. The last dose of tradipitant prior to this event was on Day 29, and this was the subject's last dose of tradipitant in the trial. The TEAE was treated with no medication. The subject was discontinued due to TEAEs on Day 63, at which time she had used 6 doses of tradipitant. The Investigator determined that the TEAE was possibly related to trial drug and not serious. The Investigator coded the AE outcome as resolved without use of concomitant medication. The timing of this TEAE suggests that the subject's adverse event was related to use of tradipitant.

7.6.2.6. Treatment-Emergent Adverse Events, Trial 3403

Table 33 below describes TEAEs occurring in $\geq 2\%$ of subjects. The most common TEAEs for subjects receiving tradipitant were somnolence, fatigue, and dizziness. The TEAEs that occurred at a higher rate in the tradipitant 170-mg arm compared to the tradipitant 85-mg arm included somnolence (12.0% versus 10.6%), fatigue (8.7% versus 5.0%), dizziness (3.8% versus 2.5%), and nausea (2.2% versus 1.0%).

Table 33. Treatment-Emergent Adverse Events¹ Occurring at $\geq 2\%$ Frequency, Safety Population, Trial 3403

Preferred Term ²	Tradipitant 85 mg N=199 n (%)	Tradipitant 170 mg N=183 n (%)
Any TEAE	65 (32.7)	63 (34.4)
Somnolence	21 (10.6)	22 (12.0)
Fatigue	10 (5.0)	16 (8.7)
Dizziness	5 (2.5)	7 (3.8)
Dry Mouth	4 (2.0)	2 (1.1)
Nausea	2 (1.0)	4 (2.2)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 25.1.

² Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

Although the TEAEs of somnolence, fatigue, dizziness, and nausea appeared to occur more frequently in the tradipitant 170-mg arm than in the 85-mg arm, the TEAEs reported by subjects could be due to motion sickness, as motion sickness may present with a variety of symptoms (e.g., belching, diaphoresis, dizziness, headache, fatigue, and somnolence). Based on Trial 3403

data alone, without a concurrent comparator arm, it is challenging to determine whether the TEAEs described above were related to tradipitant; however, given that somnolence, fatigue, and dizziness occurred at higher rates in the tradipitant arms than the placebo arms in the pooled single-dose trials (see Section [7.6.1.2](#)), it is likely that these adverse events are attributable to tradipitant.

7.6.2.7. Laboratory Findings, Trial 3403

Overall, there were no clinically relevant trends in the laboratory data. However, interpretation of the laboratory data is limited due to the design of the open-label trial. Laboratory data were collected at trial visits, which occurred every 4 months, and the visits occurred irrespective of the timing of the subjects' exposure to tradipitant. Thus, the submitted data may not accurately reflect the potential effects of recent tradipitant exposure on laboratory results.

7.6.2.8. Assessment of Drug-Induced Liver Injury, Trial 3403

No potential cases were identified for Hy's Law (i.e., AST or ALT $>3\times$ ULN, total bilirubin $>2\times$ ULN and ALP $<2\times$ ULN). There was one subject in the tradipitant 85-mg arm (1/165; 0.6%) who met criteria for Temple's Corollary with ALT $\geq 3\times$ the ULN at Visit 4. There was one subject in the tradipitant 170-mg arm who met criteria for cholestasis with bilirubin $\geq 2\times$ the ULN at Visit 4 (1/149; 0.7%).

7.6.2.9. Vital Sign Analyses, Trial 3403

There were no substantial changes over time or differences between arms in vital sign parameters during this trial, including weight, blood pressure, pulse rate, respiratory rate, and body temperature.

7.6.2.10. Electrocardiogram Analyses, Trial 3403

Subjects underwent 12-lead ECGs at the screening visit (Visit 1) and at the end-of-trial visit (Visit 5). There was an increase in the QTcB interval aggregate of ≥ 30 ms relative to baseline in 5.8% of subjects in the tradipitant 85-mg arm, and in 5.7% of subjects in the tradipitant 170-mg arm. There were no other abnormalities exceeding 5% of subjects in either treatment arm.

7.6.2.11. Subgroup Analyses, Trial 3403

[Table 34](#) describes TEAEs by demographic subgroups (sex, age group, race, ethnicity) in those receiving tradipitant 85 mg and tradipitant 170 mg. Adverse event rates were higher in the tradipitant 170-mg arm compared to the 85-mg arm for subjects who were male (40.0% versus 26.7%) and of White race (35.5% versus 29.9%). Such a difference was not observed in female subjects or subjects of Asian race. The number of subjects who were races other than White or Asian was small, precluding a clear determination regarding whether there is possible dose-response in these demographic subgroups.

Table 34. Overview of Treatment-Emergent Adverse Events by Demographic Subgroup, Safety Population, Trial 3403

Characteristic	Tradipitant 85 mg N=199 n/N_s (%)	Tradipitant 170 mg N=183 n/N_s (%)
Sex		
Female	45/124 (36.3)	45/138 (32.6)
Male	20/75 (26.7)	18/45 (40.0)
Age group, years		
<65	56/172 (32.6)	55/161 (34.2)
≥65	9/27 (33.3)	8/22 (36.4)
Race		
American Indian or Alaska Native	1/1 (100.0)	0/0 (NA)
Black or African American	5/10 (50.0)	2/12 (16.7)
White	49/164 (29.9)	54/152 (35.5)
Asian	9/20 (45.0)	6/15 (40.0)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/2 (0.0)
Other	1/4 (25.0)	1/2 (50.0)
Ethnicity		
Hispanic or Latino	5/18 (27.8)	4/14 (28.6)
Not Hispanic or Latino	59/170 (34.7)	59/165 (35.8)
Not reported or unknown	1/11 (9.1)	0/4 (0.0)

Source: adae.xpt, adsl.xpt; Software: R, JMP

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.2.12. Safety Update Report, Trial 3403

A 120-day safety update report was submitted during the review, which included additional safety data for Trial 3403, including data for an additional 69 subjects in the tradipitant 85-mg arm (268 subjects total) and 74 subjects in the tradipitant 170-mg arm (257 subjects total), resulting in a total safety population of 525 subjects. The demographics among subjects included in the safety update are generally similar compared to the population originally submitted for review. The update included a mean duration of exposure (determined by cumulative dosing days, excluding days between doses) of 24.5 days in the tradipitant 85-mg arm (previously 23.8 days) and 24.3 days in the tradipitant 170-mg arm (previously 23.9 days). There were 2 additional trial discontinuations due to TEAEs. These included one TEAE of breast cancer in the tradipitant 85-mg arm, and one TEAE of migraine in the tradipitant 170-mg arm. There was one additional SAE, which was a case of ureterolithiasis in the tradipitant 170-mg arm. There were no deaths among subjects included in the safety update. Overall, the safety update report did not identify new safety signals or affect statements of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

7.7. Key Safety Review Issues

7.7.1. Adequacy of Nonclinical Information To Assess the Toxicological Effects of Tradipitant

Issue

The Applicant proposed for tradipitant to be used for the prevention of vomiting induced by motion on an as-needed basis, with no restriction on the total duration of use. However, the Applicant has neither conducted a chronic toxicity study in a nonrodent species with tradipitant, nor have they provided adequate scientific justification that such a study is not warranted to support unrestricted use of tradipitant over a lifetime for this indication. Additionally, the Applicant has not provided any data or scientific justification to suggest that the cumulative toxicity of tradipitant will be different whether dosing occurs consecutively or as needed (e.g., intermittently). Although tradipitant will be used intermittently at the discretion of the individual for the prevention of vomiting induced by motion (i.e., for prevention of discrete episodes on an as-needed basis), this use is expected to be repeated over a lifetime, as such episodes are expected to occur whenever the motion stimulus is present. Therefore, the adequacy of the nonclinical information submitted to the current NDA to support the proposed unrestricted use for this indication, i.e., repeated intermittent use over a lifetime, was identified as a review issue.

Assessment

An NDA submission is required to contain nonclinical studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity (21 CFR 314.50(d)(2)(ii)). As vomiting induced by motion may occur whenever the motion stimulus is present, any pharmacologic intervention for this indication is expected to be used repeatedly over a lifetime. Nonclinical programs are designed to assess and inform the risks of a new drug with the most intensive use (i.e., worst-case scenario). Repeated, intermittent use of tradipitant over a lifetime (i.e., whenever an individual is trying to prevent vomiting induced by motion) is such a scenario for this indication, as clinical data with tradipitant in Trial 3403 have demonstrated that a subset of individuals are likely to use the product frequently (see Section 7.6.2.1). Additionally, the relatively long half-life of tradipitant and its major human metabolites (28+ hours) supports that even single doses spaced days apart could lead to sustained exposure to and even accumulation of drug-related material.

While the nonclinical review team acknowledges that high doses of tradipitant (up to 1500 mg/kg/day) were tested in the completed nonclinical studies, this does not provide additional assurance of safety in lieu of adequate nonclinical studies, and it is inappropriate to base a safety determination on the dose level alone. Plasma exposure to tradipitant-related compounds did not increase proportionally to the increasing dose administered in either rats or dogs. Based on human equivalent dose, the highest tested dose of 1500 mg/kg/day²³ was 85- and 171-fold the

²³ While the highest tested dose of 1500 mg/kg/day was the NOAEL in the 6-month repeat-dose toxicity study in Fischer rats, the NOAEL in the 3-month study in dogs was 275 mg/kg/day (31-fold the MPHED based on HED).

MPHD of 170 mg/day in rats and dogs, respectively. However, based on the AUC of tradipitant alone,²⁴ this dose was only 0.4/1.1- and 12/24-fold²⁵ the MPHD in male/female rats and dogs, respectively. Thus, the unrestricted use of tradipitant over a lifetime for the prevention of vomiting due to motion would expose some individuals to physiological levels of tradipitant-related material over a duration of use without adequate nonclinical assessment of the toxicological risks.

The Applicant has neither conducted a chronic repeat-dose toxicity study in a nonrodent species, nor have they provided a suitable alternative, to adequately characterize the safety of unrestricted use of tradipitant over a lifetime (see Section 12). Completed repeat-dose toxicity studies with tradipitant include studies of up to 3 months in mice, 6 months in rats, and 3 months in dogs. FDA, in concert with other international regulatory agencies, generally considers subchronic (e.g., 3-month) toxicity studies to be insufficient in predicting the long-term systemic toxicity of a drug in humans ([DeGeorge et al. 1999](#); [Ledwith and DeGeorge 2011](#); [Jacobs and Hatfield 2013](#); [Roberts et al. 2015](#); [Galijatovic-Idrizbegovic et al. 2016](#); [Monticello et al. 2017](#)). More specifically, a chronic toxicity study in a nonrodent species can identify new toxicities or demonstrate the progression of minor or adaptive events to adverse effects that may be missed or unreported in shorter duration toxicity studies. Moreover, testing in a minimum of two mammalian animal species (i.e., one rodent and one nonrodent) provides adequate assurance of detecting toxicities that may be relevant to humans, as unique toxicities may occur in one species versus another ([Broadhead et al. 2000](#); [Olson et al. 2000](#); [Bailey et al. 2014](#); [Monticello et al. 2017](#)). Thus, chronic toxicity studies in two species are important to support the safety of a drug such as tradipitant for marketing approval (i.e., a drug for which there will be unrestricted use over a lifetime, without clinical trial safeguards in place). In the absence of a chronic toxicity study in a nonrodent species or a suitable alternative, the available nonclinical data are inadequate to support marketing approval for unrestricted use of tradipitant over a lifetime.

The Applicant proposed²⁶ that their additional in vitro studies with tradipitant (i.e., in vitro liver safety pharmacology and special toxicology studies using a four organ MPS), as part of a totality of evidence approach, adequately supported the safety of unrestricted use of tradipitant over a lifetime in the absence of a chronic toxicity study in a nonrodent species. Following review of these in vitro studies, the review team determined that these studies did not substantially contribute to the characterization of the long-term safety of tradipitant, based on limitations including lack of technical characterization, lack of established biological relevance, and short duration (see Section 13.2.3 and Section 13.2.6). As such, the review team concluded that a chronic toxicity study in a nonrodent species, or a suitable alternative, was still warranted to support the safety of unrestricted use of tradipitant over a lifetime.

As real-world use of an approved drug is not highly controlled like in a clinical trial, the recommended duration of nonclinical data to support marketing is longer than for clinical trials, with the intention of identifying as many risks as possible to inform safe use of a new product prior to approval. In the case of tradipitant for the prevention of vomiting induced by motion,

²⁴ A comparison of total tradipitant-related exposure (i.e., tradipitant + M2 + M3 + M4 + M8) in animals versus humans could not be made for the 6-month study in Fischer rats or the 3-month study in dogs, as the metabolites were not measured in these studies.

²⁵ With the NOAEL in dogs being 275 mg/kg/day (9.5/7.8-fold the MPHD in males and females, based on AUC of tradipitant alone).

unrestricted, repeat intermittent use over a lifetime should be supported by chronic toxicity studies in two species (i.e., a 6-month study in a rodent species and a ≥ 6 -month study in a nonrodent species), or a suitable alternative. As discussed, the Applicant has not adequately assessed the safety of tradipitant for unrestricted, lifetime use.

Thus, the nonclinical data are insufficient to support that tradipitant is safe for unrestricted use over a lifetime.

Conclusion

The nonclinical review team acknowledges that the clinical trial data demonstrate that tradipitant is effective at preventing vomiting induced by motion, and clinical safety data with tradipitant are available for up to 90 doses. We also acknowledge that the prescribing information will describe the limitations of the available safety data. However, there is insufficient nonclinical information to adequately support the safety of unrestricted use of tradipitant over a lifetime in human subjects, and the lack of adequate nonclinical data to support the unrestricted use of tradipitant over a lifetime is an approvability issue.

7.7.2. Adequacy of Nonclinical Information To Assess the Toxicological Effects of Metabolites M2, M4, and M8

Issue

The Applicant has identified four major metabolites of tradipitant in human plasma: M2, M3, M4, and M8. These metabolites have been investigated in a series of nonclinical studies, and their plasma levels were measured in select toxicity studies conducted in rats and mice. Based on available data, these metabolites are considered to be pharmacologically active, toxicologically relevant, and present at significant levels compared to the parent drug, tradipitant. These factors support that the safety of levels of these metabolites should be qualified based on nonclinical data. Whether the nonclinical data are sufficient to qualify the safety of these metabolites was identified as a review issue.

Background

Based on PK studies in humans, the Applicant identified “four major metabolites” of tradipitant: M2, M3, M4, and M8.²⁷ Nonclinical and clinical data to assess the safety of the four major human metabolites were limited during clinical development. At the time that phase 3 trials with tradipitant were initiated (i.e., the point at which qualification of metabolites is typically expected), the Applicant’s available nonclinical data supported that M2, M4, and M8 were likely to be present at significantly lower levels in tested nonclinical species compared to humans (i.e., that these were *disproportionate metabolites*).²⁸ However, at no point during development were the available clinical pharmacology data sufficient to definitively determine whether any metabolite exceeded the typical threshold of 10% of drug-related exposure at steady state²⁹ at the

²⁷ See Module 2.6.4 Pharmacokinetics Written Summary, pg. 9.

²⁸ See Module 2.6.4 Pharmacokinetics Written Summary, Table 26, pgs. 43 to 44.

²⁹ FDA guidance for industry *Safety Testing of Drug Metabolites Revision 2* ([March 2020](#)).

proposed clinical doses that would warrant qualification by nonclinical data. Additionally, clinical trials with tradipitant have not exceeded 12 weeks or 90 dosing days for any indication. Therefore, the potential for unqualified metabolites was not considered a safety issue for tradipitant prior to the submission of this marketing application.

Assessment

Typically, “human metabolites that can raise a safety concern are those present at greater than 10 percent of total drug-related exposure at steady state,” based on area under the concentration-time curve (AUC).²⁹ In this case, clinical pharmacology data with tradipitant were previously limited such that it could not be determined whether these metabolites meet the criteria for further evaluation. However, in this NDA submission,³⁰ the available data supported that the levels of all four metabolites represent a notable proportion of exposure in humans relative to tradipitant itself. Additionally, based on information submitted to the current NDA, these metabolites are considered pharmacologically active (Section [13.2.1](#)) and were shown to induce hepatocyte death in vitro using human donor-derived cells (Section [13.2.3](#)). As such, the review team determined that the potential toxicity of these major human metabolites should be adequately evaluated in nonclinical studies, despite the unclear contribution of individual metabolites to total drug-related exposure at steady state.

Metabolites M2, M3, and M4 were measured and/or directly evaluated in select nonclinical pharmacology, pharmacokinetics, in vitro liver safety pharmacology, repeat-dose toxicity (rats only), genetic toxicology (in vitro), reproductive toxicity (pre- and postnatal development study only), carcinogenicity, special toxicology, and/or in silico studies (see Sections [13.1.4](#), [13.1.5](#), [13.1.7](#), [13.1.8](#), [13.2.1](#), [13.2.2](#), [13.2.3](#), [13.2.4](#), [13.2.5](#), [13.2.6](#), and [13.2.7](#)). M8, a glucuronide conjugate, was evaluated for binding and activity in vitro as well as in secondary pharmacology, PK, in vitro safety liver pharmacology, and in silico studies (see Sections [13.1.4](#), [13.2.1](#), [13.2.2](#), [13.2.3](#), and [13.2.7](#)).

Qualification Based on In Vivo Nonclinical Data

As levels of M3 were similar³¹ in rats compared to humans, the safety of M3 is considered adequately qualified by nonclinical data.³²

In rats and mice, M2 and M4 were not present or were observed at lower levels compared to the single-dose or steady-state levels in humans, such that under no condition was at least 50% of human M2 or M4 exposure achieved in animals. M2 and M4 were not measured in any study in a nonrodent species, while M8 was not measured in any nonclinical animal study. Based on the

³⁰ New data were submitted during the review of NDA 220152 that were not available during the review of NDA 218489 or previously submitted to any IND for tradipitant. See discussion of the timeline for the review of metabolite data in the Nonclinical Supplementary NDA Review dated December 30, 2025.

³¹ “...characterization of metabolite toxicity would generally be considered adequate when animal exposure is at least 50 percent the exposure seen in humans.” See FDA guidance for industry *M3(R2) Questions and Answers (R2)* ([March 2013](#)).

³² Unlike investigational drugs, for which toxicity is generally evaluated in two pharmacologically relevant species (i.e., a rodent and a nonrodent), major human metabolites should be adequately qualified in at least one pharmacologically relevant nonclinical species. See FDA guidance for industry *Safety Testing of Drug Metabolites* ([November 2016](#)).

available information, metabolites M2, M4, and M8 are disproportionate human metabolites that have not been qualified based on the available in vivo nonclinical data.

Qualification Based on Toxicological Similarity to Tradipitant

Safety qualification of metabolites is generally established by either 1) dosing of the parent drug in a nonclinical species determined to produce the metabolite(s) at sufficient levels compared to the human exposure; or 2) direct dosing of the unqualified metabolite(s) at doses sufficient to evaluate toxicity at exposures similar to or greater than levels formed in humans. In the absence of such data, the review team considered an alternative approach for NDA 220152, specifically, a Weight of Evidence (WoE) analysis to support that metabolites M2, M4, and M8 were not expected to be toxicologically different from tradipitant itself, thereby allowing for qualification based on total tradipitant drug-related exposure rather than on an individual basis. While this approach had been suggested previously, during early clinical development of tradipitant with the originating sponsor, the review team notes that this approach was only feasible because of data that were submitted recently (i.e., between September 2023 and October 2025). Pivotal new data included primary pharmacology (binding and/or functional activity), secondary pharmacology, liver safety pharmacology, in vitro distribution (protein binding), and in vitro genotoxicity studies with the metabolites, as well as population PK modeling supporting the relevance of healthy volunteer PK parameters for the motion sickness population and in silico analyses using various computational tools and databases.

Full discussion of the WoE analyses for each metabolite can be found in the Nonclinical Supplementary NDA Review dated December 30, 2025. Briefly, Quantitative Structure-Activity Relationship ([Q]SAR) analyses of the di-aryl alcohol and/or N-oxide moieties present on M2, M3, and M4 compared to tradipitant were conducted by FDA/CDER's Division of Applied Regulatory Science (DARS) Computational Toxicology Consultation Service (CTCS),³³ and comparative computational prediction analyses were conducted by the Applicant.^{34,35,36,37} These analyses supported that the structural differences would not result in new or exaggerated toxicities with the metabolites compared to tradipitant itself ([Table 35](#)). Analysis of the recently provided in vitro pharmacology, pharmacokinetic, and genotoxicity data further supported the toxicological similarity of tradipitant and all four major metabolites ([Table 36](#)). Therefore, the WoE supported that qualification of the disproportionate human metabolites (M2, M4, and M8) using total drug-related exposure, rather than on an individual basis, was scientifically appropriate.

³³ NDA 220152: Hepatobiliary Toxicity (Q)SAR analysis and Chemical Structural Similarity Search for Metabolites of Tradipitant. CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service. October 31, 2025.

³⁴ NDA 220152: Information Request. October 1, 2025.

³⁵ NDA 220152, SDN 23: October 15, 2025.

³⁶ NDA 220152: Information Request. October 20, 2025.

³⁷ NDA 220152, SDN 24: October 22, 2025.

Table 35. Structural Analyses of Potential Metabolite Toxicities Compared to Tradipitant

Nonclinical Data		Structural Toxicity Predictions			
		Tradipitant	M2	M3	M4
Structure					
		Parent drug	Ketone reduction	N-oxide	N-oxide + ketone reduction
CDER (Q)SAR analysis of hepatobiliary toxicity	CU Model	Positive prediction signals for: • Liver damage • Liver enzyme abnormalities • Cholestasis • Bile duct disorders • Drug-induced liver injury • Gall bladder disorders	No new or increased toxicity concerns identified	Not assessed	No new or increased toxicity concerns identified
	LMA Model	Positive prediction signals for: • Liver damage • Liver enzyme abnormalities • Cholestasis • Bile duct disorders	No new or increased toxicity concerns identified	Not assessed	No new or increased toxicity concerns identified

Nonclinical Data		Structural Toxicity Predictions			
		Tradipitant	M2	M3	M4
Applicant Analyses	Structural Alerts	1,2,3-triazole core with halogenated substituents results in high lipophilicity and bioaccumulation risk	No new structural alerts	- N-oxide elevates risk of oxidative stress, genotoxicity, and hepatotoxicity - Alpha, beta-unsaturated ketone elevates risk of covalent binding	N-oxide elevates risk of oxidative stress, genotoxicity, and hepatotoxicity
	In Silico Toxicity Profile Comparisons	- Moderate risk of hepatotoxicity and cardiotoxicity - Low risk of acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, skin sensitization, nephrotoxicity, neurotoxicity	- Predicted increase in risks of hepatotoxicity and cardiotoxicity (mitigated by existing nonclinical data) - No significant differences from tradipitant in PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, skin sensitization, nephrotoxicity, neurotoxicity	- Predicted increase in risks of oxidative stress, hepatotoxicity and cardiotoxicity (mitigated by existing nonclinical data) - No significant differences from tradipitant in PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, skin sensitization, nephrotoxicity, neurotoxicity	- Predicted increase in risks of oxidative stress, hepatotoxicity, and cardiotoxicity (mitigated by existing nonclinical data) - No significant differences from tradipitant in PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, skin sensitization, nephrotoxicity, neurotoxicity

Source: Reviewer analysis. See Nonclinical Supplementary NDA review, Sections 11 and 12.2.5, for full description of the study methods, findings, and comparison of predictions with completed nonclinical studies

Abbreviations: CU, CASE Ultra 1.9.2.4; LMA, Leadscape Model Applier 2025.0.1-3; PK, pharmacokinetic; (Q)SAR, Quantitative Structure-Activity Relationship

Table 36. Comparison of Nonclinical Findings With Tradipitant and Metabolites M2, M4, and M8

Nonclinical Data	Nonclinical Findings			
	Tradipitant	M2	M4	M8
Primary pharmacology	- Inhibited binding to NK1R $\geq 99\%$ at $10\mu\text{M}$; $\text{IC}_{50}=0.40\text{nM}/3.3\text{nM}$ - Inhibited substance P-mediated calcium release $\text{IC}_{50}=0.63\text{nM}$	- Inhibited binding to NK1R $\geq 99.3\%$ at $10\mu\text{M}$; $\text{IC}_{50}=1.55\text{nM}$ - Functional effect not tested	- Inhibited binding to NK-1R 100% at $10\mu\text{M}$; $\text{IC}_{50}=2.23\text{nM}$ - Functional effect not tested	- Inhibited binding to NK1R 99.3% at $10\mu\text{M}$; $\text{IC}_{50}=0.49\text{nM}$ - Inhibited substance P-mediated calcium release $\text{IC}_{50}=6.3\text{nM}$
Secondary pharmacology	- Significantly inhibited: - Rat benzothiazepine L-type calcium channel - Rat dihydropyridine L-type calcium channel - Rat GABA_A TBOB chloride channel	- Significantly inhibited: - Rat benzothiazepine L-type calcium channel - Rat GABAA TBOB chloride channel Human estrogen receptor alpha	No significant off-target binding	No significant off-target binding
Pharmacokinetics ¹	T_{max} (hours): 1.5 $t_{1/2}$ (hours): 28.2 - Protein binding (human): $\geq 99.9\%$ - Significantly inhibited transporters BCRP, OATP1B1 ($\text{IC}_{50}=2.83\mu\text{M}$), OATP1B3, MATE1 ($\text{IC}_{50}=3.20\mu\text{M}$), and MATE2-K in vitro	T_{max} (hours): 4.0 $t_{1/2}$ (hours): 29.5 - Protein binding (human): $>99.7\%$ - Significantly inhibited transporters OATP1B1 ($\text{IC}_{50}=2.06\mu\text{M}$) and MATE1 ($\text{IC}_{50}=2.89\mu\text{M}$)	T_{max} (hours): 4.0 $t_{1/2}$ (hours): 28.6 - Protein binding (human): $>95.4\%$ - No significant inhibition of transporters in vitro; substrate of P-gp and BCRP	T_{max} (hours): 30 $t_{1/2}$ (hours): 31.4 - Protein binding (human): not determined - Effects on transporters not determined

Nonclinical Data	Nonclinical Findings			
	Tradipitant	M2	M4	M8
General toxicity (notable findings)	• Body weight loss or decreased body weight gain (dogs) • Adaptive changes in the liver and/or thyroid related to induction of CYP enzymes (rats and dogs) • Adverse changes in liver including dose-dependent hepatocyte hypertrophy and foci of inflammatory cells with hepatocyte necrosis (HW rats only)	• Levels were too low to be informative	• Levels were too low to be informative	• Levels were not measured
Other toxicity evaluations	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (15 µg/mL) • Four-organ system: no evidence of toxicity at 7 days; sporadic evidence of toxicity in all organs at 14 days	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: inconsistent, qualitative findings of hepatocyte toxicity (1.4 µg/mL) • Four-organ system: no evidence of toxicity at 7 days (high media concentration of M2); sporadic evidence of toxicity in all organs at 14 days (low media concentration and tissue exposure to M2)	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: no toxicity observed • Four-organ system: levels were too low to be informative for either study	• 3D human hepatocyte spheroids: inconsistent, quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (≥0.04 µg/mL) • Four-organ system: M8 not measured in either study

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Nonclinical Data	Nonclinical Findings			
	Tradipitant	M2	M4	M8
Genotoxicity	Negative in: - Ames assay - In vitro chromosomal aberration assay in human lymphocytes - In vivo micronucleus assay in mice	Negative in: - Ames assay - In vitro chromosomal aberration assay in human lymphocytes	Negative in: - Ames assay - In vitro chromosomal aberration assay in human lymphocytes	Not tested

Source: Reviewer analysis. See Sections [13.1](#) and [13.2](#) for specific study information

Bold text highlights potentially increased or novel toxicities with a metabolite compared to tradipitant

¹Human T_{max} and t_{1/2} data derived from Trial VP-VLY-686-1002 following a single dose of 170 mg under fasted conditions

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; HW, Han Wistar; IC₅₀, half-maximal inhibitory concentration; M, metabolite, MATE, multidrug and toxin extrusion; MPS, microphysiological system; N/A, not applicable; NK1R, neurokinin 1 receptor; OAT, organic anion transporter; P-gp, P-glycoprotein; t_{1/2}, half-life; TBOB, (tert-butylbicycloorthobenzoate; T_{max}, time to maximum concentration

Comparison of the total tradipitant drug-related exposure (i.e., tradipitant plus all measured metabolites) between animals and humans demonstrated sufficient exposure margins such that metabolites M2, M4, and M8 were considered qualified based on the available nonclinical data.

Conclusion

Based on all data available at the time of this review, it was determined that adequate nonclinical assessment of the major human metabolites, M2, M3, M4, and M8, was warranted to support the safety of tradipitant for its intended clinical use. Only M3 was considered qualified based on the levels measured in repeat-dose toxicity studies in animals compared to those in humans, while M2, M4, and M8 were considered disproportionate human metabolites. A WoE approach, including in silico toxicology analyses of the structural differences between tradipitant and its metabolites as well as recently submitted in vitro pharmacology, pharmacokinetic, and genotoxicity data, supported that tradipitant and the disproportionate human metabolites were expected to be toxicologically similar. This conclusion allowed for the qualification of these metabolites based on total tradipitant drug-related exposure, rather than individually. Thus, all identified major human metabolites of tradipitant are considered qualified for safety based on available nonclinical data. However, as the nonclinical data supporting the safety of unrestricted use of tradipitant over a lifetime are considered inadequate, the safety of the metabolites is likewise not considered to be adequately supported by nonclinical data for unrestricted use of tradipitant over a lifetime.

Notably, it is not generally expected that such a WoE approach will be appropriate for the qualification of metabolites in other development programs, as each situation must be evaluated on its own merits based on the totality of data and information. Although in silico analyses are highly valuable in certain situations, they are unlikely to routinely address safety concerns in lieu of typical in vivo toxicity studies.

7.7.3. Adequacy of the Clinical Safety Database To Characterize Safety of Tradipitant for Vomiting Induced by Motion

Issue

Tradipitant is proposed for the indication of the prevention of vomiting induced by motion, which is a condition that is likely to occur repeatedly over the course of an individual's lifetime. The Applicant proposes unrestricted use of tradipitant with no limitation on the total duration of use. Thus, understanding the safety of long-term intermittent repeated dosing is important to inform the safe use of this product as a preventive medication for vomiting induced by motion.

Background

Vomiting induced by motion is one manifestation of the complex and multisystem disorder commonly referred to as "motion sickness." Motion sickness is expected to recur in susceptible individuals upon reintroduction of the triggering motion stimulus, notwithstanding the potential for habituation that typically occurs when the triggering motion stimulus is experienced repeatedly and predictably. Generally, for conditions such as vomiting induced by motion (i.e., conditions that are likely to require repeated intermittent use over the long-term – e.g., migraine,

erectile dysfunction, asthma), the safety evaluation of a drug is expected to characterize the safety profile for a duration of time consistent with the intended long-term use. However, depending on the frequency of the need for treatment for the condition, it may not be feasible for a clinical trial to collect data in a sufficient number of subjects with long-term exposure in the intended use population, as would be expected for chronic conditions that require daily treatment. Thus, the characterization of safety for vomiting induced by motion is supported by the clinical safety data, which serves to characterize safety in the anticipated use conditions, and the nonclinical data, which serves to characterize the toxicological risks for the proposed duration of use.

The Applicant provided safety data from three placebo-controlled trials assessing the effects of a single dose of tradipitant (Trials 2401, 3401, and 3404) and a fourth trial assessing multiple doses (Trial 3403). Trial 3403, the only repeat-dose trial in the intended use population, was an open-label, uncontrolled trial in which subjects could take tradipitant as needed prior to any motion sickness-inducing event for up to 90 total doses over the 12-month trial duration. Notably, Trial 3403 had infrequent safety assessments, potential under-reporting of adverse events, variability in the type of travel events, and no concurrent comparator arm. Therefore, it is difficult to attribute AEs to tradipitant versus other factors. Additional safety information was provided from clinical trials assessing the use of tradipitant for other indications, including gastroparesis; however, the longest duration of controlled trials in these other indications was 12 weeks. As described in Section [7.7.1](#), the Applicant has not provided sufficient nonclinical information to adequately characterize the safety of unrestricted use of tradipitant over a lifetime in human subjects.

Assessment

Among the data submitted from trials conducted in the intended use population, placebo-controlled clinical safety data are available from 516 subjects who received a single dose of tradipitant; 227 received the 85-mg dose and 289 received the 170-mg dose. The remaining safety data were from open-label, uncontrolled, as-needed use of tradipitant in 382 subjects enrolled in Trial 3403 (up to 90 doses over the course of 12 months, see Section [7.6.2](#)). The review team's safety analysis of the placebo-controlled clinical safety data identified that the TEAEs that occurred most commonly and at higher rates in subjects receiving tradipitant compared to placebo were somnolence, headache, and fatigue. Each of these TEAEs occurred at a higher rate for the pooled 170-mg arms versus pooled placebo arms compared to the pooled 85-mg arms versus pooled placebo arms. For example, somnolence occurred at a rate of 12.5% in the pooled 170-mg arm versus 5.8% in the pooled placebo arm, resulting in a risk difference of 6.7%, whereas the rate of somnolence in the pooled 85-mg arm was 6.2% versus 3.9% in the pooled placebo arm, resulting in a risk difference of 2.3%. Although there are several limitations that affect the interpretability of the results of Trial 3403, the safety data from Trial 3403 showed similar adverse events and did not identify any new safety signals (see Section [7.6.2](#)). Additionally, Trial 3403 showed that tradipitant usage was intermittent (e.g., the maximum number of doses in a 30-day period for the majority of subjects was 4 or fewer; the maximum number of consecutive dosing days for the majority of subjects was 2 or fewer) and infrequent (e.g., the majority of subjects did not exceed 30 total dosing days during the 12 month trial) suggesting that individuals with motion sickness are unlikely to take a drug for the prevention of vomiting induced by motion frequently (see Section [7.6.2.1](#)).

The analysis of the data from the pooled single-dose trials and the multiple-dose open-label trial shows that the 170 mg dose is associated with higher rates of adverse events compared to the 85 mg dose. However, this increased risk is small, and the overall benefit-risk assessment is favorable for both the 85 mg and 170 mg doses.

The clinical safety database also includes data from trials conducted in other patient populations, all with controlled trial durations of no more than 12 weeks. In the clinical program evaluating tradipitant for treatment of gastroparesis, subjects received tradipitant 85 mg twice daily in one phase 2 (4-week placebo-controlled phase) and one phase 3 trial (12-week placebo-controlled duration). The safety data from these trials were considered as part of the review. While the data from these trials provides some assurance of safety for up to 12 weeks, tradipitant was not approved for treating gastroparesis, and the generalizability of the safety information in subjects with other conditions to the safety in individuals with motion sickness is low due to differences in pathogenesis, intended use, comorbidities, and concomitant treatments.

Taken together, the available safety data support the safe use of tradipitant in the intended use population for 90 total doses; however, the safety of the unrestricted use of tradipitant has not been adequately characterized. There are no clinical trial safety data for the use of tradipitant for greater than 90 doses or 12 weeks, and there are insufficient nonclinical data to characterize the safety of unrestricted, lifelong use of tradipitant (see Section [7.7.1](#)). Thus, a description in the label that the safety of more than 90 doses has not been established is warranted to ensure the safe and effective use of tradipitant for the proposed indication.

Conclusion

The data provided in the submission do not support unrestricted use of tradipitant, due to insufficient data to adequately characterize such use for a lifetime. The clinical review team determined that the available safety data support the safe use of tradipitant for up to 90 doses. Although some individuals may use a preventative treatment for vomiting induced by motion for more than 90 doses over their lifetime, the typical individual is anticipated to use such a treatment infrequently due to the intermittent and predictable nature of vomiting induced by motion (as evidenced by the use data from Trial 3403). Thus, the label will describe the upper limit beyond which safety has not been established and will state in the dosing and administration section that the safety of tradipitant for more than 90 doses has not been established in clinical trials. This information is warranted to inform prescribers of the safe use of the product because some individuals would be expected to exceed the duration of use supported by the available safety data.

Additionally, the overall benefit-risk assessment is favorable for both the 85-mg and 170-mg doses. In the clinical trials, the 170-mg dose was associated with slightly higher rates of adverse events compared to the 85-mg dose. Because of this dose-dependent increase in adverse events, both doses of tradipitant should be approved with a recommendation that individuals use the lowest effective dose.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Pharmacokinetic difference between subjects with history of motion sickness and healthy subjects were not identified based on the available data.

Hepatic Impairment

Use of tradipitant in subjects with mild, moderate, or severe hepatic impairment is not recommended. In the mass balance study, following a single 25 mg (100 µCi) oral dose administration of ¹⁴C-radiolabeled tradipitant, about 80% of the radioactivity was recovered mainly as metabolite forms in feces within 312 hours postdose. While hepatobiliary excretion in the main elimination pathway of tradipitant and its metabolites, no dedicated study in hepatic impaired subjects have been performed.

The Applicant's proposal to not recommend tradipitant for patients with mild, moderate, or severe hepatic impairment is acceptable. However, given the main elimination pathway is hepatobiliary excretion, the review team recommends a hepatic impairment study be completed as a postmarketing commitment.

Renal Impairment

Based on a mass balance study, renal excretion is not a major elimination pathway of tradipitant and its metabolites. No dedicated study in renally impaired subjects has been conducted. Based on the Applicant's population PK analysis, the estimated apparent clearance (CL/F) was similar between subjects with mild renal impairment (N=79) and normal renal function (N=366) while 23% lower in subjects with moderate renal impairment (N=11) compared to subjects with normal renal function. However, this difference is not considered clinically significant. Tradipitant was not studied in subjects with severe renal impairment. The review team recommends a severe renal impairment study be completed as a postmarketing commitment.

Age, Race, and Sex

In clinical trials supporting motion sickness indication, the impact of age, race and sex on pharmacokinetics of tradipitant and its metabolites was not assessed.

CYP3A4*22 Genotype

Tradipitant undergoes extensive metabolism through several pathways including CYP3A4. The Applicant evaluated the impact of CYP3A4*22 (a decreased function allele, as reviewed in [Pratt et al. \(2023\)](#)) on the pharmacokinetics of tradipitant and its metabolites. A total of 57% (292/515) of subjects in Trial 3403 and 48% (82/170) of subjects in Trial 3404 had genotyping data available. Because of the large fraction of subjects with missing data, the Applicant did not include CYP3A4 genotype into the population PK models. Therefore, the impact of CYP3A4*22 genotype on tradipitant pharmacokinetics remains unclear.

8.2. Extrinsic Factors

Food Effect

Tradipitant should be administered without food.

In Trial 1002, when a single oral dose of 85-mg tradipitant was administered in healthy subjects within 30 minutes of consumption of a high-fat high-calorie meal, tradipitant C_{max} and AUC_{0-inf} was increased by 4.74-fold and 2.63-fold, respectively, and the median time to maximum concentration (T_{max}) was delayed by 2 hours (from 2 hours to 4 hours) as compared to tradipitant administered under the fasted condition.

In the same study, following administration of a single oral dose of 170 mg of tradipitant under similar fed conditions, tradipitant C_{max} and AUC_{0-inf} was increased by 7.03-fold and 3.81-fold, respectively, and the median T_{max} was delayed by 2.5 hours (from 1.5 hours to 4 hours) compared to the fasted state. For the active metabolites M2, M3, M4, and M8, a high-fat high-calorie meal increased the C_{max} by 4.08, 3.70, 3.40, 4.29-fold, respectively, and increased AUC_{0-inf} by up to 2.39, 2.64, 2.39, 2.73-fold, respectively, as compared to the fasted condition for the single 85-mg dose arm. On the other hand, for the single 170-mg dose arm, for the active metabolites M2, M3, M4, and M8, a high-fat high-calorie meal increased the C_{max} by 6.54, 5.26, 5.47, 5.6-fold, respectively, and increased AUC_{0-inf} by up to 3.5, 3.56, 3.2, 3.53-fold, respectively, compared to the fasted condition.

In the phase 2 and 3 randomized controlled clinical trials supporting the indication of prevention of vomiting induced by motion, subjects were instructed to take tradipitant approximately 60 minutes prior to boat travel on empty stomach.

Potential Effects of Other Drugs on Tradipitant

Tradipitant is extensively metabolized. The in vitro studies were conducted to identify the enzymes responsible to form some known metabolites. These in vitro studies were reviewed during NDA218489 review. No new in vitro drug interaction assessment was provided. The Applicant's in vitro studies showed non-CYP450-mediated processes (unspecified) and CYP3A4 were involved in tradipitant metabolism to M2 and M3, respectively and M8, a glucuronide metabolite can be formed by uridine glucuronosyltransferase [UGT]1A4 and UGT2B7. Notably, M8 is a more potent active metabolite with a 6.7-fold lower IC_{50} than tradipitant. However, the relative contribution of a specific metabolizing enzyme and potential contribution of other CYP enzymes to overall tradipitant metabolism have not been fully characterized. In vitro studies to measure disappearance tradipitant in presence of recombinant CYP enzymes and/or inhibitors of a specific CYP enzyme can provide such information. Therefore, it is recommended that the Applicant conducts additional in vitro assessment as a post-marketing commitment to evaluate the potential roles of other CYP enzymes and the relative contribution of specific CYP enzymes to inform the major metabolizing enzymes of tradipitant and its active metabolites and assess the potential for metabolism-mediated drug interactions. Based on the in vitro study results the need for clinical drug- drug interaction studies should be determined.

Potential Effects of Tradipitant on Other Drugs

Although tradipitant inhibits and induces CYP3A4 in vitro, when coadministered with multiple doses of tradipitant 85 mg BID, oral midazolam (a sensitive CYP3A substrate) exposure (C_{max} and AUC_{inf}) increased up to 16% as compared to when midazolam was administered alone. The change of the systemic exposure for midazolam is unlikely to be clinically significant. This in vivo drug interaction study was also reviewed under NDA 218489.

8.3. Plans for Pediatric Drug Development

An Agreed Initial Pediatric Study Plan letter was issued December 23, 2024, for the proposed deferral of pediatric studies until additional safety and effectiveness data from adult studies have been collected, as well as for a partial waiver for patients less than 2 years of age. Motion sickness symptoms, including vomiting induced by motion, are very uncommon in individuals less than 2 years of age, which would make the necessary studies impossible or highly impracticable, and thus warrants a partial waiver for assessment of tradipitant in this age group.

(b) (4)

These plans for pediatric drug development of tradipitant were determined to be acceptable, and were used to develop post-marketing requirements (PMRs) further described in Section [24](#).

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

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. Based on animal reproduction studies, oral administration of tradipitant did not demonstrate developmental toxicity in rats or rabbits. The Division of Pediatrics and Maternal Health (DPMH) recommends including information about the available clinical data under the Risk Summary and the nonclinical data under the Risk Summary and Animal Data sections.

DPMH recommends issuing a pregnancy exposure registry and complementary database study as 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 no human pregnancy data available. See Section [24](#).

Lactation

Tradipitant is present in rat milk. DPMH recommends 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 labeling that breastfed infants should be monitored for adverse reactions that occur in adults, such as somnolence.

DPMH recommends that a PMR be issued 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. See Section [24](#).

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.

9. Product Quality

The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, tradipitant and the drug product, NEREUS (tradipitant) Capsules, 85 mg at release and throughout its proposed expiration dating period of 48 months. The proposed expiration dating period is supported by the stability data provided in the application. Therefore, this application is recommended for approval from the OPQ perspective with an expiration dating period of 48 months.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Three clinical investigators (Drs. Kaminetsky, Maitra, and Thein) were inspected as routine inspections during the review. Refer to the Clinical Inspection Summary dated December 16, 2025 (DARRTS Reference ID: 5712480). For Trial 3401, clinical investigators (CIs) Drs. Kaminetsky and Thein were inspected (as Dr. Maitra was not a CI for Trial 3401), and the inspections revealed no significant discrepancies or regulatory violations.

For Trial 3404, inspections of all three CIs revealed no significant discrepancies or regulatory violations.

Based on the inspection results of the three CIs, the data generated by the CIs and submitted by the Applicant were acceptable in support of the application.

11. Advisory Committee Summary

An advisory committee meeting was not held during the review of this NDA because the application did not raise questions regarding the benefit-risk analysis that warranted convening an advisory committee. The benefit-risk analysis is summarized in Section [2.1](#) and described in more detail throughout this interdisciplinary review.

III. Additional Analyses and Information

12. Summary of Regulatory History

On October 2, 2018, IND 141315 was submitted by Vanda Pharmaceuticals Inc, the Applicant, for the development of VLY-686 (tradipitant),³⁸ an orally administered NK-1 receptor antagonist, for motion sickness. IND 141315 was opened with Trial VP-VLY-686-2401 (Trial 2401), “Motion Sifnos: A Randomized, Double-Blind, Placebo-Controlled Study To Investigate The Efficacy Of Tradipitant In Subjects Affected by Motion Sickness During Vehicle Travel.” The trial was found safe to proceed on November 1, 2018, following the Applicant’s agreement to limit enrollment to subjects with normal baseline liver biochemistry results and the addition of trial-stopping criteria.

On December 19, 2018, the Division issued an advice/information request letter regarding Trial 2401. Specifically, the Division provided the following comments and recommendations:

- The Division sought clarification from the Applicant whether they intend to seek an indication for (b) (4), or (b) (4).
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4) The Division provided recommendations on developing a fit-for-purpose COA measure and on the use of anchor-based analyses.
- The Division raised concerns with the proposed COA measure, the MSSS, and recommended the Applicant consider other COA measures to assess trial endpoints.

On March 12, 2019, the Division issued an advice/information request letter reiterating the recommendations provided in the advice/information request letter dated December 19, 2018.

On December 16, 2019, the Applicant submitted the phase 3 protocol for VP-VLY-686-3401 (Trial 3401, “Motion Syros: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in subjects affected by motion sickness during travel.”

An end-of-phase 2 meeting was held on May 13, 2020 (meeting minutes dated May 21, 2020). During the meeting, the following comments and recommendations were provided:

- The Applicant informed the Division of their intention to pursue an indication of the prevention of vomiting induced by motion. The Applicant planned to use a new COA

³⁸ VLY-686 (tradipitant) was formerly known as LY686017, originally developed by Eli Lilly and Company (b) (4)

measure to evaluate vomiting, and described their plan to assess nausea with a nausea severity scale.

- The Division stated their disagreement that Trial 2401 would be considered adequate to support a future marketing application, and that the acceptability of the proposed safety database would be determined during review of the future marketing application.
- The Division expressed concerns with other COA measures (e.g., MSSS, MSAQ) (b) (4) as insufficient information had been provided to support that the measures were fit-for-purpose.
- The Division recommended that the Applicant conduct a thorough QT study to address the potential effects of tradipitant on the QT interval, as well as an in vivo drug-drug interaction study with strong CYP4A4 inhibitors and further characterize tradipitant metabolism into various metabolites.

On November 8, 2021, the Division issued an advice letter/information request regarding an amendment of Trial 3401.

- The Division reiterated past advice to focus on assessing the prevention of vomiting induced by motion, (b) (4)
- The Division recommended repositioning the MSAQ and PGI-S as exploratory endpoints, (b) (4)
- The Division recommended submitting a statistical analysis plan and requesting a Type C written responses only meeting to obtain feedback on the proposed efficacy analyses before database lock and unblinding.
- The Division reiterated to the Applicant that two adequate and well-controlled trials are generally expected to demonstrate substantial evidence of effectiveness.

On September 14, 2022, the Applicant submitted a new phase 3 protocol for VP-VLY-686-3403 (Trial 3403), “Motion Delos: An Open-Label Study to Investigate the Safety and Efficacy of Tradipitant in Participants Affected by Motion Sickness During Travel.”

On November 21, 2022, the Division issued a deficiency - potential hold issues letter to the Applicant regarding Trial 3403. The key safety concerns communicated in the potential hold comments are summarized below:

- Revise the study protocol to clearly specify the maximum daily dose and maximum dosing frequency of tradipitant.
- Update the protocol to exclude enrollment of subjects who are being treated with prohibited medications.

On January 6, 2023, the Applicant submitted a protocol amendment incorporating the changes that adequately addressed the comments conveyed in the November 21, 2022, letter. The Division determined that the Applicant’s responses were acceptable, and Trial 3403 was considered safe-to-proceed, as amended.

On February 28, 2023, the Division issued an advice/information request regarding the design of Trial 3403.

- The Division expressed significant concerns with the proposed trial design, and its ability to generate interpretable data to support a future marketing application. The Division's concerns included the open-label, uncontrolled design that lacked a control arm, and the potential for significant variability in travel events, timing of drug administration, and tradipitant dosing. Due to these concerns, the Division did not agree that Trial 3403 could serve as an adequate and well-controlled investigation.
- The Division noted that Trial 3403 was the only trial that proposed to evaluate repeated administration of tradipitant for the proposed indication; however, this trial may not result in interpretable data due to the trial design.
- The Division informed the Applicant that to support an eventual marketing application for tradipitant as a pharmaceutical therapy for the prevention of vomiting induced by motion, in addition to the studies conducted thus far, a 6-month toxicity study in a nonrodent species should be conducted to adequately assess the risk of cumulative toxicity following repeated short-term exposures to tradipitant.

On November 8, 2023, the Division held a pre-NDA meeting with the Applicant (meeting minutes finalized on December 8, 2023). The discussion during the pre-NDA meeting, the Division made the following comments:

- The Division raised concerns about the Applicant's plan to submit results from Trial 2401 and Trial 3401 to support a marketing application. Specifically, for Trial 2401, the Division noted a lack of control for overall type I error and previously communicated concerns with the MSSS instrument that was used to measure the endpoints. The Division also noted that for Trial 3401, the 85-mg tradipitant arm was not statistically significant due to the prespecified multiple-testing procedure. According to the multiple testing procedure, the worst nausea severity score for the 170-mg tradipitant arm was tested and failed to show statistical significance, thus, the percentage of subjects with vomiting in the 85-mg tradipitant arm was only nominally significant. The Division also expressed concerns that only Trial 3401 evaluated the 85-mg tradipitant arm, which was not assessed in Trial 2401.
- The Division recommended that the Applicant finish Trial 3404, a second phase 3 trial similar in design to Trial 3401, prior to a future NDA submission.
- The Division noted that it was premature to agree to the adequacy of the safety database to support a future marketing application. The Division stated that the assessment of safety would focus on safety data from the intended use population that received the to-be-marketed dosage.
- The Division stated that the proposed nonclinical safety database may not be adequate to inform the repeated use of tradipitant for the prevention of vomiting induced by motion. The Division noted that although vomiting induced by motion may occur intermittently, it is likely that a patient will require multiple courses of treatment. Thus, it would be important to adequately characterize the risks of cumulative toxicity following repeated short-term exposures to tradipitant. The Division (b) (4)

(b) (4) invited the Applicant to provide an alternative approach with rationale for the proposed vomiting induced by motion NDA.

On October 11, 2024, the Applicant submitted a protocol amendment for Trial 3403, seeking to modify the duration of treatment with tradipitant from a maximum of 90 dosing days to a maximum of 180 dosing days and to extend the treatment period from 12 months to 24 months. A deficiency - potential hold issues letter was issued on November 15, 2024, that stated the following:

The nonclinical information submitted to the IND supports a maximum treatment duration of 3 months (i.e., 90 dosing days). Therefore, we are concerned that the IND does not contain sufficient information to assess the risks to subjects for the proposed duration of treatment. You have the option to withdraw the protocol amendment or provide a response by November 21, 2024.

The Applicant replied on November 20, 2024, with the following comments:

- The Applicant noted that most subjects (“approximately 80%”) took less than half of the maximum allowed doses (i.e., 45 doses). The Applicant expected “the majority of participants in the proposed amendment would be expected to take fewer than 90 doses over 24 months.”
- The Applicant stated that their proposed indication is for the “acute prevention of motion induced vomiting” and referred the Division to other drugs that were approved for an “acute, infrequent condition” as rationale to support their position that additional nonclinical studies were not necessary to support the proposed protocol amendment.

On November 26, 2024, the Division provided the following response to the Applicant:

As we had noted in our previous correspondence, we are concerned that the IND does not contain sufficient information to assess the risks to clinical trial subjects beyond the maximum of 90 dosing days, regardless of the frequency and/or duration of use.

You stated in your response that “many participants took only a few doses in the 12-month period, and the vast majority (approximately 80%) took fewer than half (45) of the maximum allowed doses.” Therefore, you expect that the majority of subjects will take no more than 90 dosing days over 24 months, the total treatment duration proposed in the protocol amendment. Based on the information you provided, if you amend the protocol to specify that dosing for each clinical trial subject would be limited to a maximum of 90 dosing days over the intended 24-month total treatment duration, that would satisfactorily resolve the potential hold concern. You also have the option to withdraw the protocol amendment.

(b) (4)

The Division also sent an advice/information request regarding the proposed protocol amendment for Trial 3403 on November 26, 2024. The following comments were conveyed to the Applicant:

- The Division reiterated concerns about the interpretability of Trial 3403 due to the trial design (as previously noted) and the concern that Trial 3403 was the only source of data for repeated administration of tradipitant in the intended use population. The Division noted that characterizing the safety and efficacy of repeated administration would be important, as most patients will likely require multiple courses of treatment over time, since vomiting induced by motion may recur over that patient's lifetime.
- The Division stated their concern that increasing the sample size of Trial 3403 (from 300 to 500) was a missed opportunity to gather interpretable data that could be obtained from a different trial design.

On December 4, 2024, the Division replied and reiterated the comments from the November 26, 2024, response. The Division also noted that the November 26, 2024, response was intended to satisfactorily resolve the matter by providing a path forward for the proposed protocol amendment, based on the information provided by the Applicant. The Division also stated they were open to a teleconference to discuss the proposed path forward; however, the Division requested the Applicant clarify whether there are any potential challenges with amending the protocol to specify a maximum of 90 dosing days.

On December 9, 2024, the Applicant replied with the following communication, and did not seek a teleconference to discuss the matter.

Vanda believes the body of safety data for tradipitant is sufficient to support the protocol amendment referenced above. We see no valid scientific basis to conduct additional lethal studies in dogs as a prerequisite to execute this study. As such, we do not intend to withdraw or modify the amended protocol.

On December 23, 2024, Trial 3403 was placed on partial clinical hold based on insufficient information to assess risks to human subjects.⁴⁰ Trial 3403 could not be continued except as specified below:

This partial clinical hold applies to the portion of the amendment to Study 3403 which, as proposed, would have modified treatment with tradipitant from a maximum of 90 dosing days to a maximum of 180 dosing days. Accordingly, you may enroll new subjects in Study 3403, and current subjects may continue in Study 3403, for a maximum of 90 dosing days over the course of the proposed 24-month duration.

The available nonclinical data support dosing with tradipitant for up to 90 dosing days. The nonclinical information submitted to the IND includes a 6-month study in a rodent species and a 3-month study in a nonrodent species, which support the maximum allowable 90 dosing days regardless of the frequency of use and/or duration of the study. Therefore, the current amendment (180 dosing days) exceeds the maximum 90 dosing days that is supported by the information submitted to the IND.

⁴⁰ 21 CFR 312.42(b)(2)(i)

The Division stated that to resolve the partial clinical hold, the Applicant should conduct a toxicology study in a nonrodent species of at least 6 months duration, as recommended previously, to characterize the risk of cumulative toxicity of tradipitant and to support dosing beyond 90 dosing days. Alternatively, you may amend the protocol such that a subject does not receive tradipitant for more than 90 dosing days over the course of the entire study, regardless of the length of time of their enrollment.

An Agreed Initial Pediatric Study Plan agreement letter was issued December 23, 2024, for the proposed deferral of pediatric studies until additional safety and effectiveness data from adult studies have been collected and partial waiver for pediatric subjects <2 years old.

On December 30, 2024, the Applicant submitted the NDA that is the subject of this review.

At the time of the NDA submission, Trial 3403 was on partial clinical hold as described above. On December 4, 2025, in response to an appeal of the decision to place the partial clinical hold, the CDER Center Director granted the Applicant's request to lift the partial clinical hold on Trial 3403. Refer to the Appeal Granted letter dated December 18, 2025.

13. Pharmacology Toxicology

Where appropriate, effect margins are reported relative to the clinical $C_{\max}$ under three different conditions: following a single dose of 85 mg, following a single dose of 170 mg, or following repeated dosing (i.e., at steady state) at a dose of 170 mg/day.⁴¹ As tradipitant is intended for the prevention of vomiting induced by motion, an individual may take a single dose or otherwise use the drug so infrequently that PK parameters from a single dose are most relevant. Alternatively, an individual may use tradipitant frequently, or many days in a row (e.g., daily on a week-long cruise, daily during commute to and from work), such that steady-state PK parameters are most relevant. Thus, multiple safety/effect margins are reported to best represent the wide range of potential scenarios with tradipitant under the proposed conditions of use.

While safety margins are reported relative to AUC, when possible, other effect or safety margins in this section are reported relative to HED (assuming a 60 kg adult) at the maximum clinical dose of 170 mg/day, due to the limitations of the nonclinical and clinical pharmacokinetic data with tradipitant and its major human metabolites. The review team notes that tradipitant margins based on HED are likely overestimating safety, based on the known pharmacokinetic properties (i.e., nonlinear exposure such that large increases in dose level result in marginal changes in AUC). Therefore, all HED-based margins should be interpreted with caution.

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Most nonclinical studies were cross-referenced from IND [REDACTED] (b) (4) [REDACTED]. Select PK studies, the PPND study in rats, the neonatal toxicity study

⁴¹ Steady-state $C_{\max}$ is derived from Trial VP-VLY-686-1102, in which healthy volunteers were administered tradipitant at 85 mg BID (i.e., 170 mg/day) for 12 days. Steady-state parameters are not available for 85 or 170 mg/day as a single dose. Thus, the reported steady-state $C_{\max}$ at 170 mg/day (with BID administration) is likely lower than would be expected with a single daily dose at 170 mg/day but similar to $C_{\max}$ at 85 mg/day.

in rats, the 6-month carcinogenicity study in transgenic mice, and the 2-year carcinogenicity study in rats were submitted to IND 141315. Full nonclinical reviews of these studies were completed under INDs (b) (4) (b) (4) and/or (b) (4)

13.1.1. Primary Pharmacology

Tradipitant is a selective, competitive inhibitor of the human cell membrane neurokinin (NK)-1 receptor. Tradipitant binds to the human NK-1 receptor with sub-nanomolar affinity in cells/tissues from a variety of species, including human. See Section [13.2.1](#) for additional pharmacology studies with tradipitant and its metabolites.

In a study in male Beagle dogs, a single oral dose of tradipitant at ≥ 0.3 mg/kg administered 2 hours prior to challenge with the pro-emetogenic drug, apomorphine, resulted in significantly decreased incidence of emesis compared to no treatment (less than the maximum clinical dose of tradipitant of 170 mg [2.8 mg/kg], based on HED).

13.1.2. Secondary Pharmacology

No significant activity ($\geq 50\%$ binding inhibition) of tradipitant was observed against a panel of 74 other receptors, enzymes, and ion channels, including the NK-2 and NK-3 receptors. See Section [13.2.2](#) for an additional secondary pharmacology panel.

13.1.3. Safety Pharmacology

See Section [13.2.3](#) for additional safety pharmacology studies with tradipitant and its metabolites.

Central Nervous System

In a central nervous system safety pharmacology study in male CD-1 mice, a single oral dose of tradipitant at 1500 mg/kg resulted in significantly increased spontaneous ambulatory and nonambulatory activity, mild hyperactivity, and mild hyperthermia, as well as altered sensitivity to auditory stimuli relative to controls (effect margin of 43-fold relative to the maximum clinical dose of 170 mg, based on HED). Neurological examinations were also conducted in the 1- and 3-month repeat-dose oral toxicity studies in dogs, and no adverse neurological effects were reported up to the highest tested dose of 1500 mg/kg/day (294-fold the clinical dose).

Respiratory System

In a respiratory safety pharmacology study in male Sprague Dawley rats, single oral doses of tradipitant up to 1500 mg/kg (85-fold the clinical dose, based on HED) had no significant effects on respiratory parameters.

Cardiovascular System

Tradipitant significantly inhibited the hERG channel current in vitro, with an IC_{50} value of 3.91 μ M (2,299 ng/mL; approximately 27-, 21-, and 7.0-fold the clinical C_{max} in healthy

volunteers following administration of a single dose of 85 mg, a single dose of 170 mg,⁴² and 170 mg/day at steady state,⁴³ respectively). Of note, while this hERG assay was not conducted in compliance with U.S. FDA good laboratory practice (GLP) regulations, FDA will take note of positive findings in a noncompliant study.⁴⁴

Table 37. Inhibition of hERG Channel Current by Tradipitant

Tradipitant Dose	Duration	Human C _{max} (ng/mL)	In Vitro IC ₅₀ ¹ (ng/mL)	Effect Margin
85 mg	Single dose	84.7		27
170 mg	Single dose	112	2299	21
170 mg/day	Steady state	327		7.0

Source: Trial VP-VLY-686-1002 (single-dose human data), Trial VP-VLY-686-1102 (steady-state human data from subjects administered 85 mg Q12H for 12 days), Study LLY02-12, and analysis by reviewer

¹ The in vitro equivalent (ng/mL) is calculated, briefly, by multiplying the IC₅₀ (3.91μM) by the molecular weight of tradipitant (587.9 g/mol)

Abbreviations: C_{max}, maximum plasma concentration; hERG, human ether-a-go-go-related gene; IC₅₀, half-maximal inhibitory concentration; Q12H, every 12 hours

Tradipitant also shortened the action potential duration in dog Purkinje fibers by 9% to 20% at a concentration of 20μM (11,758 ng/mL; 139-, 105-, and 36-fold the clinical C_{max} values, respectively), with no significant effects at ≤3μM. These findings were consistent with a possible blockade of cardiac sodium and/or calcium channels. In a cardiovascular safety pharmacology study in conscious male and female Beagle dogs, single oral doses of tradipitant up to 800 mg/kg had no significant effects on qualitative or quantitative ECG parameters (157-fold the maximum clinical dose of 170 mg, based on HED). ECG parameters were also monitored in the 1- and 3-month repeat-dose oral toxicity studies in dogs, and no significant findings were reported up to the highest tested dose of 1500 mg/kg/day (294-fold the clinical dose). Overall, while these studies evaluated the potential for cardiovascular safety risks with tradipitant in the context of the completed and ongoing clinical trials, they are not considered adequate in lieu of a clinical thorough QT (TQT) study, (b) (4)

⁴² Based on data from Trial VP-VLY-686-1002. Following single doses of 85 and 170 mg, C_{max} =84.7 and 112 ng/mL, respectively.

⁴³ Based on data from Trial VP-VLY-686-1102. Following 12 days of dosing at 85 mg BID in healthy volunteers, C_{max} =327 ng/mL. This study was inconclusive as to whether steady state was achieved. However, steady state was achieved within 7 days of daily dosing in healthy male subjects in Study H8R-EW-HJAD. Therefore, steady state is reasonably achieved with tradipitant within 7 days of repeated dosing, which is further supported by the population PK modeling. As subjects with vomiting induced by motion are considered otherwise healthy in the absence of a motion stimulus, and in the absence of robust multidose PK data from Trial VP-VLY-686-3403 for this indication, data from healthy volunteers was deemed the most appropriate for this evaluation.

⁴⁴ “FDA will take note of positive findings of toxicity in a study even though that study was not conducted in compliance with good laboratory practices. While a technically bad study can never establish absence of a safety risk, it may establish the presence of an unsuspected hazard or untoward effect.” See FDA guidance for industry *Good Lab Practice Regulations Management Briefings, Post Conference Report, Aug 1979* ([August 1979](#)).

Table 38. Shortening of Action Potential Duration in Dog Purkinje Fibers With Tradipitant

Tradipitant Dose	Duration	Human C _{max} (ng/mL)	In Vitro IC ₅₀ ¹ (ng/mL)	Effect Margin
85 mg	Single dose	84.7		139
170 mg	Single dose	112	11758	105
170 mg/day	Steady state	327		36

Source: Trial VP-VLY-686-1002 (single-dose human data), Trial VP-VLY-686-1102 (steady-state human data from subjects administered 85 mg Q12H for 12 days), Study 1263DE10.002, and analysis by reviewer

¹ The in vitro equivalent (ng/mL) is calculated, briefly, by multiplying the IC₅₀ (20 μM) by the molecular weight of tradipitant (587.9 g/mol)

Abbreviations: C_{max}, maximum plasma concentration; IC₅₀, half-maximal inhibitory concentration; Q12H, every 12 hours

13.1.4. Pharmacokinetics

See Section [13.2.4](#) for additional pharmacokinetic studies with tradipitant and its metabolites.

Absorption, distribution, metabolism, and excretion studies with tradipitant have been conducted in vitro and in vivo in mice, rats, rabbits, and dogs. Systemic exposure to tradipitant generally increased less than proportionally with increasing dose and was generally higher in females compared to males in all species.

Tradipitant was highly bound to plasma proteins in all species.

The major metabolic pathways of tradipitant were different in nonclinical species compared to humans. All metabolites detected in the human liver microsomes and slices were detected in preparations from one or more nonclinical species in vitro; however, metabolites M4 and M8 were not detected in liver microsomes or slices from rats and dogs, the species used for toxicity testing.⁴⁵

In humans, tradipitant is extensively metabolized, primarily through non-CYP-mediated processes and secondarily through CYP3A4, CYP2C19, and CYP2C8. The major circulating metabolites in humans have been identified as M2, M3, M4, and M8, which are produced by ketone reduction (M2, M4), N-glucuronidation (M8), and/or pyridine N-oxidation (M3, M4).

Tradipitant significantly inhibited transporters BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K in vitro, with IC₅₀ values in the micromolar range. Metabolite M2 also significantly inhibited OATP1B1 and MATE1, while M3 significantly inhibited OATP1B1, OATP1B3, and MATE1. No significant inhibition of transporters was observed with metabolite M4. Tradipitant was a weak substrate of P-glycoprotein (P-gp). M2 was not a substrate of P-gp or BCRP, while M3 and M4 were strong substrates of P-gp and weak substrates of BCRP.

Fecal excretion was the major excretion route for tradipitant-related material following oral administration of tradipitant.

13.1.5. Repeat-Dose Toxicity

Repeat-dose oral toxicity studies with tradipitant have been conducted in mice (13 weeks), rats (up to 6 months), and dogs (up to 3 months). Target organs were identified as liver and thyroid. Again, it should be noted that the HED-derived safety margins stated here are likely

⁴⁵ Module 2.6.4 Pharmacokinetics Written Summary, Table 26.

overestimating safety, based on the known pharmacokinetic properties of tradipitant, and these margins should be interpreted with caution.

In a 13-week toxicity study in albino mice, tradipitant was orally administered once daily at doses of 0 (vehicle), 15, 150, or 1500 mg/kg/day. No significant toxicity was reported in this study. Increased liver weights were observed at ≥ 150 mg/kg/day compared to controls with no histopathological correlates. These findings were considered secondary to the CYP450 enzyme induction also observed in these groups. Exposure to tradipitant increased less than proportionally with increasing dose in this study. Decreased exposure was observed between Days 1 and 14 and was attributed to enzyme induction that accelerated clearance of tradipitant. Based on the lack of adverse effects, the no-observed-adverse-effect level (NOAEL) was considered the highest tested dose of 1500 mg/kg/day (43-fold the maximum clinical dose of 170 mg, based on HED). Notably, only marginal differences in AUC values were observed among all dosing groups, such that the differences in AUC between 15 and 1500 mg/kg/day (i.e., a 100-fold increase in dose) were only 3.4- to 4.1-fold.

In a 3-month toxicity study in Fischer 344 rats, tradipitant was orally administered once daily at doses of 0 (vehicle), 15, 150, or 1500 mg/kg/day. No drug-related mortality, clinical signs of toxicity, body weight or food consumption changes, or ophthalmology findings were reported in this study. Hemolysis of blood samples from all dose groups significantly compromised detection and/or assessment of several clinical pathology parameters. Increased gamma-glutamyl transferase (GGT) activity (up to 2.1-fold control level) was observed in all treated groups. Dose-dependent increases in liver weight were reported compared to controls. Slight increases in thyroid, kidney, and adrenal gland weights were also reported. Per the Applicant, the organ weight increases were considered secondary to enzyme induction. Histopathological findings of minimal hepatocellular hypertrophy and minimal multifocal hepatocellular single cell necrosis were noted at 1500 mg/kg/day. Minimal to mild thyroid hyperplasia was observed in all treated groups. Histopathological findings in liver and thyroid were also considered secondary to enzyme induction, based on available information. Exposure to tradipitant did not increase significantly with increasing dose in this study. Decreased exposure after repeated dosing was observed in all treatment groups, consistent with typical CYP450 enzyme induction effects. Based on the lack of adverse findings, the NOAEL was considered the highest tested dose of 1500 mg/kg/day (85-fold the maximum clinical dose, based on HED); however, confidence in this finding is limited by the inadequate clinical pathology data, data suggesting loss of exposure to tradipitant after repeated administration, and marginal differences in AUC among all dosing groups (i.e., similar to 1.9-fold increase in AUC for a 100-fold increase in dose).

In a 6-month toxicity study in Fischer 344 rats, tradipitant was orally administered once daily at doses of 0 (vehicle), 15, 150, or 1500 mg/kg/day. No drug-related mortality, clinical signs of toxicity, body weight changes, ophthalmology findings, urinalysis abnormalities, or gross pathology findings were reported. A reversible increase in activated partial thromboplastin time was observed in males at ≥ 150 mg/kg/day and in females at all doses compared to controls. Reversible, dose-dependent increases in GGT activity were observed in males at ≥ 150 mg/kg/day and in females at all doses compared to controls. No other clinical chemistry findings indicative of liver injury were reported. Significant histopathological findings were observed in liver, thyroid, and kidney, including minimal to mild hepatocellular hypertrophy at all doses, minimal thyroid follicular cell hypertrophy in males at 1500 mg/kg/day and in females at all doses, and an increased incidence of minimal to mild chronic nephropathy at all doses

compared to controls. Findings in liver and thyroid were considered secondary to metabolic enzyme induction by the Applicant. Chronic nephropathy appeared to be an age-related finding, as it was also observed in the control group; however, the increase in incidence/severity noted in males at 1500 mg/kg/day was considered treatment-related. Considering that all findings were resolved following the recovery period, no other histopathological findings indicative of hepatic or renal injury were observed, and there were no findings indicative of renal function impairment, the toxicological significance of the liver, thyroid, and kidney findings was considered limited. Systemic exposure to tradipitant decreased markedly with time, especially over the first 3 months of dosing. The Applicant attributed this to induction of metabolizing enzymes accelerating the clearance of tradipitant; the review team agrees. Based on the lack of adverse findings, the NOAEL was considered to be the highest tested dose of 1500 mg/kg/day (85-fold the maximum clinical dose, based on HED); however, confidence in this finding is limited by data suggesting loss of exposure to tradipitant after repeated administration and marginal differences in AUC among all dosing groups (i.e., similar to 1.8-fold increase in AUC for a 100-fold increase in dose).

In a 3-month toxicity study in Han Wistar rats, tradipitant was orally administered once daily at doses of 0 (vehicle), 15, 150, or 1500 mg/kg/day. No drug-related mortality, clinical signs of toxicity, body weight changes, ophthalmology findings, urinalysis abnormalities, or gross pathology findings were reported. Dose-dependent increases in GGT activity were observed at ≥ 150 mg/kg/day and correlated with increased liver and thyroid weights as well as histopathological findings of hepatocyte hypertrophy, foci of inflammatory cells with hepatocyte necrosis (with dose-dependent incidence and severity), and hypertrophy of thyroid follicular cells. These findings were generally similar to the findings in the 3-month study in Fischer rats and were generally consistent with induction of metabolic enzymes. However, liver findings were considered to be more severe in this study compared to the 3-month and 6-month studies in Fischer rats, as foci of inflammatory cells with hepatocyte necrosis were not reported in Fischer rats at doses up to 1500 mg/kg/day for up to 6 months but were noted in 6/10 males at 150 mg/kg/day, 9/10 males at 1500 mg/kg/day, and 3/10 females at 1500 mg/kg/day in this study. The reason for the apparent strain-related differences in liver toxicity is unknown.⁴⁶ Systemic exposure to tradipitant decreased markedly with time. The Applicant attributed this to induction of metabolizing enzymes accelerating the clearance of tradipitant; the review team agrees. Based on the adverse findings of necrosis in the liver of males at ≥ 150 mg/kg/day and females at 1500 mg/kg/day, the NOAEL was considered the lowest dose of 15 mg/kg/day in males (less than the maximum clinical dose, based on HED) and the mid dose of 150 mg/kg/day in females (8.5-fold the maximum clinical dose); however, confidence in this finding is limited by data suggesting loss of exposure to tradipitant after repeated administration and marginal differences in AUC among all dosing groups (i.e., 2.2- to 3.1-fold increase in AUC for a 100-fold increase in dose).

⁴⁶ Exposures to tradipitant and M3 were slightly lower in Han Wistar rats compared to Fischer rats following 13 weeks/3 months of dosing at 150 mg/kg/day (the dose at which both strains have data including metabolites M2, M3, and M4). C_{max} values for tradipitant and M3 in Han Wistar rats were 0.6- to 0.7-fold and 0.4- to 0.6-fold those observed in Fischer rats, respectively. AUC values for tradipitant and M3 in Han Wistar rats were 0.9-fold and 0.4- to 0.6-fold those observed in Fischer rats, respectively. Metabolites M2 and M4 were below the limit of quantification in Han Wistar rats but observed at low levels in Fischer rats. C_{max} and AUC values for tradipitant at 1500 mg/kg/day were similar between the two strains (0.8- to 1.1-fold; metabolites not measured). Therefore, differences in exposure to tradipitant, M2, M3, and M4 do not explain the strain differences in observed toxicity.

In a 1-month toxicity study in Beagle dogs, tradipitant was orally administered once daily at doses of 0 (vehicle), 50, 200, 800, or 1500 mg/kg/day. No drug-related mortality, clinical signs of toxicity, or changes in feed consumption, body weight, ophthalmology, neurological parameters, ECG parameters, hematology and urinalysis parameters, or histopathology were reported. Treatment resulted in increased liver weights, increased hepatic cytochrome P450 content, macroscopic liver enlargement, and increases in ALT (≥ 800 mg/kg/day) and ALP (all dose groups). However, there were no microscopic correlates in the liver, and these effects were considered likely to be secondary to the observed hepatic CYP450 enzyme induction. No loss of exposure or accumulation was observed with repeated dosing of tradipitant in this study. Based on the lack of adverse effects, the NOAEL was considered the highest tested dose of 1500 mg/kg/day (294-fold the maximum clinical dose, based on HED). Notably, only marginal differences in AUC values were observed among all dosing groups, such that the differences in AUC between 50 and 1500 mg/kg/day (i.e., a 30-fold increase in dose) were only 1.9- to 4.0-fold.

In a 3-month toxicity study in Beagle dogs, tradipitant was orally administered once daily at doses of 0 (vehicle), 50, 275, or 1500 mg/kg/day. No drug-related mortality or changes in feed consumption, ophthalmology, neurological parameters, ECG parameters, hematology and urinalysis parameters, or gross pathology were reported. Drug-related clinical observations included white material in feces in males and females at ≥ 275 mg/kg/day and emesis in males at 1500 mg/kg/day. Body weight loss was observed in males at 1500 mg/kg/day (considered adverse), and decreased body weight gain was reported in males and females at all doses compared to controls. Minimal to mild, dose-dependent increases in hepatic enzymes (ALP, GGT, and ALT) were observed at 275 and/or 1500 mg/kg/day with no histopathological correlates; these findings were considered secondary to hepatic microsomal enzyme induction, as hepatic CYP450 enzyme induction was observed in the 1-month oral toxicity study in dogs. Minimal to mild diffuse vacuolation of follicular epithelial cells in the thyroid gland was observed in females at all doses but not in males; these findings were considered not adverse. No loss of exposure or accumulation was observed with repeated dosing of tradipitant in this study. Based on the observed weight loss in males at 1500 mg/kg/day, the NOAEL was considered the mid dose of 275 mg/kg/day (54-fold the maximum clinical dose, based on HED). Notably, only marginal differences in AUC values were observed among all dosing groups, such that the differences in AUC between 50 and 1500 mg/kg/day (i.e., a 30-fold increase in dose) were only 2.3- to 2.6-fold.

13.1.6. Genetic Toxicology

Tradipitant was negative in a complete battery of genetic toxicity studies, including the Ames assay, an in vitro chromosomal aberration assay in human lymphocytes, and an in vivo micronucleus assay in mice. See Section [13.2.5](#) for genotoxicity data with the metabolites.

13.1.7. Carcinogenicity

The carcinogenic potential of tradipitant was evaluated in a 26-week study in CB6F1-TgN (Rash2) transgenic mice and a 104-week study in Han Wistar rats. In transgenic mice, no tumors were attributed to treatment with tradipitant at doses up to 1500 mg/kg/day. In male and female

rats, the incidence of thyroid follicular cell adenomas was significantly higher compared to controls at the mid and high doses (30 and 150 mg/kg/day or 1.7- and 8.5-fold the maximum clinical dose, respectively, based on HED; less than the exposure to tradipitant in males and 2.8- to 3.4-fold the exposure to tradipitant in females at the MRHD, based on AUC). Combined incidences of thyroid follicular cell adenoma and carcinoma were significantly higher compared to controls in male rats at the high dose of 150 mg/kg/day only and in female rats at ≥ 30 mg/kg/day.

13.1.8. Reproductive and Developmental Toxicology

No effects on fertility, maternal health, or embryo-fetal development were observed in rats treated with tradipitant during the periods of mating and organogenesis at doses up to 1000 mg/kg/day (57-fold the maximum clinical dose, based on HED; 2.2-fold based on AUC). No effects on maternal health or embryo-fetal development were observed in rabbits treated with tradipitant during the period of organogenesis at doses up to 1000 mg/kg/day (114-fold the maximum clinical dose; 1.4-fold based on AUC). In rats treated with tradipitant during gestation and lactation, no maternal toxicity or developmental effects on the offspring were observed at doses up to 1000 mg/kg/day (57-fold the maximum clinical dose; 2.2-fold based on AUC).

In a juvenile animal study in Han Wistar rats, tradipitant was orally administered at doses of 0 (vehicle), 15, 50, or 150 mg/kg/day for 11 weeks, from Postnatal Day 10 to 90. No juvenile-specific toxicities were observed. Dose-dependent increases in liver, thyroid, and parathyroid weights were observed compared to the controls. Increased liver weights correlated with elevated liver enzymes and microscopic finding of hepatocellular hypertrophy, while increased thyroid weights correlated with hypertrophy of the thyroid follicular cells. Consistent with the findings in adult animals, changes observed in the liver and thyroid were considered secondary to metabolic enzyme induction.

13.1.9. Special Toxicology

Tradipitant showed little to no light absorption in the 290 nm to 800 nm wavelength range; thus, the phototoxicity potential of tradipitant was considered low.

See Section [13.2.6](#) for additional special toxicology studies with tradipitant.

13.2. Summary Review of Studies Submitted With the New Drug Application

Twenty-three additional primary pharmacology, safety pharmacology, pharmacokinetic, genetic toxicology, and special toxicology studies with tradipitant and/or its major human metabolites were submitted to the current NDA without being previously submitted to IND 141315 or cross-referenced from other INDs. Full reviews of these studies were conducted under the current NDA 220152 (see Nonclinical Supplementary NDA Review dated December 30, 2025).

13.2.1. Primary Pharmacology

Tradipitant completely inhibited ligand binding to the human NK-1 receptor in vitro at a concentration of 10 μ M. The IC₅₀ values of tradipitant for ligand binding at the NK-1 receptor were 0.40 and 3.3nM, respectively, in two separate in vitro studies. Tradipitant was also shown to inhibit substance P-mediated calcium release in HEK293 cells with an IC₅₀ value of 0.63nM.

The four major human metabolites of tradipitant, M2, M3, M4, and M8, have been shown or are presumed to be pharmacologically active based on available data. All four metabolites inhibited ligand binding to the NK-1 receptor by $\geq 99.0\%$ at a concentration of 10 μ M. M8 was shown to inhibit ligand binding at the receptor with an IC₅₀ of 0.49nM and to inhibit substance P-mediated calcium release in vitro with an IC₅₀ of 6.3nM. M2, M3, and M4 were reported by the Applicant¹² to inhibit binding to the NK-1 receptor with IC₅₀ values of 1.55, 0.38, and 2.23nM, respectively; the functional activity of these metabolites was not tested.

13.2.2. Secondary Pharmacology

Among a panel of 189 receptors, channels, and transporters, tradipitant was shown to significantly inhibit the rat benzothiazepine and dihydropyridine L-type calcium channels (65% and 63%, respectively) as well as the rat gamma-aminobutyric acid type A receptor (GABA_A) t-butyl bicycloorthobenzoate (TBOB) chloride channel (62%). M2 also significantly inhibited the rat benzothiazepine L-type calcium channel (52%), human estrogen receptor alpha (ER α ; 64%), and rat GABA_A TBOB chloride channel (53%). No significant inhibition of the tested receptors, channels, and transporters was observed with M3, M4, or M8.

13.2.3. Safety Pharmacology

A potential risk for hepatotoxicity with tradipitant was identified in the completed repeat-dose toxicity studies (see Section [13.1.5](#)). In the 13-week toxicity study in Han Wistar rats, foci of inflammatory cells and minimal to slight hepatocyte necrosis were observed in the livers of 6/10 mid dose males, 9/10 high dose males, and 3/10 high dose females (clinical effect margins of 8.5 in males and 85 in females, respectively, relative to the maximum clinical dose of 170 mg, based on HED). These adverse liver findings were not observed in studies of up to 6 months in Fischer rats or studies of up to 3 months in dogs; however, nonadverse liver findings attributed to adaptive effects following induction of metabolic enzymes and/or not correlated with adverse histopathological findings in the liver were observed in all nonclinical species/strains. It is well-established that prolonged exposure to a drug at levels previously shown to be adaptive may eventually result in liver cell injury due to a failure of adaptive mechanisms. Given the presence of adaptive changes in all species tested, it is plausible that evidence of hepatotoxicity could be observed in a chronic toxicity study in Han Wistar rats (i.e., the more susceptible strain) or a chronic toxicity study in a nonrodent species.

In addition to the in vivo studies, the Applicant later conducted five human cell-based in vitro safety pharmacology studies⁴⁷ that further demonstrated the potential for tradipitant and its

⁴⁷ Four liver safety pharmacology studies (HPTOX-3550, HPTOX-3560, HPTOX-3540, and SRV-0028) were previously submitted to and reviewed under NDA 218489. The fifth study, HPTOX-3610, was submitted to NDA 220152 during the review cycle following a nonclinical information request (SDN 9; March 25, 2025).

metabolites to induce hepatotoxicity. The objectives of these studies were to quantify the hepatotoxic potential of tradipitant, compare the toxicity profiles of tradipitant and its major metabolites (in the presence and absence of inflammatory cytokines), and to further evaluate tradipitant's underlying toxicity mechanisms. Four studies were conducted using static cultured 3D human donor-derived hepatocyte spheroids, and one study was conducted using an in vitro human liver-chip MPS.

In the four non-GLP studies using cultured 3D human donor-derived hepatocyte spheroids, significant variability was observed between donors, including variability in the toxicity induced by the positive control (when included) as well as variability in the toxicity observed between studies, even when the same donors were used. In the initially submitted Studies HPTOX-3550, HPTOX-3560, and HPTOX-3540, biologically significant hepatocyte toxicity⁴⁸ was observed following tradipitant treatment for 2 or 4 weeks at concentrations as low as 1.05 µg/mL (approximately 12-, 9.4-, and 3.2-fold the clinical C_{max} in healthy volunteers following administration of a single dose of 85 mg, a single dose of 170 mg,⁴² and 170 mg/day at steady state,⁴³ respectively) but more consistently in the range of 3.5 to 7.0 µg/mL (11- to 83-fold the clinical C_{max} values), with no clear concentration- or time-dependent effects reported. It should be noted that the Applicant did not conduct in vitro to in vivo extrapolation (IVIVE) analyses to determine how the in vitro concentration relates to that observed in humans, and, thus, the actual effect margins should be interpreted with caution. Additionally, no potential mechanism for the observed hepatocyte toxicity was identified in these studies.

Table 39. Hepatocyte Toxicity in Human Donor-Derived 3D Liver Spheroids Treated With Tradipitant for 2 or 4 Weeks

Tradipitant Dose		Duration	Human C _{max} (ng/mL)	Toxic Concentration (µg/mL)	Effect Margin ¹
Lowest observed toxic concentration					
85 mg	Single dose	84.7	1.05	12	
170 mg	Single dose	112		9.4	
170 mg/day	Steady state	327		3.2	
Consistent toxicity					
85 mg	Single dose	84.7	3.5-7.0	41-83	
170 mg	Single dose	112		31-63	
170 mg/day	Steady state	327		11-21	

Source: Trial VP-VLY-686-1002 (single-dose human data), Trial VP-VLY-686-1102 (steady-state human data from subjects administered 85 mg Q12H for 12 days), Study HPTOX-3550, Study HPTOX-3560, and HPTOX-3540, and analysis by reviewer

¹ Effect margins were calculated by direct comparison of the human C_{max} and in vitro concentrations. The Applicant did not conduct in vitro to in vivo extrapolation (IVIVE) analyses to determine how the in vitro concentration relates to that observed in humans. However, comparing in vitro and in vivo concentrations should occur after the establishment of an IVIVE process using in vitro data to predict in vivo exposure. IVIVE accounts for factors such as drug metabolism, distribution, and integrated physiological processes within the body to determine an in vitro-in vivo scaling factor. This scaling factor informs how much higher the in vitro concentration must be compared to the in vivo plasma concentration to cause similar biological effects in target cells. In the absence of such a threshold to determine whether the assay findings are positive or negative, the effect margins presented here have limited clinical utility.

Abbreviations: C_{max}, maximum plasma concentration; Q12H, every 12 hours

⁴⁸ Defined as viability reduced to <80% of control levels. This model (including the toxic threshold) was previously shown to detect hepatotoxic drugs with 69% sensitivity and 100% specificity, based on a panel of 123 drugs with or without clinically observed drug-induced liver injury. See [Vorrink et al. \(2018\)](#).

In the more recently submitted Study HPTOX-3610, biologically significant hepatocyte toxicity⁴⁸ was observed following tradipitant treatment for 2 weeks at concentrations as low as 0.350 µg/mL (4.1- 3.1- and 1.1-fold the clinical C_{max} values).⁴⁹ In the same study, hepatocyte toxicity was also observed with tradipitant metabolites M2 at concentrations as low as 0.350 µg/mL (3.4- to 25-fold the clinical C_{max} values), M3 as low as 1.05 µg/mL (11- to 61-fold the clinical C_{max} values) but more commonly at 10.5 or 35 µg/mL, M4 as low as 0.350 µg/mL (3.4- to 20-fold the clinical C_{max} values), and M8 in 2/4 donors only (0.350 and 10.5 µg/mL, respectively; 16- and 26-fold the single-dose clinical C_{max} values). Again, the reported effect margins should be interpreted with caution, as no IVIVE analyses were conducted.

Table 40. Hepatocyte Toxicity in Human Donor-Derived 3D Liver Spheroids Treated With Tradipitant or Metabolites for 2 Weeks

Compound	Tradipitant Dose	Duration	Human C _{max} (ng/mL)	Lowest Toxic Concentration (µg/mL)	Effect Margin ¹
Tradipitant	85 mg	Single dose	84.7	0.35	4.1
	170 mg	Single dose	112		3.1
	170 mg/day	Steady state	327		1.1
M2	85 mg	Single dose	14.2	0.35	25
	170 mg	Single dose	18.7		19
	170 mg/day	Steady state	102		3.4
M3	85 mg	Single dose	17.1	1.05	61
	170 mg	Single dose	21.9		48
	170 mg/day	Steady state	97.7		11
M4	85 mg	Single dose	17.4	0.35	20
	170 mg	Single dose	21.4		16
	170 mg/day	Steady state	104		3.4
M8	85 mg	Single dose	13.3	0.35	26
	170 mg	Single dose	21.7		16
	170 mg/day	Steady state	NM		n/a

Source: Trial VP-VLY-686-1002 (single-dose human data), Trial VP-VLY-686-1102 (steady-state human data from subjects administered 85 mg Q12H for 12 days), Study HPTOX-3610, and analysis by reviewer

¹ Effect margins were calculated by direct comparison of the human C_{max} and in vitro concentrations. The Applicant did not conduct in vitro to in vivo extrapolation (IVIVE) analyses to determine how the in vitro concentration relates to that observed in humans. However, comparing in vitro and in vivo concentrations should occur after the establishment of an IVIVE process using in vitro data to predict in vivo exposure. IVIVE accounts for factors such as drug metabolism, distribution, and integrated physiological processes within the body to determine an in vitro-in vivo scaling factor. This scaling factor informs how much higher the in vitro concentration must be compared to the in vivo plasma concentration to cause similar biological effects in target cells. In the absence of such a threshold to determine whether the assay findings are positive or negative, the effect margins presented here have limited clinical utility.

Abbreviations: C_{max}, maximum plasma concentration; M, metabolite; n/a, not applicable; NM, not measured; Q12H, every 12 hours

In a non-GLP study using the liver co-culture MPS, mild to moderate hepatocyte toxicity⁵⁰ (assessed qualitatively using immunofluorescent staining) was observed with tradipitant in all

⁴⁹ Three donors were used in both Studies HPTOX-3550 and HPTOX-3610. Findings for individual donors were inconsistent between studies. Toxicity was observed following 2 weeks of treatment with tradipitant at a notably lower concentration for 2/3 donors (0.350 versus 17.5 µg/mL) and at a higher concentration for the remaining donor (35 versus 7.0 µg/mL) in Study HPTOX-3610 compared to Study HPTOX-3550. The source of this variability is unknown.

⁵⁰ Where the definition of mild toxicity included <20% dead cells and the definition of moderate toxicity included <50% dead cells. See study report for further characterization of the scoring system (Study SRV-0028).

donors at the highest tested concentration of 26.3 μ M (183-, 138-, and 47-fold the clinical C_{max} values), while no toxicity was observed in liver sinusoidal endothelial cells under the tested conditions. Minimal⁵¹ to mild toxicity was also observed sporadically in hepatocytes and liver sinusoidal endothelial cells treated with metabolites M2, M3, M4, and/or M8 at the latest timepoint of 168 hours (7 days). No clear effects of tradipitant or its metabolites were observed on isolated endpoints selected by the Applicant to represent liver function and injury including albumin, AST, ALT, reactive oxygen species generation, CCK-18 protein expression, or microRNA-122 expression. Although four positive controls were used in this study, no explanation was given for their selection. At least one positive control resulted in statistically significant changes for each chosen endpoint. However, thresholds for biologically or clinically significant changes in each endpoint were not prespecified. Additionally, no potential mechanism for the observed hepatocyte toxicity was identified.

Table 41. Hepatocyte Toxicity in the Human Liver Co-Culture Chip Treated With Tradipitant for 7 Days

Tradipitant Dose	Duration	Human C_{max} (ng/mL)	Lowest Toxic Concentration (μ g/mL)	Effect Margin ¹
85 mg	Single dose	84.7		183
170 mg	Single dose	112	15.5	138
170 mg/day	Steady state	327		47

Source: Trial VP-VLY-686-1002 (single-dose human data), Trial VP-VLY-686-1102 (steady-state human data from subjects administered 85 mg Q12H for 12 days), Study SRV-0028, and analysis by reviewer

¹ Effect margins were calculated by direct comparison of the human C_{max} and in vitro concentrations. The Applicant did not conduct in vitro to in vivo extrapolation (IVIVE) analyses to determine how the in vitro concentration relates to that observed in humans. However, comparing in vitro and in vivo concentrations should occur after the establishment of an IVIVE process using in vitro data to predict in vivo exposure. IVIVE accounts for factors such as drug metabolism, distribution, and integrated physiological processes within the body to determine an in vitro-in vivo scaling factor. This scaling factor informs how much higher the in vitro concentration must be compared to the in vivo plasma concentration to cause similar biological effects in target cells. In the absence of such a threshold to determine whether the assay findings are positive or negative, the effect margins presented here have limited clinical utility.

Abbreviations: C_{max} , maximum plasma concentration; Q12H, every 12 hours

Overall, the utility of these in vitro liver safety pharmacology studies is limited due to their short duration and lack of clear relationship to clinical risk. However, these studies demonstrate that the potential for liver toxicity is not an animal-specific finding, as toxicity was consistently observed with human donor-derived hepatocytes. This safety concern was not identified in clinical trials with tradipitant up to 90 doses (see Section 7.6)

13.2.4. Pharmacokinetics

Tradipitant and its metabolites M2, M3, and M4 were highly bound in vitro using plasma from rat, mouse, and human. Plasma binding of tradipitant or its metabolites was not affected by concentration in any species. M8 was not tested for plasma protein binding.

Using recombinant human enzymes, UGT1A4 and UGT2B7 were identified as UGTs capable of converting tradipitant to the metabolite M8.

⁵¹ Where the definition of minimal toxicity included >95% healthy hepatocyte morphology and <5% dead cells. See study report for further characterization of the scoring system (Study SRV-0028).

In studies using human liver microsomes, tradipitant competitively inhibited CYP3A activity with an inhibitory constant (K_i) of 0.92 μ M and noncompetitively inhibited CYP3A activity with a K_i of 11 μ M. Tradipitant competitively inhibited both CYP2C19 and CYP2C9 activities with K_i values of 9.0 and 4.7 μ M, respectively. Tradipitant also noncompetitively inhibited CYP2C8 activity with a K_i value of 17 μ M. No significant effects were observed on CYP1A2, CYP2D6, CYP2E1, or CYP2B6 activity.

In a study using primary human hepatocytes, tradipitant was considered a potential inducer of CYP3A4 activity in vitro. No biologically significant effects of tradipitant were observed on CYP1A2 activity.

13.2.5. Genetic Toxicology

Metabolites M2, M3, and M4 were negative for genotoxicity in the Ames assay and in vitro chromosomal aberration assays using human lymphocytes. M8 was not assessed for genotoxicity, but the risk is considered low given the structural similarity to tradipitant and the other major human metabolites, all of which were negative for genotoxicity.

13.2.6. Special Toxicology

The Applicant conducted two special toxicology studies using a “four-organ” MPS comprised of human hepatocytes, cardiomyocytes, proximal tubular epithelial cells, and cortical neurons, with the objective of prospectively evaluating the safety of tradipitant in a human-based system.

In the first study, the Applicant stated that no effects of tradipitant were observed on selected biomarkers of function⁵² for any of the four cell types following 7 days of treatment when administered once per day at concentrations of 3 or 100 μ M. These concentrations were determined to result in cellular exposure to tradipitant at 500 and 3,500 ng/mL, respectively (approximately 5.9/41-, 4.5/31-, and 1.5/11-fold the clinical C_{max} in healthy volunteers following administration of a single dose of 85 mg, a single dose of 170 mg,⁴² and 170 mg/day at steady state,⁴³ respectively). Importantly, limitations of the assay precluded accurate interpretation of the study findings (see below).

In the second study, evidence of potential toxicity with tradipitant was observed with select endpoints under select conditions at select timepoints (up to 14 days) in hepatocytes (substantial cell detachment), cardiomyocytes (increased troponin-I, decreased cardiac force, increased field potential duration), renal proximal tubular epithelial cells (increased kidney injury molecule-1 [KIM-1] release), and cortical neurons (increased firing rate). The Applicant concluded that “chronic” exposure of tradipitant in the four-organ system yielded only “minor adverse effects in all organ constructs.” When comparing the safety of tradipitant across systems containing either high, moderate, or low metabolic activity (based only on CYP3A4 activity), significant effects of metabolic activity could be observed, suggesting that differences in hepatic expression of metabolizing enzymes (e.g., polymorphisms leading to activity of metabolic enzymes that is higher or lower than that seen in the general population) may influence physiological outcomes

⁵² Hepatocytes: CYP3A4 activity, hepatocyte viability, albumin production; cardiomyocytes: cardiac force, beat frequency, and conduction velocity; renal proximal tubule cells: kidney-injury molecule 1 (KIM-1) release; cortical neurons: half-peak width activity, spike amplitude, and firing rate.

in this test, including outcomes related to safety. As with the first four-organ study, limitations of the assay precluded accurate interpretation of the study findings (see below).

Based on the available information,⁵³ it appears that the two studies in the four-organ system were not conducted in compliance with US FDA GLP regulations. The Applicant provided a statement from the contract research organization conducting the studies, (b) (4) indicating that, in their view, US FDA GLP regulations, “did not apply [to] our organization as we are not doing biomarker or similar analysis but really trying to augment or replace animal studies.”⁵³ However, based on the stated objectives, the four-organ MPS studies are prospective in vitro nonclinical laboratory studies intended to support the safety and approval of tradipitant under this NDA. Therefore, the GLP regulations are applicable.⁵⁴ The validity and reliability of the results from nonclinical safety studies depend on careful adherence to certain standards for study conduct that help to ensure the quality, integrity, and reliability of the data (Carroll 2016).⁵⁵ establishing confidence in the scientific merit of the study so that accurate interpretation of the results is possible. Compliance with U.S. FDA GLP regulations or, when appropriate, an adequate justification of why noncompliance does not affect interpretation or validity of the study findings, is critical to assure the quality and integrity of the safety data obtained from nonclinical studies and use these data to assess risk in humans. The lack of U.S. FDA GLP compliance and absence of adequate justification by the Applicant for noncompliance are considered limitations of these studies.

In addition to the lack of compliance with U.S. FDA GLP regulations, other limitations in the design and conduct of these studies preclude their use for regulatory decision-making in this matter.

⁵³ (b) (4)

⁵⁴ See 21 CFR 58.1(a), “This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including...human and animal drugs...” See also 21 CFR 58.3(d). “Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety.”

⁵⁵ See 21 CFR Part 58.

- The evaluation of potential toxicity using the four-organ system was limited in scope (i.e., not comprehensive) for the reasons including but not limited to:
 - The MPS used human-derived cells from the heart, liver, kidney, and brain, a limited subset of tissues compared to those present in a whole animal or human. Furthermore, there was no rationale for the specific subset of organs chosen for these studies or how an investigation using cells from these organs can evaluate toxicity within fully integrated physiological systems (i.e., including any effects of metabolism, immune responses, and hormones) to provide a broad, tissue-agnostic assessment of toxicity and to inform safe use of a drug.
 - Within an individual “organ,” only a single cell type was cultured and exposed to tradipitant. A single cell type only represents a portion of an organ and ignores the unique and functionally important architecture of the organ; thus, such a construct cannot adequately or comprehensively assess potential toxicities within that organ, precluding a recapitulation of full in vivo physiology and pathophysiology.
 - These studies evaluated a small number of endpoints (one to three factors per “organ”) which do not provide enough information to evaluate potential toxicity in each tissue.
- The biological relevance of the system or the chosen endpoints to support the safety of tradipitant was neither justified nor established.
 - Some evaluated endpoints (1) are not considered representative of toxicity (i.e., CYP activity), (2) were used as biomarkers of organ injury despite a lack of validation or clinical acceptance (i.e., KIM-1⁵⁶), and/or (3) were inconsistent with the results of other studies, including the in vitro liver assays described above and the completed toxicity studies in rats and dogs (i.e., CYP activity, hepatocyte viability).
 - Positive controls were either not used to demonstrate assay validity and potential toxicity in this system using the chosen endpoints (Study HSTOX-7619), or the utility of the data generated with the positive control compounds was limited due to lack of effects or overt cytotoxicity limiting measurement of the specific endpoint (Study HSTOX-2008-002).
 - As acknowledged by the Applicant, the metabolism of tradipitant in the four-organ system was significantly different than that observed in humans or in nonclinical species. Although the Applicant attempted to address this issue by using three hepatocyte donors with differing metabolic activities in Study HSTOX-2008-002, unexplained differences in metabolism remained compared to data from nonclinical and clinical studies.
 - These studies were conducted using a single donor for each primary tissue type (with the exception of the liver construct in Study HSTOX-2008-002). Any findings in these

⁵⁶ KIM-1 has not been qualified as a stand-alone biomarker of kidney injury for any context of use. Urinary KIM-1 has been qualified as part of a panel of six urinary biomarkers (clusterin, cystatin-C, KIM-1, N-acetyl-beta-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and osteopontin) whose composite measure is used in conjunction with traditional measures to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause renal tubular injury in humans. See [FDA \(2020\)](#). A similar panel of urinary biomarkers (KIM-1, albumin, total protein, β 2-microglobulin, cystatin C, clusterin, and trefoil factor-3) has been qualified for the detection of acute drug-induced nephrotoxicity in rats (in conjunction with traditional clinical chemistry markers and histopathology) in toxicology studies. See [FDA \(2009\)](#). Another biomarker panel including urinary KIM-1 is in the qualification process.

assays may reflect the response of an individual donor and may not be predictive of the general population.

- The duration of treatment in these studies was only 7 or 14 days; short-duration experiments do not provide data on the chronic toxicity of the drug.

Based on these limitations, the four-organ studies as designed, conducted, and reported do not contribute to the assessment of unrestricted use of tradipitant over a lifetime for the prevention of vomiting induced by motion.

13.2.7. Other Toxicology

In silico analyses of tradipitant and metabolites M2, M3, M4, and M8 were conducted using various tools and databases and provided in a 2015 report.⁵⁷ Although potential toxicities with tradipitant and/or its major metabolites were identified, this nonclinical test was conducted to assess “the biochemical and biomedical properties of tradipitant and four metabolites,” not as a prospective assessment to determine the safety of tradipitant nor as a supportive study to further understand the safety of tradipitant to support a marketing application. Therefore, the findings in this report are not considered scientifically relevant for this application.

Updated in silico analyses were conducted by the Applicant to support the safety of metabolites M2, M3, and M4 for this application.^{58,59,60,61} These analyses were intended to assess if and how structural differences in the metabolites might affect their toxicity profile compared to tradipitant. Briefly, these in silico analyses were conducted using a machine learning-assisted workflow developed by xAI's Grok system, an advanced large language model trained on scientific datasets and further validated via the Applicant's in-house Python scripts. Notably, the Applicant's comparative structural prediction data were inferred based on RDKit-computed descriptors and qualitative thresholds aligned with best practices from consensus classifiers, rather than direct execution of these models. It is not clear why the Applicant chose to design a workflow using a large language model and a custom set of molecular descriptors and use information from existing classifier techniques to ‘infer’ predictions, rather than directly using existing (Q)SAR modeling software. Additionally, insufficient detail was provided on the consensus classifiers used in the analyses to fully define the approach. However, enough information was provided to facilitate review of the findings.

For metabolite M2, no additional reactive groups were identified compared to tradipitant, and no significant differences between tradipitant and M2 were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M2 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. Compared to tradipitant, M2 was predicted to have slightly increased risk of hepatotoxicity (increased oxidation potential, potential drug-induced liver injury [DILI] alerts) and cardiotoxicity (increased hERG affinity, with predicted IC₅₀ >5μM or approximately 29-fold

⁵⁷ Submitted following an Information Request: March 14, 2025. See NDA 220152, SDN 9: March 25, 2025.

⁵⁸ NDA 220152: Information Request. October 1, 2025.

⁵⁹ NDA 220152, SDN 23: October 15, 2025.

⁶⁰ NDA 220152: Information Request. October 20, 2025.

⁶¹ NDA 220152, SDN 24: October 22, 2025.

the clinical $C_{max,ss}$). Despite the slight increase in risk presented by these analyses, the potential liver toxicity of M2 is considered to be consistent with tradipitant based on the CDER (Q)SAR analyses and findings in the completed in vitro liver safety pharmacology studies. The potential for M2-related cardiotoxicity due to hERG channel binding, while not directly assessed in nonclinical studies, has been assessed in completed clinical studies (with no risk identified, although the high-exposure scenario has not been addressed) and will be further assessed in a clinical TQT study (b) (4)

Metabolite M3 was shown to have structural alerts for oxidative stress, hepatotoxicity, and genotoxicity related to the N-oxide moiety and increased covalent binding risk (e.g., sensitization and hepatotoxicity) related to the alpha, beta-unsaturated ketone moiety that are not present in tradipitant. Compared to tradipitant, M3 had no significant differences predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M3 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. M3 was predicted to have slightly increased risk of oxidative stress, hepatotoxicity, and cardiotoxicity compared to tradipitant.

For metabolite M4 compared to tradipitant, no significant differences were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M4 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. Compared to tradipitant, M4 was predicted to have slightly increased risk of oxidative stress (structural alert based on the N-oxide), hepatotoxicity (with potential DILI alerts) and cardiotoxicity (increased hERG affinity, with predicted $IC_{50} > 5\mu M$ or approximately 29-fold the clinical $C_{max,ss}$). Despite the slight increase in risk presented by these analyses, the potential liver toxicity of M4 is considered to be consistent with tradipitant based on the CDER (Q)SAR analysis and findings in the completed in vitro liver safety pharmacology studies. The potential for M4-related cardiotoxicity due to hERG channel binding, while not directly assessed in nonclinical studies, has been assessed in completed clinical studies with no risk identified, although the high-exposure scenario has not been addressed, and will be further assessed in a clinical TQT study (b) (4)

Although a structural alert for genotoxicity was identified based on the N-oxide, both M3 and M4 were demonstrated to be negative for genotoxicity in the Ames assay and an in vitro chromosomal aberration assay in human lymphocytes.

Overall, the updated in silico analyses predicted that metabolites M2, M3, and M4 were unlikely to present additional toxicity concerns compared with tradipitant. The review team acknowledges that this type of computational toxicology analysis is not validated for this intended use. However, in conjunction with the internally conducted (Q)SAR analysis and following consideration of all available data, we generally agree with the Applicant's stated position.

13.2.8. Qualification of Metabolites

The Applicant has identified four major metabolites of tradipitant in human plasma: M2, M3, M4, and M8. These metabolites have been investigated in a series of nonclinical studies, and their plasma levels were measured in select toxicity studies conducted in rats and mice. Based on available data, these metabolites are considered to be pharmacologically active, toxicologically relevant, and present at significant levels compared to the parent drug, tradipitant. These factors support that the safety of levels of these metabolites should be qualified based on nonclinical

data. However, only M3 was present in tested nonclinical species at sufficient levels to be qualified for safety. M2, M4, and M8 are disproportionate human metabolites.

Using a WoE approach deemed appropriate for this drug and this application, the review team determined that, based on the in silico structural comparisons in conjunction with the available pharmacological, PK, and toxicological information about tradipitant and its metabolites, the metabolites are not expected to result in differing or exaggerated toxicity compared to tradipitant. Therefore, qualification of M2, M4, and M8 using total drug-related exposure, rather than on an individual basis, was deemed scientifically appropriate, and the levels of these metabolites were considered qualified based on this approach.

Therefore, all identified major human metabolites of tradipitant are considered qualified for safety based on available nonclinical data. However, as the nonclinical data supporting the safety of unrestricted use of tradipitant over a lifetime are considered inadequate, the safety of the metabolites is likewise not considered to be adequately supported by nonclinical data for unrestricted use of tradipitant over a lifetime.

13.2.9. Excipients

There are no novel excipients or excipients of human or animal origin used in the manufacturing of the tradipitant drug product.

All excipients used in the manufacture of tradipitant capsules are at levels below those used in previously approved, orally administered products as reported in the FDA Inactive Ingredient Database ([Table 42](#)). The proposed commercial drug product is size 1, white opaque body and black opaque cap, hard gelatin capsules, printed with 'VANDA 85 mg' in white on the cap, containing 85 mg of tradipitant per capsule. The gelatin capsule consists of gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6, and white ink. There are no nonclinical safety concerns with the composition of the capsule.

Table 42. Formulation of Tradipitant 85 mg Capsules

Component	Grade	Function	mg/Capsule	%w/w
Tradipitant	In house	API	85.00	(b) (4)
(b) (4) lactose (b) (4)	USP/NF/Ph.Eur	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose (b) (4)	USP/NF/Ph.Eur			
(b) (4)	USP/NF/Ph.Eur			
Croscarmellose sodium (b) (4)	USP/NF/Ph.Eur			
Povidone (b) (4)	USP/Ph.Eur			
Sodium lauryl sulfate	USP/NF/Ph.Eur			
Magnesium stearate (b) (4)	USP/NF/Ph.Eur			
Total fill weight				
Capsules size 1, weight				
Total weight				

Source: Table created by reviewer, based on Applicant's provided information (Quality Overall Summary, 2.3P Drug Product, Description and Composition, pgs. 1-2).

Abbreviations: API, active pharmaceutical ingredient; N/A, not applicable; NF, National Formulary; Ph.Eur., European Pharmacopoeia; USP, United States Pharmacopoeia; %w/w, percent weight per weight

13.2.10. Impurities

Overall, there are no safety concerns with the levels of impurities in tradipitant, and all impurities are adequately controlled. Notable impurities in tradipitant include potentially genotoxic impurities, related substances, residual solvents, elemental impurities, and potential nitrosamines.

The Applicant identified six impurities which were considered potentially genotoxic and are controlled as such at the drug substance level ([Table 43](#)). Notably, three of these impurities were considered International Council for Harmonisation (ICH) M7 Class 5 (i.e., nonmutagenic impurities) based on the available information ([April 2023](#)), including Ames assay, expert rule and statistical-based bacterial mutagenicity predictions, and/or expert review; however, the Applicant is controlling these impurities as though they were genotoxic (i.e., Class 2 or 3). We have no safety concerns with this approach.

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] This is acceptable.
- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] This is acceptable.
- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] This is acceptable.
- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
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[REDACTED]
[REDACTED]
- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
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[REDACTED]
[REDACTED]
[REDACTED]

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Additionally, as there are more than two Class 2 or Class 3 genotoxic impurities in tradipitant, total genotoxic impurities are controlled in the drug substance at a level of NMT (b) (4) ppm (equivalent to (b) (4)/day based on the clinical dose of tradipitant of 170 mg/day). Although not necessary, the Applicant has set this specification to include the total level of all impurities they have categorized as potentially genotoxic, including the Class 5 impurities listed in [Table 43](#); we have no safety concerns with this approach. As this level is less than the ICH M7 AI of 5 µg/day for total genotoxic impurities in drugs with expected lifetime exposure ([April 2023](#)), there are no safety concerns with the levels of total genotoxic impurities in tradipitant.

Table 43. Genotoxic Impurities Controlled in the Tradipitant Drug Substance

Chemical Name	Structure	ICH M7 Class	Specification (MDE Based on 170 mg/Day Dose)
(b) (4)			

Chemical Name	Structure	ICH M7 Class	Specification (MDE Based on 170 mg/Day Dose)
(b) (4)			
Total genotoxic impurities			(b) (4)

Source: Table created by reviewer, based on Applicant's provided information (3.2.S.3.2 Impurities, 3.2.S.4.1 Specification, and 3.2.S.4.5 Justification of Specification).

Abbreviations: ICH, International Council for Harmonisation; MDE, maximum daily exposure; NMT, not more than

Individual specified impurities include related substances (b) (4). These specified impurities are controlled at a level of NMT (b) (4)% in the drug substance. Unspecified impurities are controlled at a level of NMT (b) (4)% (w/w) in the drug substance, and total impurities are controlled at a level of NMT (b) (4)% (w/w). No impurities exceed the ICH Q3A qualification threshold of 0.15% (April 2023).

Residual solvents in the tradipitant drug substance are controlled in accordance with ICH Q3C (R8) (April 2021).

Elemental impurities with the potential of being introduced during the drug substance manufacturing process are controlled in accordance with ICH Q3D (R2) ([April 2022](#)).

A nitrosamine risk assessment conducted by the Applicant (b) (4)

[REDACTED]. Based on these findings, there are no safety concerns regarding the levels of individual or total nitrosamines in tradipitant.

13.2.11. Extractables and Leachables

Tradipitant 85 mg capsules are packaged in high-density polyethylene bottles with child-resistant closures containing aluminum foil-lined induction seals. Each bottle also contains a 2-g silica gel desiccant (b) (4). The materials of construction of the container closure system components are routinely used in the pharmaceutical industry for solid oral dosage forms, and the components comply with 21 CFR 211.94 requirements for drug product containers and closures. Based on the oral formulation (capsules) and container closure system, there are no nonclinical safety concerns regarding extractables and leachables.

14. Clinical Pharmacology

14.1. In Vitro Studies

Note that in this review, drug code names LY686017 or VLY-686 are also used to refer to tradipitant. Thirteen in vitro study reports were submitted characterizing protein binding, metabolism, and DDI potential. A summary of in vitro studies is provided in [Table 44](#). All in vitro studies were reviewed during current NDA review as well as during review of NDA 218489.

A summary of the in vitro DDI assessments for tradipitant is listed in [Table 44](#) and [Table 45](#). For in vitro DDI assessment, $C_{\max}$ from Trial 1102 were utilized. In Trial 1102, following 85 mg single dose for 1 day and 85 mg BID dose for 13 days, the observed mean $C_{\max}$ was 327 (± 42.4) ng/mL, in healthy subjects.

Table 44. In Vitro Studies of Tradipitant and Its Major Metabolites Using Human Biomaterials

Assessment	Conclusions	Study/Report
Distribution	Using the ultracentrifugation method, the mean ($\pm$ SEM) percentage of tradipitant (LY686017) bound to plasma proteins was 96.2%$\pm$0.6% in human plasma, 96.6%$\pm$1.5% in dog plasma, 90.1%$\pm$2.9% in gerbil plasma, 89.6%$\pm$4.2% in rat plasma, and 88.7%$\pm$4.7% in mouse plasma. Using the dextran coated charcoal adsorption method, the average percentage of tradipitant bound to plasma proteins was 93.2%$\pm$0.4% in human plasma and 92.8%$\pm$0.4% in gerbil plasma. The extent of binding to plasma proteins was independent of LY686017 concentrations in the 3 to 3000 ng/mL range.	ADME Report 06
Plasma protein binding	The plasma protein binding of tradipitant (VLY-686) was 98.5 ->99% at the concentration range investigated (300 ng/mL, 3000 ng/mL, and 30,000 ng/mL). The plasma protein binding was >99% for M2, 94.6->99% for M3, and 92.8%-98.3% for M4. There was no evidence for notable concentration-dependent binding in all species with tradipitant, M2, M3, and M4.	VW85WJ
Metabolism	The in vitro metabolism of tradipitant (LY686017) was studied by incubation with human, rat, dog, primate, and gerbil liver microsomes; and human, rat, dog, and primate liver slice incubations. Overall, a total of 17 major metabolites and 29 total metabolites were detected in the various matrices. M2 was detected as the major metabolite in human liver microsomes. The N-glucuronide conjugate of the reduced ketone (M9) was the major metabolite detected in human liver slices. Other significant metabolites observed in the human liver slices were M2, M4 (N-oxide of the reduced ketone), and an N-glucuronide metabolite, M8. M8, a glucuronide, was detected only in human material. In the mass balance study in humans, all major metabolites were <10% of total drug exposure (H8R-MC-HJAK). In vitro studies indicated that tradipitant (LY686017) is metabolized to M2 (2081070) in incubations with human liver microsomal samples by non-CYP-mediated processes. Further metabolism of M2 appears to be CYP-mediated. Tradipitant is metabolized to M3 (21954113) mainly by CYP3A4, although CYP2C19 and CYP2C8 are also capable of forming M3. In incubations with recombinant human UGT (rhUGT) enzymes, conversion of tradipitant to M8 was observed with rhUGT1A4 at 5 and 50μM tradipitant, and with rhUGT2B7 at 50μM tradipitant, indicating UGT1A4 and UGT2B7 are capable of converting tradipitant to M8.	ADME Report 01 2004IV-EI002 XT164094

NDA 220152
NEREUS (tradipitant)

Assessment	Conclusions	Study/Report
DDI potential- CYP inhibition	Less than 50% direct inhibition was observed for UGT1A4 activity (maximum of 7.3%) by tradipitant (0.001 to 1µM) and the IC ₅₀ value was reported as >1µM.	XT205023
	The catalytic activities selective for CYP2E1 and CYP2B6 were not substantially inhibited by LY686017. LY686017 noncompetitively inhibited the biotransformation of paclitaxel to 6a-hydroxypaclitaxel, a marker activity for CYP2C8, yielding an apparent K _i value of 17µM.	CD-0822
	The biotransformation of bupropion to hydroxybupropion, a marker for CYP2B6 activity, was not substantially inhibited by LY686017, yielding <45% inhibition over a range of LY686017 concentrations from 0.009µM to 20µM.	
	The CYP3A mediated biotransformation of midazolam was competitively inhibited by LY686017, yielding a K _i value of 0.92µM in vitro. Testosterone metabolism, an additional marker activity for CYP3A, was noncompetitively inhibited by LY686017, yielding a K _i value of 11µM. LY686017 was found to competitively inhibit both CYP2C19 and CYP2C9 mediated metabolism yielding K _i values of 9µM and 4.7µM, respectively.	21-250-TC; 22-250-TC
	Metabolism mediated by CYP1A2 and CYP2D6 was not significantly inhibited by LY686017, exhibiting ≤35% and ≤41% inhibition, respectively, over a LY686017 concentration range of 0.15µM to 200µM.	
	VLY-686 directly inhibited CYP3A4/5 (testosterone 6β-hydroxylation and midazolam 1'-hydroxylation) with IC ₅₀ values of 3.3µM and 1.2µM, respectively. VLY-686 may be a metabolism-dependent inhibitor of CYP3A4/5 and the inhibition is irreversible. There was evidence of weak direct inhibition of CYP2C8 (24.9%) and CYP2C9 (28.6%) by VLY-686 at 5µM concentration. There was little or no evidence of direct inhibition of CYP1A2, CYP2B6, CYP2C19, or CYP2D6 by VLY- 686. There was little or no evidence of time-dependent or metabolism dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 by VLY-686.	XT135114

Assessment	Conclusions	Study/Report
DDI potential- CYP induction	LY686017 is not likely to be a clinically significant inducer of CYP1A2; however, clinically significant induction of CYP3A is possible. In vitro evaluation of VLY-686 as a potential inducer of cytochrome P450 expression and activity in cultured human hepatocytes indicated that treatment with up to 25µM VLY-686: • Had little or no effect on CYP1A2 activity and mRNA (≤ 2-fold change and/or $\leq 20\%$ compared to the positive control). • Caused concentration-dependent increases in CYP2B6 activity and mRNA (up to 15- and 8-fold change in activity and mRNA, respectively). • Caused inconsistent responses of CYP2C8 activity and mRNA levels in the three cultures: concentration-dependent decreases (0.3-fold change or 72% decrease compared to the vehicle control); little or no change (< 2-fold change), or a concentration-dependent increase (up to 3.7-fold increase and 33% as effective as the positive control) in CYP2C8 activity with concentration-dependent increases in CYP2C8 mRNA levels (up to 3.8-fold change and more effective than the positive control). • Had little or no effect on CYP2C9 activity and mRNA levels in two of the three cultures (< 2-fold change) and a concentration-dependent increase in CYP2C9 mRNA levels (up to 4.66-fold and more effective than the positive control) in one of the three cultures. • Caused concentration-dependent decreases (down to 0.1-fold change or 88% decrease compared to the vehicle control) in CYP2C19 activity with little or no change in mRNA levels in two cultures (< 2-fold change), while the third culture had an increase in mRNA levels (2.8-fold change) at 10µM VLY-686. • Caused a bell-shaped trend in CYP3A4/5 activity (highest was up to 5.4-fold change and 40% as effective as the positive control; and lowest was down to 0.4-fold change or a 61% decrease compared to the vehicle control) and concentration-dependent increases in CYP3A4 mRNA (up to 8.5-fold change and more effective than the positive control).	2003IV-HI02, Amend 01 XT133124

NDA 220152
NEREUS (tradipitant)

Assessment	Conclusions	Study/Report
DDI potential transporter	LY686017 may be a poor substrate of P-gp. LY686017 is unlikely to cause a clinically relevant P-gp inhibition interaction in human subjects.	2006TP-Pgp01
	• Tradipitant inhibited BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K with calculated IC₅₀ values of 7.42, 2.82, 6.64, 3.20, and 4.47μM, respectively. Tradipitant did not demonstrate >50% inhibition of OAT1, OAT3, or OCT2. Tradipitant was not a substrate of BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K. • M2 inhibited OATP1B1 and MATE1 with calculated IC₅₀ values of 2.06 and 2.89μM, respectively. M2 did not demonstrate >50% inhibition of P-gp, BCRP, OATP1B3, OAT1, OAT3, OCT2, or MATE2-K at concentrations up to 10μM. M2 was not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K. • M3 inhibited OATP1B1, OATP1B3, and MATE1 with IC₅₀ values of 3.43, 6.51, and 7.47μM, respectively. M3 did not demonstrate >50% inhibition of P-gp, BCRP, OAT1, OAT3, OCT2, or MATE2-K at concentrations up to 10μM. M3 was a substrate of P-gp, as evidenced by efflux ratios of 36.9, 31.9, and 21.2 at 0.1, 1 and 10μM, respectively. These efflux ratios were reduced in the presence of the P-gp inhibitor, valspodar. M3 at 0.1 and 1μM showed weak BCRP substrate potential, as evidenced by efflux ratios of two that were partially reduced in the presence of the BCRP inhibitor, Ko143. M3 was not a substrate of OATP1B1, OATP1B3, MATE1, or MATE2-K. • M4 did not demonstrate >50% inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K. M4 was a substrate of P-gp, as evidenced by efflux ratios of 33.2, 52.3, and 41.2 at 0.1, 1, and 10μM, respectively. These efflux ratios were reduced in the presence of the P-gp inhibitor, valspodar. M4 at 1μM showed weak BCRP substrate potential, as evidenced by efflux ratio of 2.11, which was reduced in the presence of the BCRP inhibitor, Ko143. M4 was not a substrate of ATP1B1, OATP1B3, MATE1, or MATE2-K.	XT168118

Source: Reviewer's summary from NDA 220152; Adapted from Non-Clinical Pharmacokinetics Written Summary (eCTD Section 2.6.4); Note that these data were also reviewed during review of NDA218489

LY686017 or VLY-686 refer to tradipitant

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DDI, drug-drug interaction; IC₅₀, half-maximal inhibitory concentration; K_i, inhibitory constant; M, metabolite; MATE, multidrug and toxin extrusion transporter; mRNA, messenger ribonucleic acid; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; SEM, standard error of the mean; UGT, uridine glucuronosyltransferase

Table 45. Assessment of In Vivo Drug Interaction Potential Based on In Vitro Studies Evaluating Inhibition of CYP Enzymes and Transporters by Tradipitant

Inhibition	Ki Value	IC50 (μM)#	R (or alternate R)*	In vivo CYP inhibition potential (based on in vitro R value)	In vivo study conducted (yes or no)	In vitro study report #
CYP1A2		<35% inhibition over a range of LY686017 concentrations from 0.15 μM to 200 μM	N/A	no	no	21-250-TC
		little or no evidence of direct inhibition	N/A	no	no	XT135114
CYP2B6	N/A	<45% inhibition over a range of LY686017 concentrations from 0.009 μM to 20 μM	N/A	no	no	CD-0822
		little or no evidence of direct inhibition	N/A	no	no	XT135114
CYP2C8	17 μM		1.0003	no	no	CD-0822
	24.9% inhibition at 5 μM VLY	> 5 μM	1.0011	no	no	XT135114
CYP2C9	4.7 +/- 0.6 μM		1.001	no	no	21-250-TC
	28.6% inhibition at 5 μM VLY	> 5 μM	1.001	no	no	XT135114
CYP2C19	9.0 +/- 2.5 μM		1.0006	no	no	21-250-TC
	little or no evidence of direct inhibition	N/A	N/A	no	no	XT135114
CYP2D6	<41% inhibition over a range of LY686017 concentrations from 0.15 μM to 200 μM	N/A		no	no	21-250-TC
	little or no evidence of direct inhibition	N/A		no	no	XT135114
CYP3A4	0.92 +/- 0.11 uM		1.006	yes	yes	21-250-TC
		1.2 μM	1.004	yes	yes	XT135114
CYP2E1		no inhibition over a range of LY686017 concentrations from 0.009 μM to 20 μM	N/A	no	no	CD-0822

P-gP		2.99 ± 0.53 uM	1.0018	no	no	2006TP
BCRP		7.42 uM	1.0007	no	no	XT168118
OATP1B1		2.82 uM	1.0019	no	no	XT168118
OATP1B1 portal vein^		2.82 uM	1.07	no	no	XT168118
OATP1B3		6.64 uM	1.0008	no	no	XT168118
OATP1B3 Portal vein^		6.64 uM	1.03	no	no	XT168118
MATE1		3.20 uM	1.0017	no	no	XT168118
MATE2-K		4.47 uM	1.0012	no	no	XT168118
OAT1	No > than 50% inhibition		N/A	no	no	XT168118
OAT3	No > than 50% inhibition		N/A	no	no	XT168118
OCT2	No > than 50% inhibition		N/A	no	no	XT168118

(b) (4)

* R-calculation for tradipitant is $R1=1 + (I_{max}/K_i)$ where:

Human plasma C_{max} : 327 ng/ml (0.556μM) from Trial VP-VLY-686-1102

Plasma free fraction: 1%

$I_{max}=0.01 \times 0.556=0.00556$

Regulatory guidance is based upon K_i value rather than IC_{50} values, however, under these reported assay conditions $IC_{50} = K_i$ value

$R = 1 + ((f_{u,p} \times I_{in,max})/IC_{50}) \geq 1.1$ for OATP1B1/3 receptors

Abbreviations: AR, accumulation ratio; BCRP, breast cancer resistance protein; C_{max} , maximum plasma concentration; CYP, cytochrome P450; $f_{u,p}$, unbound fraction in plasma; IC_{50} , half-maximal inhibitory concentration; $I_{in,max}$, estimated maximum plasma inhibitor concentration at the inlet to the liver; K_i , inhibitory constant; I_{max} , maximum lesion count during treatment; MATE, multidrug and toxin extrusion transporter; N/A, not applicable; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; R1, reversible inhibition

14.2. In Vivo Studies

This NDA submission consists of 27 clinical and clinical pharmacology studies, including 11 phase 1 studies in healthy subjects, 1 phase 2 and 2 completed phase 3 studies and one ongoing open-label phase 3 study in subjects with history of motion sickness, and 12 studies in subjects with other conditions. In addition, seven population PK analysis and exposure-response analysis reports, and one pharmacogenetic report were submitted and reviewed. The proposed to-be-marketed formulation (i.e., 85 mg capsules) was used in seven trials.

Note that in this review, drug code names LY686017 or VLY-686 are also used to refer to tradipitant. For phase 1 clinical pharmacology studies H8R-EW-HJAE, H8R-FW-HJAN, VPVLY-686-1101, and H8R-MC-HJAF, considering the nature of study design and objectives, including the use of preliminary formulations, different dosing regimen, and different population, these four clinical trials are not considered relevant to the proposed indication and/or proposed dosage and therefore, are not discussed in this review. The clinical pharmacology studies reviewed for the current NDA are listed in [Table 46](#). Refer to the OCP review memo in DARRTS for details.

Table 46. List of Relevant Clinical Pharmacology Studies

Study Number/Phase	Study Title	Study Population	Study Formulation	Study Dosing Regimen
H8R-EW-HJAC/Phase 1	Single oral dose-escalating study to assess the safety and pharmacokinetics of LY686017 in healthy subjects	Healthy subjects (N=28)	1, 10, 100 mg capsules (Size 0)	Single dose 1, 3, 10, 30, 50, 100, 200, 400, 800 mg
H8R-EW-HJAD/Phase 1	Part A: A multiple dose safety, pk, and pd study of LY686017 in healthy male subjects Part B: A PET imaging study with Carbon-11 GR205171 to determine occupancy of cerebral Neurokinin-1 Receptors by LY686017 in Healthy Subjects	Healthy subjects (N=14)	1, 10, 100 mg capsules (Size 0)	1, 10, 100 mg QD
H8R-MC-HJAP/Phase 1	A multiple-dose, fixed sequence, two-period crossover, LY686017-ethanol interaction study in healthy volunteers	Healthy subjects (N=23)	10 mg capsules	50 mg QD
H8R-MC-HJAK/Phase 1	Disposition after oral administration of ¹⁴ C-Labeled NK-1 Antagonist II (LY686017)	Healthy subjects (N=5)	25 mg LY686017- ¹⁴ C solution	Single dose 25 mg
VP-VLY-686-1102/Phase 1	An open-label, single-sequence study to assess the effect of multiple doses of tradipitant on cytochrome P450 3A4 using midazolam as a substrate in healthy subjects	Healthy subjects (N=24)	85 mg capsules*	85 mg BID
VP-VLY-686-1002/Phase 1	A four-period, two-way crossover open-label study evaluating the pharmacokinetics of a single dose of tradipitant in healthy participants	Healthy subjects (N=31)	85 mg capsules*	Single dose 85, 170 mg
VP-VLY-686-1301/Phase 1	A single center, randomized, double-blind, placebo-controlled study to evaluate the effects of tradipitant on satiation, gastric volume, gastric accommodation, and gastric emptying in healthy volunteers	Healthy subjects (N=27)	85 mg capsules*	85 mg BID
VP-VLY-686-3404/Phase 3	Motion Serifos: a randomized, double-blind, Placebo-controlled study to investigate the efficacy of tradipitant in participants Affected by motion sickness during travel	Subjects with history of motion sickness N=316; 85 mg (n=104); 170 mg (n=106); Placebo (n=106)	85 mg capsules*	Single dose of 85 mg or 170 mg orally versus Placebo

Study Number/Phase	Study Title	Study Population	Study Formulation	Study Dosing Regimen
VP-VLY-686-3401/Phase 3	Motion Syros: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in participants affected by motion sickness travel	Subjects with history of motion sickness; N=365; 170 mg (n=120); 85 mg (n=23); Placebo (n=122)	85 mg capsules*	Single dose of 85 mg or 170 mg orally vs. Placebo
VP-VLY-686-2401/Phase 2	Motion Sifnos: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in subjects affected by motion sickness during travel	Subjects with history of motion sickness; N=126; 170 mg (n=63); Placebo (n=63)	85 mg capsule*	Tradipitant/Placebo 85 mg capsules; single dose; oral
VP-VLY-686-3403/Phase 3 ongoing study	Motion Delos: An open-label study to investigate the safety and efficacy of tradipitant in participants affected by motion sickness during travel	Subjects with history of motion sickness N=382; 85 mg (n=199); 170 mg (n=183)	85 mg capsule*	85 mg or 170 mg orally
Pharmacogenetic report	2301: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy of Tradipitant in Relieving Symptoms of Gastroparesis 3301: Pharmacogenetic Findings of CYP3A4*22 Allele Relevant to Reduced Clearance of Tradipitant			
Population PK/Exposure-response analysis reports	- VP-VLY-686-2301 Population PK Analysis - VP-VLY-686-2301 Exposure-Response Analysis - VP-VLY-686-3301 Population PK Analysis - VP-VLY-686-3301 Exposure-Response Analysis - VP-VLY-686-3301 Exposure-Response Analysis for Safety - Pooled Population Pharmacokinetic Analysis Report: Studies VP-VLY-686-1002, VP-VLY-686-1102, VP-VLY-686-1301, VP-VLY-686-2301, VP-VLY-686-3301, VP-VLY-686-3404, and VP-VLY-686-3403, Dated 6/30/2025 - Pooled Population Pharmacokinetic Analysis Report: Studies VP-VLY-686-1002, VP-VLY-686-1102, VP-VLY-686-1301, VP-VLY-686-2301, VP-VLY-686-3301, VP-VLY-686-3404, and VP-VLY-686-3403, Dated 7/21/2025			

Source: Reviewer's summary
LY686017 or VLY-686 refer to tradipitant

* The proposed to-be-marketed formation. No relative bioavailability study was conducted between preliminary formulations and the proposed to-be-marketed formation.

Abbreviations: BID, twice daily; ¹⁴C, carbon-14; CYP, cytochrome P450; N, number of subjects in study population; NK-1, neurokinin; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; QD, once daily

14.3. Bioanalytical Method Validation and Performance

Concentrations of tradipitant and its metabolites (M3, M4, M6 and M8) in human plasma samples have been measured using adequately validated high performance LC-MS/MS assays in clinical pharmacology studies. All clinical samples were analyzed within the established stability periods.

Table 47. Bioanalytical Methods Utilized in the Clinical Trials Supporting the Current NDA

Validation Report	Analyte and Matrix	Platform	Assay Range	Relevant Studies
2172.013103.2	Tradipitant in human plasma	LC-MS/MS Full validation	0.2 to 50 ng/mL	H8R-EW-HJAC H8R-EW-HJAD H8R-MC-HJAF H8R-MC-HJAP
3265.061405	Tradipitant, M2, M3, and M4 in human plasma	LC-MS/MS Full validation	Tradipitant: 0.2 to 50 ng/mL M2: 0.2 to 50 ng/mL M3: 0.2 to 50 ng/mL M4: 0.2 to 50 ng/mL	H8R-MC-HJAK
(b) (4) 208-1505	Tradipitant, M2, M3, and M4 in human plasma	LC-MS/MS Full validation	Tradipitant: 1 to 1000 ng/mL M2: 0.5 to 500 ng/mL M3: 0.5 to 500 ng/mL M4: 0.5 to 500 ng/mL	VP-VLY-686-1002 VP-VLY-686-1102 VP-VLY-686-1301 VP-VLY-686-2301 VP-VLY-686-3301 VP-VLY-686-3404
(b) (4) 208-1801	M8 in human plasma	LC-MS/MS Full validation	0.5 to 500 ng/mL	VP-VLY-686-1002 VP-VLY-686-3301 VP-VLY-686-3404

Source: Summarized from APPENDIX 9 of Summary of Biopharmaceutic Studies and Associated Analytical Methods under Module 2.7.1

Abbreviations: LC-MS/MS, liquid chromatographic separation with tandem mass spectrometry; M, metabolite

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Executive Summary

The Applicant’s initial population pharmacokinetic (PPK) analysis (submitted on December 30, 2024) included no PK data from subjects with motion sickness. An information request (IR) was sent on April 2, 2025, requesting the Applicant conduct additional PPK modeling and simulation analysis incorporating the PK data for tradipitant and its metabolites (M2, M3, M4, and M8) in subjects with motion sickness obtained from Trial 3404 and 3403 (if

available). In response to the IR, an updated PPK report was submitted on July 22, 2025, based on pooled tradipitant and metabolite concentration data from 7 trials (1002, 1102, 1301, 2301, 3301, 3403, and 3404). Key highlights of the PPK models are described below:

- The Applicant's NONMEM executions finished with unsuccessful minimization, probably due to the over-parameterization of the models. However, the PPK analysis generally captured the concentration data reasonably well and the predicted tradipitant and metabolite exposures appear generally reasonable.
- The observed PK exposures of tradipitant and metabolites of Trial 3403 are higher than other trials (including Trial 3404, another trial in motion sickness). Per the Applicant, these differences may reflect the small number of postdose samples obtained in each trial and the short interval of these samples relative to dosing.
- In addition, each dosing amount was derived via averaging the total dosing micrograms over a period of time for subjects with poor compliance (as low as 46.4%) added uncertainty to the PPK modeling and simulation analysis. It might be rational to exclude PK data from subjects with confirmed low compliance in the PPK analysis. The FDA reviewer's independent PPK analysis of tradipitant suggested one-compartmental model could also be used to describe the PK data (with low-compliance subject and Trial 1002 excluded). However, this model also under-predicted the elevated concentrations observed in Trial 3403.

See the OCP review memo in DARRTS for additional details.

14.6. Pharmacogenetics

Refer to Section [8.1](#).

15. Study/Trial Design

Trials 3401 and 3404 are summarized in Section [6.2.1.1](#) and Section [6.2.2.1](#), respectively.

16. Efficacy

16.1. Subgroup Analyses by Demographic Characteristics

Subgroup analyses were conducted to assess the potential for differences in the treatment effect on vomiting for various demographic characteristics for Trials 3401 and 3404, as detailed in [Table 48](#) and [Table 49](#), respectively. Overall, for Trial 3401, the percentage of subjects with vomiting was numerically lower in each tradipitant arm compared to placebo across almost all subgroups with the exception of a few subgroups that had very small sample sizes. For Trial 3404, the percentage of subjects with vomiting was generally lower in both tradipitant arms compared to placebo across most subgroups with a reasonable sample size. In the Black or African American subgroup, the placebo arm had a lower percentage of vomiting than either tradipitant arm. However, due to the small sample size in this subgroup, statistical conclusions

cannot be made. In addition, this trend was not observed in the Black or African American subgroup in Trial 3401.

Table 48. Percentage of Subjects With Vomiting During the Vehicle Travel by Subgroups of Sex, Age Group, Race, and Ethnicity, ITT Population, Trial 3401

Characteristic	Tradipitant 85 mg n (%)	Tradipitant 170 mg n (%)	Placebo n (%)	Treatment Difference (Tradipitant 85 mg–Placebo) (95% CI) ¹	Treatment Difference (Tradipitant 170 mg–Placebo) (95% CI) ¹
Sex					
Female	(N=82) 19 (23)	(N=87) 17 (20)	(N=75) 38 (51)	-27.5 (-42.0, -13.0)	-31.1 (-45.2, -17.1)
Male	(N=41) 5 (12)	(N=33) 5 (15)	(N=47) 16 (34)	-21.8 (-38.7, -5.0)	-18.9 (-37.1, -0.6)
Age group, years					
<65	(N=100) 20 (20)	(N=101) 18 (18)	(N=112) 51 (46)	-25.5 (-37.6, -13.4)	-27.7 (-39.6, -15.8)
≥65	(N=23) 4 (17)	(N=19) 4 (21)	(N=10) 3 (30)	-12.6 (-45.0, 19.7)	-8.9 (-42.7, 24.9)
Race					
American Indian or Alaska Native	(N=0) NA	(N=1) 0	(N=2) 1 (50)	NA	-50.0 (-100, 19.3)
Asian	(N=9) 3 (33)	(N=7) 1 (14)	(N=11) 3 (27)	6.1 (-34.4, 46.6)	-13.0 (-49.9, 23.9)
Black or African American	(N=5) 1 (20)	(N=10) 0	(N=5) 4 (80)	-60.0 (-100, -10.4)	-80.0 (-100, -44.9)
Native Hawaiian or Other Pacific Islander	(N=1) 1 (100)	(N=0) NA	(N=0) NA	NA	NA
White	(N=105) 19 (18)	(N=102) 21 (21)	(N=102) 46 (45)	-27.0 (-39.1, -14.9)	-24.5 (-36.9, -12.1)
Other racial categories ²	(N=3) 0	(N=0) NA	(N=2) 0	NA	NA
Ethnicity					
Hispanic or Latino	(N=12) 1 (8)	(N=13) 2 (15)	(N=14) 8 (57)	-48.8 (-79.1, -18.5)	-41.8 (-74.3, -9.3)
Not Hispanic or Latino	(N=102) 21 (21)	(N=99) 17 (17)	(N=105) 44 (42)	-21.3 (-33.6, -9.0)	-24.7 (-36.7, -12.7)
Not reported or unknown	(N=9) 2 (22)	(N=8) 3 (38)	(N=3) 2 (67)	-41.7 (-100, 19.5)	-29.2 (-92.2, 33.8)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

² There is no description provided regarding specific classifications included under “Other” racial categories.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the corresponding subgroup; n, number of subjects in specified population or group; NA, not applicable

Table 49. Percentage of Subjects With Vomiting During the Vehicle Travel by Subgroups of Sex, Age Group, Race, and Ethnicity, ITT Population, Trial 3404

Characteristic	Tradipitant 85 mg n (%)	Tradipitant 170 mg n (%)	Placebo n (%)	Treatment Difference (Tradipitant 85 mg–Placebo) (95% CI) ¹	Treatment Difference (Tradipitant 170 mg–Placebo) (95% CI) ¹
Sex					
Female	(N=62) 14 (23)	(N=56) 7 (13)	(N=60) 25 (42)	-19.1 (35.3, -2.8)	-29.2 (-44.3, -14.0)
Male	(N=42) 5 (12)	(N=50) 4 (8)	(N=46) 15 (33)	-20.7 (-37.4, -4.0)	-24.6 (-40.1, -9.1)
Age group, years					
<65	(N=92) 19 (21)	(N=93) 8 (9)	(N=93) 33 (35)	-14.8 (-27.6, -2.1)	-26.9 (-38.1, -15.6)
≥65	(N=12) 0	(N=13) 3 (23)	(N=13) 7 (54)	-53.8 (-80.9, -26.7)	-30.8 (-66.2, 4.7)
Race					
American Indian or Alaska Native	(N=0)	(N=0)	(N=1) 1 (100)	NA	NA
Asian	(N=9) 2 (22)	(N=15) 1 (7)	(N=12) 5 (42)	-19.4 (-58.4, 19.5)	-35.0 (-65.6, -4.4)
Black or African American	(N=4) 3 (75)	(N=5) 2 (40)	(N=6) 2 (33)	41.7 (-15.1, 98.4)	6.7 (-50.5, 63.8)
Multiple	(N=2) 1 (50)	(N=3) 0	(N=4) 1 (25)	25.0 (-56.3, 100)	-25.0 (-67.4, 17.4)
Native Hawaiian or Other Pacific Islander	(N=0) NA	(N=2) 0	(N=0) NA	NA	NA
White	(N=88) 13 (15)	(N=80) 8 (10)	(N=78) 29 (37)	-22.4 (-35.4, -9.4)	-27.2 (-39.8, -14.6)
Other racial categories ²	(N=1) 0	(N=1) 0	(N=5) 2 (40)	-40.0 (-82.9, 2.9)	-40.0 (-82.9, 2.9)
Ethnicity					
Hispanic or Latino	(N=16) 5 (31)	(N=11) 1 (9)	(N=16) 6 (38)	-6.3 (-39.1, 26.6)	-28.4 (-57.6, 0.8)
Not Hispanic or Latino	(N=84) 14 (17)	(N=91) 10 (11)	(N=82) 29 (35)	-18.7 (-31.8, -5.6)	-24.4 (-36.6, -12.2)
Not reported	(N=4) 0	(N=4) 0	(N=8) 5 (63)	-62.5 (-96.1, -28.9)	-62.5 (-96.1, -28.9)

Source: Reviewer-generated table using data submitted by the Applicant in NDA 220152, SDN 1, dataset adqs.xpt, module 5.3.5.1.

¹ Difference (%) and its 95% CI are tradipitant minus placebo and based on estimated unadjusted risk difference and Wald interval.

² There is no description provided regarding specific classifications included under "Other" racial categories.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the corresponding subgroup; n, number of subjects in specified population or group; NA, not applicable

17. Clinical Safety

The safety data for TEAEs for the individual trials are described in this section. Refer to Section [7.6.1](#) for the pooled safety analyses.

17.1. Safety Results, Trial 3401

17.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 3401

[Table 50](#) below provides an overview of TEAEs that occurred during the evaluation period of Trial 3401 (i.e., during the vehicle travel assessment). There were no deaths and no SAEs reported in the tradipitant or placebo arms. There were no TEAEs that led to study discontinuation. Overall, TEAEs were reported in a greater proportion of subjects in the tradipitant 85-mg arm (26.8%) and the tradipitant 170-mg arm (28.3%) compared to the placebo arm (9.0%). The majority of TEAEs were of mild severity.

Table 50. Overview of Adverse Events,¹ Safety Population, Trial 3401

Event Category	Tradipitant 85 mg N=123 n (%)	Tradipitant 170 mg N=120 n (%)	Placebo N=122 n (%)
Any TEAE ²	33 (26.8)	34 (28.3)	11 (9.0)
Severe	0	0	0
Moderate	6 (4.9)	5 (4.2)	5 (4.1)
Mild	27 (22.0)	29 (24.2)	6 (4.9)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent adverse event defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 23.0.

² Severity as assessed by the investigator. For subjects who experienced more than one TEAE, the severity of the most severe TEAE is represented.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

17.1.2. Treatment-Emergent Adverse Events, Trial 3401

[Table 51](#) below describes TEAEs occurring in $\geq 2\%$ of subjects and higher in those receiving tradipitant compared to placebo in Trial 3401. The TEAEs that occurred at a higher rate in the tradipitant 85-mg arm compared to the placebo arm included somnolence (6.5% versus 0.8%), headache (5.7% versus 2.5%), fatigue (4.1% versus 0%), dizziness (4.1% versus 1.6%), and abdominal discomfort (2.4% versus 0%). The TEAEs that occurred at a higher rate in the tradipitant 170-mg arm compared to the placebo arm included somnolence (8.3% versus 0.8%), headache (8.3% versus 2.5%), and fatigue (8.3% versus 0%).

Table 51. Treatment-Emergent Adverse Events¹ by Preferred Term² Occurring in ≥2% of Subjects and at Higher Frequency Than Placebo, Safety Population, Trial 3401

Preferred Term	Tradipitant 85 mg N=123 n (%)	Tradipitant 170 mg N=120 n (%)	Placebo N=122 n (%)
Any TEAE	33 (26.8)	34 (28.3)	11 (9.0)
Somnolence	8 (6.5)	10 (8.3)	1 (0.8)
Headache	7 (5.7)	10 (8.3)	3 (2.5)
Fatigue	5 (4.1)	10 (8.3)	0 (0)
Dizziness	5 (4.1)	1 (0.8)	2 (1.6)
Abdominal discomfort	3 (2.4)	0 (0)	0 (0)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 23.0

² Coded as MedDRA preferred terms.

Duration is one dose during evaluation period.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

TEAEs of somnolence, headache, and fatigue occurred more commonly in both tradipitant arms compared to the placebo arm. Dizziness occurred at a higher rate than placebo only in the tradipitant 85-mg arm (4.1% versus 1.6%). Of note, the TEAEs reported by subjects could be due to motion sickness, as motion sickness may present with a variety of symptoms (e.g., nausea, vomiting, belching, diaphoresis, dizziness, headache, fatigue, and somnolence). However, the TEAEs described above were likely related to tradipitant, as they occurred more frequently in the tradipitant arms than the placebo arm and are consistent with the mechanism of action of tradipitant (i.e., centrally-acting NK-1 receptor antagonist).

17.2. Safety Results, Trial 3404

17.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 3404

[Table 52](#) below provides an overview of TEAEs that occurred during the evaluation period of Trial 3404 (i.e., during and after the vehicle travel assessment). There were no deaths and no SAEs reported in the tradipitant or placebo arms. No subjects withdrew due to adverse events. Overall, TEAEs were reported in a greater proportion of subjects in the tradipitant 85-mg arm (31.7%) and tradipitant 170-mg arm (34.9%) compared to the placebo arm (26.4%). The majority of TEAEs were of mild severity.

Table 52. Overview of Adverse Events,¹ Safety Population, Trial 3404

Event Category	Tradipitant 85 mg N=104 n (%)	Tradipitant 170 mg N=106 n (%)	Placebo N=106 n (%)
Any TEAE ²	33 (31.7)	37 (34.9)	28 (26.4)
Severe	0	0	0
Moderate	7 (6.7)	4 (3.8)	8 (7.5)
Mild	26 (25.0)	33 (31.1)	20 (18.9)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 26.0.

² Severity as assessed by the investigator. For subjects who experienced more than one TEAE, the severity of the most severe TEAE is represented.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

17.2.2. Treatment-Emergent Adverse Events, Trial 3404

[Table 53](#) below describes TEAEs occurring in $\geq 2\%$ of subjects and higher in those receiving tradipitant compared to placebo in Trial 3404. The TEAEs that occurred at a higher rate in the tradipitant 85-mg arm compared to the placebo arm included fatigue (8.7% versus 5.7%) and dizziness (1.9% versus 0.9%). The TEAEs that occurred at a higher rate in the tradipitant 170-mg arm compared to the placebo arm included fatigue (11.3% versus 5.7%), headache (9.4% versus 8.5%), somnolence (8.5% versus 7.5%), dizziness (2.8% versus 0.9%), and hyperhidrosis (2.8% versus 0.9%).

Table 53. Treatment-Emergent Adverse Events¹ Occurring at $\geq 2\%$ Frequency, Safety Population, Trial 3404

Preferred Term²	Tradipitant 85 mg N=104 n (%)	Tradipitant 170 mg N=106 n (%)	Placebo N=106 n (%)
Any TEAE	33 (31.7)	37 (34.9)	28 (26.4)
Fatigue	9 (8.7)	12 (11.3)	6 (5.7)
Headache	9 (8.7)	10 (9.4)	9 (8.5)
Somnolence	6 (5.8)	9 (8.5)	8 (7.5)
Dizziness	2 (1.9)	3 (2.8)	1 (0.9)
Hyperhidrosis	0 (0.0)	3 (2.8)	1 (0.9)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 26.0.

² Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

TEAEs of fatigue and dizziness occurred more commonly in both tradipitant arms compared to the placebo arm. Somnolence and hyperhidrosis occurred at a higher rate in the tradipitant 170-mg arm than placebo (8.5% versus 7.5% and 2.8% versus 0.9%, respectively). Of note, the TEAEs reported by subjects could be due to motion sickness, as motion sickness may present with a variety of symptoms (e.g., nausea, vomiting, belching, diaphoresis, dizziness, headache, fatigue, and somnolence). However, the TEAEs described above were likely related to tradipitant, as they occurred more frequently in the tradipitant arms than the placebo arm and are

consistent with the mechanism of action of tradipitant (i.e., centrally-acting NK-1 receptor antagonist).

17.3. Safety Results, Trial 2401

Subjects in Trial 2401 were assigned to take a single dose of either tradipitant 170 mg or placebo during the evaluation phase. All subjects in the safety population were exposed to a single dose of trial drug.

17.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 2401

[Table 54](#) below provides a summary of TEAEs reported in Trial 2401. There were no deaths and no SAEs reported in the tradipitant or placebo arms. No subjects withdrew due to TEAEs. Overall, TEAEs were reported in a slightly lower proportion of subjects in the tradipitant 170-mg arm (66.7%) compared to the placebo arm (73.0%). The majority of TEAEs were of mild severity. The rates of TEAEs in both arms of Trial 2401 are higher than in the phase 3 trials, due to “motion sickness” being reported as a TEAE.

Table 54. Overview of Adverse Events,¹ Safety Population, Trial 2401

Event Category	Tradipitant 170 mg	Placebo
	N=63 n (%)	N=63 n (%)
Any TEAE ²	42 (66.7)	46 (73.0)
Severe	1 (1.6)	0
Moderate	10 (15.9)	8 (12.7)
Mild	31 (49.2)	38 (60.3)

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 21.0.

² Severity as assessed by the investigator. For subjects who experienced more than one TEAE, the severity of the most severe TEAE is represented.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

17.3.2. Treatment-Emergent Adverse Events, Trial 2401

[Table 55](#) shows TEAEs in Trial 2401 occurring in $\geq 2\%$ of subjects in the tradipitant arm and higher in the tradipitant arm than placebo.⁶² The most common TEAE in the tradipitant arm was somnolence (27.0%), and the next most common TEAEs were headache (12.7%), nausea (6.3%), and fatigue (3.2%).

⁶² “Motion sickness” was reported as a TEAE; however, it was reported more frequently in the placebo arm (42.9%) than in the tradipitant arm (30.2%).

Table 55. Treatment-Emergent Adverse Events¹ Occurring at ≥2% Frequency, Safety Population, Trial 2401

Preferred Term^{2,3}	Tradipitant 170 mg N=63 n (%)	Placebo N=63 n (%)
Any TEAE	42 (66.7)	46 (73.0)
Somnolence	17 (27.0)	8 (12.7)
Headache	8 (12.7)	5 (7.9)
Nausea	4 (6.3)	2 (3.2)
Fatigue	2 (3.2)	0

Source: adae.xpt; Software: JMP

¹ Treatment-emergent AE defined as an adverse event that is newly occurring or worsening from treatment dosing until 3 days after the final dose of trial medication. Medical Dictionary for Regulatory Activities, version 21.0.

² Coded as MedDRA preferred terms

³ "Any TEAE" includes subjects who reported a TEAE of "motion sickness;" however, "motion sickness" is not specifically listed due to the higher rate of occurrence in the placebo arm and high likelihood of occurring as a result of the trial conditions.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

TEAEs of somnolence, headache, fatigue, and nausea occurred more commonly in the tradipitant arm compared to the placebo arm. Of note, the TEAEs reported by subjects could be due to motion sickness, as motion sickness may present with a variety of symptoms (e.g., nausea, vomiting, belching, diaphoresis, dizziness, headache, fatigue, and somnolence). However, the TEAEs described above were likely related to tradipitant, as they occurred more frequently in the tradipitant arms than the placebo arm and are consistent with the mechanism of action of tradipitant (i.e., centrally-acting NK-1 receptor antagonist).

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

21.1. Clinical Outcome Assessment

In both phase 3 trials, motion-induced vomiting and nausea symptoms were assessed using the VA and NA instruments, respectively. The VA is a single-item patient-reported questionnaire that assesses the incidence of vomiting on a Yes/No response scale. The NA is a single-item patient-reported questionnaire that assesses nausea severity at its worst on a 5-point Likert scale, with score ranging from 0 to 4, where 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very

severe. Subjects completed the VA and NA approximately every 30 minutes throughout the boat travel.

The VA and NA questionnaires are simplistic measures that appear straightforward for patients to complete and comprehend. 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 trials 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 Trial 3404, defined as worst nausea ≥ 3 on the NA instrument, represents severe to very severe symptoms and appears to be clinically meaningful. 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.

21.2. Abuse Potential

The Applicant provided an Abuse Liability Justification Report and the Controlled Substance Staff (CSS) reviewed this report to evaluate the abuse potential of tradipitant. 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 was also determined to have no significant activity ($\geq 50\%$ inhibition) in a broad panel of receptors, transporters, ion channel receptors, and enzymes associated with abuse. Based on these in vitro findings, additional studies including nonclinical abuse potential assessments and a human abuse potential study were not requested. In addition, AEs associated with abuse from the clinical development program were reviewed. This analysis indicated that the most prevalent AEs observed in clinical trials were somnolence, headache, and fatigue. CSS notes that these AEs are 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 has a potential for abuse or physical dependence. Based on these data, CSS provides the following recommendations:

- Tradipitant does not appear to have a potential for abuse and does not require scheduling under the Controlled Substances Act.
- Tradipitant does not require a Section 9 (Drug Abuse and Dependence section) in its label, should tradipitant be approved.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to Section [10](#).

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 56](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 56. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
BOXED WARNING	Not applicable
1 INDICATIONS AND USAGE	The indication was modified from "acute prevention of vomiting induced by motion" to "prevention of vomiting induced by motion." The word "acute" is not necessary as vomiting induced by motion is a self-limited condition.
2 DOSAGE AND ADMINISTRATION	- Because the available safety data do not support the unrestricted use of tradipitant, a statement that the safety of NEREUS for the prevention of vomiting induced by motion in adults for more than 90 doses has not been established in clinical trials was added. Refer to review Section 1.1 and Section 7.7. - The recommended dosage was specified to indicate that the drug should be used "as a single oral dose." This reflects how the drug was assessed in the clinical trials that support its safety and efficacy. - The recommendation to "[u]se the lowest effective dose" was added as a result of the dose-dependent increased risk of adverse events observed in the clinical trials. - The maximum dosage in a 24-hour period was modified from (b) (4) to "a single dose of 85 mg or 170 mg." This modification was to avoid the potential for an individual to take 85 mg twice in a 24-hour period, which was not evaluated in the vomiting induced by motion clinical development program. - The recommendation "(b) (4)" was modified to "Administer NEREUS on an empty stomach, at least 1 hour prior to or 2 hours after a full meal." This change was to provide more specific guidance to individuals using tradipitant, as exposure to tradipitant was increased in the fed state and the potential effects of higher exposure of tradipitant on QT prolongation has not been adequately addressed (See review Section 5.2).
4 CONTRAINDICATIONS	No changes
5 WARNINGS AND PRECAUTIONS	Section 5.1 "Effects on the Ability to Drive or Operate Machinery" was added, including warnings regarding the incidence of adverse events of somnolence and fatigue and their effect on mental and physical abilities, as well as increased risk with CNS depressants and strong CYP3A4 inhibitors. This section was added because these adverse reactions may affect individuals' ability to drive or operate machinery, and tradipitant has not been assessed for its impact on individuals' ability to drive or operate

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	machinery. - The description of the safety database that includes “(b) (4)” was deleted, and the remaining text was revised to focus on data from subjects in the safety database from the clinical trials specific to the proposed indication. This change was made because the adverse reactions described in this subsection are based on the three placebo-controlled clinical trials for the prevention of vomiting induced by motion (Trials 3401, 3404, and 2401, numbered as Studies 1, 2, and 3, respectively). - Table 1 was modified to compare the rates of adverse reactions between subjects who received each dose of tradipitant with the pooled placebo group from trials that included that specific dose arm (i.e., tradipitant 85 mg vs. placebo in Trials 3401 and 3404; tradipitant 170 mg vs. placebo in Trials 3401, 3404, and 2401). This distinction is necessary because the 85 mg dose was not assessed in Trial 2401, and comparing subjects who received placebo in Trial 2401 to subjects in other trials could be misleading. - The description of the Trial 3403 was modified to describe how tradipitant was administered in that trial (e.g., the timing of each dose relative to travel events, the total number of doses allowed during the trial), as well as the patterns of use (e.g., median exposure was 18 doses, a majority of subjects did not take more than 30 doses during the 12-month trial). This change was made to inform prescribers of the pattern of use in the only multiple-dose trial for this indication and support the language in Section 2 that describes that the safety of tradipitant for more than 90 doses has not been established.
7 DRUG INTERACTIONS	Section 7.1 was renamed “Effects of Other Drugs on NEREUS,” and revised to state that “[t]radipitant is a CYP3A4 substrate. Strong CYP3A4 inhibitors may increase tradipitant exposure, which may increase the risk of adverse reactions to NEREUS.” These changes were made to describe clinically significant drug interactions with CYP3A4 inhibitors. The Applicant’s proposed (b) (4) were determined not to be clinically significant and were removed.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	(b) (4) - In Section 8.1, the “Risk Summary” subsection was modified to state that “[a]vailable data from clinical trials with NEREUS use in pregnant women are insufficient to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.” This modification was made to specifically convey that safety data related to pregnancy is insufficient to identify potential risks. - In Section 8.1, the “Risk Summary” subsection was modified

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	to include more specific information regarding adverse developmental effects in animal reproduction studies, including safety margins relative to the maximum recommended human dose (MRHD). A description of the risk of major birth defects and miscarriage in the general population was also added. These additions are intended to provide prescribers more specific information regarding the safety of tradipitant if given during pregnancy. • In Section 8.1, the "Animal Data" subsection was modified to separately describe studies assessing combined fertility and embryofetal toxicity in rats, embryofetal development in rabbits, and pre- and post-natal development in rats, each of which reference the margins relative to the MRHD. These modifications are intended to provide prescribers more specific information regarding the safety of tradipitant if given during pregnancy. • In Section 8.2, a reference to data describing the presence of tradipitant in rat milk was added, as well as an explanation that "[w]hen a drug is present in animal milk, it is likely that the drug will be present in human milk." A statement was added advising to "[m]onitor breastfed infants for somnolence." This modification was made to reflect FDA's current approach to informing prescribers of the potential presence of drug in human milk when only animal lactation data are present. Additionally, a description of data from studies assessing tradipitant excretion in the milk of lactating rats was added, including the margins relative to the MRHD. • In Section 8.4, the subsection on "(b) (4)" was removed in order to prevent misinterpretation of a lack of toxicity in animals to correspond to a lack of toxicity in pediatric patients. • Section 8.5 was modified to follow examples in the Geriatric Use section labeling guidance when information is sufficient to detect differences between geriatric and younger adult subjects. • Section 8.6 was modified to clarify that the recommended dosage of tradipitant for individuals with mild and moderate renal impairment is the same as the recommended dosage for individuals with normal renal function. Avoidance of use of tradipitant in individuals with severe renal impairment was recommended, in order to specifically inform prescribers of the potential risk in this population, as subjects with severe renal impairment were not included in clinical trials. • Section 8.7 was modified to clarify that individuals with any degree of hepatic impairment should avoid tradipitant, as subjects with any degree of hepatic impairment were not included in clinical trials. • A subsection for "(b) (4)" was deleted because data were insufficient to support inclusion in labeling.
9 DRUG ABUSE AND DEPENDENCE	Not applicable
10 OVERDOSAGE	This section was removed, as there were no toxicity findings

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	associated with overdosage of the drug, (b) (4) (b) (4)
12 CLINICAL PHARMACOLOGY	- In Section 12.1, (b) (4) was deleted. - In Section 12.2, the "Cardiac Electrophysiology" subsection was modified to specify that the maximum recommended single dose administered without food did not result in clinically significant QTc prolongation. This modification, particularly with the addition of "without food" was important to inform prescribers and patients of the conditions of use that resulted in this statement regarding QTc prolongation. A PMC will be issued to evaluate the effects of tradipitant on QT intervals in the fed state (see review Section 24). - In Section 12.2, the "(b) (4)" subsection was deleted as this information is not relevant to the intended use population. - In Section 12.3, the "Absorption" subsection was modified to include clinically relevant data, including PK parameters (i.e., C_{max}, AUC_{0-inf}, and median T_{max}) for a single dose of tradipitant 85 mg and 170 mg. Data were also added to inform providers of the differences in PK values between the fed and fasted states. (b) (4) were removed from this section that is meant to contain data and cross-references to the relevant clinical sections were added. - In Section 12.3, the "Elimination" subsection was modified to include the elimination half-life, as this information is likely to be important to prescribers. - In Section 12.3, the "Specific Populations" subsection was modified to remove information (b) (4) as the information was not relevant to the intended use population. - In Section 12.3, the "Drug Interaction Studies" subsection was re-organized into "Clinical Studies" and "In Vitro Studies,". (b) (4)
13 NONCLINICAL TOXICOLOGY	- Section 13.1 was modified to include exposure margins that reflect animal to human tradipitant exposure using AUC rather than BSA. (b) (4) was removed, (b) (4)
14 CLINICAL STUDIES	- The two phase 3 single-dose trials (Trials 3401 and 3404) were referred to as "Study 1" and "Study 2," respectively. The descriptions of the study design and data (e.g., demographics) were pooled, due to the similarity of both studies. - The table describing the incidence of vomiting in each treatment arm (Table 2) was modified to remove a row for (b) (4) and a row for "Treatment Difference"

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	was added, to improve interpretability of the data. Additionally, (b) (4) were removed, and 95% confidence intervals were added in order for prescribers to more easily interpret the certainty for the estimated treatment difference. A statement was added regarding the secondary endpoint of "worst nausea score," describing data for this endpoint, and explaining that it did not reach statistical significance in either study. This section was added to provide a more complete description of the drug's efficacy profile.
17 PATIENT COUNSELING INFORMATION	Statements were added recommending that patients be advised of the following: - NEREUS may cause somnolence and/or fatigue and impair mental and/or physical abilities required for driving or operating heavy machinery - Concomitant use of other drugs with NEREUS may increase somnolence and/or fatigue, and if concomitant use is unavoidable, patients should be warned against activities requiring complete mental alertness - NEREUS should be taken 60 minutes before an event expected to cause vomiting induced by motion, the maximum dosage in a 24-hour period is a single dose of 85 or 170 mg, and NEREUS should be administered on an empty stomach, at least 1 hour prior to or 2 hours after a full meal (b) (4) - Breastfeeding women using NEREUS should monitor infants for somnolence and seek medical care if they notice this sign
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	A statement was added in Section 16 "How Supplied/Storage and Handling" specifying that the product is "packaged as 36-count in an HDPE bottle with child-resistant cap and a 2-g desiccant pouch." Other language was edited for clarity.

Source: "Draft Labeling Text" included in NDA submission (12/30/2024); Finalized PI

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA approved:

- Prescribing information

24. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) will be issued:

- PMR 4946-1 Conduct a clinical trial to evaluate the pharmacokinetics and safety of an age-appropriate formulation of tradipitant in pediatric patients 2 to <18 years of age with history of motion sickness.
- Final Protocol Submission: June 2026
Study Completion: December 2026
Final Report Submission: March 2027
- * Milestone dates were extended from the dates agreed upon in the iPSP to allow additional time to reach agreement on a final protocol.*
- PMR 4946-2 Conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of tradipitant in pediatric patients 2 to <18 years of age with a history of motion sickness.
- Final Protocol Submission: January 2027
Study Completion: January 2028
Final Report Submission: June 2028
- * Milestone dates were extended from the dates agreed upon in the iPSP to allow additional time to reach agreement on a final protocol.*
- PMR 4946-3 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 U.S. 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.
- Draft Protocol Submission: June 2026
Final Protocol Submission: December 2026
Study Completion: December 2036
Final Report Submission: June 2037

- PMR 4946-4 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).
Draft Protocol Submission: June 2026
Final Protocol Submission: December 2026
Study Completion: December 2032
Final Report Submission: December 2033
- PMR 4946-5 Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received tradipitant to measure concentrations of tradipitant and its major metabolites in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.
Draft Protocol Submission: June 2026
Final Protocol Submission: December 2026
Study Completion: December 2028
Final Report Submission: June 2029

The following postmarketing commitments (PMCs) will also be issued:

- PMC 4946-6 Conduct a clinical pharmacology study to evaluate the effects of hepatic impairment on the pharmacokinetics of tradipitant and its major metabolites compared to subjects with normal hepatic function.
Draft Protocol Submission: June 2026
Final Protocol Submission: December 2026
Study Completion: December 2027
Final Report Submission: June 2028
- PMC 4946-7 Conduct a clinical pharmacology study to evaluate the effects of severe renal impairment on the pharmacokinetics of tradipitant and its major metabolites compared to subjects with normal renal function.
Draft Protocol Submission: June 2026
Final Protocol Submission: December 2026
Study Completion: December 2027
Final Report Submission: June 2028

- PMC 4946-8 Conduct in vitro assessment(s) to evaluate the contribution of all major CYP enzymes to the overall metabolism of tradipitant and its active metabolites, and to assess the relative contribution of specific CYP enzymes to tradipitant metabolism. The in vitro study results will determine the need for subsequent clinical drug-drug interaction study(ies).
Draft Protocol Submission: June 2026
Final Protocol Submission: October 2026
Study Completion: April 2027
Final Report Submission: October 2027
- PMC 4946-9 Conduct a study to evaluate the effects of tradipitant on QT intervals in the fed state.
Final Protocol Submission: February 2026
Study Completion: February 2027
Final Report Submission: August 2027

25. Financial Disclosure

Table 57. Covered Clinical Studies: Trials 3401 and 3404

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 18		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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NDA 220152
NEREUS (tradipitant)

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ICH Guidance for Industry *Guideline for Elemental Impurities Q3D(R2)* (April 2022)

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FDA Guidance for Industry *M3(R2)Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: Questions and Answers* (March 2013)

FDA Guidance for Industry *Safety Testing of Drug Metabolites (Revision 2)* (March 2020)

FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

FDA Guidance for Industry *Safety Testing of Drug Metabolites* (November 2016)

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27. Review Team

Table 58. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Mary Chung
Nonclinical reviewer	Sarah Morgan
Nonclinical team leader	Jackye Peretz
OCP reviewer(s)	Sanjida Mahjabeen, Hongshan Li, Karryn Crisamore
OCP team leader(s)	Shen Li, Vishnu Sharma, Sarah Dorff
Clinical reviewer	Joshua Eisenberg
Clinical team leader	Matthew Kowalik
Biometrics reviewer	Dapeng Hu
Biometrics team leader	Paul Imbriano
Cross-discipline team leader	Matthew Kowalik
Division director (pharm/tox)	Andrew Goodwin
Division director (OCP)	Chandras Sahajwalla
Deputy Division director (clinical)	Juli Tomaino
Office director (designated signatory authority)	Nikolay Nikolov

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 59. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Hamid Shafiei
Drug Product	Zhengfang Ge/ Hamid Shafiei (ATL)
Drug Substance	Fred (Friedrich) Burnett/ Lawrence (Larry) Perez
Manufacturing	Amit Kokate/ Vaikunth Prabhu
Biopharmaceutics	Leah Falade/ Tapash Ghosh
OPDP	Meeta Patel
OSI	Courtney McGuire/ Michele Fedowitz
OSE/DEPI	Benjamin Booth/ Wei Hua
OSE/DMEPA	Sherly Abraham/Damon Birkemeier
OSE/DRM	Brian Caruth/ Yasmeen Abou-Sayed
OSE/DPV	Michelle Hines
OSE/DMAMES	Yelena Maslov
Other:	
CDER/OTS/OCP/DARS/CTCS	Jahan Cooper and Naomi Kruhlak
DCOA	Ji Li/ Onyekachukwu Iloh/ David Reasner
IRT	Lars Johannesen/ Devi Kozeli
CSS	Chad Reissig/ Dominic Chiapperino
DPMH	Charlotte Jones/ Shetarra Walker (pediatrics) Katherine Kratz/ Miriam Dinatale (maternal health)

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRM, Division of Risk Management; DPV, Division of Pharmacovigilance; DMAMES, Division of Mitigation Assessment and Medication Error Surveillance; DARS, Division of Applied Regulatory Science; CTCS, Computational Toxicology Consultation Service; IRT, Interdisciplinary Review Team for Cardiac Safety; CSS, Controlled Substance Staff; DMAMES, Division of Mitigation Assessment and Medication Error Surveillance; DPMH, Division of Pediatric and Maternal Health

27.1. Reviewer Signatures

Table 27-60 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Consultant Discipline Primary Reviewer	Chad Reissig CSS	Sections: 21.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chad Reissig Digitally signed by Chad Reissig Date: 12/30/2025 12:30 PM EST GUID: 20251230173037				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Ji Li ODES DCOA	Sections: 21	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ji Li Digitally signed by Ji Li Date: 12/30/2025 12:30 PM EST GUID: 20251230173057				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Consultant Discipline Secondary Reviewer	Chad Reissig CSS	Sections: 21.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chad Reissig Digitally signed by Chad Reissig Date: 12/30/2025 12:31 PM EST GUID: 20251230173117				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Sanjida Mahjabeen OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2,14.1, 14.2, 14.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sanjida Mahjabeen Digitally signed by Sanjida Mahjabeen Date: 12/30/2025 12:32 PM EST GUID: 20251230173249				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Shen Li OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shen Li Digitally signed by Shen Li Date: 12/30/2025 12:34 PM EST GUID: 20251230173448				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Secondary Reviewer	Sarah Dorff OCP DTPM	Sections: 8.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sarah Dorff Digitally signed by Sarah Dorff Date: 12/30/2025 12:36 PM EST GUID: 20251230173638				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Primary Reviewer	Karryn Crisamore OCP DTPM	Sections: 8.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Karryn Crisamore		Digitally signed by Karryn Crisamore Date: 12/30/2025 12:36 PM EST GUID: 20251230173639		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Paul Imbriano OB DBIII	Sections: 1, 2, 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Paul Imbriano		Digitally signed by Paul Imbriano Date: 12/30/2025 12:41 PM EST GUID: 20251230174127		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Mary Chung ORO DROII	Sections: Section III,12.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mary Chung		Digitally signed by Mary Chung Date: 12/30/2025 12:42 PM EST GUID: 20251230174258		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Mary Chung ORO DROII	Sections: Section III, 12.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mary Chung		Digitally signed by Mary Chung Date: 12/30/2025 12:44 PM EST GUID: 2025123017440		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Jackye Peretz OII DPTII	Sections: 2, 5.1, 7.1, 7.7.1, 7.7.2, 13	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jackye Peretz Digitally signed by Jackye Peretz Date: 12/30/2025 12:44 PM EST GUID: 20251230174424				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Dapeng Hu OB DBIII	Sections: Sections 1, 2, 6, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dapeng Hu Digitally signed by Dapeng Hu Date: 12/30/2025 12:45 PM EST GUID: 2025123017456				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Andrew Goodwin OII DPTII	Sections: 5,7,13	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrew Goodwin		Digitally signed by Andrew Goodwin Date: 12/30/2025 12:52 PM EST GUID: 20251230175215		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Sarah Morgan OII DPTII	Sections: 2, 5.1, 7.1, 7.7.1, 7.7.2, 13	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sarah Morgan		Digitally signed by Sarah Morgan Date: 12/30/2025 12:53 PM EST GUID: 2025123017531		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Matthew Kowalik OII DG	Sections: 1, 2, 3, 4, 7, 10, 11, 12, 16, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew Kowalik Digitally signed by Matthew Kowalik Sign on behalf of Joshua Eisenberg Date: 12/30/2025 12:55 PM EST GUID: 2025123017550				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Matthew Kowalik OII DG	Sections: 1, 2, 3, 4, 7, 10, 11, 12, 16, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew Kowalik Digitally signed by Matthew Kowalik Date: 12/30/2025 12:56 PM EST GUID: 20251230175621				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Chandrabhas Sahajwalla OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chandrabhas Sahajwalla		Digitally signed by Chandrabhas Sahajwalla Date: 12/30/2025 1:06 PM EST GUID: 2025123018650		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Chandrabhas Sahajwalla OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chandrabhas Sahajwalla		Digitally signed by Chandrabhas Sahajwalla Date: 12/30/2025 1:08 PM EST GUID: 2025123018841		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Onyekachukwu Illoh ODES DCOA	Sections: 21	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Onyekachukwu Illoh Digitally signed by Onyekachukwu Illoh Date: 12/30/2025 1:16 PM EST GUID: 2025123018167				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Vishnu Sharma OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Vishnu Sharma Digitally signed by Vishnu Sharma Date: 12/30/2025 1:22 PM EST GUID: 2025123018223				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Vishnu Sharma OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Vishnu Sharma Digitally signed by Vishnu Sharma Sign on behalf of Signed for Hongshan Li as he is out-of-office. Date: 12/30/2025 1:30 PM EST GUID: 20251230183035				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Tertiary Reviewer	David Reasner ODES DCOA	Sections: 21	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: David Reasner Digitally signed by David Reasner Date: 12/30/2025 2:46 PM EST GUID: 20251230194634				

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/

MATTHEW R KOWALIK
12/30/2025 03:01:38 PM

JULI A TOMAINO
12/30/2025 03:35:51 PM

Signing as myself; for technical reasons selected signing as someone else: The insufficient nonclinical data were an approvability issue for the originally proposed unrestricted use. Based on the available safety data, this application is recommended for approval with a description in the label that the safety of tradipitant has not been established for more than 90 total doses to adequately inform prescribers of the safe use of tradipitant for this indication. Refer to Sections 1 and 2.

NIKOLAY P NIKOLOV
12/30/2025 05:07:11 PM

Signing as myself (for technical reasons I selected signing as "Someone else" option): I concur with the CDTL and Division Signatory's recommendation to approve this application with the description in the label that the safety of tradipitant has not been established for more than 90 total doses to adequately inform prescribers of the safe use of tradipitant for this indication. Refer to Sections 1 and 2.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA ASSESSMENT AND EVALUATION

Application Number*: 220152

Supporting Document Number/s: 1, 9, 21, 22, 23, 24

CDER Receipt Date: SDN 1: December 30, 2024
SDN 9: March 25, 2025
SDN 21: July 30, 2025
SDN 22: September 19, 2025
SDN 23: October 15, 2025
SDN 24: October 22, 2025

Sponsor: Vanda Pharmaceuticals, Inc.

Product: Tradipitant (VLY-686)

Pharmacologic Class: Substance P/neurokinin-1 (NK-1) receptor antagonist

Indication: Acute prevention of vomiting induced by motion

Therapeutic area: Gastroenterology

Clinical Review Division: Division of Gastroenterology (DG)

Pharm/Tox Division: Division of Pharm/Tox for Immunology and Inflammation (DPT-II)

Reviewer: Sarah J. Morgan, PhD

Supervisor/Team Leader: Jackye Peretz, PhD

Project Manager: Mary Chung, PharmD

Purpose of Review: Supplementary Pharm/Tox NDA review

Alternative Assays: 3D spheroid cultures of primary human hepatocytes, human liver co-culture microphysiological system (co-cultured primary human hepatocytes and liver sinusoid endothelial cells), "four-organ" microphysiological system (liver primary biopsy, iPSC-derived cardiac cells, kidney primary biopsy, and iPSC-derived neuronal cells)

Reviewer Completion Date: December 30, 2025

Template Version: Sep 11, 2020

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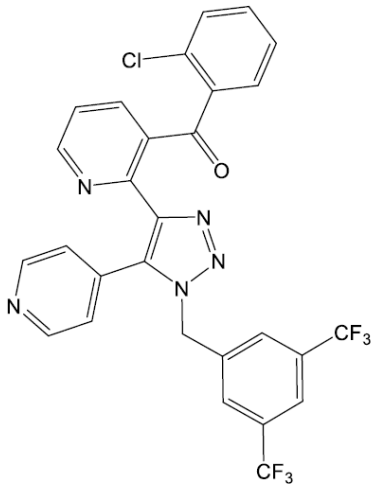
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Nonclinical Summary

Drug Information⁺

Type of Product:	Small molecule (oral capsule)
Code/ Generic Name:	Tradipitant (VLY-686, LY686017)
Chemical Name (optional):	{2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone
CAS# or UNII (if available):	CAS: 622370-35-8 UNII: NY0COC51FI
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	C ₂₈ H ₁₆ ClF ₆ N ₅ O 587.9 g/mol
Proposed 505(b)(2):	N
Biosimilar:	N

Pharmacology/ Toxicology Summary

Only studies reviewed in this document are summarized in the following sections.

Pharmacology (primary & secondary/ MoA)

Key Findings:

The inhibitory potential of tradipitant and metabolites M2, M3, M4, and M8 were evaluated in a series of in vitro binding assays. Tradipitant, M2, M3, M4, and M8 all inhibited binding to the human tachykinin NK-1 receptor by $\geq 99.0\%$ at 10 μM . Tradipitant inhibited binding to the NK-1 receptor with an IC_{50} of 3.3 nM, while M8 inhibited binding to the receptor with an IC_{50} of 0.49 nM. The Applicant reported similar IC_{50} values for the other metabolites, although these were not included in the provided study reports.

In functional assays, tradipitant and M8 inhibited substance P-mediated calcium release with IC_{50} values of 0.63 and 6.3 nM, respectively. These data confirm that M8 is pharmacologically active at the NK-1 receptor. Functional assays were not conducted

with M2, M3, or M4. Based on data from binding assays and their structural similarity to tradipitant, M2, M3, and M4 are presumed to be active metabolites as well.

Tradipitant significantly inhibited the rat benzothiazepine and dihydropyridine L-type calcium channels (65% and 63%, respectively) and rat GABAA t-butyl bicyclo-orthobenzoate (TBOB) chloride channel (62%). M2 also significantly inhibited the rat benzothiazepine L-type calcium channel (52%), human estrogen receptor (ER) alpha (64%), and rat GABA_A TBOB chloride channel (53%). No significant off-target effects were observed with M3, M4, or M8.

Safety Pharmacology

Key Findings:

The Applicant conducted four non-GLP safety pharmacology studies using cultured 3D human hepatocyte spheroids and one non-GLP safety pharmacology study using an in vitro human liver co-culture microphysiological system (MPS) with the objective of quantifying the in vitro hepatotoxic potential of tradipitant and its metabolites and to evaluate their underlying toxicity mechanisms. High variability of the positive controls, between donors, and between studies was observed. The rationale for the chosen positive controls was not provided, and the biological and/or clinical context for chosen endpoints and observed effects was not established. No primary mechanism was identified by which tradipitant or its metabolites may induce liver injury. In light of the limitations stated above, the clinical risk of liver injury with tradipitant administration remains poorly defined; however, these studies support that the risk of drug-induced liver injury is not an animal-specific finding and is relevant to humans.

PK/ADME/TK

Key Findings:

Tradipitant and its metabolites M2, M3, and M4 were highly bound in vitro using plasma samples from rat, mouse, and human. Protein binding of M8 was not assessed. There was no clear effect of concentration on plasma binding of tradipitant or its metabolites in any species.

Using recombinant human enzymes, UGT1A4 and UGT2B7 were identified as UDP-glucuronosyltransferases capable of converting tradipitant to the metabolite M8.

In studies using human liver microsomes, tradipitant competitively inhibited CYP3A activity with a K_i of 0.92 μ M and non-competitively inhibited CYP3A activity with a K_i of 11 μ M. Tradipitant competitively inhibited both CYP2C19 and CYP2C9 activity with K_i values of 9.0 μ M and 4.7 μ M, respectively. Tradipitant also non-competitively inhibited CYP2C8 activity with a K_i value of 17 μ M. No significant effects were observed on CYP1A2, CYP2D6, CYP2E1, or CYP2B6 activity.

In a study using primary human hepatocytes, tradipitant was considered a potential inducer of CYP3A4 activity in vitro. No biologically significant effects on CYP1A2 activity were observed.

Toxicology

Genotoxicity

Key Findings:

Tradipitant metabolites M2, M3, and M4 were negative for genotoxicity in the in vitro bacterial reverse mutation assay and the in vitro mammalian chromosome aberration assay using human lymphocytes. M8 was not tested for genotoxic potential.

Special Toxicology Studies

Key Findings:

The Applicant conducted two studies using a “four-organ” MPS comprised of primary human hepatocytes, induced pluripotent stem cell (iPSC)-derived cardiomyocytes, primary human renal proximal tubular epithelial cells, and iPSC-derived cortical neurons with the objective of evaluating the safety of tradipitant. Although the Applicant positioned these studies as pivotal to determining the safety of tradipitant, these studies were not conducted in compliance with US FDA GLP regulations; given the absence of adequate details regarding deviations from GLP and the potential impact of any deviations on the study validity, this was considered a limitation of these studies. Other limitations were identified that precluded use of these studies to support regulatory decision-making in this application, including the narrow scope of toxicity evaluations, unjustified biological relevance of the system and chosen endpoints, use of a single donor/cell source per organ, and short duration of the studies (7 or 14 days). Ultimately, due to these limitations, these studies do not substantively contribute to the safety profile of tradipitant.

Other Toxicology Studies

Key Findings:

An in silico analysis of tradipitant and metabolites M2, M3, M4, and M8 using various tools and databases was conducted in 2015 and submitted to the current NDA. Potential toxicities were identified; *however, in light of the completed in vitro and in vivo toxicity studies with tradipitant and/or its metabolites, the findings in this report are not considered toxicologically relevant.*

Updated in silico analyses were conducted by the Applicant to support the safety of metabolites M2, M3, and M4 for tradipitant for the prevention of vomiting induced by motion. These analyses were intended to assess if and how structural differences in the metabolites might affect their toxicity profile compared to tradipitant. Briefly, these in silico analyses were conducted using a machine learning-assisted workflow developed by xAI's Grok system, an advanced large language model trained on scientific datasets and further validated via the Applicant's in-house Python scripts. Notably, the Applicant's comparative structural prediction data were inferred based on RDKit-computed descriptors and qualitative thresholds aligned with best practices from consensus classifiers, rather than direct execution of these models. It is not clear why the Applicant chose to design a workflow using a large language model and a custom set of molecular descriptors and use information from existing classifier techniques to ‘infer’ predictions, rather than directly using existing (Q)SAR modeling software. Although insufficient detail was provided on the consensus classifiers used in the analyses to fully define the approach, enough information was provided to facilitate

review of the findings. Overall, the updated in silico analyses predicted that metabolites M2, M3, and M4 were unlikely to present additional toxicity concerns compared with tradipitant.

Nonclinical Assessment and Recommendation

The NDA submission included reports of 24 new nonclinical studies that had not been previously submitted to IND 141315 or cross-referenced from IND (b) (4). These included reports of primary pharmacology, safety pharmacology, pharmacokinetics, genetic toxicology, special toxicology, and other toxicology studies with tradipitant and/or its metabolites. In addition to review of the individual studies, this document contains an assessment of the available nonclinical data with tradipitant with regard to two major issues:

1. If the available nonclinical information, including additional in vitro assays, adequately support the safety of unrestricted use of tradipitant over a lifetime for the prevention of vomiting induced by motion; and
2. How the available nonclinical information addresses the safety of the four major human metabolites of tradipitant, M2, M3, M4, and M8.

Adequacy of Nonclinical Data to Support the Safety of Unrestricted Use

As previously documented, the Applicant has not conducted a chronic toxicity study in a nonrodent species. The available nonclinical data with tradipitant, including repeat-dose toxicity studies of up to 6 months in rats and up to 3 months in dogs, do not support the safety of unrestricted, repeated intermittent use of tradipitant over a lifetime for the prevention of vomiting induced by motion. While the duration of the nonclinical toxicity studies supports the safety of tradipitant itself for repeat intermittent dosing for a limited duration, it does not support unrestricted use over a lifetime.

As an alternative to conducting a chronic toxicity study in a nonrodent species, the Applicant submitted a total of seven additional in vitro assays to support the long-term safety of tradipitant.

Four studies using cultured 3D human hepatocyte spheroids and one study using an in vitro human liver co-culture MPS were conducted with tradipitant and/or its major metabolites with the objective of validating/quantifying the drug's hepatotoxic potential and to evaluate its underlying toxicity mechanisms. Treatment with tradipitant and all four major metabolites resulted in decreased hepatocyte viability that was deemed biologically relevant by the Applicant. Despite their limitations, these studies support the risk for tradipitant to cause liver injury, initially identified in Han Wistar rats, and that the potential for liver injury is not animal-specific, as these studies used human cells.

It should be noted that, while adaptive liver changes were observed in all animal toxicity studies with tradipitant and adverse liver findings were only observed in the 3-month Han Wistar rat study, the metabolites M2, M4, and M8 were not present in the rat studies. Therefore, the toxicological impact of these compounds, including the potential for hepatotoxicity, has not been adequately elucidated in animal studies.

Two additional in vitro studies using a “four-organ” MPS comprised of human hepatocytes, cardiomyocytes, renal proximal tubule epithelial cells, and cortical neurons were conducted to evaluate the safety of tradipitant. Limitations in the design and conduct of the studies were identified, including the narrow scope of toxicity evaluations, unjustified biological relevance of the system and chosen endpoints, lack of compliance with US FDA GLP regulations, and short duration of treatment (up to 14 days) relative to the intended clinical use.

Ultimately, the submitted alternative in vitro assays do not substantially contribute to the safety profile of tradipitant, and a chronic toxicity study in a nonrodent species is still scientifically warranted to support unrestricted use over a lifetime. Moreover, the in vitro liver safety pharmacology studies support a human-relevant risk of hepatotoxicity with tradipitant use that was initially identified in the animal studies, though the clinical risk of liver injury with tradipitant administration remains poorly defined.

Overall, there continues to be insufficient nonclinical safety information to support the safety of unrestricted, repeated intermittent use of tradipitant over a lifetime in humans, and this is an approvability issue for the current application.

Nonclinical Qualification of Major Human Metabolites

The Applicant has identified four major metabolites of tradipitant in human plasma: M2, M3, M4, and M8. These metabolites have been investigated in a series of nonclinical studies, and their plasma levels were measured in select toxicity studies conducted in rats and mice. Metabolite levels were not measured in any toxicity study conducted in dogs. Based on available data, these metabolites are considered to be pharmacologically active, toxicologically relevant, and present at significant levels compared to the parent drug, tradipitant. These factors support that the safety of levels of these metabolites should be qualified based on nonclinical data. Among these metabolites, only M3 was present in nonclinical studies in sufficient levels to be qualified for safety; M2, M4, and M8 are disproportionate human metabolites, and their safety was not adequately addressed with in vivo animal studies.

The Applicant proposed, and the review team considered, a Weight of Evidence (WoE) analysis to support that metabolites M2, M4, and M8 were not expected to be toxicologically different from tradipitant itself, thereby allowing for qualification based on total tradipitant drug-related exposure rather than on an individual basis. (Q)SAR analyses of the di-aryl alcohol and/or N-oxide moieties present on M2, M3, and M4 compared to tradipitant were conducted by FDA/CDER, and comparative computational prediction analyses were conducted in parallel by the Applicant. These analyses supported that the structural differences would not result in new or exaggerated toxicities with the metabolites compared to tradipitant itself. Analysis of the recently provided in vitro pharmacology, pharmacokinetic, and genotoxicity data (reviewed in this document) further supported the toxicological similarity of tradipitant and all four major metabolites. Therefore, the WoE supported that qualification of the disproportionate human metabolites (M2, M4, and M8) using total drug-related exposure, rather than on an individual basis, was scientifically appropriate.

Comparison of the total tradipitant drug-related exposure (i.e., tradipitant plus all measured active metabolites) between animals and humans demonstrated sufficient exposure margins such that metabolites M2, M4, and M8 were considered qualified based on the available nonclinical data. Thus, there is no safety concern with the levels of the major human metabolites.

Notably, it is not generally expected that such a WoE approach will be appropriate for the qualification of metabolites in other development programs, as each situation must be evaluated on its own merits based on the totality of data and information. Although in silico analyses are highly valuable in certain situations, they are unlikely to routinely address safety concerns in lieu of typical in vivo toxicity studies.

1 Background

1.1 Regulatory History

NDA 220152 for tradipitant for the acute prevention of vomiting induced by motion in adults was submitted on December 30, 2024 (SDN 1). This submission included 20 reports of nonclinical studies that had not been previously submitted to IND 141315 or cross-referenced from other INDs with tradipitant. Following the nonclinical filing review, additional information requests were communicated in the Filing Review Issues Identified Letter.¹ In response, the Applicant submitted three additional reports of nonclinical studies (SDN 9: March 25, 2025). Finally, following the Applicant's suggestion that the levels of the major human metabolites of tradipitant were qualified for safety based on their structural similarity and thus toxicological similarity to tradipitant (SDN 22: September 19, 2025) and resulting information requests,^{2,3} the Applicant submitted updated in silico analyses of the metabolites to support their safety in lieu of additional nonclinical studies (SDNs 23 and 24: October 15 and 22, 2025). This document contains reviews of these 24 new studies as well as a detailed scientific discussion of the nonclinical review issues relevant to this application.

1.2 Relevant INDs, NDAs, BLAs or DMFs

IND 141315: Treatment of motion sickness (DG); active

NDA 218489: Treatment of [symptoms of] or [nausea in] in gastroparesis (DG);

Complete Response Letter issued September 18, 2024

(b) (4)

¹ NDA 220152: [Filing Review Issues Identified Letter](#). March 14, 2025.

² NDA 220152: Information Request. October 1, 2025.

³ NDA 220152: Information Request. October 20, 2025.

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
NDA 218489	Sarah Morgan, PhD	September 18, 2024	Nonclinical NDA Review
	Matthew Kowalik, MD	September 18, 2024	NDA Integrated Review
(b) (4)	Yolanda Branch, PhD	January 21, 2021	PK, neonatal tox, PPND
	Jackye Peretz, PhD	September 21, 2016	30-Day IND Review
	Jianyong Wang, PhD	May 12, 2016	SPA Review – 2-year carci study in rats, 6-month carci study in Tg mice
	Jianyong Wang, PhD	April 29, 2016	30-Day IND Review
	Elizbieta Chalecka-Franasz, PhD	January 11, 2006	Nonclinical PK Amendment Review

3 Studies Submitted

3.1 Studies Reviewed

Twenty nonclinical studies not previously reviewed under IND were provided in the initial NDA submission (SDN 1: December 30, 2024). Three additional nonclinical studies were submitted in response to information requests in the Filing Review Issues Identified Letter¹ (SDN 9: March 25, 2025).

Pharmacology – Primary	4.2.1.1
Radioligand Binding of Tradipitant and its Metabolite M2	ab28300-1190604
Radioligand Binding of Tradipitant and its Metabolite M3	ab28300-1190601
Radioligand Binding of Tradipitant and its Metabolite M4	ab28300-1190602
Radioligand Binding of VLY-686	ab28300-1190603
In Vitro Pharmacology Study of VLY-686 and VLY-686 M8	FR095-0045286 (aka 100071541)
Evaluation of the activity of tradipitant and its M8 metabolite at the neurokinin-1 receptor	HPPK-3621
Pharmacology – Safety	4.2.1.3
Mechanistic analysis of tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model	HPTOX-3550
Analysis of the interaction between inflammatory signaling and tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model	HPTOX-3560
In vitro hepatotoxicity assessment of compounds in (b) (4) 3D spheroid model	HPTOX-3540
Evaluation of Toxicity of Tradipitant in the Human Co-Culture Liver-Chip	SRV-0028
HSTOX 7619: Evaluating the safety and toxicology of tradipitant in (b) (4) multi-organ, microphysiological system	HSTOX 7619
HSTOX 2008-002: Safety Evaluation of Supraphysiological Tradipitant Dosing under Differential Liver Metabolism	HSTOX 2008-002
Mechanistic analyses of tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model	HPTOX-3610

Pharmacokinetics – Absorption	4.2.2.2
In Vitro Permeability and Gastrointestinal Fluid Stability of Tradipitant (VLY-686) According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States FDA, the EMA, and the ICH	20VNDAP1GLPS607
Pharmacokinetics – Distribution	4.2.2.3
VLY-686 and Major Metabolites M2, M3 and M4: Investigation of Plasma Protein Binding In Vitro in Rat, Mouse and Human by Rapid Equilibrium Dialysis	WW85WJ
Pharmacokinetics – Metabolism	4.2.2.4
UGT Reaction Phenotyping of Tradipitant	XT164094
Pharmacokinetics – Drug Interactions (Nonclinical)	4.2.2.6
In Vitro Interaction of LY686017 with Human Cytochromes P450 CYP3A, CYP2D6, CYP2C19, CYP2C9, and CYP1A2	21-250-TC, 22-250-TC
Effects of LY686017 on CYP1A2 and CYP3A in Primary Cultures of Human Hepatocytes	2003IV-HI02
In Vitro Interaction of LY686017 with CYP2E1, CYP2C8, and CYP2B6 in Human Liver Microsomes	CD-0822
Tradipitant: UDP-glucuronosyltransferase Inhibition in Human Liver Microsomes	XT205023
Other Toxicity Studies	4.2.3.7.7
VLY-686 metabolites: Bacterial Reverse Mutation Test	TAJ0042
VLY-686 Metabolites: In Vitro Mammalian Chromosome Aberration Test In Human Lymphocytes	TAJ0043
Toxicology Assessment of Tradipitant and Four Corresponding Metabolites Performed via the TEST, ILab2, and ToxTree Software and augmented by analog searches from the DSSTox, SuperToxic and ACToR databases – 2015-01-30	In Silico Toxicologic Assessment
Chemical and structural analysis of tradipitant and its metabolites M2, M3, and M4	Response to Non-Clinical Information Request dated 01 October 2025

3.2 Studies Not Reviewed

All other nonclinical studies submitted to the NDA were previously reviewed under INDs

(b) (4)

4 Pharmacology

4.1 Primary Pharmacology

Radioligand Binding of Tradipitant and Its Metabolites M2, M3, and M4

Tradipitant: [ab28300-1190604](#)

M2: [ab28300-1190601](#)

M3: [ab28300-1190602](#)

M4: [ab28300-1190603](#)

The radioligand binding of tradipitant (named VLY-686 in this report) and its metabolites M2, M3, and M4 to a panel of 189 receptors, channels, and transporters was evaluated using rodent tissues or recombinant expression of human proteins in cell lines, as appropriate. As only a single concentration (10 μ M) of each test article was used, IC₅₀ values were not calculated. Inhibition of > 50% was considered biologically significant.

Tradipitant significantly inhibited the rat benzothiazepine and dihydropyridine L-type calcium channels (65% and 63%, respectively), rat GABA_A t-butyl bicyclo-orthobenzoate (TBOB) chloride channel (62%), and human tachykinin NK-1 receptor (100%). Metabolite M2 significantly inhibited the rat benzothiazepine L-type calcium channel (52%), human estrogen receptor (ER) alpha (64%), rat GABA_A TBOB chloride channel (53%), and human tachykinin NK-1 receptor (100%). Metabolites M3 and M4 significantly inhibited the human tachykinin NK-1 receptor (100%), with no significant inhibitory effects observed on other targets.

Table 1. Significant Inhibitory Effects of Tradipitant and its Metabolites

Target	Species	% Inhibition (10 μ M)			
		Tradipitant	M2	M3	M4
Calcium Channel L-Type, Benzothiazepine	Rat	65	52	ns	ns
Calcium Channel L-Type, Dihydropyridine	Rat	63	ns	ns	ns
Estrogen ER α	Human	ns	64	ns	ns
GABA _A , Chloride Channel, TBOB	Rat	62	53	ns	ns
Tachykinin NK-1	Human	100	100	100	100

NS: not significant (< 50% inhibition).

Table created by reviewer, based on Sponsor's provided data (Study ab28300-1190604; Study ab28300-1190601; Study ab28300-1190602; Study ab28300-1190603).

In Vitro Pharmacology Study of VLY-686 and VLY-686 M8
[FR095-0045286 \(aka 100071541\)](#)

The radioligand binding of tradipitant (named VLY-686 in this report) and metabolite M8 to a panel of 43 receptors, channels, and transporters was evaluated using rodent tissues or recombinant expression of human proteins in cell lines, as appropriate. Inhibition of >50% was considered biologically significant.

Both tradipitant and M8 inhibited the NK-1 receptor $\geq 99.0\%$ at the highest tested concentration of 10 μM . M8 was approximately 3 times more potent at the NK-1 receptor compared to tradipitant (IC_{50} values of 0.49 and 3.3 nM, respectively).

Table 2. Significant Inhibitory Effects of Tradipitant and Metabolite M8

Target	Species	Tradipitant		M8	
		% Inhibition (10 μM)	IC_{50} (nM)	% Inhibition (10 μM)	IC_{50} (nM)
Tachykinin NK-1	Human	99	3.3	99.3	0.49

NS: not significant (< 50% inhibition).

Table created by reviewer, based on Sponsor's provided data (Study 100071541).

Evaluation of the activity of tradipitant and its M8 metabolite at the neurokinin-1 receptor
[HPPK-3621](#)

The ability of tradipitant and metabolite M8 to inhibit activation of TACR1 (i.e., the NK-1 receptor) was evaluated in vitro using a functional assay. HEK293 cells were treated with tradipitant or M8 over the concentration range 10 pM-10 mM for 30 minutes prior to the addition of substance P at 100 nM (the EC_{80} as determined in a preliminary experiment). Intracellular calcium release was measured using a commercial kit (further information not provided).

Tradipitant and M8 similarly inhibited substance P-mediated calcium release in a concentration-dependent manner, with IC_{50} values of 0.63 and 6.3 nM, respectively.

Figure 1. Inhibition of Substance P (NK-1 Receptor)-Mediated Calcium Release by Tradipitant or M8

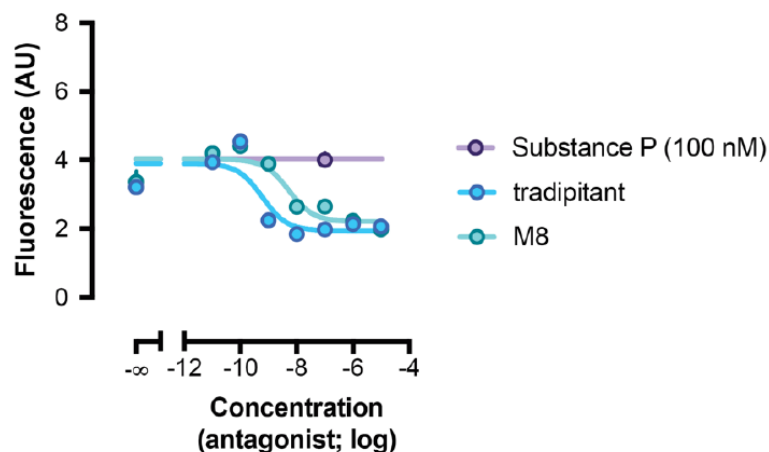


Figure copied directly from study report (Study HPPK-3621, Figure 2).

4.3 Safety Pharmacology Studies

Reviewer Note: The safety pharmacology study reviewed below were not conducted in accordance with US FDA GLP regulations. Despite that limitation, evidence of hepatotoxicity was identified, as described below.

4.3.1 Mechanistic analysis of tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model

[HPTOX-3550](#)

Methods:

As stated in the study report, the objective of this non-GLP study⁴ was to quantify the in vitro hepatotoxic potential of tradipitant and to evaluate its underlying toxicity mechanisms. Tradipitant was evaluated using 3D spheroid cultures of primary human hepatocytes as previously reported by Bell et al.⁵ In each experiment, primary human hepatocytes from a single human donor were seeded into ultra-low attachment plates and cultured for seven days until spontaneous self-aggregation was observed. Cells were then cultured overnight in serum free medium prior to treatment with tradipitant (Lot # DVVE18001M⁶) at approximately 3.5, 7.0, 10.5, 17.5, or 35 µg/mL (i.e., approximately 10, 20, 30, 50, or 100x the Applicant's reported clinical C_{max} of 350 ng/mL).

Reviewer note: Steady state PK data for subjects who experience vomiting induced by motion are derived from Trial VP-VLY-686-1102, in which healthy volunteers were administered tradipitant at 85 mg twice daily (BID) for 12 days (assumed but not

(b) (4)

confirmed to represent steady state) under fasted conditions. In this Trial, the C_{max} for tradipitant was reported as 327 ng/mL. Thus, the concentrations used in this study represent tradipitant exposure approximately 1.1-, 3.2-, 11-, 21-, 32-, or 107-fold the C_{max} , respectively, in this population. It should be noted that the Applicant did not conduct *in vitro* to *in vivo* extrapolation (IVIVE) analyses to determine how the *in vitro* concentration relates to that observed in humans. In fact, a direct comparison of C_{max} and *in vitro* concentrations is scientifically inappropriate as such an “approach oversimplifies the complex relationship between *in vitro* and *in vivo* drug behavior and can lead to inaccurate conclusions.”⁷ Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

DMSO was used as the negative control in all experiments. Drug-containing medium was replaced every 48-72 hours for a total of 2 or 4 weeks.

A total of five donors were used in this study for five individual experimental cultures; the cells from each donor were not pooled. Donors included three females and two males ranging in age from 27-50 years old, of varying ethnicity, who died of non-liver-related causes, and were not reported to be on any medication at the time of death. At least eight spheroids per donor per endpoint were evaluated.

Table 3. Characteristics of Human Hepatocyte Donors in Study HPTOX-3550

	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5
Age	30	48	27	50	25
Ethnicity	Hispanic	Polynesian	African American	Caucasian	Hispanic
Gender	Female	Female	Female	Male	Male
BMI	30.8	N/A	28.2	31.3	32.2
Cause of death	Head trauma	Trauma	Anoxia	CVA/Stroke	Head trauma
HEP-B, HEP-C, HIV	Negative	Negative	Negative	Negative	Negative
Medications	None reported	None reported	None reported	None reported	None reported

Table copied directly from study report (Study HPTOX-3550, Appendix).

Endpoints tested in this study included cell viability as determined via quantification of ATP using a commercial kit; cholestatic potential as determined via ATP quantification following co-culture of spheroids with a physiological, non-toxic mixture of bile acids per Hendriks et al⁸; effects of inflammation on cell viability following co-culture of spheroids

⁷ Albrecht, W. Which concentrations are optimal for *in vitro* testing? *Excli j*, 2020. 19: p. 1172-1173.

⁸ Hendriks, D., Fredriksson Puigvert, L., Messner, S. et al. Hepatic 3D spheroid models for the detection and study of compounds with cholestatic liability. *Sci Rep* 6, 35434 (2016).

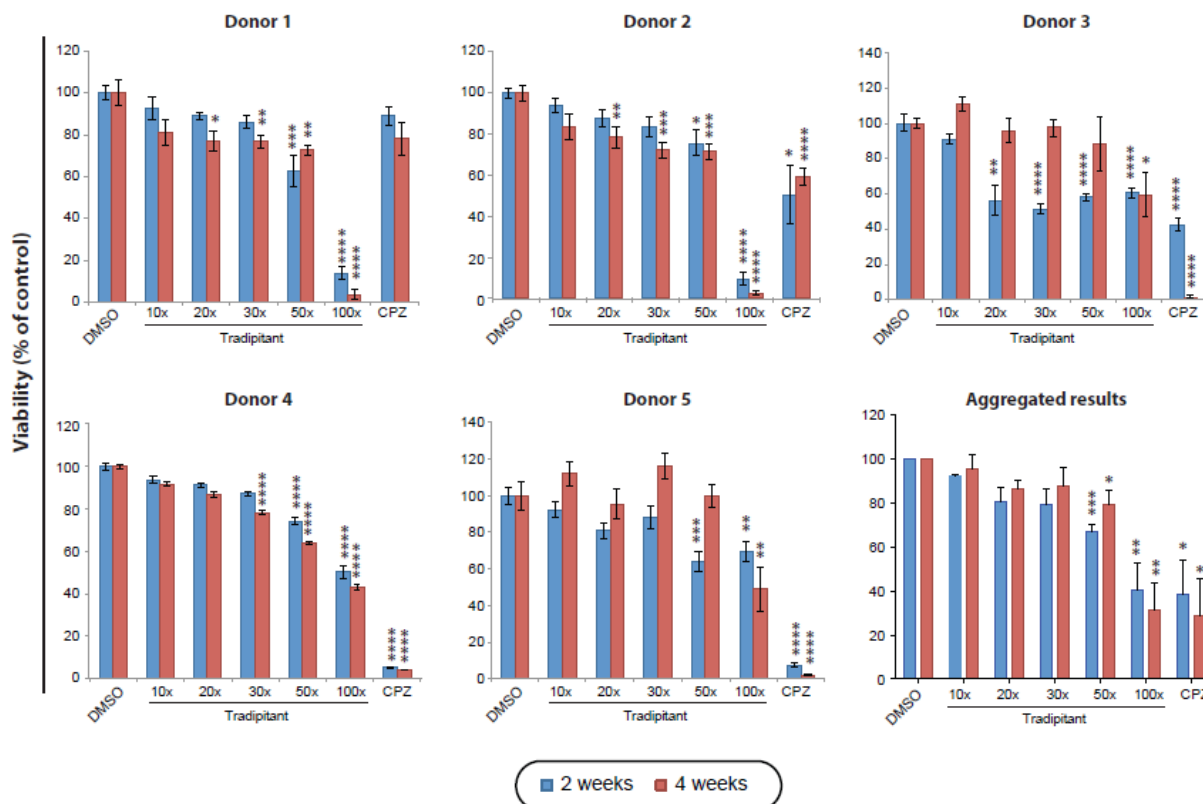
with 10 ng/ml each of pro-inflammatory cytokines tumor necrosis factor alpha (TNF α), interferon gamma (INF γ), and interleukin (IL)-6; generation of reactive oxygen species (ROS) using a commercial kit; and effects on intracellular triglyceride levels using staining with a commercial dye and measurement of fluorescence at 572 nm. Tradipitant was considered hepatotoxic if viability was reduced to < 80% of control levels in experiments measuring cell viability.⁹

Results:

Although notable inter-donor variability was observed, cell viability generally decreased in spheroids treated with tradipitant in a time- and concentration-dependent manner. Toxicity was observed in Donors 1 and 2, with cell viability reduced to $\approx$ 80% of controls at ≥ 7.0 μ g/mL following 4 weeks of tradipitant exposure, and to < 20% of controls at 35 μ g/mL following 2 or 4 weeks of treatment. Treatment with the positive control, chlorpromazine, induced limited or moderate toxicity in these donors (viability $\approx$ 60%-90% of controls). In Donors 3 and 5, toxicity (viability $\approx$ 60%-80% of controls) was observed at ≥ 7.0 and ≥ 17.5 μ g/mL, respectively, after 2 weeks of treatment; however, no biologically significant toxicity was observed following 4 weeks of treatment except at the highest concentration of 35 μ g/mL (viability $\approx$ 60% of controls). Toxicity in Donor 4 was observed to be the most clearly dose- and time-dependent, with biologically significant decreases in cell viability observed following treatment at ≥ 10.5 μ g/mL for 2 weeks and ≥ 17.5 μ g/mL for 4 weeks.

Decreased cell viability was observed at 7.0 μ g/mL in 3/5 donors. However, when combining the results for all 5 donors, biologically significant decreases in cell viability were observed at ≥ 17.5 μ g/mL following 4 weeks of treatment.

⁹ Vorrink, S. U.; Zhou, Y.; Ingelman-Sundberg, M.; Lauschke, V. M. Prediction of Drug-Induced Hepatotoxicity Using Long-Term Stable Primary Hepatic 3D Spheroid Cultures in Chemically Defined Conditions. *Toxicological Sciences* 2018, 163, 655–665.

Figure 2. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids

Viability was evaluated by quantifying ATP levels. Error bars indicate SEM. * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 using heteroscedastic two-tailed t-tests compared to the respective DMSO control at the same time point. N=8 spheroids per measurement.

CPZ: chlorpromazine (positive control).

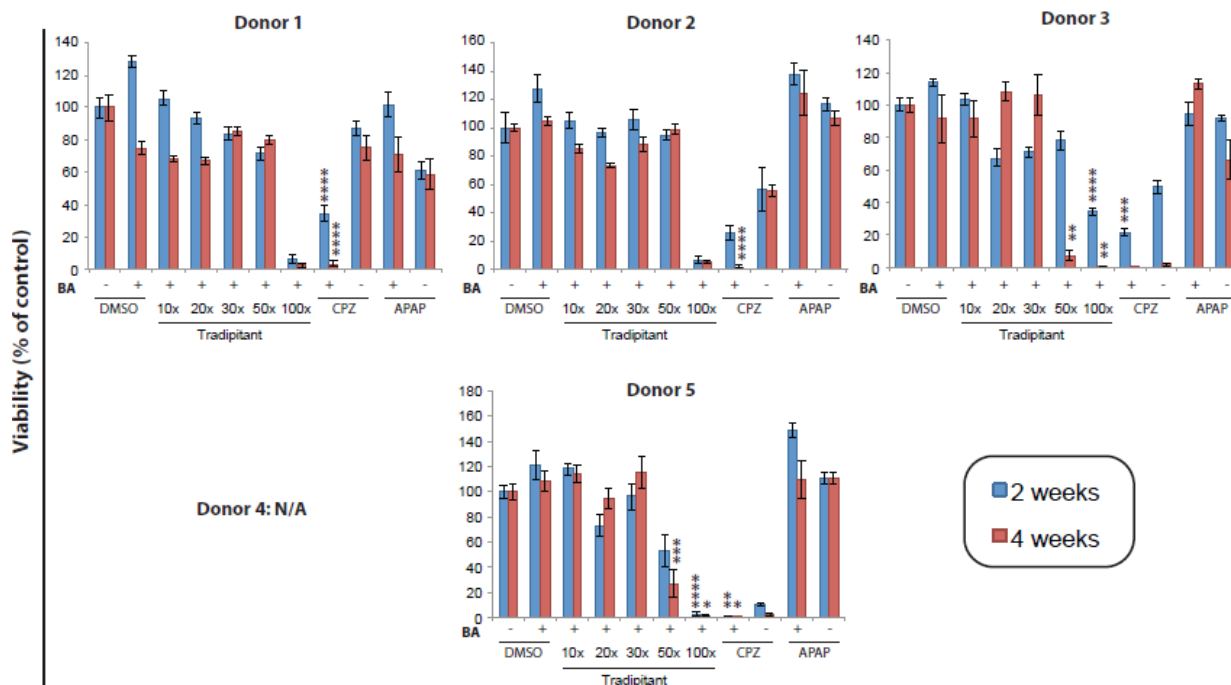
10x, 20x, 30x, 50x, and 100x = 3.5, 7.0, 10.5, 17.5, and 35 µg/mL, respectively.

Figure copied directly from study report (Study HPTOX-3550, Figure 1).

The cholestatic potential of tradipitant in the hepatocyte spheroids was determined via the cholestatic index (Cix), which is calculated by dividing the viability of spheroids co-treated with bile acids by the viability of spheroids treated with compound only. Compounds are assumed to induce cholestasis if the Cix is ≤ 0.8 (see Table 4).

Decreased cell viability resulting from the induction of cholestasis in the hepatocyte spheroids (Cix ≤ 0.8 ; i.e., tradipitant toxicity was amplified by the physiological bile acid mixture at these concentrations) was observed in four donors at 35 µg/mL for 2 weeks and in Donors 3 and 5 only at ≥ 17.5 µg/mL for 4 weeks. The experiment with Donor 4 failed for technical reasons.

Figure 3. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids Co-Cultured with Bile Acids



Viability was evaluated by quantifying ATP levels. Error bars indicate SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ are indicated for bile acid (BA) treated samples compared to the respective non-BA treated control. Only those samples are indicated where the Cix is ≤ 0.8 . $n = 8$ spheroids per measurement.

APAP: acetaminophen; CPZ: chlorpromazine.

10x, 20x, 30x, 50x, and 100x = 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3550, Figure 2).

Table 4. Cholestatic Index of Tradipitant in Primary Human Hepatocyte Spheroids

	Donor	1	2	3	5
2w	10x tradipitant	1.14	1.12	1.14	1.27
	20x tradipitant	1.05	1.10	1.20	0.90
	30x tradipitant	0.97	1.26	1.38	1.09
	50x tradipitant	1.15	1.25	1.34	0.82
	100x tradipitant	0.5	0.71	0.57****	0.04****
	CPZ	0.4****	0.45	0.44***	0.11**
	APAP	1.66	1.18	1.03	1.34
4w	10x tradipitant	0.85	1.01	0.83	1.02
	20x tradipitant	0.88	0.94	1.14	0.99
	30x tradipitant	1.12	1.22	1.09	0.99
	50x tradipitant	1.10	1.38	0.08**	0.27***
	100x tradipitant	0.82	2.03	0.01**	0.04*
	CPZ	0.05****	0.03****	0.06	0.04*
	APAP	1.21	1.16	1.70	0.99

* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 are indicated for bile acid (BA) treated samples compared to the respective non-BA treated control.

APAP: acetaminophen; CPZ: chlorpromazine.

10x, 20x, 30x, 50x, and 100x = 3.5, 7.0, 10.5, 17.5, and 35 µg/mL, respectively.

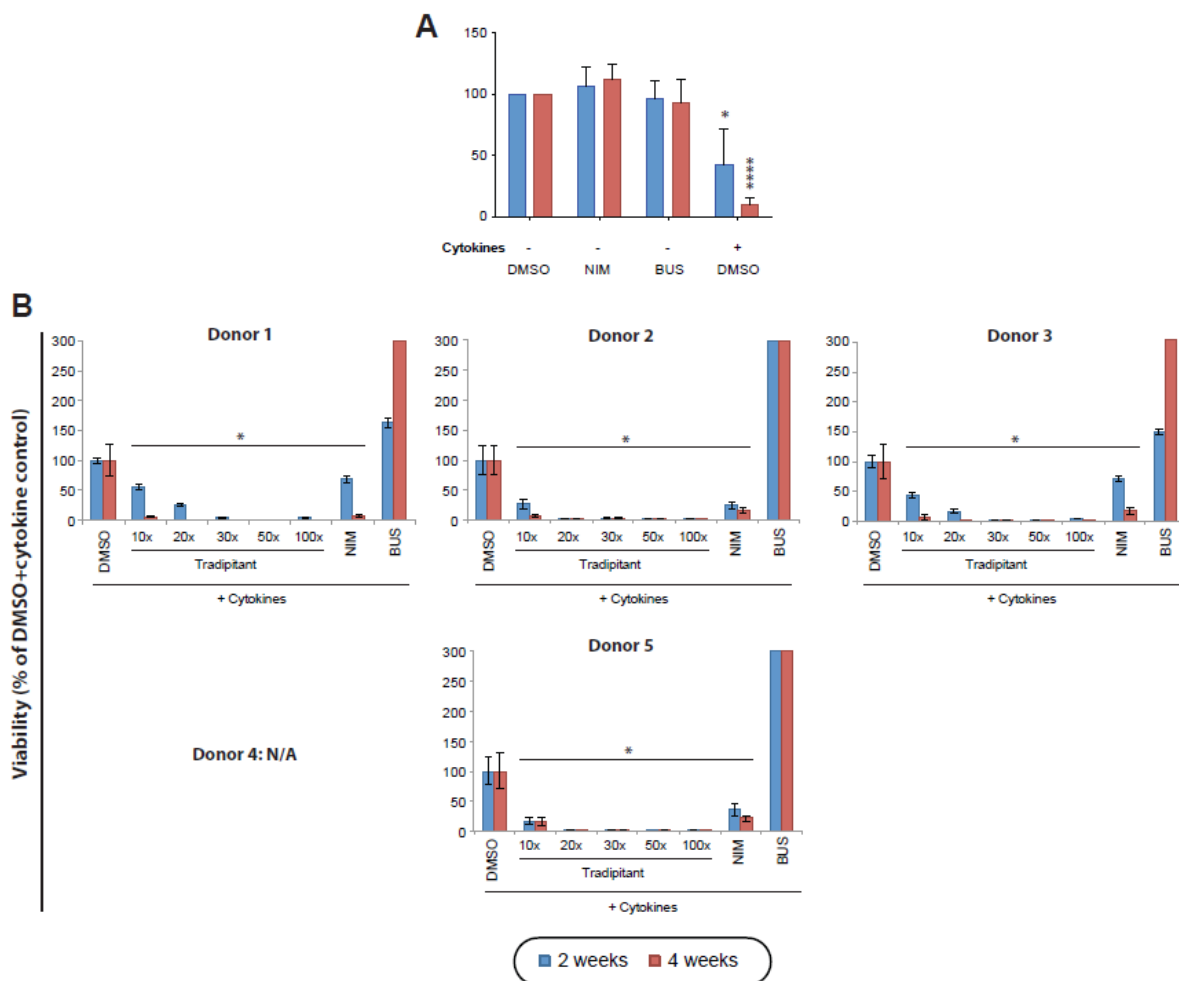
Table copied directly from study report (Study HPTOX-3550, Table 1).

The Applicant investigated the synergistic effects of tradipitant and pro-inflammatory cytokines (TNF α , INF γ , and IL-6) on cell viability.

Reviewer note: Based on the Applicant's presentation of data in this section and the lack of raw data provided, it is difficult to distinguish between effects that are additive (or sub-additive) and synergistic. As the cytotoxic effects of the cytokine mixture alone were strong, the overall nature of the combined effect may be obscured under the tested conditions. Additionally, the expected effects of control compounds nimesulide and buspirone were not defined.

The combination of cytokines alone was strongly cytotoxic, decreasing viability by 58% and 90% after 2 weeks and 4 weeks, respectively. Again, the experiment with donor 4 failed for technical reasons. In the other 4 donors, treatment with tradipitant at all tested concentrations (≥ 3.5 µg/mL) for 2 or 4 weeks resulted in larger decreases in cell viability compared to the cytokines alone. Based on these findings, inflammation may increase the risk of liver injury with tradipitant.

Figure 4. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids Co-Cultured with Pro-Inflammatory Cytokines

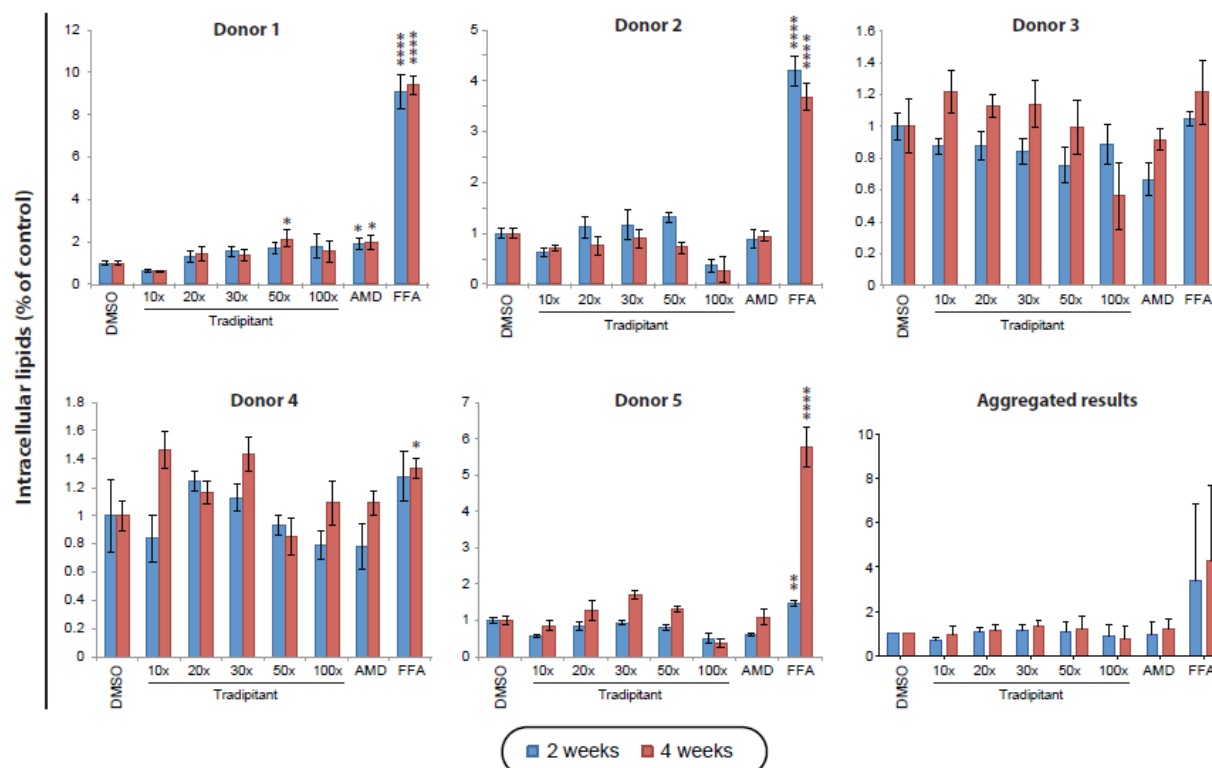


A. Evaluation of cytokines and control compounds nimesulide (NIM) and buspirone (BUS) in vitro hepatotoxicity in 3D spheroids. **B.** Results of co-exposure of tradipitant, NIM and BUS together with cytokines are shown. Error bars indicate SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ using heteroscedastic two-tailed t-tests compared to the respective DMSO+cytokine control at the same time point. N=8 spheroids per measurement. Cytokines: 10 ng/ml each of tumor necrosis factor alpha (TNF α), interferon gamma (INF γ), and interleukin (IL)-6.

Figure copied directly from study report (Study HPTOX-3550, Figure 3).

Intracellular triglyceride accumulation was used as a marker of potential hepatic steatosis following treatment with tradipitant. No consistent effect of tradipitant on intracellular triglyceride levels was observed. Effects of the positive controls, amiodarone (AMD) and free fatty acids (FFA), were also variable. This was considered related to the inter-donor variability in intracellular lipid levels/extent of steatosis at the time of hepatocyte recovery, rather than effects of the experimental treatment (see Figure 6).

Figure 5. Effects of Tradipitant on Intracellular Triglyceride Accumulation in Primary Human Hepatocyte Spheroids

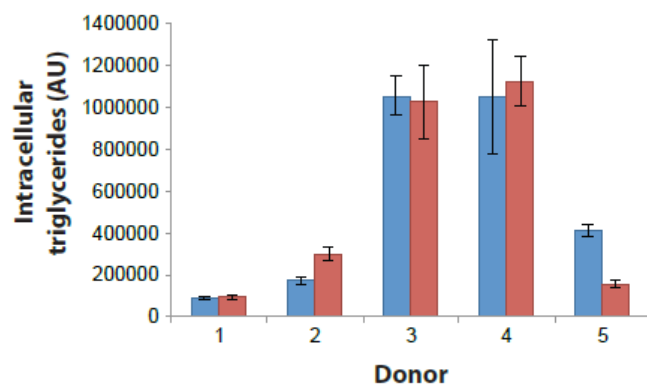


Error bars indicate SEM. * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 using heteroscedastic two-tailed t-tests compared to the respective DMSO control at the same time point. N=8 spheroids per measurement.

AMD: amiodarone; FFA: free fatty acids.

Figure copied directly from study report (Study HPTOX-3550, Figure 4).

Figure 6. Donor Variability in Intracellular Triglyceride Levels (Untreated) in Primary Human Hepatocyte Spheroids



Error bars indicate SEM. N=8 spheroids per donor.

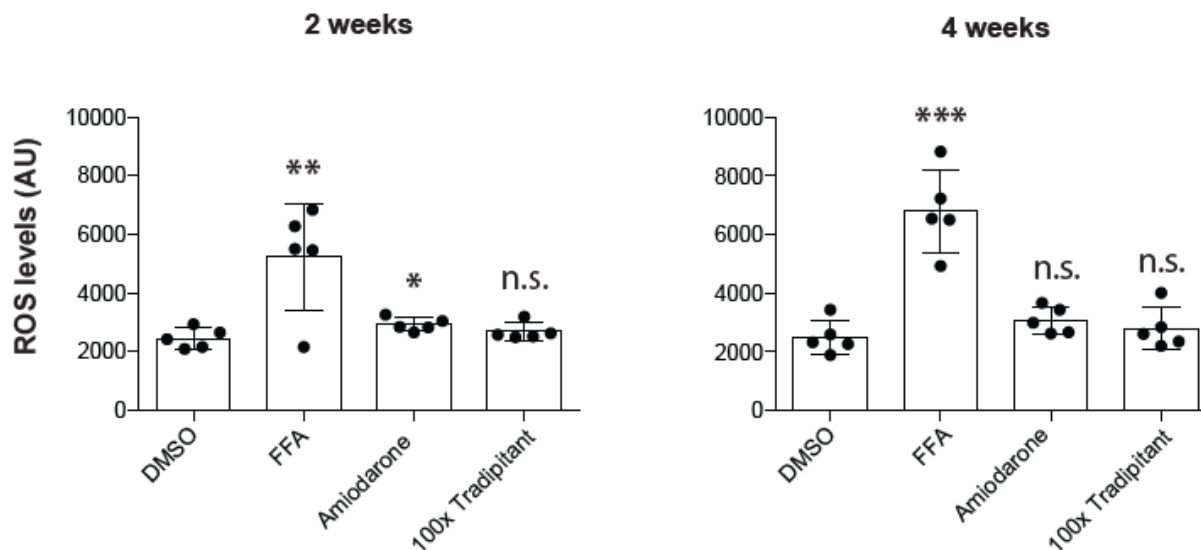
Blue bars: 2 weeks; red bars: 4 weeks.

Data in this figure are from untreated spheroids.

Figure copied directly from study report (Study HPTOX-3550, Figure 5).

Tradipitant had no significant effect on ROS generation following either 2 or 4 weeks of treatment at 35 µg/mL.

Figure 7. Effects of Tradipitant on ROS Generation in Primary Human Hepatocyte Spheroids



Error bars indicate SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ using heteroscedastic two-tailed t-tests compared to the respective DMSO control at the same time point. Each measurement corresponds to one donor and 48 spheroids were pooled per donor, condition and time point. FFA: free fatty acids; ns: not significant; ROS: reactive oxygen species (as a marker of oxidative stress). Figure copied directly from study report (Study HPTOX-3550, Figure 6).

4.3.2 Analysis of the interaction between inflammatory signaling and tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model

[HPTOX-3560](#)

Methods:

As stated in the study report, the objective of this non-GLP study⁴ was to quantify the in vitro hepatotoxic potential of tradipitant and to evaluate its underlying toxicity mechanisms. Tradipitant was evaluated using 3D spheroid cultures of primary human hepatocytes as previously reported by Bell et al.⁵ In each experiment, primary human hepatocytes from a single human donor were seeded into ultra-low attachment plates and cultured for 7 days until spontaneous self-aggregation was observed. Cells were then cultured overnight in serum free medium prior to treatment with tradipitant (Lot # DVVE18001M⁶) at approximately 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, or 35 µg/mL (i.e., approximately 1, 3, 10, 20, 30, 50, or 100x the Applicant's reported clinical C_{max} of 350 ng/mL); this concentration range was selected by the Applicant based on the findings in Study HPTOX-3550.

Reviewer note: As stated previously, the concentrations used in this study represent tradipitant exposure at approximately 11-, 21-, 32-, 54-, or 107-fold the clinical C_{max} of 327 ng/mL, respectively, as determined in healthy volunteers following 12 days of

dosing at 85 mg BID. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. In fact, a direct comparison of C_{max} and in vitro concentrations is scientifically inappropriate as such an “approach oversimplifies the complex relationship between in vitro and in vivo drug behavior and can lead to inaccurate conclusions.”⁷ Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

DMSO was used as the negative control in all experiments. Drug-containing medium was replaced every 48-72 hours for a total of 2 or 4 weeks.

A total of five donors were used in this study; the cells from each donor were not pooled. Demographic and health information were not provided for the donors. Eight spheroids per donor per endpoint were evaluated.

Cell viability was determined via quantification of ATP using a commercial kit following treatment with tradipitant alone and following co-culture of spheroids with pro-inflammatory cytokines (TNF α , INF γ , and IL-6; each individually and in combination at 0.1, 1, and 10 ng/mL). Treatments were considered hepatotoxic if cell viability was reduced to < 80% of control levels.⁹

Results:

Reviewer note: The Applicant’s interpretation of these results does not clearly report or identify effects that are synergistic versus those that are additive or sub-additive. As no raw data were provided and the presentation of the data did not allow for potential synergistic effects to be directly determined, the results reported here should be interpreted with caution. Synergistic effects were identified by the reviewer as those being greater or equal to 1.1 times the estimated additive effect (i.e., the sum of the tradipitant only effect and the cytokines only effect, as estimated from the bar graph). Synergistic effects were only analyzed for the cytokine mixtures, not for the individual cytokines, due to the large number of conditions tested. Notably, the Applicant did not provide any rationale to explain how the cytokine conditions are relevant to the indication of vomiting induced by motion, as these subjects are generally considered healthy in the absence of the motion stimulus.

Summary of Findings

Tradipitant induced hepatotoxicity in 4/5 donors after 2 or 4 weeks of treatment, evidenced by decreased cell viability of the hepatocyte spheroids compared to controls. The concentration(s) at which biologically significant toxicity occurred were highly donor-dependent.

Overall, no clear synergistic effects of tradipitant with pro-inflammatory cytokines (TNF α , INF γ , IL-6, or the combination) were observed on the viability of hepatocyte spheroids. However, interpretation of these data was severely limited by the lack of raw data provided, the Applicant’s method of analysis, the high variability of data generated for

each individual donor, and the frequently large effects observed with tradipitant or cytokines alone.

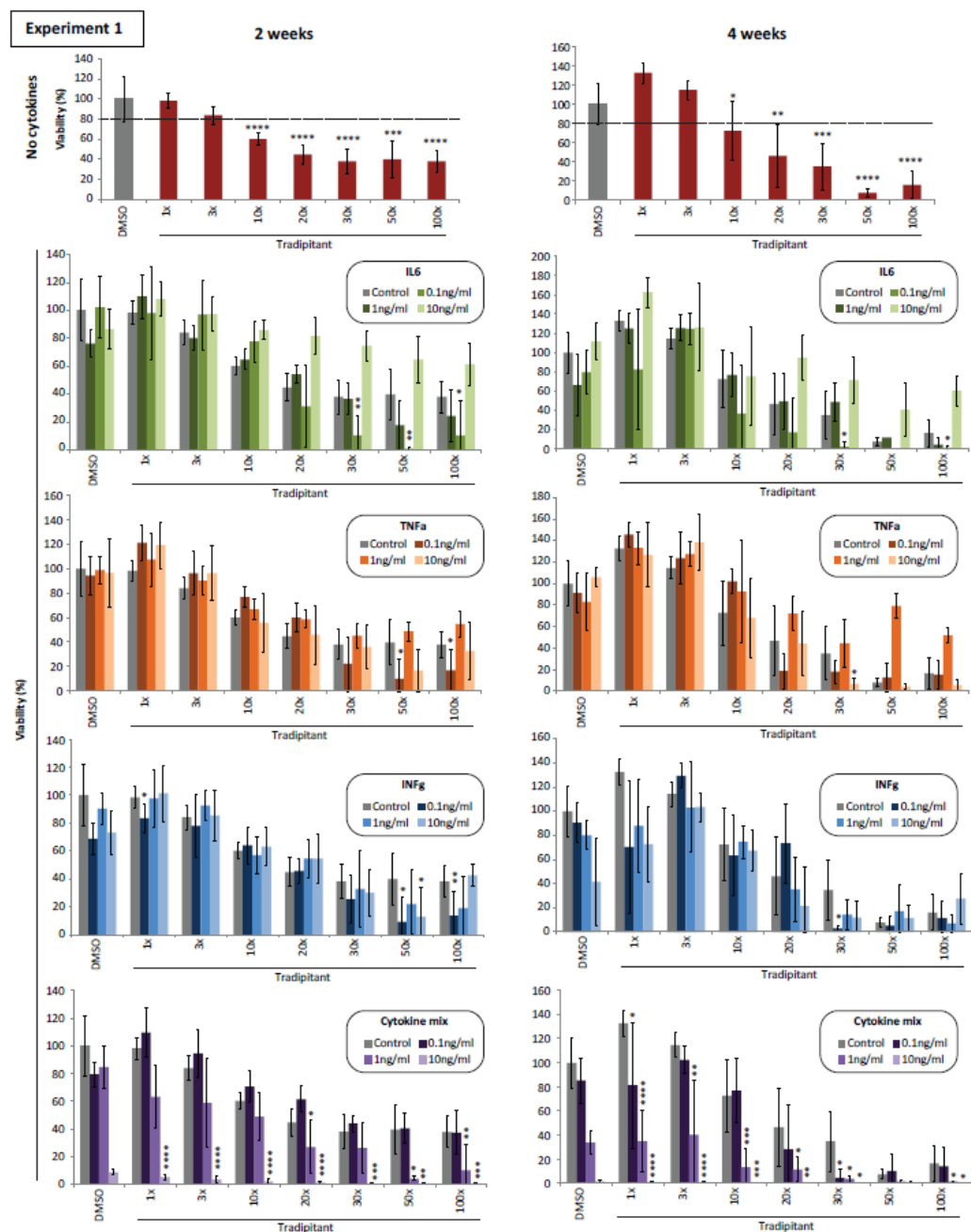
Reviewer note: In this study, treatment with tradipitant at 3.5 µg/mL (or less) for 2 or 4 weeks resulted in biologically significant decreases in cell viability in 4/5 donors. This is a lower concentration than that observed in Study HPTOX-3550 (7.0 µg/mL). A possible explanation for the increased sensitivity could not be determined, and no explanation was provided.

Individual Donor Findings

For Donor 1, biologically significant, dose-dependent hepatotoxicity was observed at tradipitant concentrations ≥ 3.5 µg/mL following treatment for both 2 and 4 weeks.

None of the cytokines (TNF α , INF γ , IL-6) alone significantly impacted cell viability; however, treatment with the cytokine mixture resulted in decreased cell viability at 10 ng/mL at 2 weeks and at ≥ 1 ng/mL at 4 weeks.

No combined effects of tradipitant and individual cytokines were reported for this donor. Sporadic instances of synergistic effects of tradipitant and the cytokine mixture on cell viability were identified in this review, but no consistent or concentration-dependent synergy was observed in this donor following 2 weeks of treatment. Synergistic effects were identified with tradipitant at 0.35 µg/mL only using all concentrations of the cytokine mixture following 4 weeks of treatment, but not with other combinations.

Figure 8. Effect of Cytokines on the Hepatotoxicity of Tradipitant – Donor 1

Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability using heteroscedastic two-tailed t-tests. For the top row (no cytokines), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (panels in rows 2-5), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and tradipitant concentration. $n = 8$ spheroids per measurement.

IL-6: interleukin 6; INF γ : interferon gamma; TNF α : tumor necrosis factor alpha.

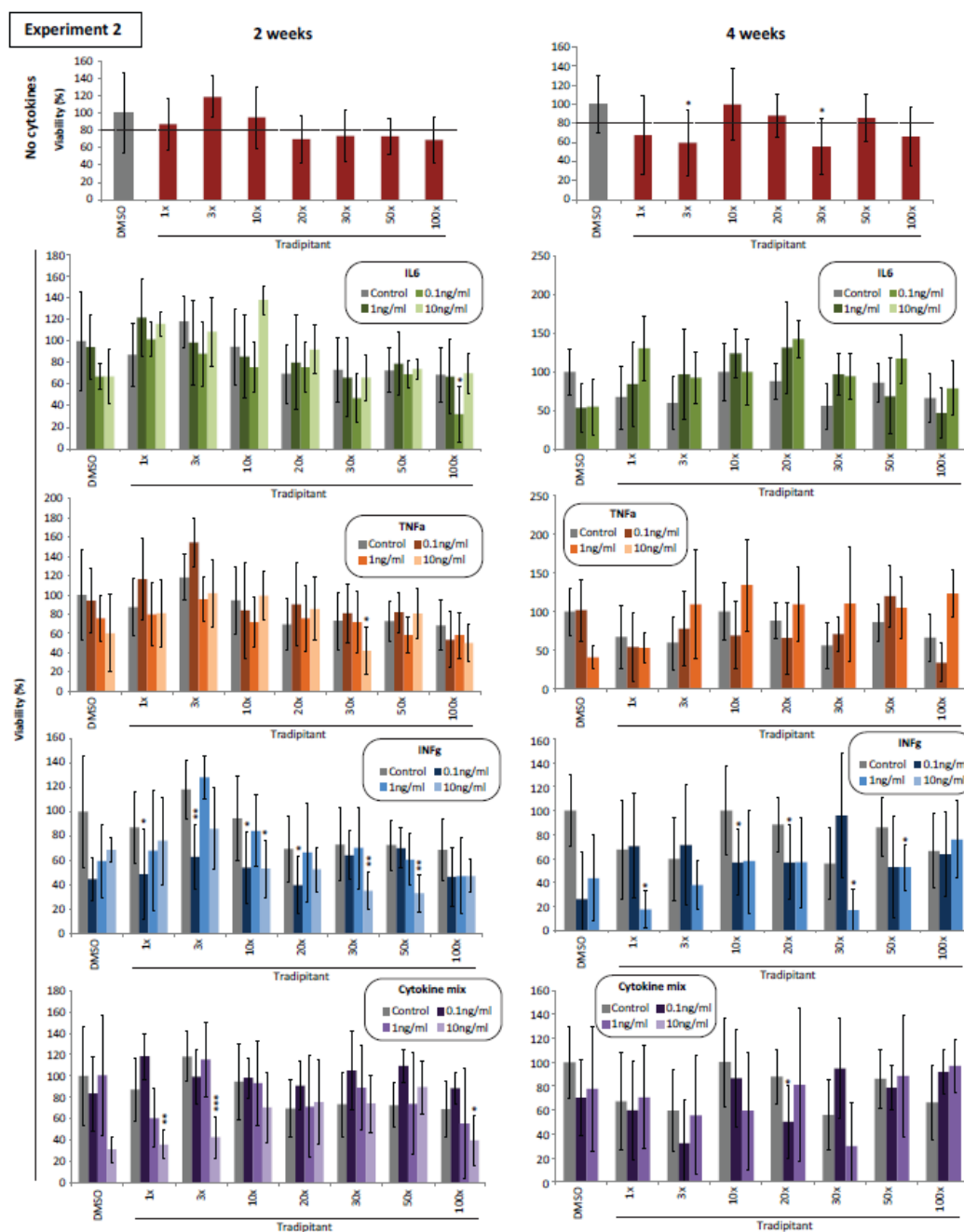
1x, 3x, 10x, 20x, 30x, 50x, and 100x = 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3560, Figure 1).

For Donor 2, no clear effect of tradipitant on cell viability was observed under the tested conditions, although notable variability was observed between spheroids.

None of the cytokines alone had a clear or significant impact on cell viability; however, treatment with the cytokine mixture tended to result in decreased cell viability at 10 ng/mL at 2 weeks; data with the 10 ng/mL cytokine mixture were not reported for the 4-week timepoint (with no rationale provided).

Synergistic effects were identified with tradipitant at 0.35 µg/mL only in combination with all concentrations of the cytokine mixture following two weeks of treatment, but not with other combinations. Sporadic instances of synergistic effects of tradipitant and the cytokine mixture on cell viability were identified following two weeks of treatment, but no consistent or concentration-dependent synergy was observed in this donor at this timepoint.

Figure 9. Effect of Cytokines on the Hepatotoxicity of Tradipitant – Donor 2

Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability using heteroscedastic two-tailed t-tests. For the top row (no cytokines), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (panels in rows 2-5), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and tradipitant concentration. $n=8$ spheroids per measurement.

IL-6: interleukin 6; IFN γ : interferon gamma; TNF α : tumor necrosis factor alpha.

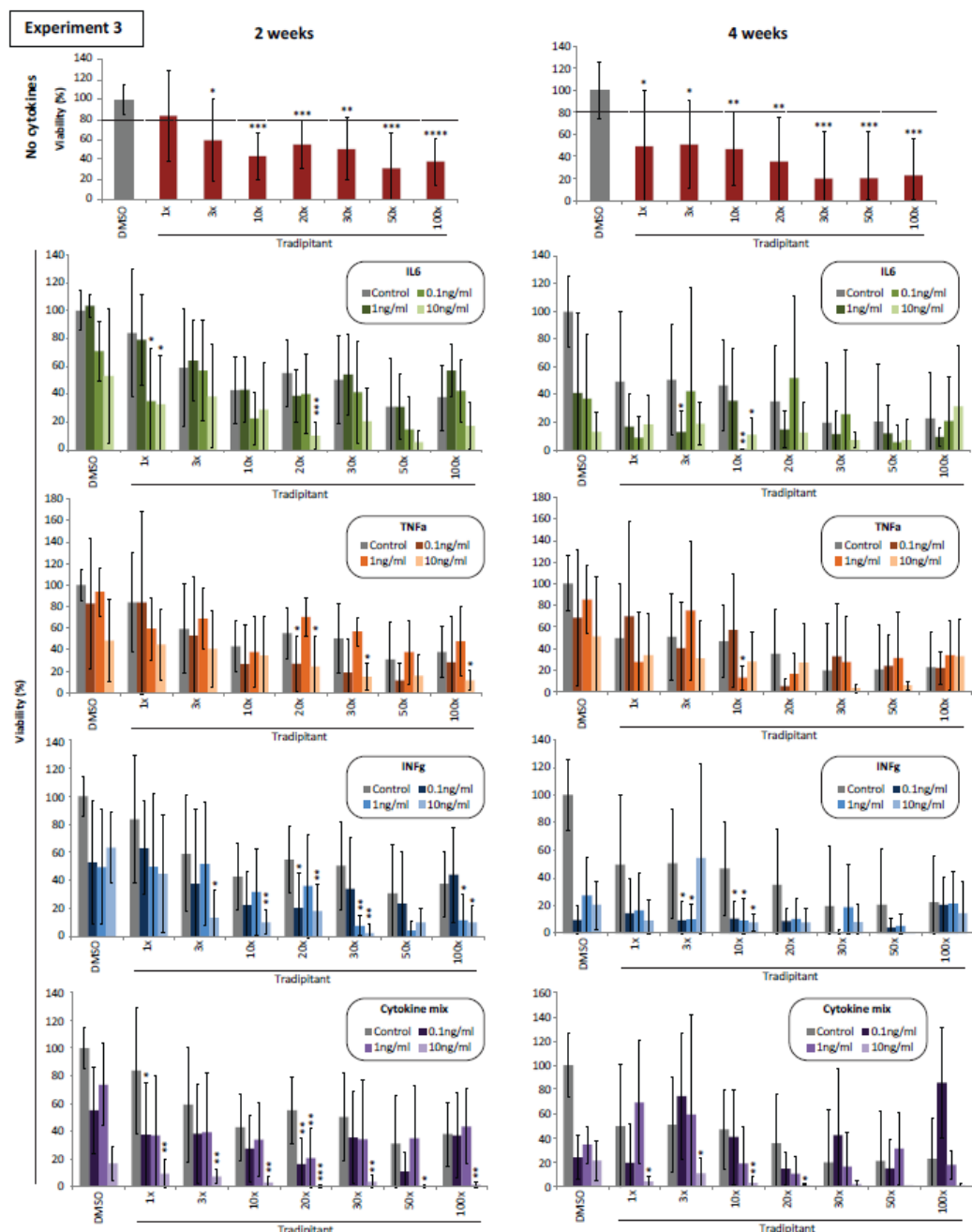
1x, 3x, 10x, 20x, 30x, 50x, and 100x = 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3560, Figure 2).

Interpretation of data from Donor 3 was impacted by high variability. Biologically significant, dose-dependent hepatotoxicity was observed at tradipitant concentrations $\geq 1.05 \mu\text{g/mL}$ following treatment for 2 weeks and at all concentrations for 4 weeks.

None of the cytokines alone had a clear or significant impact on cell viability; however, treatment with the cytokine mixture resulted in decreased cell viability at 10 ng/mL after 2 weeks and at all concentrations after 4 weeks.

The Applicant reported synergistic effects of tradipitant in combination with IL-6, $\text{TNF}\alpha$, or $\text{IFN}\gamma$ alone in this donor; however, these findings could not be substantiated by the reviewer, especially in light of the high variability and strong effects of tradipitant alone. Sporadic instances of synergistic effects of tradipitant and the cytokine mixture on cell viability were identified, but no consistent or concentration-dependent synergy was observed in this donor under the tested conditions.

Figure 10. Effect of Cytokines on the Hepatotoxicity of Tradipitant – Donor 3

Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability using heteroscedastic two-tailed t-tests. For the top row (no cytokines), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (panels in rows 2-5), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and tradipitant concentration. $n = 8$ spheroids per measurement.

IL-6: interleukin 6; INF γ : interferon gamma; TNF α : tumor necrosis factor alpha.

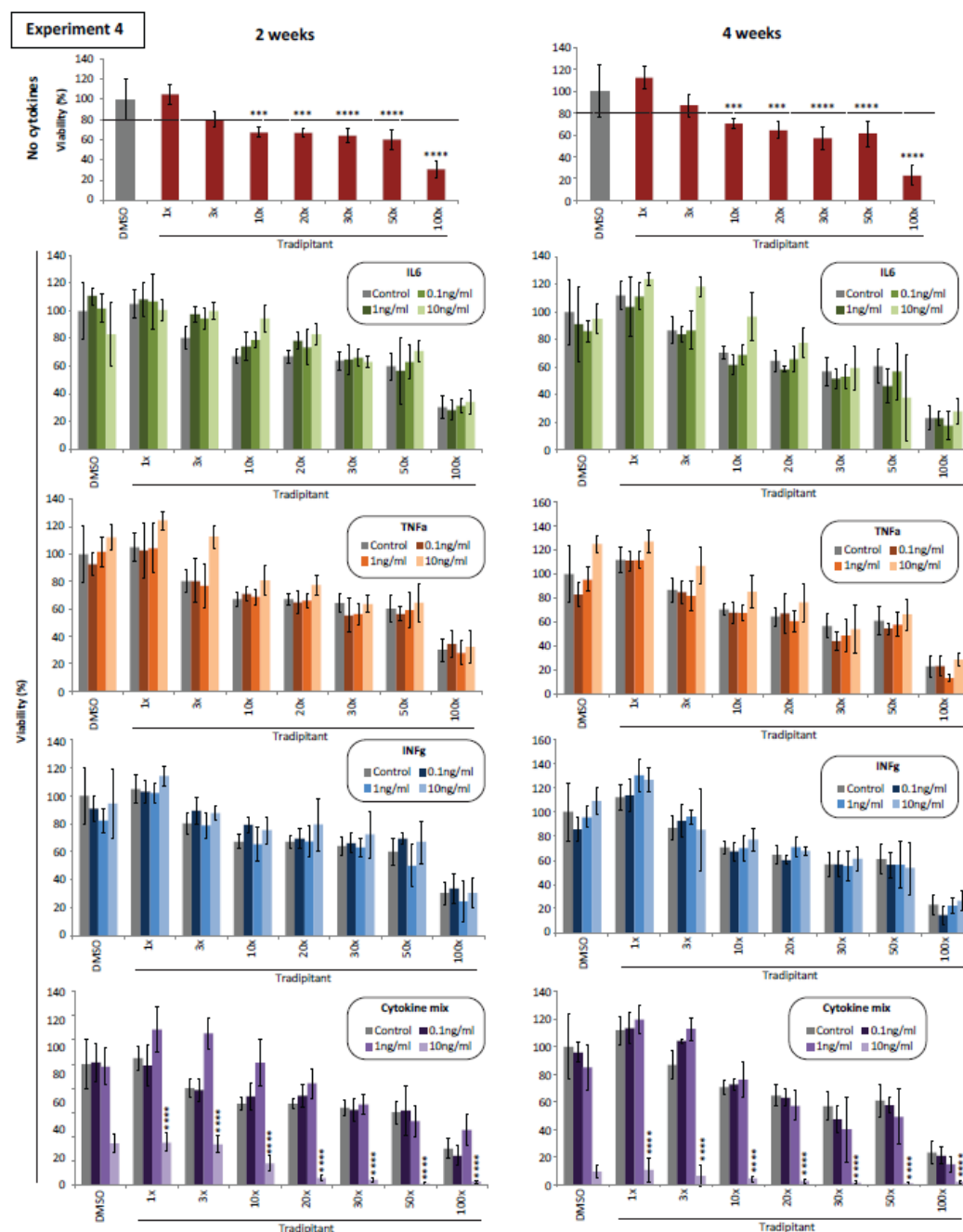
1x, 3x, 10x, 20x, 30x, 50x, and 100x = 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3560, Figure 3).

For Donor 4, biologically significant, dose-dependent hepatotoxicity was observed at tradipitant concentrations $\geq 3.5 \mu\text{g/mL}$ following treatment for both 2 and 4 weeks.

None of the cytokines alone significantly impacted cell viability; however, treatment with the cytokine mixture resulted in decreased cell viability at 10 ng/mL following 2 or 4 weeks of treatment.

The Applicant reported synergistic effects of tradipitant in combination with the cytokine mixture at 10 ng/mL; however, these findings could not be substantiated by the reviewer, especially in light of the strong individual effects of tradipitant and the cytokine mixture. Sporadic instances of synergistic effects of tradipitant and the cytokine mixture on cell viability were identified, but no consistent or concentration-dependent synergy was observed in this donor under the tested conditions.

Figure 11. Effect of Cytokines on the Hepatotoxicity of Tradipitant – Donor 4

Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability using heteroscedastic two-tailed t-tests. For the top row (no cytokines), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (panels in rows 2-5), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and tradipitant concentration. $n = 8$ spheroids per measurement.

IL-6: interleukin 6; IFN γ : interferon gamma; TNF α : tumor necrosis factor alpha.

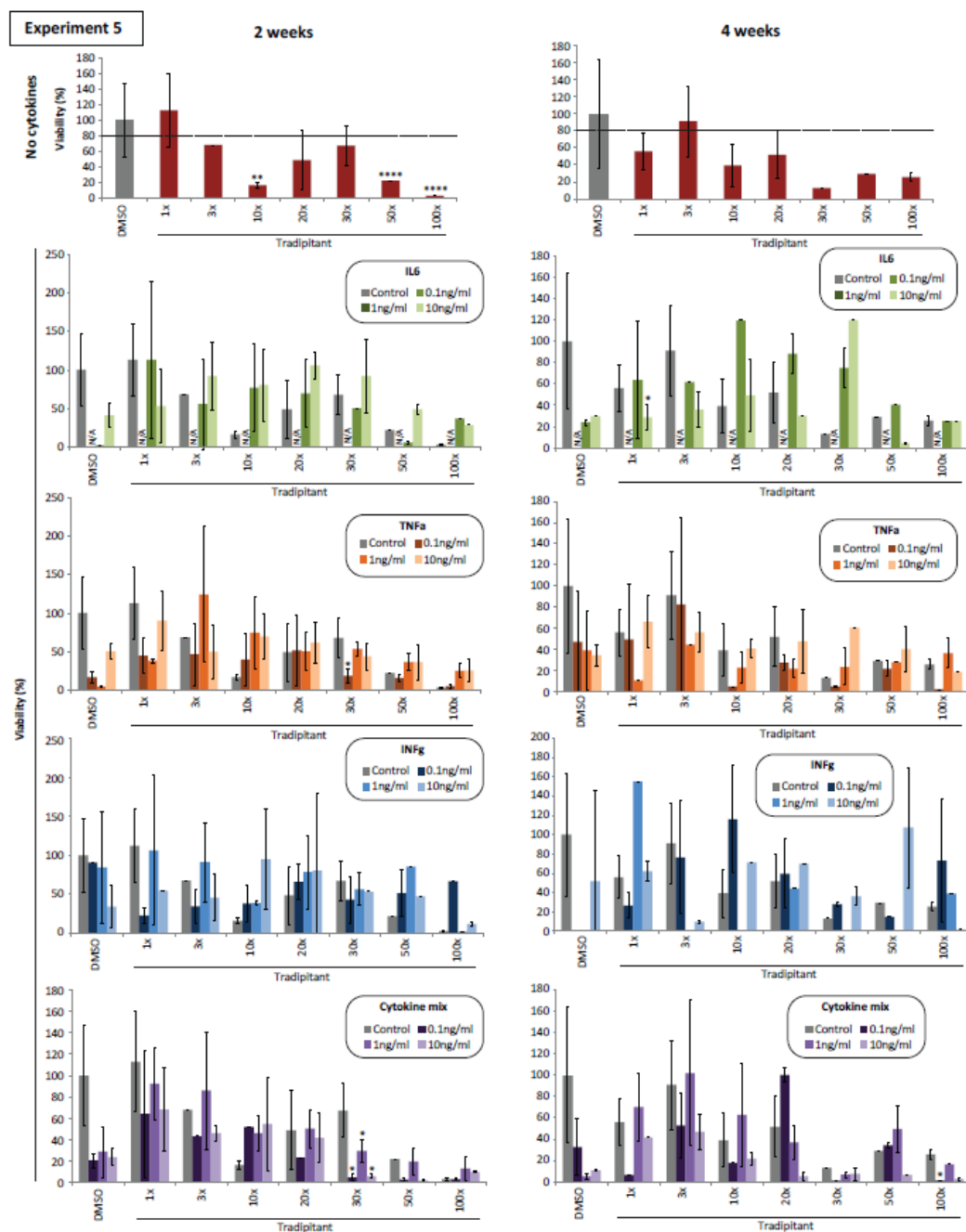
1x, 3x, 10x, 20x, 30x, 50x, and 100x = 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3560, Figure 4).

For Donor 5, biologically significant hepatotoxicity was observed at tradipitant concentrations $\geq 1.05 \mu\text{g/mL}$ following treatment for 2 weeks and at 1x and $\geq 3.5 \mu\text{g/mL}$ for 4 weeks.

Analysis of the effects of cytokines alone was impacted by high variability of the data and technical issues with some experimental conditions; however, the overall trend suggested that each cytokine individually as well as the mixture had a biologically significant effect on cell viability.

No synergistic effects of tradipitant and the cytokine mixture on cell viability were identified in this donor.

Figure 12. Effect of Cytokines on the Hepatotoxicity of Tradipitant – Donor 5

Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability using heteroscedastic two-tailed t-tests. For the top row (no cytokines), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (panels in rows 2-5), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and tradipitant concentration. $n=8$ spheroids per measurement.

IL-6: interleukin 6; IFN γ : interferon gamma; TNF α : tumor necrosis factor alpha.

1x, 3x, 10x, 20x, 30x, 50x, and 100x = 0.35, 1.05, 3.5, 7.0, 10.5, 17.5, and 35 $\mu\text{g/mL}$, respectively.

Figure copied directly from study report (Study HPTOX-3560, Figure 5).

4.3.3 In vitro hepatotoxicity assessment of compounds in (b) (4) 3D spheroid model

[HPTOX-3540](#)

Methods:

As stated in the study report, the objective of this non-GLP study⁴ was to quantify the in vitro hepatotoxic potential of tradipitant and to evaluate its underlying toxicity mechanisms. Tradipitant was evaluated using 3D spheroid cultures of primary human hepatocytes as previously reported by Bell et al.⁵ In each experiment, primary human hepatocytes from a single human donor were seeded into ultra-low attachment plates and cultured for 7 days until spontaneous self-aggregation was observed. Cells were then cultured overnight in serum free medium prior to treatment with tradipitant (Lot # DVVE18001M⁶) at approximately 1, 5, 20, or 50x the Applicant's reported clinical C_{max} of 350 ng/mL (i.e., approximately 0.35, 1.75, 7.0, or 17.5 μ g/mL).

Reviewer note: As stated previously, the concentrations used in this study represent tradipitant exposure at approximately 1.1-, 5.4-, 21-, or 54-fold the clinical C_{max} of 327 ng/mL, respectively, as determined in healthy volunteers following 12 days of dosing at 85 mg BID. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. In fact, a direct comparison of C_{max} and in vitro concentrations is scientifically inappropriate as such an "approach oversimplifies the complex relationship between in vitro and in vivo drug behavior and can lead to inaccurate conclusions."⁷ Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

DMSO was used as the negative control in all experiments. Positive controls for different mechanisms of hepatotoxicity included fialuridine ($1 \times C_{max} = 0.5 \mu$ M), chlorpromazine (0.84μ M), bosentan (7.43μ M), acetaminophen (136μ M), and troglitazone (6.08μ M); however, the mechanisms and expected effects of the various positive controls were not defined. Drug-containing medium was replaced every 48-72 hours for a total of 2 or 4 weeks.

A total of three donors were used in this study. Donors included two males and one female, ranging from 25-28 years of age, of varying ethnicity, negative for hepatitis virus infections and HIV, who died of non-liver-related causes, and were not reported to be on any medication at the time of death. An average of 37 ± 18 spheroids per donor per endpoint were evaluated.

Table 5. Characteristics of Human Hepatocyte Donors in Study HPTOX-3540

	Donor 1	Donor 2	Donor 3
Age	25	27	28
Ethnicity	Hispanic	African American	Caucasian
Gender	Male	Female	Male
BMI	N/A	28.2	N/A
Cause of death	Head Trauma	Anoxia	Head Trauma
HEP-B, HEP-C, HIV	Negative	Negative	Negative
Medications	None reported	None reported	None reported
Social and medical history	Substance abuse (unspecified)	Respiratory disease: vent dependent d/t quadriplegia	None reported

Table copied directly from study report (Study HPTOX-3540, Appendix).

Cell viability was determined via quantification of ATP using a commercial kit following treatment. Treatments were considered hepatotoxic if cell viability was reduced to less than 80% of control levels.⁹

Results:

Clear dose- and time-dependent hepatotoxicity was observed with all five positive control compounds. Hepatotoxic concentrations of bosentan, troglitazone, acetaminophen and chlorpromazine closely resembled the previously reported values.^{9,10,11} In contrast, while fialuridine (noted with # in the figure below) was clearly hepatotoxic, the severity of toxicity was much lower than previously determined, with very similar responses in all three donors. Ultimately, this was determined to be related to a manufacturer error, and fialuridine from a different supplier (noted with * in the figure below) confirmed severe toxicity after 4 weeks of exposure at 1x the C_{max} , in agreement with previous findings.¹²

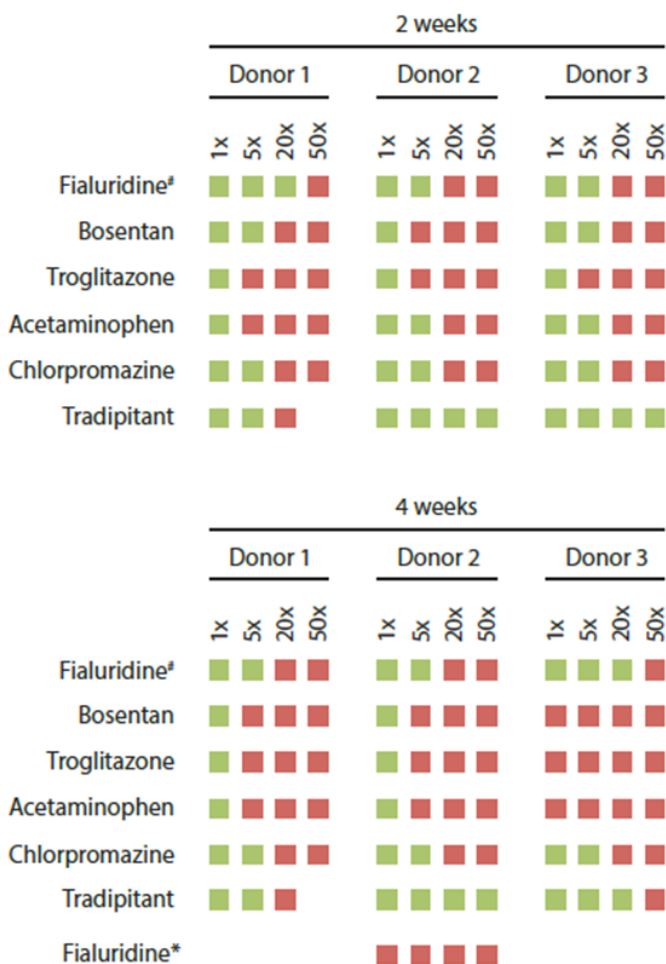
¹⁰ Bell, C. C.; Lauschke, V. M.; Vorrink, S. U.; Palmgren, H.; Duffin, R.; Andersson, T. B.; Ingelman-Sundberg, M. Transcriptional, Functional, and Mechanistic Comparisons of Stem Cell-Derived Hepatocytes, HepaRG Cells, and Three-Dimensional Human Hepatocyte Spheroids as Predictive In Vitro Systems for Drug-Induced Liver Injury. *Drug Metabolism and Disposition* 2017, 45, 419–429.

¹¹ Bell, C. C.; Dankers, A. C. A.; Lauschke, V. M.; Sison-Young, R.; Jenkins, R.; Rowe, C.; Goldring, C. E.; Park, K.; Regan, S. L.; Walker, T.; Schofield, C.; Baze, A.; Foster, A. J.; Williams, D. P.; van de Ven, A. W. M.; Jacobs, F.; Houdt, J. V.; Lähteenmäki, T.; Snoeys, J.; Juhila, S.; Richert, L.; Ingelman-Sundberg, M. Comparison of Hepatic 2D Sandwich Cultures and 3D Spheroids for Long-term Toxicity Applications: A Multicenter Study. *Toxicol. Sci.* 2018, 162, 655–666.

¹² Hendriks, D. F. G.; Hurrell, T.; Riede, J.; van der Horst, M.; Tuovinen, S.; Ingelman-Sundberg, M. Mechanisms of chronic fialuridine hepatotoxicity as revealed in primary human hepatocyte spheroids. *Toxicol. Sci.* 2019.

Toxicity was observed with tradipitant in Donor 1 at 7.0 µg/mL, with viability 54% and 32% that of controls after 2 weeks and 4 weeks, respectively. Tradipitant did not significantly reduce cell viability in Donor 2 under any tested condition. Finally, tradipitant significantly decreased cell viability in Donor 3 after 4 weeks at 17.5 µg/mL, but not under any other tested condition.

Figure 13. Hepatotoxicity of Tradipitant in Primary Human Hepatocyte Spheroids – Individual Heat Maps



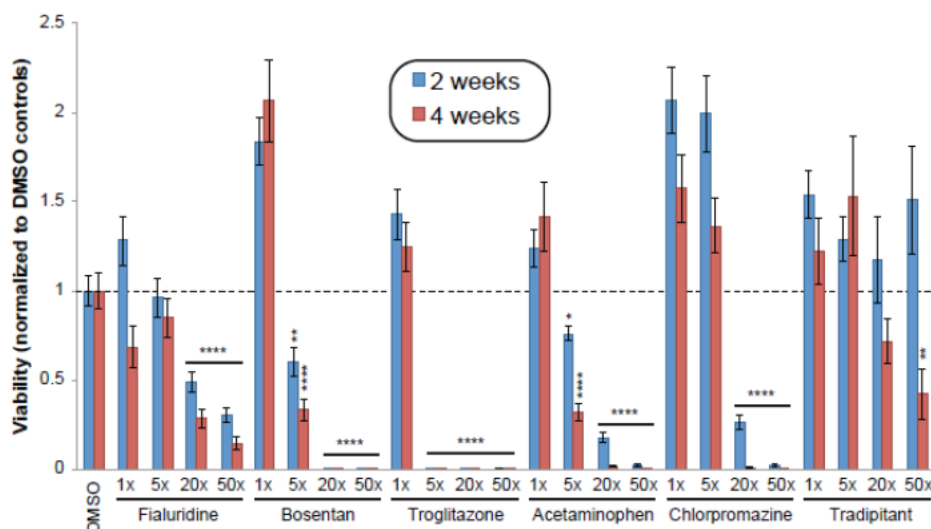
Red boxes indicate that the average hepatocyte viability was decreased to <80% of the respective controls with statistical significance ($p < 0.05$). If these conditions are not met, the evaluation is classified negative (green). The asterisk (*) and the hashtag (#) indicate fialuridine from different commercial suppliers. See text for explanation.

1x, 5x, 20x, and 50x = 0.35, 1.75, 7.0, and 17.5 µg/mL, respectively.

Figure slightly adapted from study report, to remove irrelevant treatments (Study HPTOX-3540, Figure 1).

Combining the results from the three donors tested, tradipitant at 17.5 µg/mL significantly decreased the viability of hepatocyte spheroids after 4 weeks of treatment. No significant effects were observed with 2 weeks of treatment up to 17.5 µg/mL or with 4 weeks of treatment up to 7.0 µg/mL.

Figure 14. Hepatotoxicity of Tradipitant in Primary Human Hepatocyte Spheroids – Summary of All Donors



Viability was evaluated by quantifying ATP levels. Error bars indicate SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ using a heteroscedastic two-tailed t-test compared to DMSO control at the same time point.

Figure slightly adapted from study report, to remove irrelevant treatments (Study HPTOX-3540, Figure 2).

Reviewer note: In this study, treatment with tradipitant only produced biologically significant toxicity at 17.5 $\mu\text{g/mL}$ (occasionally 7.0 $\mu\text{g/mL}$) for 4 weeks. This is a higher threshold than that observed in either Study HPTOX-3550 (7.0 $\mu\text{g/mL}$) or Study HPTOX-3560 (3.5 $\mu\text{g/mL}$). The lower sensitivity to tradipitant may be explained by the generally younger age of the donors used in the present study, although no explanation was provided.

4.3.4 Mechanistic analyses of tradipitant in vitro hepatotoxicity in (b) (4) 3D spheroid model

[HPTOX-3610](#)

Methods:

As stated in the study report, the objectives of this non-GLP study¹³ were 1) to compare the toxicity profiles of tradipitant and its metabolites M2, M3, M4, and M8 with or without co-exposure to cytokines in 3D primary human liver spheroids and 2) to identify the

(b) (4)

molecular signatures of aprepitant and serlopitant exposures in 3D primary human liver spheroids with or without co-exposure to cytokines.

All experiments in this study used 3D spheroid cultures of primary human hepatocytes as previously reported by Bell et al.¹⁴ Briefly, primary human hepatocytes from a single human donor were seeded into ultra-low attachment plates and cultured for at least seven days until spontaneous self-aggregation was observed. Cells were then cultured overnight in serum free medium prior to treatment.

In part one of the study, spheroids were treated with tradipitant at approximately 1, 3, 10, 20, 30, or 100x the Applicant's reported clinical C_{max} of 350 ng/mL (i.e., 0.35, 1.05, 3.5, 7.05, 10.5, or 35 µg/mL). Spheroids were alternatively treated with metabolites M2, M3, M4, or M8 at the same concentrations (although these concentrations are not considered to reflect the corresponding clinical C_{max} values of the individual metabolites). Spheroids were also treated with tradipitant or metabolites in combination with a cytokine cocktail containing TNF α , INF γ , or IL-6 at 1 ng/mL each.

Reviewer note: As stated previously, the concentrations of tradipitant used in this study represent tradipitant exposure at approximately 1.1-, 3.2-, 11-, 21-, 32-, or 107-fold the clinical C_{max} of 327 ng/mL, respectively, as determined in healthy volunteers following 12 days of dosing at 85 mg BID. The concentrations of metabolites M2, M3, and M4 used in this study represent approximately 3.4- to 343-, 3.6- to 358-, and 3.4- to 337-fold, respectively, the individual clinical C_{max} values of the metabolites; a comparison to M8 cannot be made, as no steady state parameters are available for that metabolite. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. In fact, a direct comparison of C_{max} and in vitro concentrations is scientifically inappropriate as such an "approach oversimplifies the complex relationship between in vitro and in vivo drug behavior and can lead to inaccurate conclusions."⁷ Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

DMSO was used as the negative control in all experiments. Drug-containing medium was replaced every 48-72 hours for a total of 14 days.

A total of four donors were used in this study for four individual experimental cultures; the cells from each donor were not pooled. Donors included one male and three females ranging in age from 25-42 years old, of varying ethnicity, who died of non-liver-related causes, and were not reported to be on any medication at the time of death.

¹⁴ Bell, C., Hendriks, D., Moro, S. et al. Characterization of primary human hepatocyte spheroids as a model system for drug-induced liver injury, liver function and disease. Sci Rep 6, 25187 (2016).

Table 6. Characteristics of Human Hepatocyte Donors in Study HPTOX-3610

	Donor 1	Donor 2	Donor 3	Donor 4
Age	25	27	30	42
Ethnicity	Hispanic	African American	Hispanic	Caucasian
Gender	Male	Female	Female	Female
BMI	32.2	28.2	30.8	26.9
Cause of death	Head Trauma	Anoxia	Head trauma	Anoxia
HEP-B, HEP-C, HIV	Negative	Negative	Negative	Negative
Medications	None reported	None reported	None reported	None reported

Table copied directly from study report (Study HPTOX-3610, Table 1).

Cell viability was measured via quantification of ATP using the CellTiter-Glo Luminescent Cell Viability Assay from Promega (Madison, WI, USA; catalog no. G7570/G7571/G7572/G7573). Each condition was evaluated in four independent experiments, with up to eight spheroids per timepoint. A treatment condition was considered hepatotoxic if viability was reduced to < 80% of control levels.¹⁵

In part two of the study, spheroids were treated with aprepitant or serlopitant at 0.6, 2, or 6 µg/mL in the presence or absence of the cytokine cocktail. Aprepitant and serlopitant concentrations were chosen based on a previous study. Total RNA was isolated and stored at -80°C until further processing. See study report for further details on RNA sequencing and data analysis methods. At the time of NDA submission, the results of this analysis were pending and have not been submitted. However, the lack of data from part two of the study is not considered to impact the review of the safety of tradipitant and its metabolites for this application.

Results:

Reviewer note: This study investigated the effects of tradipitant and its metabolites on hepatocyte viability in both the presence and absence of a defined cytokine cocktail. The Applicant did not provide any rationale to explain how the cytokine conditions are relevant to the indication of vomiting induced by motion, and these subjects are generally considered healthy in the absence of the motion stimulus. Thus, this review will focus on the effects of tradipitant and its metabolites alone, in the absence of cytokines. To the extent that results could be interpreted given the lack of raw data and normalization of the cytokine data in the study report, it should be noted that the combined effects of tradipitant or its metabolites and the cytokine cocktail were generally additive or sub-additive, consistent with the findings previously reported in Study HPTOX-3560 (see Section 4.3.2).

¹⁵ Vorrink, S. U.; Zhou, Y.; Ingelman-Sundberg, M.; Lauschke, V. M. Prediction of Drug-Induced Hepatotoxicity Using Long-Term Stable Primary Hepatic 3D Spheroid Cultures in Chemically Defined Conditions. *Toxicological Sciences* 2018, 163, 655–665.

Summary of Findings

Overall, biologically significant decreases in viability (i.e., viability < 80% of control) were observed with tradipitant and all tested metabolites. The concentration(s) at which biologically significant toxicity occurred and the maximum effect were highly donor-dependent.

Reviewer Note: Following two weeks of treatment with tradipitant, biologically significant decreases in cell viability in this study were observed at a notably lower concentration for 2/3 donors (0.350 versus 17.5 µg/mL) and at a higher concentration for the remaining donor (35 versus 7.0 µg/mL) compared to that observed in Study HPTOX-3550. A possible explanation for the increased sensitivity could not be determined, and no explanation was provided.

Treatment with tradipitant resulted in biologically significant decreases in viability in all donors at concentrations as low as 0.35 µg/mL (the lowest concentration tested, approximately 1.1-fold the clinical C_{max} of 327 ng/mL in healthy volunteers following administration at 85 mg BID for 12 days¹⁶). Decreased viability with tradipitant was generally not concentration-dependent. The maximum decrease in viability was observed at 10.5-35 µM and ranged from 50%-90%.

Treatment with M2 resulted in biologically significant decreases in viability in all donors at concentrations as low as 0.35 µg/mL (the lowest concentration tested). Decreased viability with M2 was generally concentration-dependent, though the incremental increases at higher concentrations tended to be small or absent. The maximum decrease in viability was observed at 7.05-10.5 µg/mL and ranged from 35%-90%.

Treatment with M3 resulted in biologically significant decreases in viability in all donors at concentrations as low as 1.05 µg/mL but more commonly at 10.5 or 35 µg/mL. The maximum decrease in viability was observed at 1.05 µg/mL in Donor 3 but at 35 µg/mL in other donors and ranged from 60%-100%.

Treatment with M4 resulted in biologically significant decreases in viability in all donors at concentrations as low as 0.35 µg/mL (the lowest concentration tested). Decreased viability with M2 was generally not concentration-dependent. The maximum decrease in viability was most often observed at 3.5 µg/mL and ranged from 30%-70%.

Treatment with M8 resulted in biologically significant decreases in viability in only two of the four tested donors. In those two donors, decreased viability was observed at concentrations as low as 10.5 and 0.35 µg/mL, respectively. The maximum decrease in viability was observed at 7.05-10.5 µg/mL and ranged from 30%-80%.

¹⁶ Based on data from Study VP-VLY-686-1102. Following 12 days of dosing at 85 mg BID in healthy volunteers, C_{max} = 327 ng/mL. Although the study was inconclusive as to whether steady state was achieved, steady state was achieved within 7 days of daily dosing in healthy male subjects in Study H8R-EW-HJAD. As subjects with vomiting induced by motion are considered otherwise healthy in the absence of a motion stimulus, and in the absence of robust multi-dose PK from Study VP-VLY-686-3403 for this indication, PK from healthy volunteers was deemed the most appropriate for this evaluation.

Table 7. Effects of Tradipitant and Its Major Metabolites on Viability in Human Hepatocyte Spheroids

Donor	Tradipitant		M2		M3		M4		M8	
	LTC (µg/mL)	Max Effect (conc, µg/mL)	LTC (µg/mL)	Max Effect (conc, µg/mL)	LTC (µg/mL)	Max Effect (conc, µg/mL)	LTC (µg/mL)	Max Effect (conc, µg/mL)	LTC (µg/mL)	Max Effect (conc, µg/mL)
1	0.35	50% (35)	0.35	95% (10.5)	10.5	85% (35)	3.5	65% (3.5)	10.5	30% (≥10.5)
2	35	90% (35)	10.5	35% (10.5)	35	90% (35)	3.5	30% (3.5)	none	n/a
3	0.35	85% (10.5)	0.35	95% (10.5)	1.05	100% (1.05)	0.35	70% (0.35)	0.35	80% (7.05)
4	3.5	55% (35)	0.35	50% (7.05)	35	60% (35)	1.05	60% (3.5)	none	n/a

Conc: concentration; LTC: lowest toxic concentration; max effect: maximum decrease in viability compared to control.

A concentration was considered toxic if it produced a biologically significant decrease in viability (i.e., to < 80% of the respective control value).

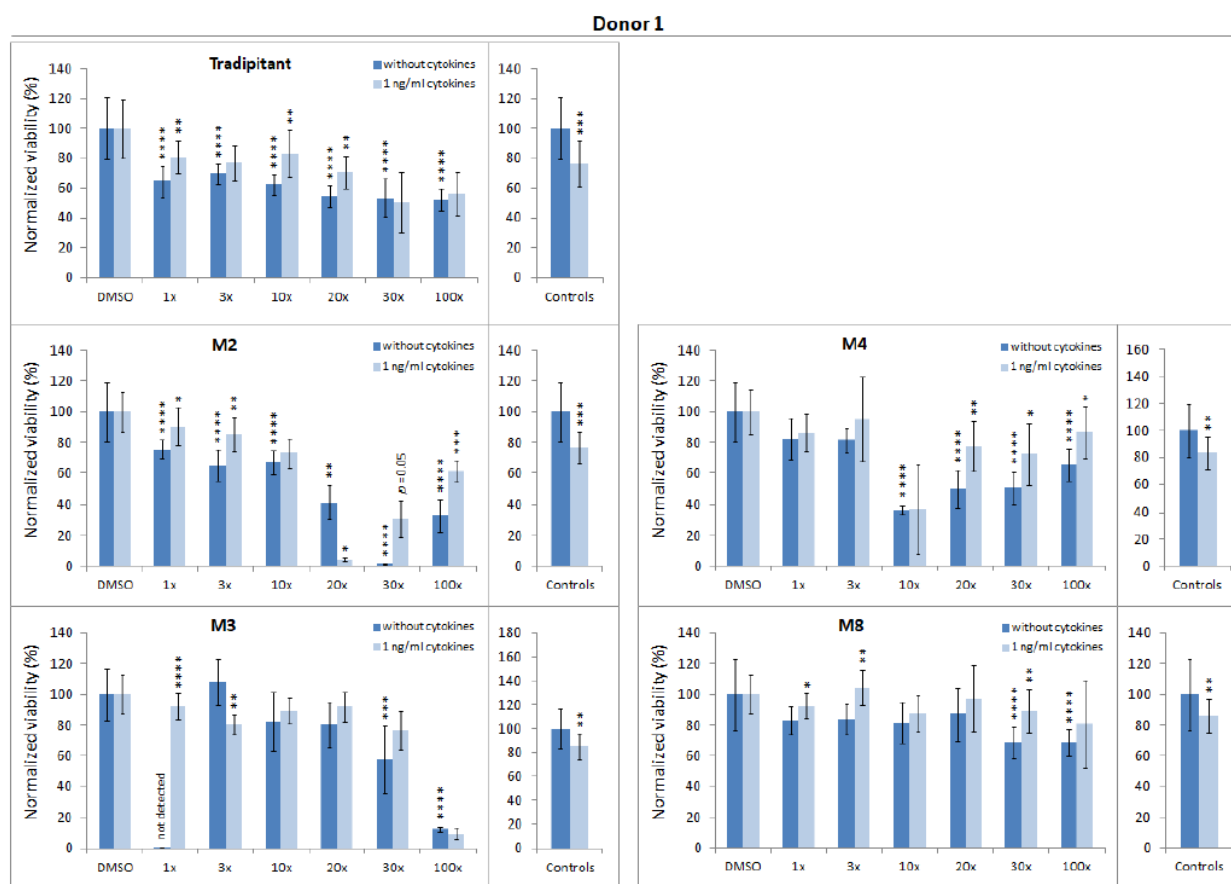
As no raw data were provided in the study report, decreases in viability were manually estimated from graphs to the nearest 5%.

Table created by reviewer, based on data from Study HPTOX-3610, Figures 1-4.

Individual Donor Findings

For Donor 1, biologically significant, concentration-dependent hepatotoxicity was observed with tradipitant at all tested concentrations ($\geq 0.35 \mu\text{g/mL}$) following treatment for two weeks, with a maximum decrease in viability of approximately 50% compared to DMSO control. Treatment with M2 resulted in decreases in viability at all tested concentrations that were generally concentration-dependent, with a maximum decrease in viability of approximately 70%. Toxicity with M3 was observed primarily at 10.5 and $35 \mu\text{g/mL}$, with a maximum decrease of 85%. Toxicity with M4 was observed at $3.5 \mu\text{g/mL}$ and higher, with a maximum decrease in viability of 65%. Finally, toxicity was observed with M8 at 10.5 and $35 \mu\text{g/mL}$, with a maximum decrease in viability of 30%.

Figure 15. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids in the Presence or Absence of Cytokines – Donor 1

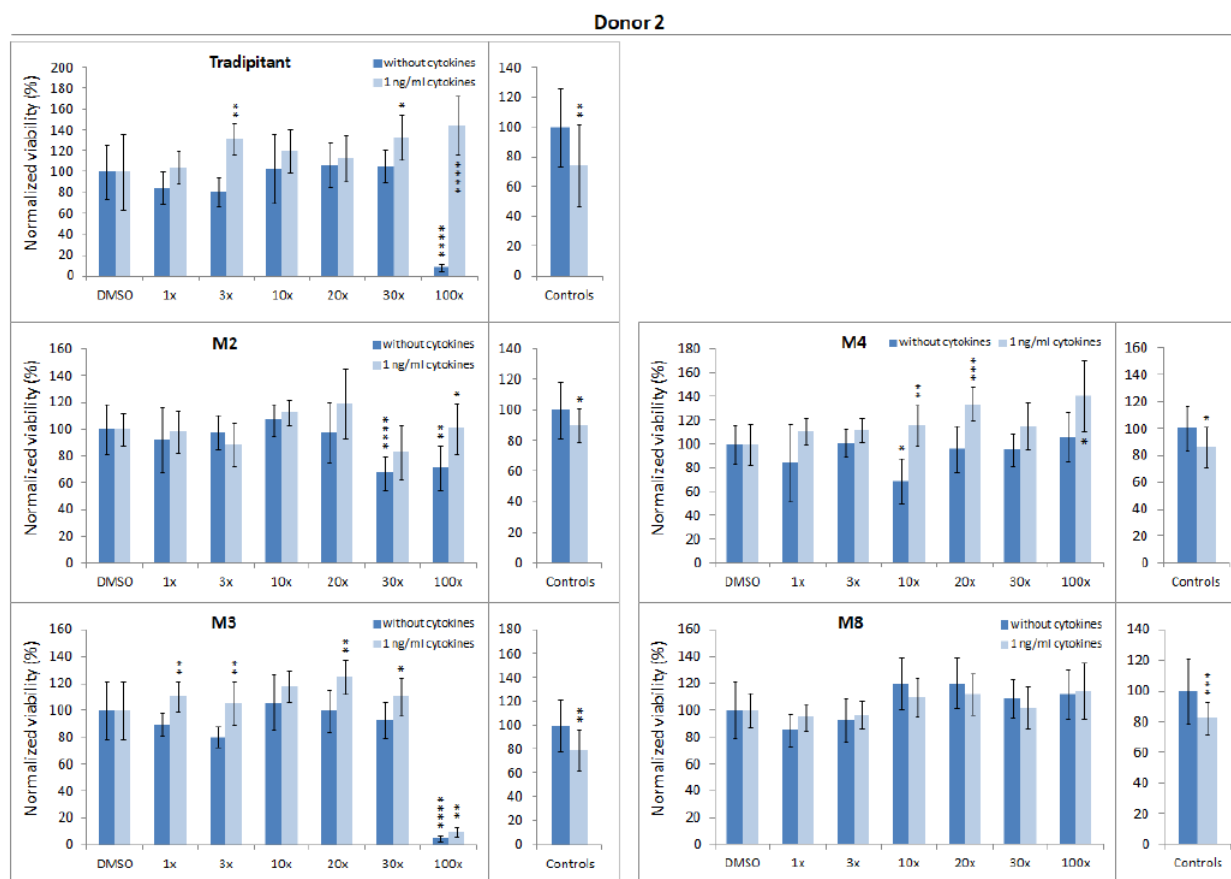


Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability. For the first row (no cytokines, dark blue), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (light blue), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and compound concentration. Control boxes show the effect of the cytokine cocktail compared to the DMSO control on the same plate. $n \leq 8$ spheroids per measurement.

Figure copied directly from study report (Study HPTOX-3610, Figure 1).

For Donor 2, biologically significant hepatotoxicity was observed with tradipitant at 35 $\mu\text{g/mL}$ only, with a decrease in viability of approximately 90% compared to DMSO control. Treatment with M2 resulted in decreases in viability at 10.5 and 35 $\mu\text{g/mL}$, with a maximum decrease in viability of approximately 35%. Toxicity with M3 was observed at 35 $\mu\text{g/mL}$ only, with a decrease in viability of 90%. Toxicity with M4 was observed at 3.5 $\mu\text{g/mL}$ only, with a decrease in viability of 30%. Biologically significant toxicity was not observed with M8 in this Donor at any tested concentration.

Figure 16. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids in the Presence or Absence of Cytokines – Donor 2

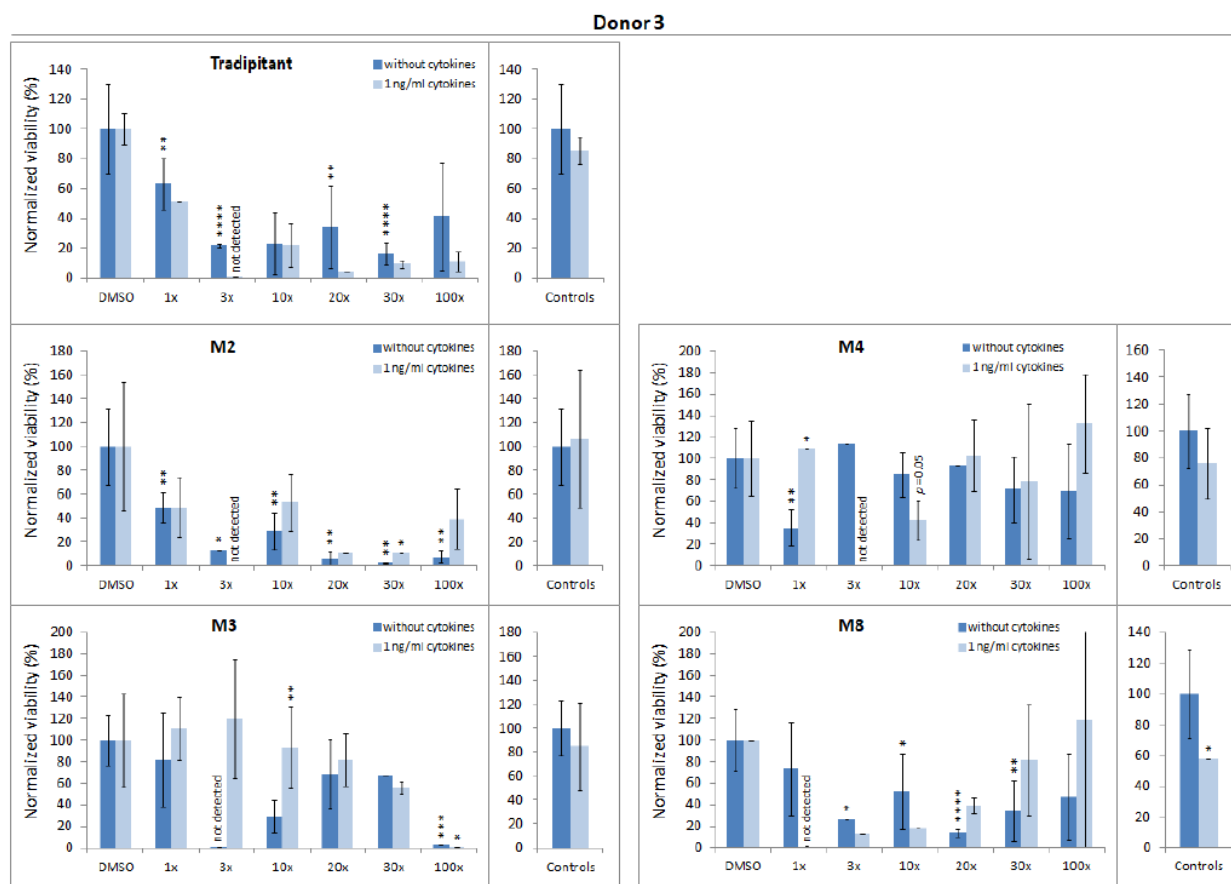


Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability. For the first row (no cytokines, dark blue), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (light blue), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and compound concentration. Control boxes show the effect of the cytokine cocktail compared to the DMSO control on the same plate. $n \leq 8$ spheroids per measurement.
Figure copied directly from study report (Study HPTOX-3610, Figure 2).

For Donor 3, toxicity was generally not concentration-dependent using any compound. Biologically significant toxicity was observed with tradipitant at all tested concentrations ($\geq 0.35 \mu\text{g/mL}$), with a maximum decrease in viability of approximately 85% compared

to DMSO control. Treatment with M2 resulted in decreases in viability at all tested concentrations, with a maximum decrease in viability of approximately 95%. Toxicity with M3 was observed at 1.05 $\mu\text{g/mL}$ and higher, with a maximum decrease in viability of 100%. Toxicity with M4 was inconsistent, with biologically significant effects observed at 0.35 $\mu\text{g/mL}$ and at $\geq 35 \mu\text{g/mL}$ and a maximum decrease in viability of 70%. Finally, toxicity was observed with M8 at all tested concentrations, with a maximum decrease in viability of 80%.

Figure 17. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids in the Presence or Absence of Cytokines – Donor 3

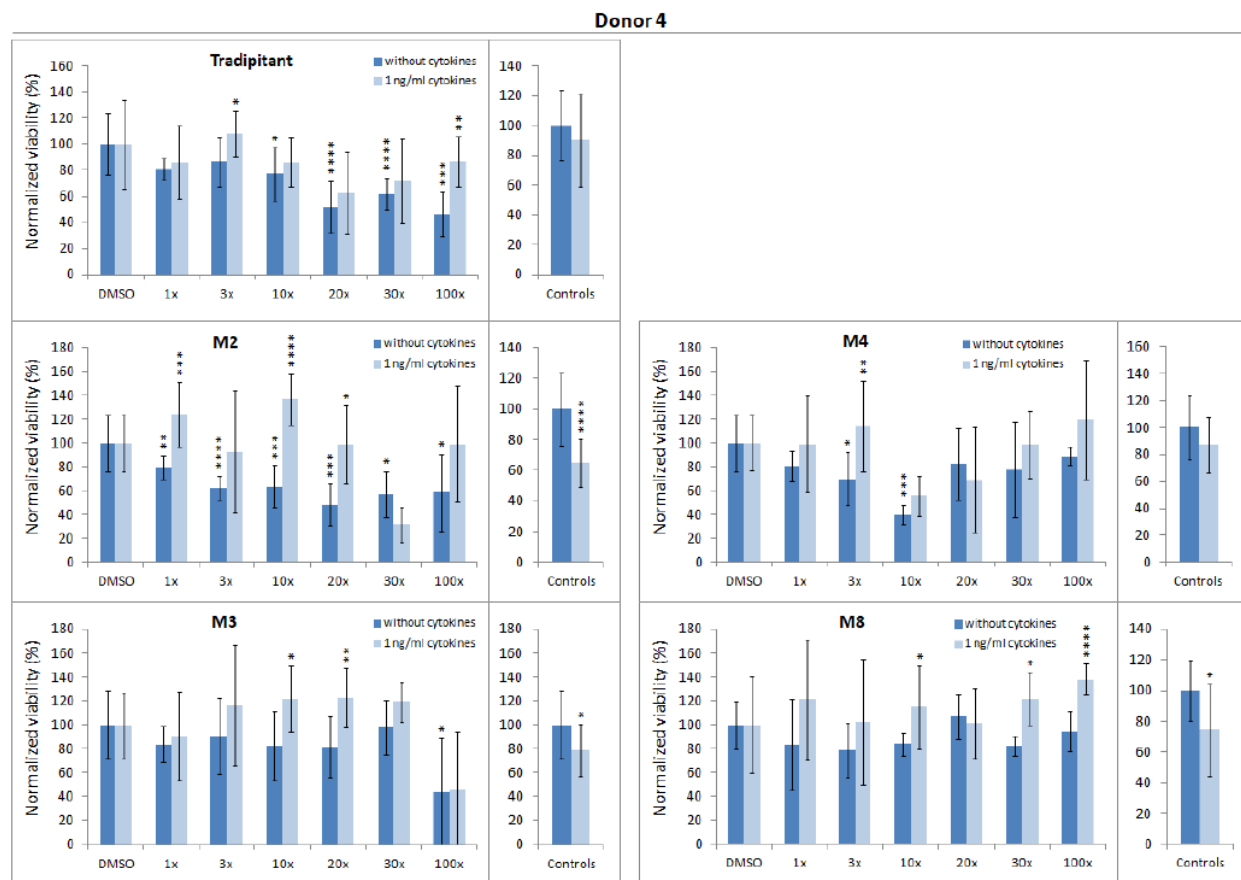


Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability. For the first row (no cytokines, dark blue), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (light blue), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and compound concentration. Control boxes show the effect of the cytokine cocktail compared to the DMSO control on the same plate. $n \leq 8$ spheroids per measurement. Figure copied directly from study report (Study HPTOX-3610, Figure 3).

For Donor 4, biologically significant hepatotoxicity was observed with tradipitant at 3.5 $\mu\text{g/mL}$ and higher, with a maximum decrease in viability of approximately 55% compared to DMSO control. Treatment with M2 resulted in decreases in viability at all tested concentrations, with a maximum decrease in viability of approximately 50%.

Toxicity with M3 was observed at 35 µg/mL only, with a decrease of 60%. Toxicity with M4 was observed at 1.05 and 3.5 µg/mL only, with a maximum decrease in viability of 60%. Biologically significant toxicity was not observed with M8 in this Donor at any tested concentration.

Figure 18. Effects of Tradipitant on Viability of Primary Human Hepatocyte Spheroids in the Presence or Absence of Cytokines – Donor 4



Viability was evaluated by quantifying ATP levels. Error bars indicate SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ for significant reduction in viability. For the first row (no cytokines, dark blue), statistical tests refer to the comparison with the respective DMSO control at the same time point. For cytokine treatments (light blue), statistical tests refer to the comparison with the respective no-cytokine control at the same time point and compound concentration. Control boxes show the effect of the cytokine cocktail compared to the DMSO control on the same plate. $n \leq 8$ spheroids per measurement.

Figure copied directly from study report (Study HPTOX-3610, Figure 4).

4.3.5 Evaluation of Toxicity of Tradipitant in the Human Co-Culture Liver-Chip

[SRV-0028](#)

Methods:

As stated in the submitted report, this non-GLP study was intended to “validate the pre-clinical toxicology safety profiles of tradipitant and its metabolites in the human Liver-chip.” and “to compare the toxicity profile of tradipitant to other known liver toxicants that have been approved for clinical use.” To do so, tradipitant was evaluated using

(b) (4) Human Co-Culture Liver-Chip, which consists of primary human hepatocytes and liver sinusoid endothelial cells (LSECs). Organ-chips were composed of polydimethylsiloxane (PDMS). Primary human hepatocytes were cultured in the top channel on an extracellular matrix (ECM)-coated membrane with an overlay of matrix to form an “ECM sandwich.” Human LSECs were seeded on the opposite side of the same membrane in the bottom channel. After 3 days in static culture, the chips were connected to the organ-chip culture instrument and cultured under constant flow until the start of compound addition, in accordance with (b) (4) Liver-Chip Co-Culture Protocol. Starting at 72 hours after connection, all cells were incubated with the appropriate compound solution under flow at 150 $\mu\text{L/h}$ for 2 days, followed by 30 $\mu\text{L/h}$ for the remainder of the study (see Results for more information on flow rate).

Chips were continuously treated for up to 168 hours (7 days) with tradipitant (Lot # RS-IN-VDDE17022⁶) at 1.3 μM (772.4 ng/mL), 7.6 μM (4,480 ng/mL), or 26.3 μM (15,448 ng/mL). According to the Applicant, these concentrations are equivalent to approximately 3x, 20x, and 68x the C_{max} of 85 mg tradipitant administered twice daily (BID) in humans at steady state, respectively, as determined in clinical study VP-VLY-686-1102.

Reviewer note: In the provided rationale for the selected tradipitant concentrations, the Applicant did not explicitly state the referenced clinical C_{max} . Based on the numbers provided, the value used was approximately 230 ng/mL, although it was inconsistent between the three concentrations/ C_{max} multiples provided (calculated values of 257, 224, and 227 ng/mL, respectively), potentially due to rounding and/or lack of significant digits. As stated previously, a clinical C_{max} of 327 ng/mL was determined in healthy volunteers following 12 days of dosing at 85 mg BID. Based on this value, the concentrations used in this study represent tradipitant exposure at approximately 2.4-, 14-, or 47-fold the clinical C_{max} in the context of the current indication. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. In fact, a direct comparison of C_{max} and in vitro concentrations is scientifically inappropriate as such an “approach oversimplifies the complex relationship between in vitro and in vivo drug behavior and can lead to inaccurate conclusions.”⁷ Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

Metabolite M2 was tested at 0.12 and 2.43 μ M, M3 at 0.11 and 2.29 μ M, M4 at 0.12 and 2.48 μ M, and M8 at 0.05 and 0.90 μ M; rationale for these concentrations was not provided. Positive controls for different mechanisms of hepatotoxicity included acetaminophen (10 mM), fialuridine (30 μ M), benzbromarone (100 μ M), and bosentan (30 μ M). Rationale for the selected positive controls or their expected effects in this system were not provided. DMSO was used as the vehicle control in all experiments.

A total of three donors were used in this study. Donors included two males and one female, ranging from 26-77 years of age, who did not smoke or drink alcohol, and who died of non-liver-related or unknown causes. Generally, six chips were used for each vehicle control condition, while four to five chips were used for each positive control, tradipitant, or metabolite condition.

Table 8. Characteristics of Human Hepatocyte Donors in Study SRV-0028

Donor	Patient Background
Hepatocyte Donor 1: HU 8305	Male, 53, No tobacco, alcohol, or drug usage, died from anoxia
Hepatocyte Donor 2: HU 8350	Male, 26, No tobacco or alcohol usage, but has a history of heroine use, died from anoxia due to drug intoxication
Hepatocyte Donor 3: HU 2005	Female, 77, No tobacco or alcohol usage, no drug history, cause of death unknown

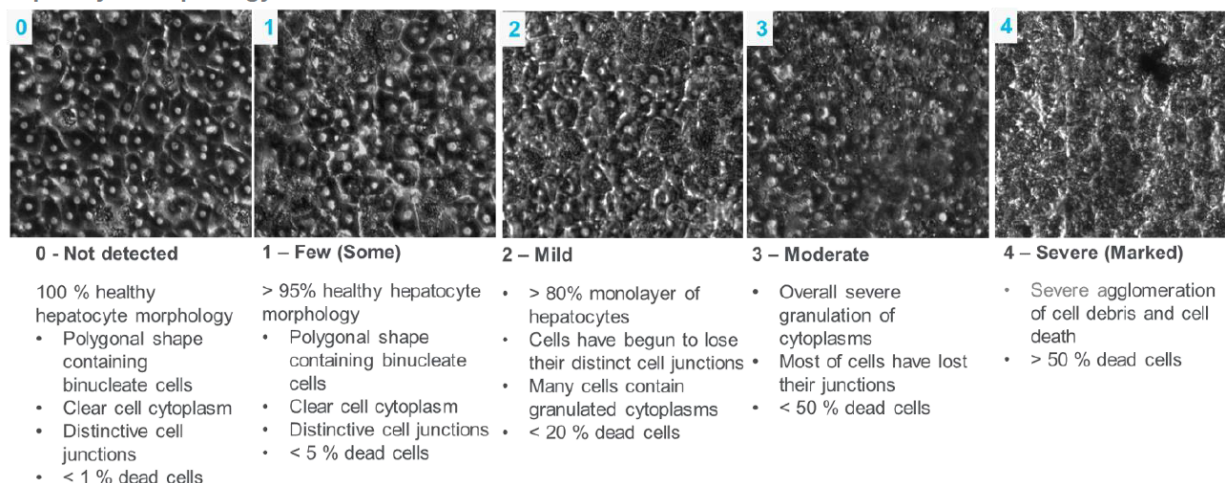
Table copied directly from study report (Study SRV-0028, Table 3).

Tradipitant and its metabolites were measured by LCMS. Evaluated endpoints included morphology, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), ROS generation, caspase-cleaved cytokeratin 18 (CCK-18) expression, and miR-122 expression. Albumin, ALT, AST, ROS, and CCK-18 were measured via commercial ELISA kits (with adjustment for cell number and dilution). miR-122 expression was measured by RT-qPCR. Finally, hepatocytes were stained with AdipoRed to qualitatively evaluate intracellular lipid droplets, while both hepatocytes and LSCECs were stained with CellROX to qualitatively evaluate ROS/oxidative stress.

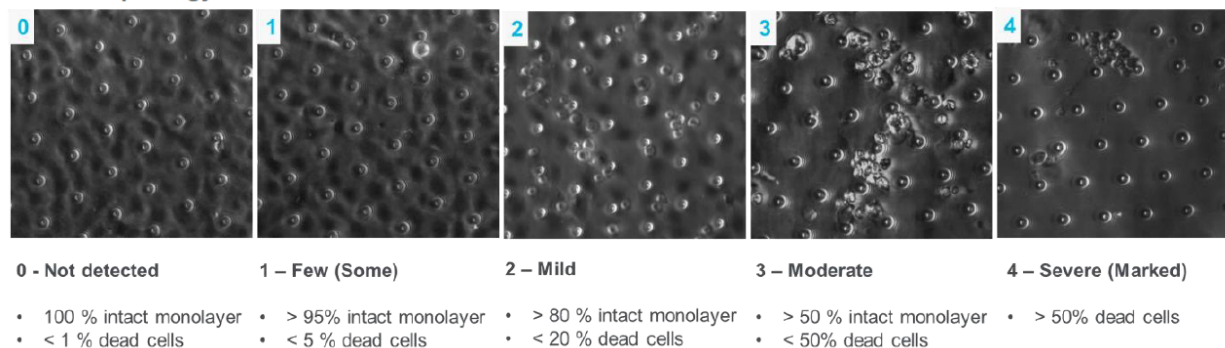
For morphology analyses, four images were obtained per chip per timepoint. Images were independently analyzed by two individuals, one of whom was blinded to the study. Morphology was scored qualitatively according to the classification below.

Figure 19. Hepatocyte and LSEC Morphology Classification Systems

Hepatocyte Morphology



LSEC Morphology



LSEC: Liver sinusoid endothelial cells.

Figures copied directly from study report (Study SRV-0028, pages 25-26).

Results:

During initial test runs, it was determined that 7.62 μM tradipitant applied at a flow rate of 30 $\mu\text{L/h}$ was highly absorbed in the chip itself, resulting in a significant decrease in exposure to hepatocytes (approaching zero) and LSECs (as low as 0.5 μM). Increasing the fluidic flow rate to 150 $\mu\text{L/h}$ improved the uniform distribution of tradipitant and increased the likelihood that cells would be exposed to the drug (range 1.063-6.384 μM for hepatocytes and 1.182-6.195 μM for LSECs). Based on these results, the flow rate was adjusted to 150 $\mu\text{L/h}$ during the treatment phase of the experiment, and an additional concentration of tradipitant (26.28 μM) was included. Additionally flow optimization was not reported for the metabolites.

Morphology

Summary of Findings

Reviewer note: Representative images for each donor can be viewed in the study report. All analyses are qualitative, and the descriptions below are based on the representative images and heat map summaries provided.

Overall, positive controls induced severe time- and dose-dependent toxicity in both hepatocytes and LSECs. At 26.28 μ M, the highest tested concentration, tradipitant induced mild toxicity in hepatocytes from Donors 2 and 3 and moderate toxicity in hepatocytes from Donor 1. Tradipitant did not induce significant toxicity in LSECs at any tested concentration. Sporadic findings of minimal to mild toxicity were observed in hepatocytes and LSECs with metabolites M2, M3, M4, and/or M8 (generally only at the high concentration of each) following 168 hours of treatment.

Figure 20. Heat Map of Morphological Scores – Donor 1

TimePoint		Top Channel			Bottom Channel		
		24 Hour	72 Hour	168 Hour	24 Hour	72 Hour	168 Hour
Vehicle Control	N/A	0	0	0	0	0	0
Acetaminophen	10 mM	3	4	4	0	2	4
Fialuridine	30 μ M	2	3	4	0	1	1
Benzbromarone	100 μ M	2	3	4	3	3	4
Bosentan	30 μ M	3	4	4	0	0	1
Tradipitant	1.31 μ M	0	0	1	0	0	0
	7.62 μ M	0	1	1	0	0	0
	26.28 μ M	0	2	3	0	0	0
M2	0.12 μ M	0	0	0	0	0	0
	2.43 μ M	0	0	0	0	0	1
M3	0.11 μ M	0	0	0	0	0	0
	2.29 μ M	0	1	2	0	1	1
M4	0.12 μ M	0	0	0	0	1	0
	2.48 μ M	0	0	0	0	1	0
M8	0.05 μ M	0	0	0	0	1	1
	0.90 μ M	0	2	2	0	2	2

Healthy	0	1	2	3	4	Damage
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Top channel: hepatocytes; bottom channel: liver sinusoid endothelial cells.

Figure copied directly from study report (Study SRV-0028, page 76)

Figure 21. Heat Map of Morphological Scores – Donor 2

TimePoint		Top Channel				Bottom Channel			
		6 Hour	24 Hour	72 Hour	168 Hour	6 Hour	24 Hour	72 Hour	168 Hour
Vehicle Control	N/A	0	0	0	0	0	0	0	0
Acetaminophen	10 mM	0	1	3	3	0	1	4	4
Fialuridine	30 μ M	0	0	0	1	0	0	0	1
Benzbromarone	100 μ M	1	3	4	4	2	3	4	4
Bosentan	30 μ M	0	0	2	3	0	0	1	3
Tradipitant	1.31 μ M	0	0	0	1	0	0	0	0
	7.62 μ M	0	0	1	1	0	0	0	0
	26.28 μ M	0	0	2	2	0	0	0	0
M2	0.12 μ M	0	0	0	0	0	0	0	0
	2.43 μ M	0	0	0	2	0	0	0	0
M3	0.11 μ M	0	0	0	0	0	0	0	0
	2.29 μ M	0	0	0	0	0	0	0	1
M4	0.12 μ M	0	0	0	0	0	0	0	0
	2.48 μ M	0	0	0	0	0	0	0	0
M8	0.05 μ M	0	0	0	2	0	0	0	0
	0.90 μ M	0	0	0	2	0	0	0	0

Healthy	0	1	2	3	4	Damage
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Top channel: hepatocytes; bottom channel: liver sinusoid endothelial cells.

Figure copied directly from study report (Study SRV-0028, page 77)

Figure 22. Heat Map of Morphological Scores – Donor 3

TimePoint		Top Channel				Bottom Channel			
		6 Hour	24 Hour	72 Hour	168 Hour	6 Hour	24 Hour	72 Hour	168 Hour
Vehicle Control	N/A	0	0	0	0	0	0	0	0
Acetaminophen	10 mM	0	1	2	3	0	1	2.5	3
Fialuridine	30 μ M	0	0	1.5	2	0	0	0.5	0.5
Benzbromarone	100 μ M	0	2	3	4	0	2	2.5	4
Bosentan	30 μ M	0	1.5	2.5	3	0	0.5	0.5	3
Tradipitant	1.31 μ M	0	0	0	0	0	0	0	0
	7.62 μ M	0	0	0.5	0	0	0	0	0
	26.28 μ M	0	0.5	1	1	0	0	0	0.5
M2	0.12 μ M	0	0	0	0	0	0	0	0
	2.43 μ M	0	0	0	1	0	0	0	0
M3	0.11 μ M	0	0	0	0	0	0	0	0
	2.29 μ M	0	0	0	0	0	0	0	0
M4	0.12 μ M	0	0	0	0	0	0	0	0
	2.48 μ M	0	0	0	0	0	0	0	0
M8	0.05 μ M	0	0	0	0	0	0	0	0
	0.90 μ M	0	0	0	1	0	0	0	0

Healthy	0	1	2	3	4	Damage
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Top channel: hepatocytes; bottom channel: liver sinusoid endothelial cells.

Figure copied directly from study report (Study SRV-0028, page 77)

Pre-Treatment

Prior to treatment, all images from all donors demonstrated healthy hepatocytes and LSECs, with morphology scores of 0.

6 Hours

Only Donors 2 and 3 were evaluated for morphology at the 6-hour timepoint. Hepatocytes and LSECs treated with 100 μ M benzbromarone both demonstrated mild toxicity ($\approx$ 20% dead cells with cells beginning to lose their distinct tight junctions and granulation of the cytoplasm). No toxicity was observed in Donor 2 with the remaining controls or in Donor 3 with any positive control after 6 hours.

Hepatocytes and LSECs from both Donors 2 and 3 demonstrated normal, healthy morphology at all tested concentrations of tradipitant and its metabolites following 6 hours of treatment.

24 Hours

Morphology was evaluated for all donors at the 24-hour timepoint. Mild to moderate hepatocyte toxicity was induced by 10 mM acetaminophen in all donors, mild toxicity was induced by 30 μ M fialuridine in Donor 1 only, and mild hepatocyte toxicity was induced by 30 μ M bosentan in Donors 1 and 3 when compared to the vehicle control at 24 hours. Treatment with acetaminophen resulted in overall severe granulation of cytoplasm, loss of junctions in most cells, and dead cells ($<$ 50%). Fialuridine treatment did not induce significant cell death in hepatocytes, but cells had begun to lose their distinct cell junctions, and many cells contained granulated cytoplasm. With benzbromarone, mild to moderate toxicity was observed in hepatocytes and moderate cell death was observed in LSECs compared to the vehicle control group in all donors at 24 hours.

No morphological changes were observed in hepatocytes or LSECs treated with tradipitant or its metabolites at any concentration in all donors after 24 hours.

72 Hours

Morphology was evaluated for all donors at the 72-hour timepoint. Hepatocyte toxicity was observed in at least one donor with all positive controls: moderate to severe toxicity in all donors with acetaminophen, severe toxicity in Donor 1 only with fialuridine, mild to moderate toxicity in all donors with bosentan, and severe toxicity in all donors with benzbromarone compared to the corresponding vehicle control at 72 hours. Mild to severe toxicity was observed in LSECs from all donors treated with acetaminophen, mild toxicity was observed in LSECs from Donor 1 only with fialuridine, and moderate to severe toxicity was observed in LSECs from all donors treated with benzbromarone. No significant toxicity was observed in LSECs treated with bosentan for 72 hours.

A concentration-dependent increase in hepatotoxicity, including observations of vesicles akin to steatosis, was observed with tradipitant in all donors compared to vehicle controls following 72 hours of treatment. No significant morphological changes were

observed in LSECs treated with tradipitant, nor was toxicity observed in either hepatocytes or LSECs treated with metabolites at this timepoint.

168 Hours

Following 168 hours of treatment, acetaminophen induced moderate to severe hepatotoxicity in all donors, fialuridine induced mild (Donors 2 and 3) or severe (Donor 1) toxicity, benzbromarone induced severe toxicity in all donors, and bosentan induced moderate toxicity in all donors. In LSECs, acetaminophen induced severe toxicity in Donors 1 and 2, while bosentan induced moderate toxicity observed in all treated donors at this timepoint. No significant effects were observed on LSECs treated with fialuridine or benzbromarone.

Low to moderate toxicity was observed in hepatocytes from all donors treated with tradipitant at 26.28 μ M for 168 hours, as indicated by altered hepatocyte morphology when compared to the vehicle control. Overall severe granulation of cytoplasm was observed, most of the cells had lost their tight junctions, and < 50% cells appeared dead. No significant morphological changes were observed in hepatocytes treated with tradipitant at lower concentrations or in LSECs treated with any concentration of tradipitant at this timepoint.

In hepatocytes, mild toxicity ($\leq$ 20% dead cells) was observed with M2 at the high concentration in Donor 2 only. Minimal toxicity was observed with M3 at the high concentration in Donor 1 only. No significant toxicity was observed in any donor with M4 treatment. Mild toxicity was observed with M8 at both the low and high concentrations in Donors 2 and 3 only.

In LSECs, minimal toxicity was observed in Donor 1 only with the high concentrations of M2, M3, and M4. No significant toxicity was observed in LSECs from Donor 1 with M8 or in Donors 2 or 3 with any metabolite at either the low or high concentrations at the 168-hour timepoint.

Immunofluorescence Imaging

AdipoRed staining (intracellular lipid accumulation, hepatocytes only) was conducted in all donors, while CellROX staining (ROS accumulation, hepatocytes and LSECs) was conducted in Donors 2 and 3 only. Assessment of immunofluorescent staining of the hepatocytes from each donor was qualitative only, with representative images provided. Significant donor-to-donor variations in the lipid accumulation were observed.

Hepatocytes from Donor 1 showed increased lipid accumulation with all positive controls compared to vehicle. No significant lipid accumulation or changes in ROS activity were observed in cells from Donors 2 and 3, although these findings may have been confounded by cell death/loss due to treatment and/or processing in these donors.

A concentration-dependent accumulation of lipids was observed in hepatocytes from Donor 1 treated with tradipitant compared to vehicle controls. In Donor 2, no significant lipid accumulation was observed in hepatocytes or LSECs treated with tradipitant, but a

slight increase in ROS activity was observed in treated compared to control cells. In Donor 3, no significant lipid accumulation was observed in hepatocytes or LSECs treated with tradipitant; ROS staining in this donor was minimal under all treatment conditions.

Lipid accumulation was observed in hepatocytes from Donor 1 with both low and high concentrations of M2, M3, and M4, and low concentrations of M8 compared to vehicle controls. In hepatocytes from Donors 2 and 3, no notable lipid accumulation or changes in ROS activity were observed. No significant effects of the metabolites were observed in LSECs from any donor.

Biomarker Analysis

Summary of Findings

The Applicant measured albumin, AST, ALT, ROS generation, CCK-18 protein expression, and miRNA-122 expression in the top channel (hepatocyte) effluent following 6, 24, 72, and/or 168 hours of treatment. Some factors were also assessed in cell lysate samples.

- No clear effects of tradipitant or its metabolites were observed on albumin levels.
- No biologically significant effect of tradipitant was observed on AST levels; however, metabolites M2, M3, M4, and/or M8 had effects on AST that were potentially biologically significant, although there was high variability between donors and the general effects were a fraction of those observed with the positive control, benzbromarone.
- No significant effect of tradipitant was observed on ALT levels; however, metabolites M2, M3, M4, and/or M8 had effects on ALT that were potentially biologically significant, with effects approximately 20-50% that of the positive control, benzbromarone, and similar to that of acetaminophen and bosentan.
- The effects of tradipitant and its metabolites on ROS generation and CCK-18 expression were inconclusive due to a lack of meaningful differences between the positive and vehicle controls.
- Although increases in miRNA-122 expression were observed with tradipitant and/or its metabolites, with effects as high as 50-75% of the positive control, acetaminophen, the biological significance of these changes was not established.

Albumin Levels

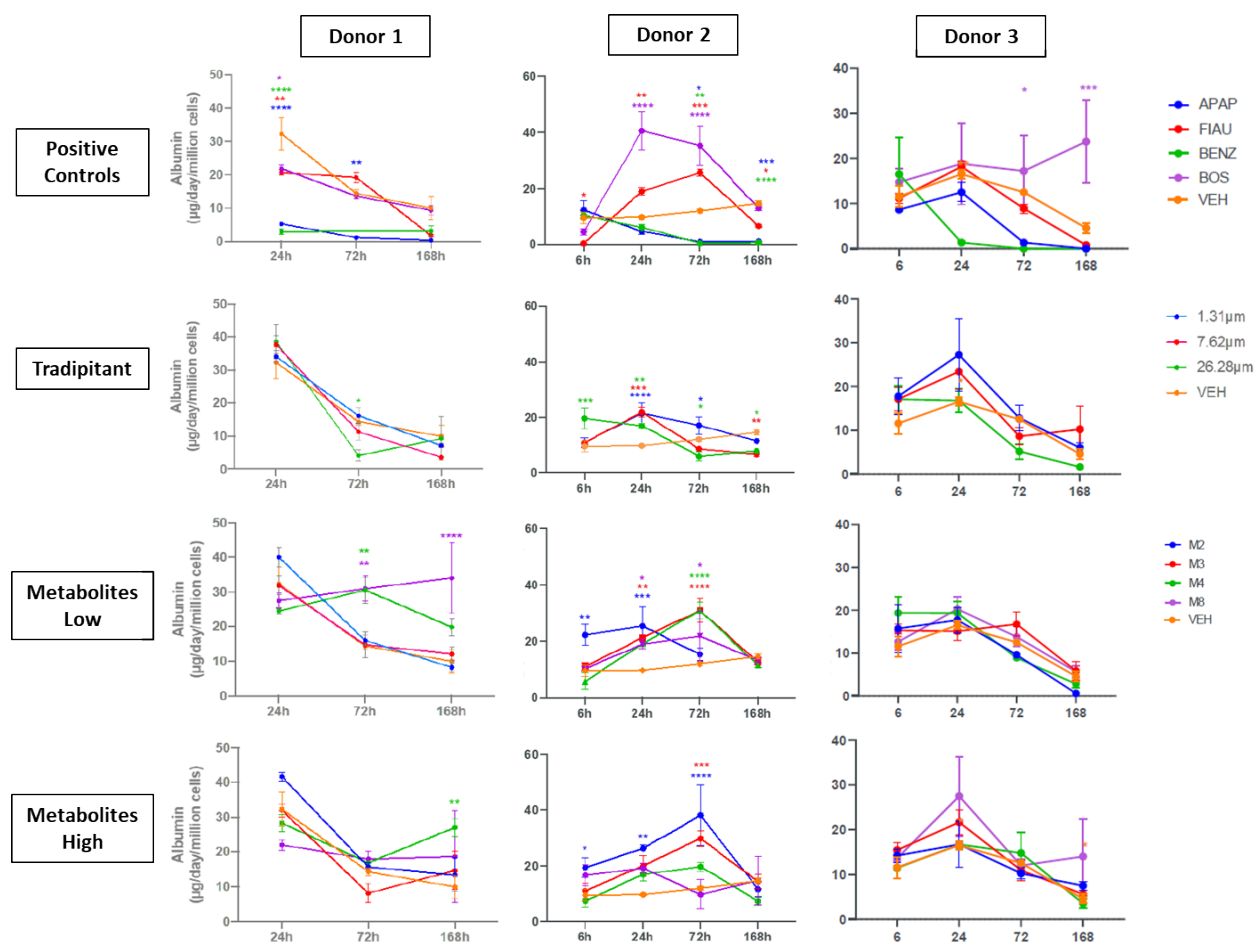
Albumin secretion was measured from the top channel (hepatocytes) effluent at 24, 72, and 168 hours for all donors. An additional timepoint of 6 hours was included for Donors 2 and 3. The Applicant interpreted a decrease in albumin secretion (compared to vehicle or over time) to indicate a decline in the health of hepatocytes, while an increase was considered to indicate an improvement in hepatocyte health.

The vehicle control for Donors 1 and 2 demonstrated a decrease in albumin levels at later timepoints, suggesting an overall decline in hepatocyte health over time.

Treatment with positive control compounds acetaminophen and benzbromarone consistently resulted in decreased albumin secretion in all three donors compared to vehicle, although the magnitude and timing of the difference was variable.

While some differences were noted between tradipitant and vehicle control groups, no clear negative effect of tradipitant or its metabolites was noted on albumin secretion. Effects were generally minimal, with no concentration-dependence, and were potentially impacted by declining hepatocyte health.

Figure 23. Albumin Release Following Treatment with Positive Controls, Tradipitant, or Metabolites



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ by 2-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint.

APAP: acetaminophen; BENZ: benzbromarone; BOS: bosentan; FIAU: fialuridine; VEH: vehicle.

Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 93-95).

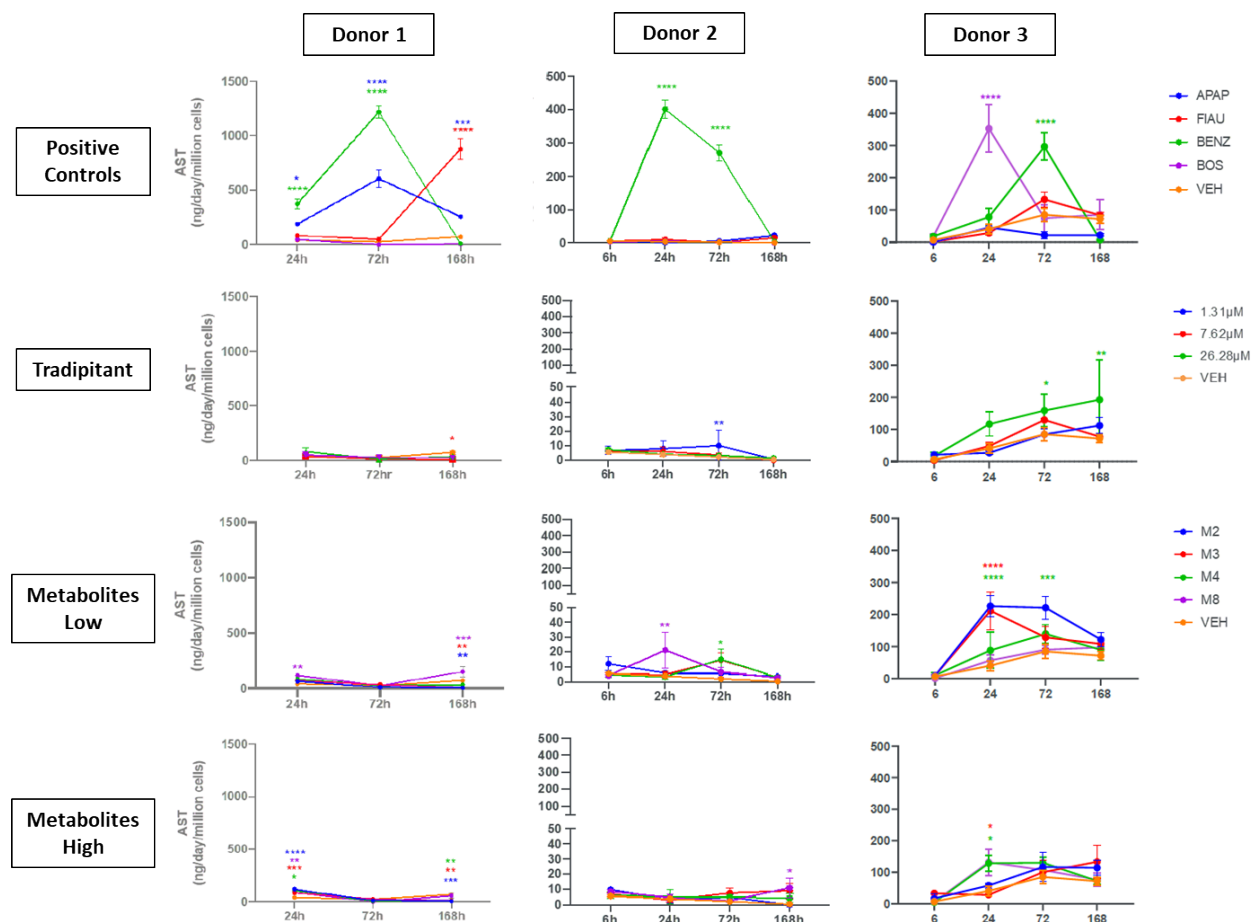
AST Levels

AST levels were measured from top channel effluent at 24 hours, 72 hours, and 168 hours of treatment for all donors, and an additional 6 hours timepoint was added for Donors 2 and 3.

Increased AST was consistently observed with benzbromarone for all donors within 72 hours. Increased AST was also observed in Donor 1 with acetaminophen (24 and 72 hours) and fialuridine (168 hours) as well as with bosentan in Donor 3 (24 hours) compared to vehicle controls.

No consistent effect of tradipitant on AST was noted. In Donor 3 only, increased AST was observed with tradipitant at 26.28 μ M by 24 hours, with levels at 168 hours reaching approximately 2-fold that of vehicle. Notable changes were not observed with lower concentrations of tradipitant in Donor 3 or at any concentration in Donors 1 and 2.

Similarly, notable changes in AST levels with tradipitant metabolites were only observed in Donor 3. Treatment with the low concentration of metabolite M2 or M3 resulted in increased AST in Donor 3 and 24 and 72 hours (up to 5-fold or more that of the vehicle control), with differences mostly resolving by 168 hours. Notable changes were not observed with lower concentrations of metabolites M2 and M3 or any concentration of M4 or M8 in Donor 3, and no effects of the metabolites were observed in Donors 1 and 2.

Figure 24. AST Levels Following Treatment with Positive Controls, Tradipitant, or Metabolites

*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 by 2-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint.

APAP: acetaminophen; AST: aspartate aminotransferase; BENZ: benzbromarone; BOS: bosentan; FIAU: fialuridine; VEH: vehicle.

Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 95-97).

ALT Levels

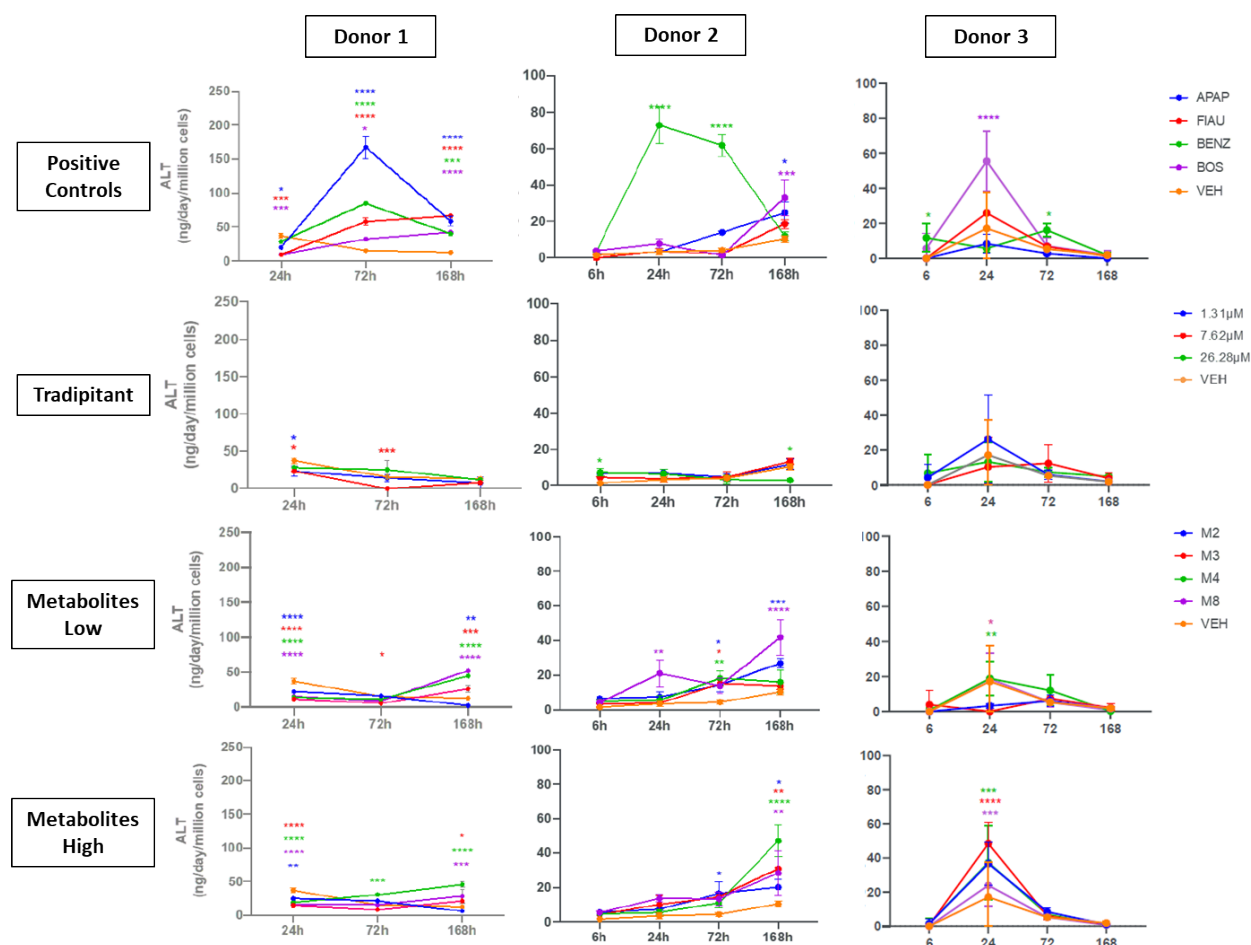
ALT levels were measured from top channel (hepatocyte) effluent at 24, 72, and 168 hours for all donors, and an additional 6 hours timepoint was added for Donors 2 and 3.

The effects of the various positive controls on ALT levels were highly variable between donors. In Donor 1, significantly increased ALT was observed at ≥ 24 hours with acetaminophen, fialuridine, and bosentan, while increased ALT was observed at ≥ 72 hours with benzbromarone. In Donor 2, significantly increased ALT was observed at 24 and 72 hours with benzbromarone and at 168 hours with acetaminophen and bosentan. In Donor 3, significantly increased ALT was observed at 6 and 72 hours with benzbromarone as well as at 24 hours with bosentan.

No notable differences in ALT were observed between tradipitant-treated conditions and the vehicle control in any donor.

The effects of the metabolites on ALT were highly variable between donors. No clear effect of any metabolite was observed compared to vehicle in Donor 1. For Donor 2, increased ALT was observed with the low and high concentrations of M2, high concentration of M3, high concentration of M4, and low and high concentrations of M8; effects generally peaked at 168 hours. For Donor 3, notable effects on ALT were observed at 24 hours only with the high concentrations of M2, M3, and M4.

Figure 25. ALT Levels Following Treatment with Positive Controls, Tradipitant, or Metabolites



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ by 2-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint.

ALT: alanine aminotransferase; APAP: acetaminophen; BENZ: benzbromarone; BOS: bosentan; FIAU: fialuridine; VEH: vehicle.

Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 99-101).

Generation of Reactive Oxygen Species

For Donor 1, ROS generation was measured in the frozen top channel effluent at 24, 72, and 168 hours. However, because no meaningful differences were detected between the vehicle and positive controls and the half-life of ROS after release is known to be short, the assay was run at an earlier timepoint and with fresh samples in later experiments.

Hence, for Donor 2, ROS was measured from the freshly collected effluent following 6, 24, 72, or 168 hours of treatment. These data were also inconclusive, and the effluent-based assay was not run for Donor 3; instead, ROS was assessed by live staining and imaging (see Immunofluorescence Imaging).

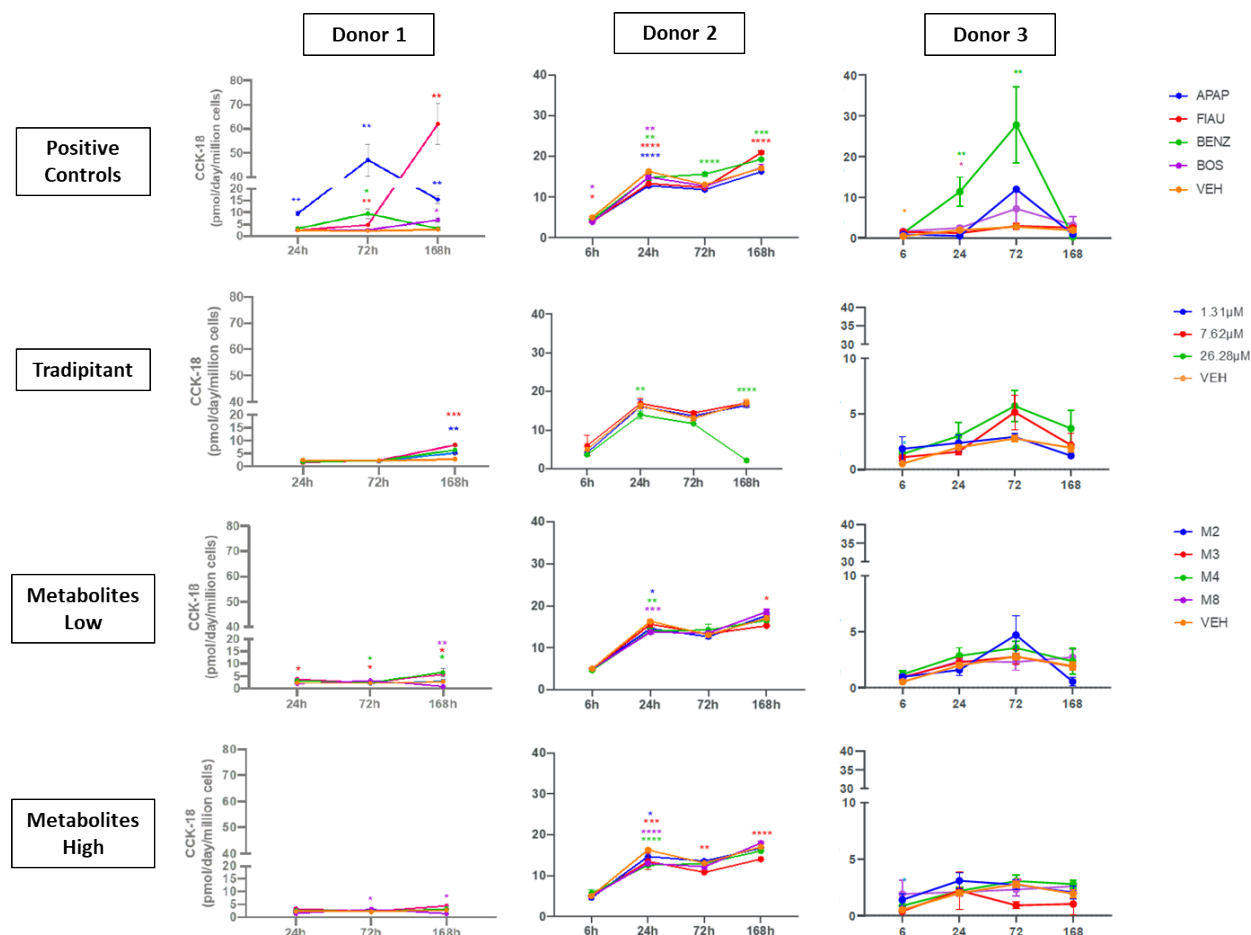
Caspase-Cleaved Cytokeratin 18 Levels

CCK-18 is a protein released from hepatocytes during apoptosis that has been proposed in the literature as a potential biomarker of liver disease¹⁷; this biomarker has not been clinically validated for this purpose. CCK-18 was measured in the top channel (hepatocyte) effluent at 24, 72, and 168 for all donors, and an additional timepoint of 6 hours was added for Donors 2 and 3.

The effects of the positive controls on CCK-18 expression were inconsistent between donors. Increased CCK-18 was observed with acetaminophen at ≥ 24 hours and fialuridine at 168 hours compared to vehicle in Donor 1, while increased CCK-18 was observed with benzbromarone at 24 and 72 hours in Donor 3; no notable effects were observed in Donor 2 at any timepoint.

While some differences were observed between the vehicle control and samples treated with tradipitant or metabolites, these differences were of small magnitude. Furthermore, a biologically significant magnitude of change was not defined. Thus, the biological significance of any changes in CCK-18 expression induced by tradipitant or its metabolites cannot be determined.

¹⁷ Li J, Verhaar AP, Pan Q, de Knecht RJ, Peppelenbosch MP. Serum levels of caspase-cleaved cytokeratin 18 (CK18-Asp396) predict severity of liver disease in chronic hepatitis B. Clin Exp Gastroenterol. 2017 Aug 11;10:203-209.

Figure 26. CCK-18 Protein Release Following Treatment with Positive Controls, Tradipitant, or Metabolites

*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 by 2-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint.

APAP: acetaminophen; BENZ: benzbromarone; BOS: bosentan; CCK-18: caspase-cleaved cytokeratin 18; FIAU: fialuridine; VEH: vehicle.

Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 104-106).

miRNA-122 Expression

miR-122 is a liver-specific miRNA that has been used as a prognostic marker for patients with hepatocellular carcinoma and has been proposed in the literature as biomarker for liver injury, including injury induced by acetaminophen¹⁸; this biomarker has not been clinically validated for this purpose. miR-122 was initially measured from the top channel (hepatocyte) effluent at 24, 72, and 168 hours for all donors, with an additional timepoint of 6 hours added for Donors 2 and 3.

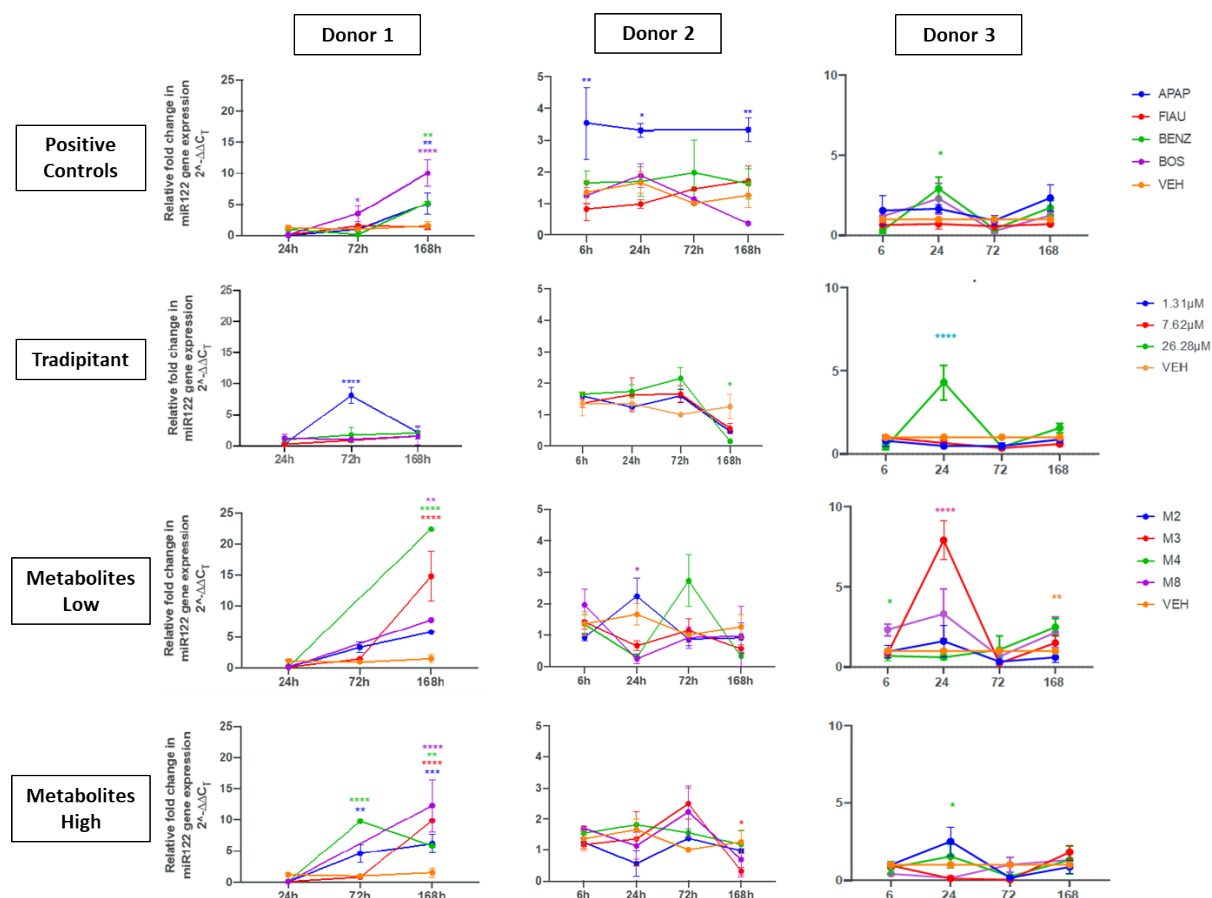
¹⁸ Thakral S, Ghoshal K. miR-122 is a unique molecule with great potential in diagnosis, prognosis of liver disease, and therapy both as miRNA mimic and antimir. *Curr Gene Ther.* 2015;15(2):142-50.

Increased miRNA-122 expression was observed with acetaminophen by 168 hours in Donors 1 and 2 (< 5-fold increase compared to vehicle). Sporadic effects were observed with other positive controls.

In Donor 1, an increase in miR-122 expression was observed with the low concentration of tradipitant at 72 hours only (estimated to be 4-fold that of the vehicle control). No effects of tradipitant were observed on miR-122 expression in Donor 2. In Donor 3, an increase in miR-122 expression was observed with the high concentration of tradipitant at 24 hours only (also estimated to be 4-fold that of the vehicle control); this effect was considered “biologically irrelevant” by the Applicant (no other explanation provided).

Increases in miR-122 expression were observed in Donor 1 with M2, M3, M4, and M8. No notable increases in miR-122 expression were observed with metabolites in Donor 2. Increased miR-122 expression was also observed with the low concentration of M3 in Donor 3.

Figure 27. miRNA-122 Release Following Treatment with Positive Controls, Tradipitant, or Metabolites



*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 by 2-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint.

APAP: acetaminophen; BENZ: benzbromarone; BOS: bosentan; FIAU: fialuridine; VEH: vehicle.

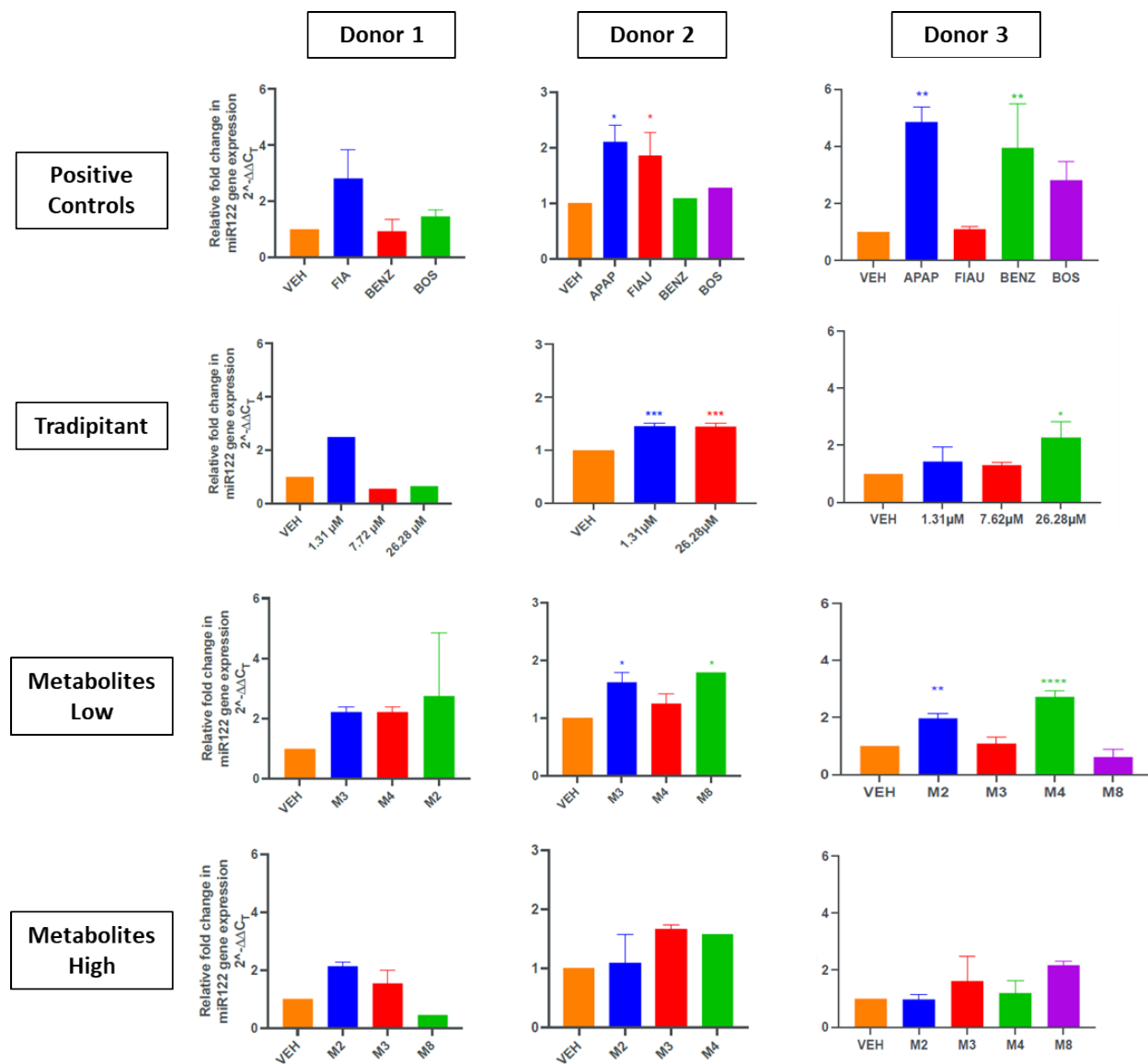
Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 108-110).

miRNA-122 expression was also analyzed in the cell lysate. One chip was lysed from each condition per donor at 168 hours only.

Increased miR-122 expression was observed in cell lysates from Donors 2 and 3 treated with acetaminophen ($\approx$ 2-fold and 5-fold vehicle control, respectively), Donor 2 treated with fialuridine ($\approx$ 2-fold), and Donor 3 treated with benzbromarone ($\approx$ 4-fold).

No clear effects of tradipitant or its metabolites were observed on miR-122 expression measured in the cell lysate.

Figure 28. miRNA-122 Expression in Cell Lysate Following Treatment with Positive Controls, Tradipitant, or Metabolites (168 Hours)



* $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$ by 1-way ANOVA, Uncorrected Fisher's LSD test, in comparison to the vehicle control at that timepoint. APAP, M8 (0.05 μ M), and M4 (2.84 μ M) had a low signal to noise ratio and were not plotted.

APAP: acetaminophen; BENZ: benzbromarone; BOS: bosentan; CCK-18: caspase-cleaved cytokeratin 18 FIAU: fialuridine; VEH: vehicle.

Figure adapted by reviewer, based on figures copied directly from study report (Study SRV-0028, pages 111-113).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

In Vitro Permeability and Gastrointestinal Fluid Stability of Tradipitant (VLY-686) According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States FDA, the EMA, and the ICH
[20VNDAP1GLPS607](#)

In this two-part study, the in vitro permeability of tradipitant (named VLY-686 in this report) was evaluated in a validated Caco-2 cell monolayer model, and the stability of tradipitant in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was determined according to the Biopharmaceutics Classification System (BCS). Samples were assayed using LC-MS/MS.

The permeability of tradipitant was higher than that of the positive control, minoxidil. As minoxidil is greater than 85% absorbed in humans, it was inferred that tradipitant should have greater than 85% absorption in humans. Therefore, tradipitant was classified as highly permeable according to the BCS criteria.

Table 9. Unidirectional (A-to-B) Permeability and Recovery of Tradipitant and Reference Compounds

Parameter	Analyte		
	VLY-686 (0.130 μ M) ^a	Minoxidil (10 μ M)	Atenolol (100 μ M)
P_{app} (10^{-6} cm/s)	18.7 $\pm$ 3.5	2.68 $\pm$ 0.67*	0.0619 $\pm$ 0.0161*
Recovery (%)	86.1 $\pm$ 13.1	102 $\pm$ 5	92.9 $\pm$ 3.0
Mass Balance (%)	144 $\pm$ 24 [#]	Not determined	Not determined

The results are presented as mean $\pm$ standard deviation (SD); n=4.

^a Mean measured concentration of the dosing solution prepared as described in [Section 9.4](#)

* The atenolol P_{app} was less than 1.00×10^{-6} cm/sec and the ratio of minoxidil P_{app} to atenolol P_{app} was greater than 3 for each replicate, confirming monolayer integrity.

[#] Mass balance was supramaximal due to the pre-incubation of the cell monolayers with the test article, followed by a post-experiment rinse with MeCN:HBSSg (1:1, v:v), which extracted the test article from all compartments, including the donor chamber.

VLY-686: tradipitant.

Table copied directly from study report (Study 20VNDAP1GLPS607, Table 1).

Based on the efflux ratio of 0.586, tradipitant was considered to permeate Caco-2 cell monolayers primarily by passive diffusion and was not considered a substrate of efflux transporters.

Table 10. Bidirectional Permeability of Tradipitant

Parameter	Direction	Mean Measured Dosing Concentration 0.615 μ M
P_{app} (10^{-6} cm/sec)	A-to-B	32.4 $\pm$ 13.3
Recovery (%)		94.0 $\pm$ 29.9
Mass Balance (%)		121 $\pm$ 14 [#]
P_{app} (10^{-6} cm/sec)	B-to-A	19.0 $\pm$ 3.4
Recovery (%)		136 $\pm$ 21 [§]
Mass Balance (%)		170 $\pm$ 27 [#]
Efflux Ratio*	B-to-A / A-to-B	0.586

The results are presented as mean $\pm$ SD; n=6 for P_{app} and recovery, n=3 for mass balance.

* Efflux ratio was calculated using the mean A-to-B and B-to-A P_{app} values.

§ B-to-A recovery was supramaximal (> 100%) because the measured 45-minute donor concentration was higher than the measured initial donor concentration. There is no impact on the calculated permeability, because P_{app} is normalized to the initial donor concentration, and the mean measured initial donor concentrations in each direction were comparable (relative percent difference less than 3%).

Mass balance was supramaximal due to the pre-incubation of the cell monolayers with the test article, followed by a post-experiment rinse with MeCN:HBSSg (1:1, v:v), which extracted the test article from all compartments, including the donor chamber.

Table copied directly from study report (Study 20VNDAP1GLPS607, Table 2).

More than 90% of the nominal concentration of tradipitant remained after incubation for 60 minutes in SGF and 180 minutes in SIF. Based on these results, tradipitant was considered stable in SGF and SIF.

Table 11. Stability of Tradipitant in Simulated Gastric Fluid (SGF)

Matrix	Time (min)	Measured Concentration (nM)	Recovery (%) [#]	Mean Recovery (%)	CV (%)
SGF	0	(b) (4)		89.8*	14.7
	60	(b) (4)		103	5.53

[#] Recovery is expressed vs. the nominal concentration (b) (4)

* The mean measured initial concentration of VLY-686, relative to the nominal concentration, was lower than expected. The observed degree of variability is consistent with the tolerance of the validated LC-MS/MS method (accuracy within 85.0-115%); the greater sensitivity of LC-MS/MS (vs. HPLC with UV detection) was required for this compound. Therefore, the stability of VLY-686 in incubated SGF samples was determined based on recovery vs. the nominal concentration.

CV: standard deviation/mean×100%

Table copied directly from study report (Study 20VNDAP1GLPS607, Table 3).

Table 12. Stability of Tradipitant in Simulated Intestinal Fluid (SIF)

Matrix	Time (min)	Measured Concentration (nM)	Recovery (%) [#]	Mean Recovery (%)	CV (%)
SIF	0	(b) (4)		93.1	13.8
	120	(b) (4)		96.5	2.40
	180	(b) (4)		98.0	3.85

[#] Recovery is expressed vs. the nominal concentration (b) (4) μM)

CV: standard deviation/mean×100%

Table copied directly from study report (Study 20VNDAP1GLPS607, Table 4).

Distribution

VLX-686 and Major Metabolites M2, M3 and M4: Investigation of Plasma Protein Binding In Vitro in Rat, Mouse and Human by Rapid Equilibrium Dialysis [WW85WJ](#)

The plasma protein binding of tradipitant (named VLX-686 in this report) and its metabolites M2, M3, and M4 were investigated using plasma samples from rat, mouse, and human. Tested concentrations were 300, 3000, and 30,000 ng/mL.

Tradipitant was highly bound in plasma in all species tested ($\geq 99\%$ bound in rat, $\geq 98.5\%$ in mouse, and $\geq 99.9\%$ in human). Tradipitant concentration had no effect on plasma protein binding in any species.

Metabolites M2, M3, and M4 were highly bound in plasma in all species tested ($\geq 92.8\%$ bound in rat, $\geq 97.4\%$ in mouse, and $\geq 95.4\%$ in human). Metabolite concentration had no effect on plasma protein binding in any species.

Table 13. Plasma Protein Binding of Tradipitant and its Metabolites

Species	Conc. (ng/mL)	Tradipitant		M2		M3		M4	
		%B	%R	%B	%R	%B	%R	%B	%R
Rat	300	99.1	87.4	99.7	89.8	94.6	94.0	96.3	91.9
	3000	99.0	91.4	99.7	91.6	96.5	86.6	95.5	93.2
	30000	99.8	91.5	99.4	93.7	97.5	79.4	92.8	78.5
Mouse	300	98.5	94.3	99.8	92.4	99.6	95.1	97.9	88.4
	3000	>99.9	95.9	99.8	92.7	99.0	94.6	97.5	88.3
	30000	98.9	97.7	99.7	103.0	98.9	95.3	97.4	88.4
Human	300	>99.9	97.1	99.7	90.3	98.8	91.7	98.3	91.0
	3000	99.9	90.3	99.9	93.3	99.4	86.9	98.1	97.0
	30000	99.9	87.0	99.7	91.9	97.9	92.7	95.4	89.3

%B: percent bound; %R: percent recovered.

Table created by reviewer, based on Applicant's provided data (Study WW85WJ).

Metabolism

UGT Reaction Phenotyping of Tradipitant [XT164094](#)

The UDP-glucuronosyltransferase (UGT) enzymes involved in the metabolism of tradipitant to metabolite M8 (N-glucuronide) were investigated using human liver microsomes and recombinant human UGT enzymes. In one experiment, tradipitant (0.5, 5, or 50 μ M) was incubated with pooled human liver microsomes and with or without the cofactor, uridine diphosphate glucuronic acid (UDPGA), for up to 120 minutes. In a second experiment, tradipitant (5 or 50 μ M) was incubated with recombinant human enzymes UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B10, or 2B15, each for 60 minutes. In both experiments, the amount of M8 was determined by LC-MS/MS.

In a preliminary experiment in which tradipitant was incubated with human liver microsomes to assess the general metabolic potential of tradipitant into M8, loss of tradipitant ranged from 0-17% in the presence of protein (liver microsomes) and cofactor (UDPGA). Overall, metabolite M8 was inconsistently formed, but M8 formation generally increased with incubation time, protein and substrate concentration, and required the presence of both protein and UDPGA cofactor.

Figure 29. Effect of Incubation Time and Protein Concentration on the Conversion of Tradipitant to M8 by Human Liver Microsomes

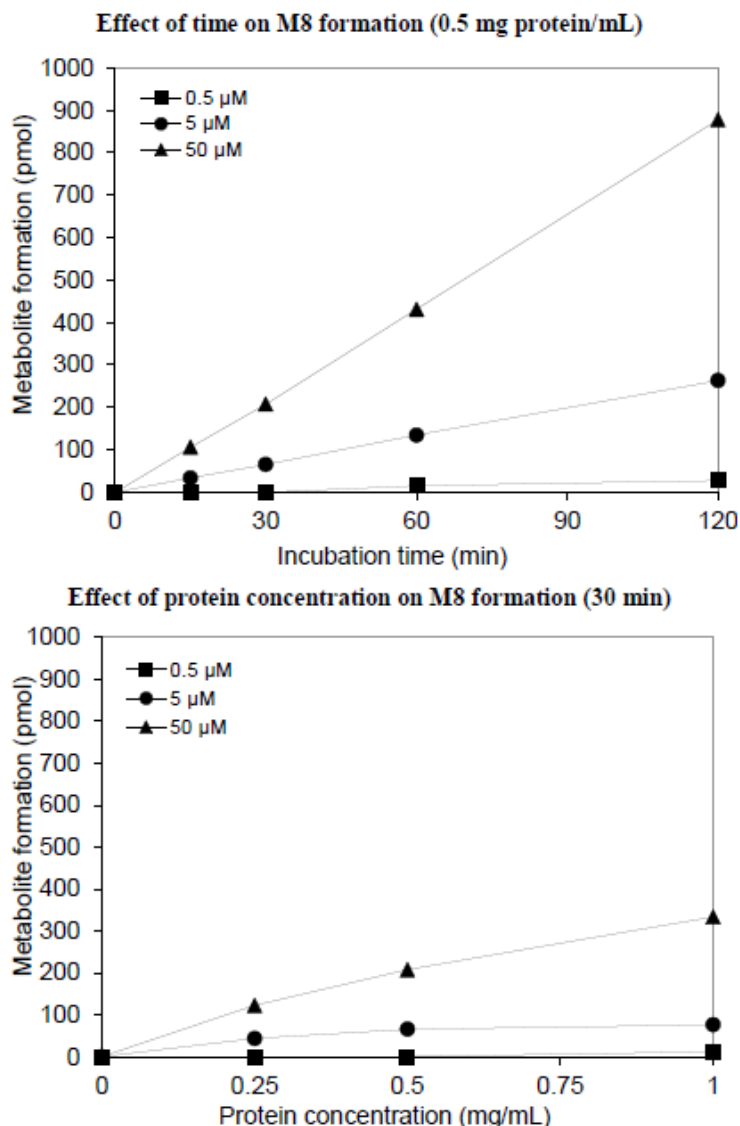


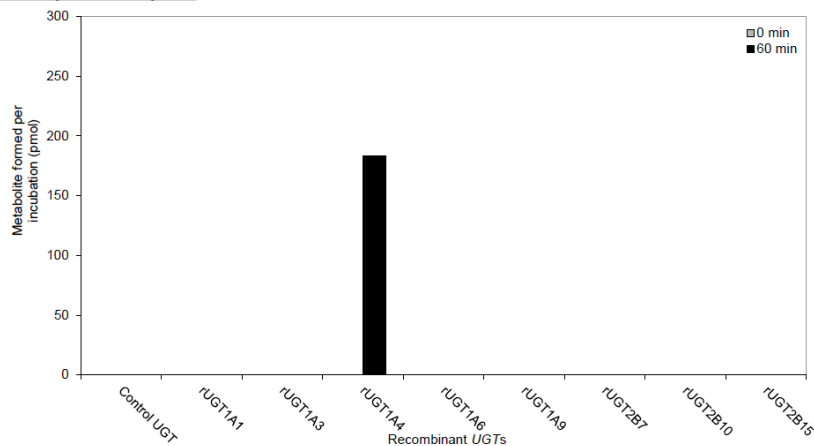
Figure copied directly from study report (Study XT164094, Figure 3).

In the main experiment using recombinant human UGT enzymes to determine which, if any, UGT enzymes are responsible for the metabolism of tradipitant to M8, conversion of tradipitant to M8 was observed with UGT1A4 at 5 and 50 μ M tradipitant and with

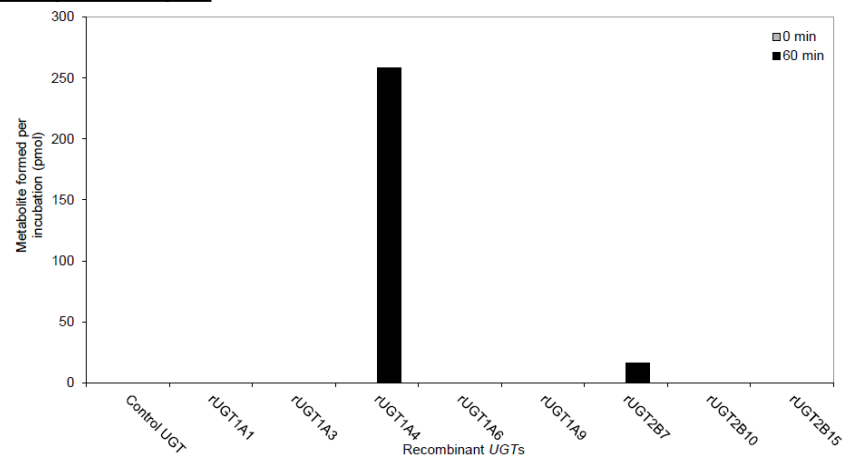
UGT2B7 at 50 μ M only. Thus, only UGT1A4 and UGT2B7 were considered capable of metabolizing tradipitant to M8.

Figure 30. Conversion of Tradipitant to M8 by Recombinant Human UGT Enzymes

Tradipitant 5 μ M:



Tradipitant 50 μ M:



Figures copied directly from study report (Study XT164094, Figures 6 and 7).

Drug Interactions (Nonclinical)

In Vitro Interaction of LY686017 with Human Cytochromes P450 CYP3A, CYP2D6, CYP2C19, CYP2C9, and CYP1A2 [21-250-TC](#), [22-250-TC](#)

The ability of tradipitant (named LY686017 in this report) to inhibit the activity of select cytochrome P450 (CYP) enzymes was evaluated using human liver microsomes. Metabolism of the appropriate substrate was evaluated by LC-MS/MS.

Tradipitant competitively inhibited CYP3A activity with a K_i of 0.92 μ M and non-competitively inhibited CYP3A activity with a K_i of 11 μ M. Tradipitant competitively

inhibited both CYP2C19 and CYP2C9 activity with K_i values of 9.0 μM and 4.7 μM , respectively. Additionally, tradipitant non-competitively inhibited CYP2C8 activity with a K_i value of 17 μM . No significant effects were observed on CYP1A2, CYP2D6, CYP2E1, or CYP2B6 activity over the tested concentration range.

Table 14. In Vitro Inhibition of CYP Enzymes by Tradipitant

Form-Selective Catalytic Activity	Type of Inhibition	Apparent K_i
CYP3A4 Midazolam 1'-Hydroxylation	competitive	$0.92 \pm 0.11 \mu\text{M}$
CYP3A4 Testosterone 6 β -Hydroxylation	noncompetitive	$11 \pm 1 \mu\text{M}$
CYP2C19 (S)-Mephenytoin 4'-Hydroxylation	competitive	$9.0 \pm 2.5 \mu\text{M}$
CYP2C9 Diclofenac 4'-Hydroxylation	competitive	$4.7 \pm 0.6 \mu\text{M}$

Table copied directly from study report (Study 21-250-TC; 22-250-TC, Table 1).

Effects of LY686017 on CYP1A2 and CYP3A in Primary Cultures of Human Hepatocytes [2003IV-HI02](#)

The ability of tradipitant (named LY686017 in this report) to induce the activity of CYP1A2 and CYP3A4 was evaluated using primary human hepatocytes. Hepatocytes (n = 5 donors) were treated for 72 hours with tradipitant over the concentration range of 0.084-8.4 μM . Metabolism of the appropriate substrate was determined by UV detection or LC-MS/MS.

Although the effects of tradipitant on CYP1A2 activity were variable, no biologically significant induction was observed in any donor tested.

Changes in CYP3A activity were also variable. Tradipitant significantly increased CYP3A4 activity in one donor each at 2.5 and 8.4 μM . Thus, tradipitant was considered a potential inducer of CYP3A4 activity.

In Vitro Interaction of LY686017 with CYP2E1, CYP2C8, and CYP2B6 in Human Liver Microsomes [CD-0822](#)

The ability of tradipitant (named LY686017 in this report) to inhibit the activity of CYP2E1, CYP2C8, and CYP2B6 was evaluated using human liver microsomes. Liver microsomes were incubated for 10-20 minutes with tradipitant at concentrations up to 20 μM . Metabolism of the appropriate substrate was determined by LC-MS/MS.

Tradipitant non-competitively inhibited CYP2C8 activity with an apparent K_i value of 17 μM . Similar to the findings in Study [21-250-TC/22-250-TC](#), no significant inhibition (< 50%) of CYP2E1 and CYP2B6 activities was observed with tradipitant up to the highest tested concentration of 20 μM .

Tradipitant: UDP-glucuronosyltransferase Inhibition in Human Liver Microsomes
[XT205023](#)

The ability of tradipitant to inhibit UGT1A4 was evaluated using human liver microsomes. Liver microsomes were incubated with tradipitant over the concentration range of 0.001-1 μM for 5 minutes, with reactions initiated every 10 seconds by the addition of the cofactor UDPGA. Reactions were analyzed by LC-MS/MS.

No significant inhibition of UGT1A4 was observed with tradipitant.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

7.1.1 VLY-686 metabolites: Bacterial Reverse Mutation Test

Study no.: [TAJ0042](#)
Study report location: EDR 4.2.3.7.7
Conducting laboratory and location:  (b) (4)

GLP compliance: Yes
Drug, lot #, and % purity: M2: Batch # E14032-05, Purity 99.77%
M3: Batch # E14032-08, Purity 99.25%
M4: Batch # E14032-10, Purity 98.33%

Methods

Strains: *S. typhimurium* TA1535, TA1537, TA98, TA100;
E. coli WP2 *uvrA* (pKM101)
Concentrations in definitive study: 5, 15, 50, 150, 500, 1500, 5000 µg/plate
Basis of concentration selection: Regulatory guidelines including ICH S2(R1)
Negative control: DMSO
Positive controls: -S9: Sodium azide (2 µg/plate), 9-aminoacridine (50 µg/plate), 2-nitrofluorene (2 µg/plate), 4-nitroquinoline-1-oxide (2 µg/plate)
+S9: 2-aminoanthracene (5 or 10 µg/plate), benzo[a]pyrene (5 µg/plate)
Formulation/Vehicle: DMSO
Incubation & sampling time: 37°C for 72 hours
Comment on Study Validity: Valid

Results

Metabolite M2

Cytotoxicity, demonstrated by a reduction in revertant colony numbers, was observed in strain WP2 *uvrA* following exposure to M2 at 1500 µg/plate in the presence of S9. No signs of cytotoxicity were observed with M2 under other tested conditions. Precipitate was observed with M2 at ≥ 500 µg/plate in the absence of S9 mix and at ≥ 1500 µg/plate in the presence of S9 mix. No biologically significant increases in the number of revertant colonies were observed with M2 up to 5000 µg/plate in the presence or absence of S9 mix. Thus, M2 was considered not genotoxic under the conditions of the assay.

Metabolite M3

Cytotoxicity, demonstrated by a thinning of the background lawn of non-revertant colonies, was observed in strains TA98, TA100, TA1535, and TA1537 following exposure M3 at ≥ 500 $\mu\text{g}/\text{plate}$ and in strain WP2 *uvrA* at ≥ 1500 $\mu\text{g}/\text{plate}$ in the presence of S9 mix. No signs of cytotoxicity were observed with M3 under other tested conditions. Precipitate was observed with M3 at ≥ 500 $\mu\text{g}/\text{plate}$ in the absence of S9 mix and at ≥ 1500 $\mu\text{g}/\text{plate}$ in the presence of S9 mix. No biologically significant increases in the number of revertant colonies were observed with M3 up to 5000 $\mu\text{g}/\text{plate}$ in the presence or absence of S9 mix. Thus, M3 was considered not genotoxic under the conditions of the assay.

Metabolite M4

Cytotoxicity, demonstrated by a reduction in revertant colony numbers, was observed in strain TA98 following exposure to M4 at 500 and 1500 $\mu\text{g}/\text{plate}$ in the absence of S9 mix. No signs of cytotoxicity were observed with M4 under other tested conditions. Precipitate was observed on all plates containing M4 at ≥ 500 $\mu\text{g}/\text{plate}$ in the absence and presence of S9 mix. No biologically significant increases in the number of revertant colonies were observed with M4 up to 5000 $\mu\text{g}/\text{plate}$ in the presence or absence of S9 mix. Thus, M4 was considered not genotoxic under the conditions of the assay.

7.2 In Vitro Assays in Mammalian Cells**7.2.1 VLY-686 Metabolites: In Vitro Mammalian Chromosome Aberration Test In Human Lymphocytes**

Study no.:	TAJ0043
Study report location:	EDR 4.2.3.7.7
Conducting laboratory and location:	 (b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	M2: Batch # E14032-05, Purity 99.77%
	M3: Batch # E14032-08, Purity 99.25%
	M4: Batch # E14032-10, Purity 98.33%

Methods

Cell line:	Primary human lymphocytes (n = 2 donors) stimulated to undergo cell division by treatment with phytohemagglutinin
Concentrations in definitive study:	23.33, 38.88, 64.8, 108, 180 µg/mL
Basis of concentration selection:	Effects on the mitotic index and/or precipitate in a preliminary toxicity test
Negative control:	DMSO
Positive controls:	–S9: mitomycin C (0.1 or 0.2 µg/mL) +S9: cyclophosphamide (7.5 µg/mL)
Formulation/Vehicle:	1% v/v DMSO
Incubation & sampling time:	3 hours ± S9, 21 hours –S9 at 34-39°C
Comment on Study Validity:	Valid

Results

Metabolite M2

No significant increase in the proportion of cells with chromosomal aberrations was observed with M2 under any tested condition compared to vehicle controls. Additionally, no significant increases in polyploid or endo-reduplicated metaphases were observed with M2 compared to controls.

Metabolite M3

No significant increase in the proportion of cells with chromosomal aberrations was observed with M3 under any tested condition compared to vehicle controls. Additionally, no significant increases in polyploid or endo-reduplicated metaphases were observed with M3 compared to controls.

Metabolite M4

No significant increase in the proportion of cells with chromosomal aberrations was observed with M4 under any tested condition compared to vehicle controls. Additionally, no significant increases in polyploid or endo-reduplicated metaphases were observed with M4 compared to controls.

10 Special Toxicology Studies

10.1 HSTOX 7619: Evaluating the safety and toxicology of tradipitant in multi-organ, microphysiological system (b) (4)

[HSTOX 7619](#)

Methods

Limited methods were provided in this study report. An information request was sent to the Applicant on March 27, 2024, requesting further detail on various aspects of the study design and conduct. Information provided by the Applicant in their response received March 26, 2024, is included in the description of the methods below.¹⁹

The potential toxic effects of tradipitant were evaluated using (b) (4) multi-organ MPS. This custom, human-based multi-organ platform was composed of liver (primary biopsy), cardiac (induced pluripotent stem cell [iPSC]-derived), kidney (primary biopsy), and neuronal (iPSC-derived) “organ” modules and was referred to as the “four-organ system.”

Initial experiments evaluated the stability of tradipitant in the four-organ system over a 7-day period. Additionally, the pharmacokinetic profiles of tradipitant and metabolites M2, M3, and M4 were determined. Samples were collected at 1, 4, 8, 24, and 48 hours and analyzed via HPLC-MS (n = 3 for each time point and concentration). Data were fit to a PK model incorporating mixing and loss of compound to adsorption; no further information was provided on this PK modeling.

To evaluate the toxicity of tradipitant, the system was treated once daily for 7 days with vehicle or tradipitant (Lot # RS-IN-VDDE17022) at 3 or 100 µM. According to the Applicant, these concentrations were selected to achieve “plasma” exposures of approximately 500 and 3500 ng/mL, respectively. The vehicle (not defined) was used as the negative control, and no positive controls were used for any assay.

Reviewer note: The low and high concentrations (plasma exposures) used in this study represent tradipitant exposure at approximately 1.5- and 11-fold the clinical C_{max} of 327 ng/mL, respectively, as determined in healthy volunteers following 12 days of dosing at 85 mg BID. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

Unless otherwise noted, endpoints evaluating cellular function were measured pre-treatment (with tradipitant being added to the culture immediately after baseline recordings) and following 1, 4, and 7 days of treatment. Each condition was tested in duplicate per experiment, and four biological replicates were used for each assay. Statistical analysis methods were not provided.

(b) (4)

Hepatocytes

Primary human hepatocytes were obtained from two donors. Both Donors 1 and 2 were used to evaluate the metabolism of tradipitant in the four-organ system, while only Donor 1 was used for the main experiments evaluating hepatocyte function and toxicity.

Primary human hepatocytes from Donor 1 were purchased from the (b) (4). This donor was a 44-year-old Caucasian female with a body mass index (BMI) of 26.4. No other information on the health status of the donor was provided.

Primary human hepatocytes from Donor 1 were purchased from (b) (4). This donor was a 42-year-old African American male, with a BMI of 31, who used alcohol approximately twice per month. The donor was on multiple medications including aspirin 81 mg, metoprolol 25 mg, Toviaz 4 mg, and botox injections in legs and bladder. The cause of death of this donor was stroke.

Hepatocytes were cultured on coverslips derivatized with an amine-containing silane. Additionally, Kasumi-1 and MEG-01 cells were suspended in alginate-based hydrogels in separate chambers. The purpose of the Kasumi-1 and MEG-01 cells was not provided by the Applicant or in their referenced publication.²⁰ Thus, the contribution of these other cell types to the function of this assay is unclear.

In this study, hepatocyte function was evaluated based on CYP3A4 activity, viability, and albumin production. CYP3A4 enzymatic activity was assessed in the liver fraction using a chemiluminescent assay (Promega p450-610TM assay), according to the manufacturer's instructions.²¹ Cell viability was assessed after disassembly via a standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.²⁰ Human serum albumin production from the liver fraction was measured in the supernatant of the culture. Samples were collected from the exchanged medium and stored at -20°C until analysis. One freeze-thaw cycle occurred before samples were analyzed following manufacturers' instructions provided in the ELISA Starter Accessory Kit. Samples were diluted as necessary in sample conjugate/diluent buffer to ensure readings measured within the range of the standard curve.²¹

Cardiomyocytes

iPSC-derived cardiomyocytes used in this study were purchased from (b) (4). The source of human fibroblasts used to derive these cells was a healthy female Caucasian donor less than 18 years of age.

Donor-derived human fibroblasts were reprogrammed to iPSCs through ectopic expression of factors (i.e., Oct4, Sox2, Nanog, Lin28) by retroviral transduction. The retroviral particles used in this process were obtained from the cell culture supernatant of HEK 293T cells transfected with plasmids containing the reprogramming factor genes as well as the coding regions of the *gag*, *pol*, and *env* retroviral genes. No retroviral

gene expression was detected by PCR in the starting fibroblast material or the resulting cell line, confirming the cell line cannot spontaneously produce infectious virus.

The iPSC-derived cell clones (cardiomyocytes) were engineered through homologous recombination to exhibit blasticidin resistance under the control of a cardiomyocyte-specific promoter. Neomycin resistance was also included in the targeting vector to allow selection of clones. None of the engineering vectors used contained oncogenes. The final cell population contained $\geq 95\%$ cardiomyocytes. Whole-genome transcript profiling and immunocytochemical characterization demonstrated that cardiomyocytes, at the time of purchase, exhibited a stable human cardiac gene expression profile with proper protein expression and localization necessary for cardiac function.

iPSC-derived cardiomyocytes obtained from the manufacturer were thawed and cultured as previously described.^{20,21}

Cardiac electrical function was measured by incorporating and chemically patterning cardiomyocytes onto customizable multi electrode arrays (cMEAs) to produce a defined conduction path along a series of surface-embedded microelectrodes.^{22,23} Cardiac contractions were measured using a cantilever deflection system in which longitudinal deflection of the cantilever due to contractions resulted in changes in position of the reflected beam on the lateral effect sensor.^{21,24,25} The voltage output from the position sensor was converted directly to force using a modified form of Stoney's equation, as published previously.^{21,26,27,28} cMEAs were fabricated to simultaneously stimulate and record electrical activity of cardiomyocytes, allowing conduction velocity to be recorded at different points (14 mm total path length). Printed circuit boards and flexible

²⁰ McAleer, C.W., Pointon, A., Long, C.J. et al. On the potential of in vitro organ-chip models to define temporal pharmacokinetic-pharmacodynamic relationships. *Sci Rep* 9, 9619 (2019).

²¹ Oleaga C., C. Bernabini, A. S. T. Smith, B. Srinivasan, M. Jackson, W. McLamb, V. Platt, R. Bridges, Y. Cai, N. Santhanam, B. Berry, S. Najjar, N. Akanda, X. Guo, C. Martin, G. Ekman, M. B. Esch, J. Langer, G. Ouedraogo, J. Cotovio, L. Breton, M. L. Shuler, J. J. Hickman. Multi-organ toxicity demonstration in a functional human in vitro system composed of four organs. *Sci. Rep.* 6, 20030 (2016).

²² Stancescu M., P. Molnar, C. W. McAleer, W. McLamb, C. J. Long, C. Oleaga, J.-M. Prot, J. J. Hickman. In vitro model of whole heart function. *Biomaterials* 60, 20–30 (2015).

²³ Natarajan A., M. Stancescu, V. Dhir, C. Armstrong, F. Sommerhage, J. J. Hickman, P. Molnar. Patterned cardiomyocytes on microelectrode arrays as a functional, high information content drug screening platform. *Biomaterials* 32, 4267–4274 (2011).

²⁴ Smith A. S. T., C. J. Long, C. W. McAleer, N. Bobbitt, B. Srinivasan, J. J. Hickman. Utilization of microscale silicon cantilevers to assess cellular contractile function in vitro. *J. Vis. Exp.* 2014, e51866

²⁵ Wilson K., M. Das, K. J. Wahl, R. J. Colton, J. J. Hickman. Measurement of contractile stress generated by cultured rat muscle on silicon cantilevers for toxin detection and muscle performance enhancement. *PLOS ONE* 5, e11042 (2010).

²⁶ Pirozzi K. L., C. J. Long, C. W. McAleer, A. S. T. Smith, J. J. Hickman. Correlation of embryonic skeletal muscle myotube physical characteristics with contractile force generation on an atomic force microscope-based biomicroelectromechanical systems device. *Appl. Phys. Lett.* 103, 083108 (2013).

²⁷ McAleer C. W., A. S. T. Smith, S. Najjar, K. Pirozzi, C. J. Long, J. J. Hickman. Mechanistic investigation of adult myotube response to exercise and drug treatment in vitro using a multiplexed functional assay system. *J. Appl. Physiol.* 117, 1398–1405 (2014).

²⁸ Oleaga C., G. Legters, L. R. Bridges, L. Kumanchik, C. Martin, Y. Cai, M. Schnepfer, C. W. McAleer, C. J. Long, J. J. Hickman. In Stem Cell-Derived Models in Toxicology, Methods in Pharmacology and Toxicology, M. Clements, L. Roquemore, Eds. (Humana Press, 2017), pp. 229–246.

elastomeric connectors (1 mm wide by 18.2 mm long by 9mm tall) were incorporated into each system to create an interface between the MEA and a commercially available 60-electrode amplifier. A stimulus generator was used to stimulate the cells (800 mV rectangular pulse, 0.5 to 3.0 Hz in 0.25 Hz increments). The multichannel systems software suite was used to control both the amplifier and stimulator and was used to record action potentials (APs).

In this study, cardiomyocyte function was evaluated based on cardiac force, beat frequency, and conduction velocity. As previously described,²⁰ cardiac velocity and spontaneous beat frequency were extracted from the data using Clampfit (Axon Instruments). Spontaneous beat frequency was obtained from spontaneous recordings of cardiac activity 30 s in length. Stimulated conduction was initiated by stimulation using 40 ms pulses at 1 Hz for 15 s. For each recording, the frequency was calculated as the number of measured APs divided by the length of time between the first and last APs during the recording interval. Cardiac velocity was measured by determining the length of time for an AP to travel from an electrically stimulated electrode along the patterned cardiomyocyte path, following the method described previously.²²

Proximal Tubular Epithelial Cells

Human primary proximal tubular epithelial cells were purchased from (b) (4). No information on the donor characteristics was included in the vendor-provided COA. Human kidney tissue was obtained from specimens obtained during surgical resection of renal cell carcinoma. Renal proximal tubule epithelial cells were grown in monolayer cultures following isolation from renal cortical tissue. Microfluidic technology allowed media perfusion, which exposed cells to fluid shear force at the apical surface and delivered nutrients continuously under normoxic conditions.²⁹ Renal proximal tubule epithelial cells were confirmed to have γ -glutamyl transferase activity.

In this study, renal proximal tubule cell function was evaluated based on kidney-injury molecule (KIM)-1 release. KIM-1 protein in the supernatant was quantified by ELISA.

Cortical Neurons

The iPSC cell line utilized for cortical neuron differentiation was purchased from the (b) (4). iPSCs were generated by four-factor (OCT4, SOX2, KLF4, CMYC) retroviral vector-mediated reprogramming from fibroblasts derived from a healthy, 64-year-old male donor.

Differentiation of cortical neurons from iPSCs consisted of a timeline of three stages, starting out with the use of small molecules, and ending with an array of neuron-specific factors. iPSCs were grown to 90% confluence in the manufacturer-specified culture

²⁹ Adler M, Ramm S, Hafner M, Muhlich JL, Gottwald EM, Weber E, Jaklic A, Ajay AK, Svoboda D, Auerbach S, Kelly EJ, Himmelfarb J, Vaidya VS. A Quantitative Approach to Screen for Nephrotoxic Compounds In Vitro. *J Am Soc Nephrol*. 2016 Apr;27(4):1015-28.

medium on a surface coated with matrigel matrix. To induce the differentiation, cells received a full medium change and were then fed every other day with differentiation medium I, differentiation medium II, and differentiation medium III, according to the differentiation timeline.

In this study, cortical neuron function was evaluated based on half-peak width activity, spike amplitude, and firing rate as previously described.³⁰ Whole-cell patch clamp recordings were performed on the 37°C heated stage of an upright microscope. The intracellular recording solution (140 mM potassium gluconate, 4 mM NaCl, 0.5 mM CaCl₂, 1 mM MgCl₂, 1 mM EGTA, 5 mM HEPES acid, 5 mM HEPES base, and 5 mM Na₂ATP) was loaded into borosilicate glass patch pipettes produced with a pipette puller. Patch pipettes with a resistance in the range of 6–10 MΩ were used for all recordings. Voltage-clamp and current-clamp experiments were performed with a Multiclamp 700B amplifier. Signals were filtered at 2 kHz and digitized at 20 kHz with an Axon Digidata 1322A interface. Offset potentials were nulled before formation of a gigaΩ seal and fast and slow capacitance was compensated for in all recordings. Membrane potentials were corrected by subtraction of a 15 mV tip potential, calculated using Axon's pClamp 10 software (Axon Instrument, Foster City, CA, USA). Recordings with an access resistance of less than 22 MΩ were not included as a high access resistance indicates poor patch quality/insufficient access to the interior of the cell. To generate a single AP, a 3 ms depolarizing current pulse of sufficient intensity (1-2 nA) was applied. Inward and outward currents were evoked by a series of 250 ms depolarizing steps from -70 to +170 mV with +10 mV increments. Depolarization-evoked repetitive firing was recorded in current clamp mode. Gapfree recordings of spontaneous activity of patched neurons were performed for up to 5 m while holding the cell membrane at optimal threshold (between -45 and -50 mV). Cells which required more than 200 pA of current to maintain voltage clamp were excluded as excessive application of current is indicative of poor patch quality or membrane integrity. All recordings and analysis were performed using the pClamp 10 software suite. Action potential rise times were calculated as the time taken to reach 90% maximum AP amplitude from 10% of the maximum amplitude. Decay slope and time were calculated from 90% to 10% of the action potential. Full width at half maximum was calculated as the width of the action potential (in ms) at half the maximum amplitude. Action potential rise time and FWHM were calculated during the flattest portion of the AP to allow for easy comparison between conditions.

GLP Compliance

This study was not GLP compliant, as confirmed by (b) (4)⁴

³⁰ Berry JA, Phan A, Davis RL. Dopamine Neurons Mediate Learning and Forgetting through Bidirectional Modulation of a Memory Trace. *Cell Rep*. 2018 Oct 16;25(3):651-662.e5.

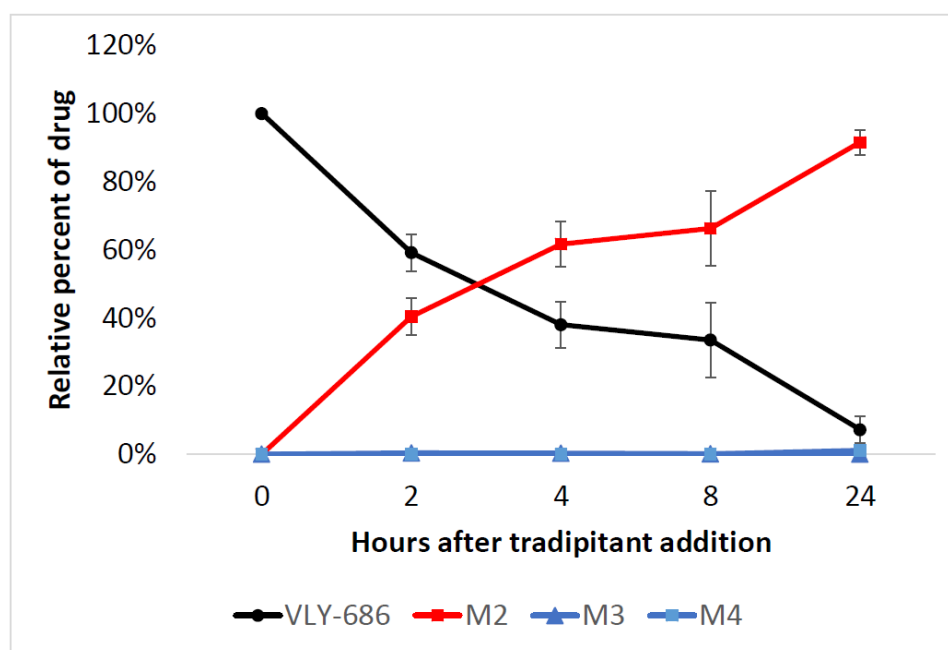
Results

Metabolism of Tradipitant in Acellular and Liver Systems

Due to the lipophilicity of tradipitant, it was necessary to evaluate the maximum solubility of the compound in the system as well as the amount absorbed onto the PDMS device material. The targeted “plasma” concentrations of tradipitant were 500 and 5000 ng/mL. However, a concentration of 5000 ng/mL could not be consistently achieved due to the high lipophilicity of the drug (data not provided), and the maximum targeted concentration was reduced to 3500 ng/mL. The dosing concentration of tradipitant that resulted in sustained “plasma” concentrations of 500 ng/mL and 3500 ng/mL were 3 μ M and 100 μ M, respectively.

Tradipitant was stable over a 7-day period in acellular systems. Metabolism of tradipitant in hepatocytes from Donor 1 resulted in 7.2% parent drug, 91.6% M2, 0.1% M3, 1.2% M4 after 24 hours.

Figure 31. Liver Metabolic Conversion of Tradipitant Over 24 Hours in the Four-Organ Microphysiological System (Donor 1)



VLY-686: tradipitant.

Figure copied directly from study report (Study HSTOX 7619, Figure 1).

Table 15. Liver Metabolic Conversion of Tradipitant Over 24 Hours in the Four-Organ Microphysiological System (Donor 1)

Compound	Hours after Drug Addition				
	0	2	4	8	24
Tradipitant	100%	59.2%	38.0%	33.5%	7.2%
M2	0%	40.4%	61.7%	66.3%	91.6%
M3	0%	0.4%	0.3%	0.1%	0.1%
M4	0%	0.1%	0.1%	0.1%	1.2%

Table created by reviewer, based on Applicant's provided data (Study HSTOX 7619, Table 1).

As this metabolite profile was different than expected (see Reviewer note below), additional testing was conducted. It was determined that the buffering agent in the medium did not affect metabolism of tradipitant in the four-organ system. However, repeat experiments using hepatocytes from Donor 2 demonstrated lower conversion of tradipitant to M2 compared to using hepatocytes from Donor 1. Liver conversion of tradipitant in hepatocytes from Donor 2 resulted in 32.9% parent drug, 58.7% M2, 0.5% M3, 7.8% M4 after 24 hours.

Based on these findings, the Applicant concluded that the source of liver affects the metabolic profile of tradipitant in this system, potentially due to differences in CYP enzyme activity.

Figure 32. Liver Metabolic Conversion of Tradipitant Over 24 Hours in the Four-Organ Microphysiological System (Donor 2)

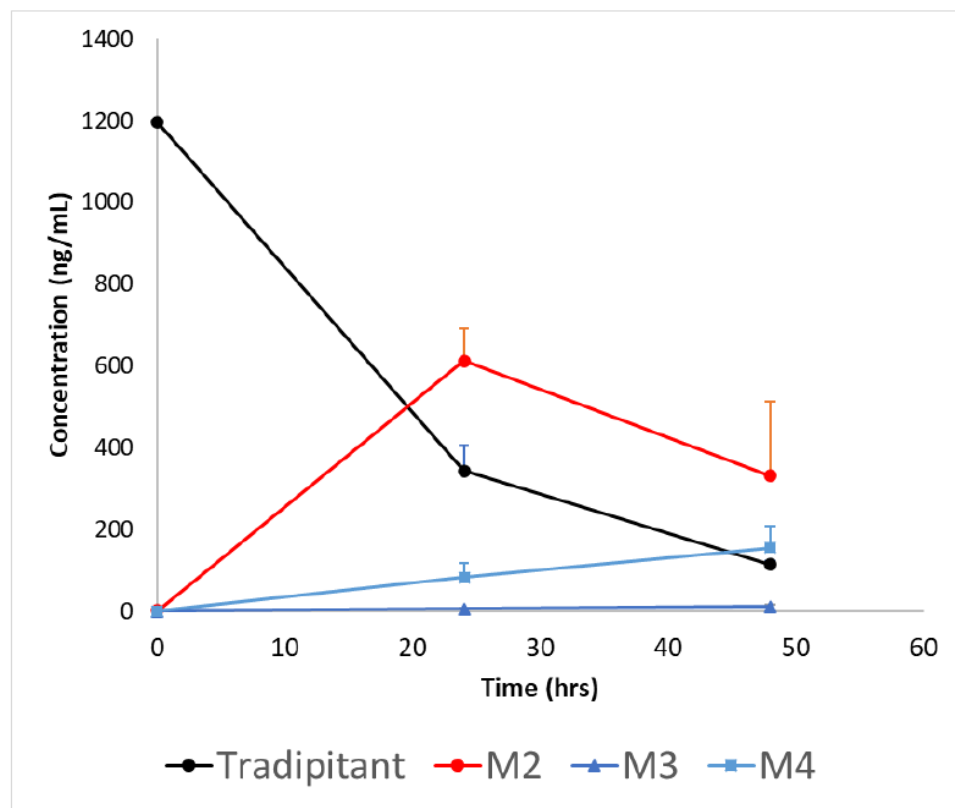


Figure copied directly from study report (Study HSTOX 7619, Figure 4).

Table 16. Liver Metabolic Conversion of Tradipitant Over 24 Hours in the Four-Organ Microphysiological System (Donor 2)

Compound	Hours after Drug Addition		
	0	24	48
Tradipitant	99.9%	32.9%	18.6%
M2	0.1%	58.7%	54.2%
M3	0%	0.5%	1.8%
M4	0%	7.8%	25.4%

Table created by reviewer, based on Applicant's provided data (Study HSTOX 7619, Table 3).

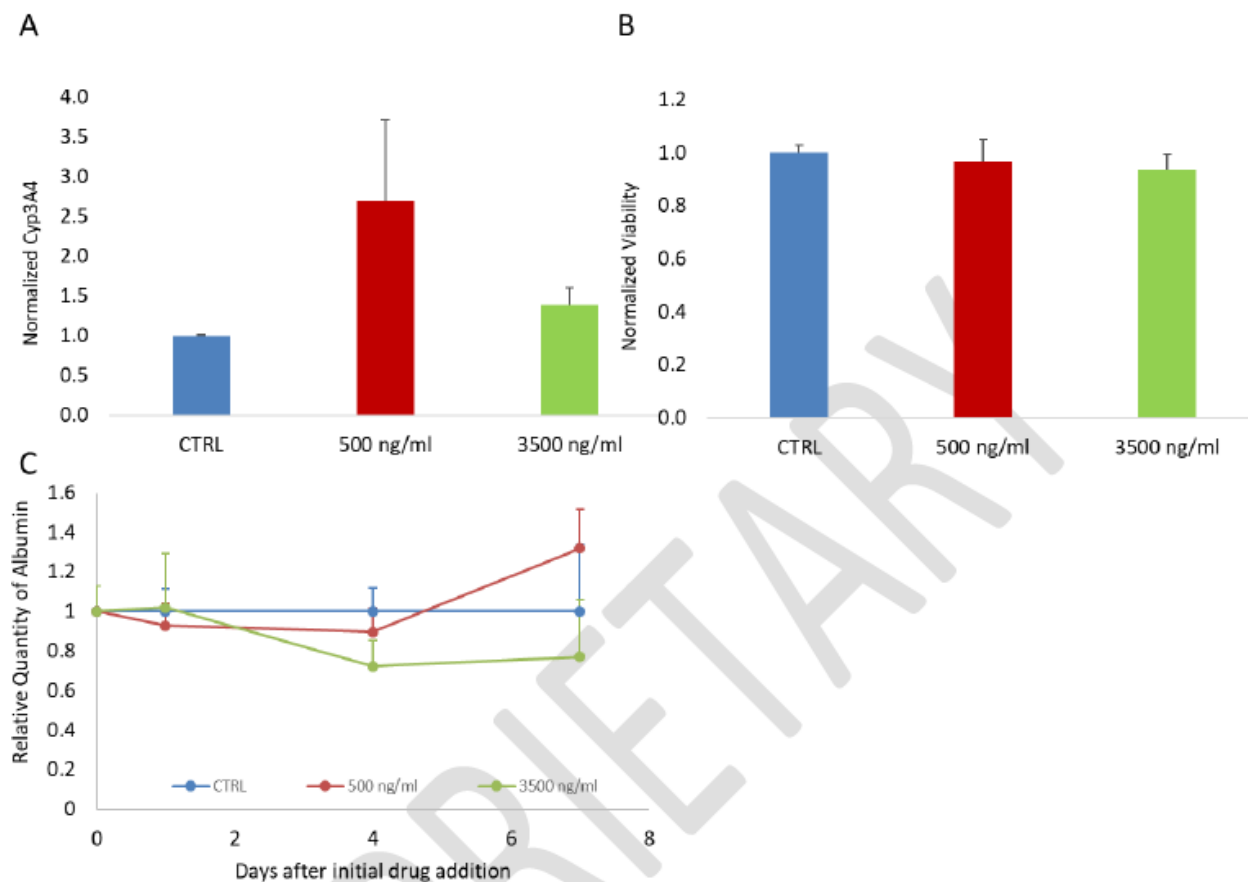
Reviewer note: The drug and metabolite pharmacokinetic profiles measured in this in vitro study (using either Donor 1 or Donor 2) are not consistent with human clinical or in vivo animal study data. Following a single dose of 25 mg radiolabeled tradipitant in healthy human volunteers, drug-related exposure measured over 24 hours was 9% parent drug, 4% M2, 5% M3, and 8% M4 (i.e., the parent drug and major identified human metabolites accounted for only 26% of drug-related exposure; see Trial H8R-MC-HKAK and 2.4 Nonclinical Overview, pg. 20). In healthy volunteers administered 85 mg tradipitant BID for 12 days, drug-related exposure measured over 24 hours was

composed of 50% parent drug, 17% M2, 16% M3, and 17% M4 (see Trial VP-VLY-686-1102, pgs. 60-63). Additionally, although data are limited, M2 represented < 1% of drug-related exposure in nonclinical toxicology studies. Overall, cells in the MPS were overexposed to M2 and underexposed to tradipitant and/or its other major metabolites during this study compared to what has been observed in animals and humans. Due to the differences in in vitro and in vivo metabolism, the clinical relevance of any findings related to toxicity in this assay is unclear.

Tissue-Specific Endpoints

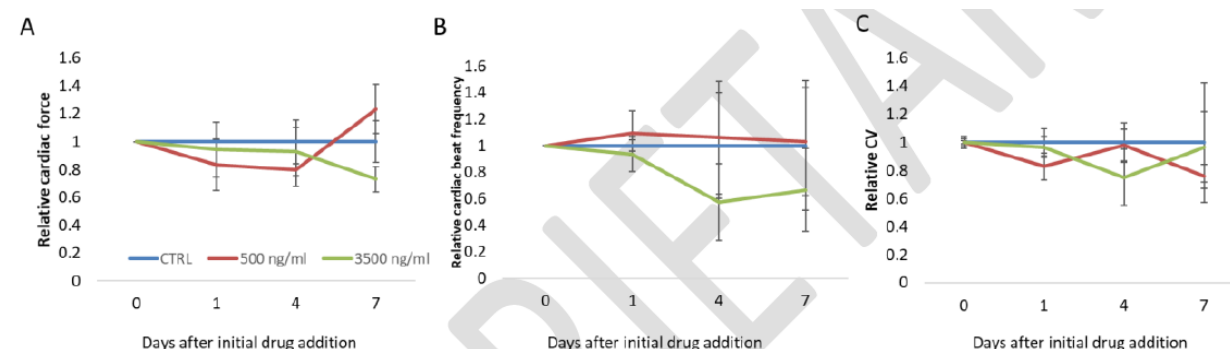
The study report states that no significant effects of tradipitant were observed on selected measures of hepatocyte function (albumin production, CYP3A4 activity, liver cell viability), cardiomyocyte function (cardiac force, cardiac beat frequency, and cardiac conduction velocity), kidney injury (KIM-1, a proposed biomarker of acute kidney injury³¹), or cortical neuron function (half-peak width, spike amplitude, and firing rate) through 7 days of treatment. In light of the limited scope of the toxicity evaluation (including lack of scientific justification for the specific parameters tested), observed differences in metabolism, lack of positive controls, and lack of compliance with US FDA GLP regulations, we disagree that any conclusions can be made based on the information available in this study report.

³¹ Song J, Yu J, Prayogo GW, Cao W, Wu Y, Jia Z, Zhang A. Understanding kidney injury molecule 1: a novel immune factor in kidney pathophysiology. *Am J Transl Res*. 2019 Mar 15;11(3):1219-1229.

Figure 33. Effects of Tradipitant on Markers of Liver Function in the Four-Organ Microphysiological System

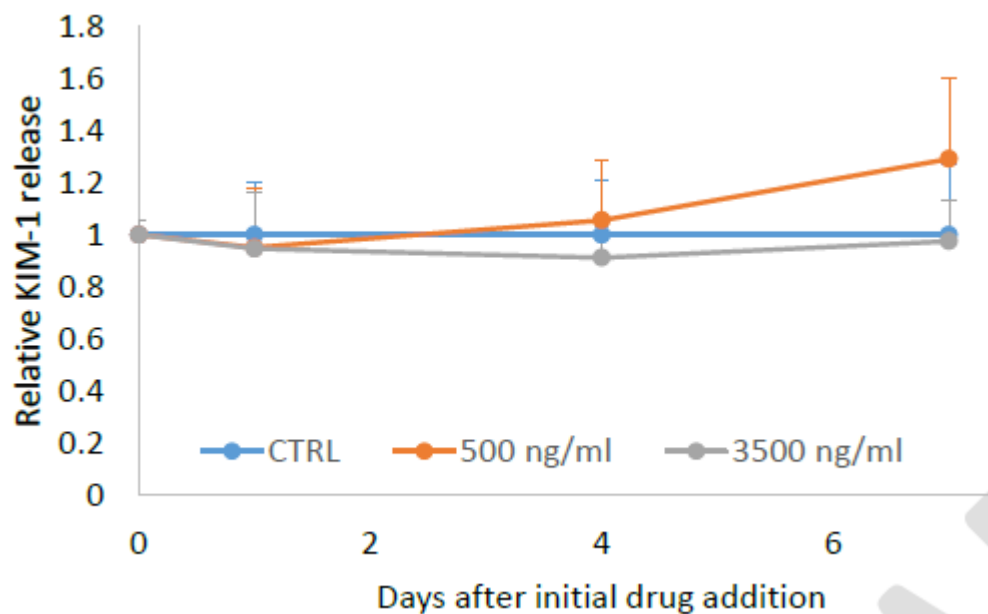
Cyp 3A4 activity (Day 7; $p > 0.15$), B) viability (Day 7; $p > 0.8$), C) albumin production ($p > 0.2$).
 Figure copied directly from study report (Study HSTOX 7619, Figure 5).

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Figure 34. Effects of Tradipitant on Markers of Cardiac Function in the Four-Organ Microphysiological System

Systemic concentrations of 500 ng/ml and 3500 ng/ml effects on A) cardiac force ($p > 0.18$), B) cardiac beat frequency ($p > 0.67$), or C) cardiac conduction velocity ($p > 0.3$).
 Figure copied directly from study report (Study HSTOX 7619, Figure 4).

Figure 35. Effects of Tradipitant on KIM-1 Release in the Four-Organ Microphysiological System

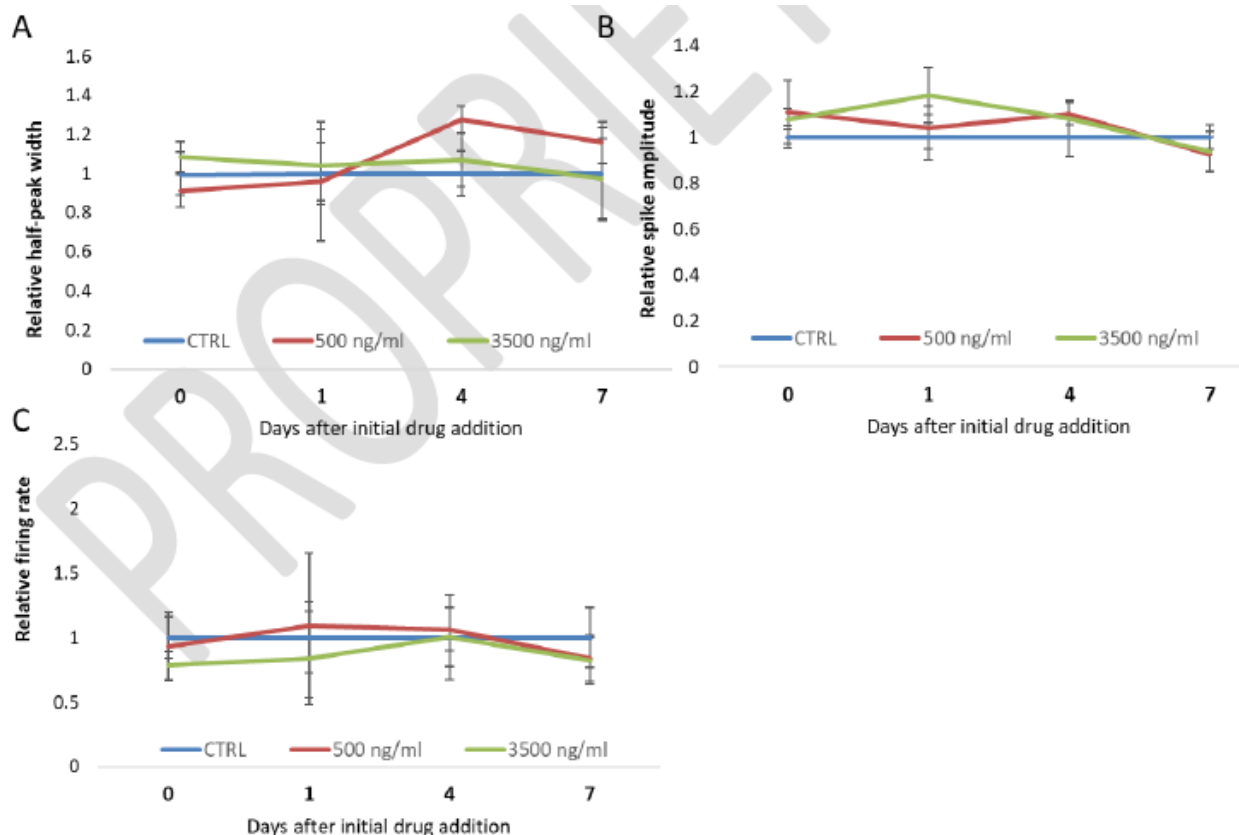


KIM-1: kidney injury molecule-1

KIM-1 release ($p > 0.16$).

Figure copied directly from study report (Study HSTOX 7619, Figure 6).

Figure 36. Effects of Tradipitant on Markers of Cortical Neuron Function in the Four-Organ Microphysiological System



Cortical neuron A) half-peak width activity ($p > 0.68$), B) spike amplitude ($p > 0.39$), or C) firing rate ($p > 0.9$).

Figure copied directly from study report (Study HSTOX 7619, Figure 7).

10.2 HSTOX 2008-002: Safety Evaluation of Supraphysiological Tradipitant Dosing under Differential Liver Metabolism

[HSTOX 2008-002](#)

Methods

The potential toxic effects of tradipitant were evaluated using (b) (4) multi-organ MPS. This custom, human-based multi-organ platform was composed of liver (primary biopsy), cardiac (induced pluripotent stem cell [iPSC]-derived), kidney (primary biopsy), and neuronal (iPSC-derived) "organ" modules and was referred to as the "four-organ system."

Based on the unexpected drug metabolism observed in Study HSTOX-7619 (Donor 1, purchased from the (b) (4)

(b) (4) this study used multiple donors for the liver construct in order to evaluate the effects of differences in metabolism on the potential toxicity of

tradipitant. Three donors were identified as having low, moderate, and high levels of metabolic activity, as defined by CYP3A4 activity, respectively (see Results). All cell types utilized in this study were cultured independently to allow for complete maturation prior to integration into the four-organ system. Following assembly, systems were maintained for 3 days before the start of the experiment.

To evaluate the toxicity of tradipitant, the system was treated once daily for 14 days with vehicle or tradipitant (Lot # RS-FP-VDDE21019) to achieve a final concentration of 3, 30, or 100 μ M. On Days 1-13, systems received daily medium changes amounting to 30% of the total system volume, with the new medium containing the appropriate concentration of tradipitant to maintain target concentrations in the full system. Concentrations of 3 and 100 μ M were previously shown to achieve “plasma” exposures of approximately 500 and 3500 ng/mL, respectively (see Study HSTOX-7619). DMSO (0.1%) was used as the vehicle/negative control, and two positive controls were included for each endpoint (see results below).

Reviewer note: Based on the information provided by the Applicant, Solubility issues were observed at the highest administered concentration of 100 M tradipitant, as the compound precipitated out of solution when added to culture medium. The degree of precipitation was not quantified.

Reviewer note: As stated previously, the low and high concentrations (plasma exposures) used in this study represent tradipitant exposure at approximately 1.5- and 11-fold the clinical C_{max} of 327 ng/mL, respectively, as determined in healthy volunteers following 12 days of dosing at 85 mg BID. The Applicant did not conduct IVIVE analyses to determine how the in vitro concentration relates to that observed in humans. Thus, the stated effect margins should be interpreted with caution, and all observed effects are discussed in terms of absolute concentration.

Unless otherwise noted, endpoints evaluating “organ” function were measured pre-treatment (with tradipitant being added to the culture immediately after baseline testing) and following 1, 4, 7, 10, and 14 days of treatment. In addition to organ-specific endpoints, the quantities of tradipitant, M2, M3, and M4 were measured in medium collected from systems on Days 1, 4, 7, 10, and 14 post-dose. On Day 14, the cells were lysed and the quantities of tradipitant, M2, M3, and M4 in both media and cell lysate samples were measured by UHPLC-MS/MS.

Unless otherwise stated, each condition was tested in duplicate per experiment, and four biological replicates each were used for the low, moderate, and high metabolizing donors. Two-way ANOVA/Fisher's LSD was utilized to compare vehicle control to the various tradipitant concentrations for each four-organ system with either the high, medium, or low metabolizing liver construct.

Hepatocytes

Primary human hepatocytes (PHH) were obtained from (b) (4)

Reviewer note: Hepatocytes used in this study are from different donors than those used in Study HSTOX-7619. No donor information was provided for these hepatocytes by the Applicant, and no information was obtainable on the manufacturer websites given the lack of lot numbers provided. Based on the study report, two vials of Sigma cells were used with different source donors and phenotypes.

Cells were thawed and plated 7 days prior to experiments. For adherence to coverslips, cells were plated and cultured using the appropriate media from each manufacturer (i.e., (b) (4), as appropriate). Each coverslip was examined under 10X magnification to ensure healthy, confluent cells with similar densities were used in the study. Hepatocytes were maintained on coverslips and monitored for 14 days. Phase images were collected to monitor cell morphology. Metabolic function was assessed on days 1, 7, and 14 to determine albumin production and CYP3A4 activity.

CYP3A4 activity was measured using a commercially available assay (Promega: Madison, WI, USA; catalog no. V9002). CYP3A4 activity was categorized as low (< 5 pmol/hr/10⁶ cells), moderate (5-50 pmol/hr/10⁶ cells), or high (>50 pmol/hr/10⁶ cells). One donor each was designated as a low, moderate, or high metabolizer; these three donors were used for the liver system (alone or in conjunction with heart, kidney, and brain systems) throughout the study to assess the impact of metabolism on the toxicity endpoints.

Reviewer note: The study report did not identify the hepatocyte donor (i.e., low, moderate, or high metabolizer) used in the four-organ system for evaluation of positive control compounds; however, it appears that only one hepatocyte donor was used in each assay.

Evaluation of cell viability was conducted in the same cells following CYP3A4 measurement using a standard MTT assay.

The conversion of tradipitant to M2, M3, and M4 was characterized in liver-only systems. Hepatocytes were treated with two concentrations of tradipitant over a 14-day time course. Each concentration was assessed in triplicate per experiment and with two biological replicates. Medium from systems was collected following 1, 4, 7, 10, and 14 days of treatment, and the quantities of tradipitant, M2, M3, and M4 were measured via HPLC-MS.

Hepatocyte function (as part of the four-organ system) was evaluated via measurement of albumin production. Media samples were collected from each system on days 0, 1, 4, 7, 10, and 14 post system assembly and were stored at -80°C until use. Albumin was

measured using a commercially available ELISA (Thermo Fisher Scientific: Waltham, MA, US; catalog no. EHAB).

Chlorpromazine and losartan were used as positive controls for measurement of albumin production. Chlorpromazine is a phenothiazine that can cause mild and transient serum enzyme elevations and is a known cause of clinically apparent acute and chronic cholestatic liver injury. Chlorpromazine administered orally at 75 mg/day for 21 days is associated with compound-induced liver injury with a latency of 2 weeks.³² The chlorpromazine concentration used in this study, 0.5 μ M (the clinical C_{max}), was selected to recapitulate the clinically observed liver injury. Losartan is an angiotensin 1 (AT1) blocker prescribed for the treatment of hypertension that has been reported to induce mild hepatotoxicity including marked elevation of aminotransferases.³³ The losartan concentration used in this study, 300 ng/mL, was selected based on the high end of the range of clinical $C_{max,ss}$ values following the recommended dosing regimen.

Cardiomyocytes

iPSC-derived human cardiomyocytes were purchased from (b) (4). The source of human fibroblasts used to derive these cells was a healthy female Caucasian donor less than 18 years of age. Donor-derived human fibroblasts were reprogrammed to iPSCs as described for Study HSTOX-7619.

Cardiomyocytes were thawed and plated onto cantilever chips and treated MEAs 8 days prior to assembly of systems. Cantilever recordings and electrophysiological measurements were performed on Days 0, 1, 4, 7, 10, and 14 post-assembly. Cardiac force, beat frequency, and conduction velocity were determined as described for Study HSTOX-7619. Troponin-I was measured on Days 0, 1, 4, 7, 10, and 14 using a commercial kit (R&D Systems: Minneapolis, MN, USA; catalog no. DY6887-05).

Terfenadine and doxorubicin were used as positive controls for cardiomyocyte functional assays. Terfenadine is an inhibitor of the human ether-à-go-go-related gene (hERG) channel current, resulting in QT prolongation in both nonclinical species and humans. Terfenadine is rapidly metabolized to fexofenadine, mainly by CYP3A4, and this metabolite does not cause QT prolongation.^{34,35} In this study, integrated cardiac MEAs were utilized to measure the external field potential, allowing for quantification of field potential duration (FPD), a surrogate for the action potential duration at 90% repolarization (APD_{90}) that enables an assessment of the impact of terfenadine (or any

³² LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Chlorpromazine. [Updated 2017 Oct 5]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548793/>.

³³ Al-Halawani MZ, Thawabi M, Asslo F, Shaaban H, Shamooh F, Baddoura WJ. Losartan-induced Ischemic Hepatocellular Hepatotoxicity: A Case Report and Literature Review. J Family Med Prim Care. 2014 Jul;3(3):272-4. doi: 10.4103/2249-4863.141635. PMID: 25374869; PMCID: PMC4209687.

³⁴ Kamiya, K. et al. Molecular determinants of hERG channel block by terfenadine and cisapride. J Pharmacol Sci 108(3), 301-7 (2008).

³⁵ Rangno, R. Terfenadine therapy: can we justify the risks? CMAJ 157(1), 37-8 (1997).

drug of interest) on the QT interval.³⁶ The terfenadine concentration used in the current study, 5 μ M, was supported by previous work in heart-only systems that showed a profound effect on cardiac repolarization at 0.5 to 1 hour, such that rhythmic cardiac beating ceased and, therefore, FPD and beat rate were unquantifiable. These changes in FPD were reduced in a two-organ heart-liver model, over the time course of the experiment, suggesting that the observed effects on FPD were due to terfenadine (the parent drug), rather than the metabolite.³⁷ Doxorubicin was selected as the second positive control based on previous work that assessed the ability of a triterpenoid saponin to modulate doxorubicin-induced cell apoptosis in various tissues in a rodent model.³⁸ Doxorubicin is an anthracycline chemotherapeutic that is utilized for the treatment of hematological and solid tumor malignancies and results in chronic toxicity in the heart through mechanisms associated with induced oxidative stress.³⁹ Doxorubicin was used at a concentration of 20 μ M in this study.

Proximal Tubular Epithelial Cells

Human primary proximal tubular epithelial cells were purchased from (b) (4)

Reviewer note: These cells were obtained from a different source than those used in Study HSTOX-7619. No donor information was provided for these cells by the Applicant, and no information was obtainable on the manufacturer website given that a lot number was not provided.

Renal proximal tubule cell toxicity was evaluated based on KIM-1 release. KIM-1 protein in the supernatant was quantified by commercial ELISA (R&D Systems: Minneapolis, MN, USA; catalog no. SKM100).

Amphotericin B and gentamicin were used as positive controls for measurement of KIM-1. Amphotericin B is an anti-fungal agent that is utilized for systemic infections and is known to induce nephrotoxicity in humans. The concentration of amphotericin B used in this study, 20 μ M, was adopted from a previously published study.⁴⁰ Gentamicin also results in renal damage. The concentration of gentamicin used in this study, 60 μ M, was

³⁶ Braam, S. R. et al. Prediction of drug-induced cardiotoxicity using human embryonic stem cell-derived cardiomyocytes. *Stem Cell Res* 4(2), 107-16 (2010).

³⁷ McAleer, C.W., Pointon, A., Long, C.J. et al. On the potential of in vitro organ-chip models to define temporal pharmacokinetic-pharmacodynamic relationships. *Sci Rep* 9, 9619 (2019). <https://doi.org/10.1038/s41598-019-45656-4>.

³⁸ Su, Z., Ye, J., Qin, Z. et al. Protective effects of madecassoside against Doxorubicin induced nephrotoxicity in vivo and in vitro. *Sci Rep* 5, 18314 (2016). <https://doi.org/10.1038/srep18314>.

³⁹ Pugazhendhi A, Edison TNJI, Velmurugan BK, Jacob JA, Karuppusamy I. Toxicity of Doxorubicin (Dox) to different experimental organ systems. *Life Sci*. 2018 May 1;200:26-30. doi: 10.1016/j.lfs.2018.03.023. Epub 2018 Mar 10. PMID: 29534993.

⁴⁰ Yano T, Itoh Y, Kawamura E, Maeda A, Egashira N, Nishida M, Kurose H, Oishi R. Amphotericin B-induced renal tubular cell injury is mediated by Na⁺ Influx through ion-permeable pores and subsequent activation of mitogen-activated protein kinases and elevation of intracellular Ca²⁺ concentration. *Antimicrob Agents Chemother*. 2009 Apr;53(4):1420-6. doi: 10.1128/AAC.01137-08. Epub 2009 Jan 12. PMID: 19139282; PMCID: PMC2663073.

adopted a previously published study focused on evaluating gentamicin exposure in renal proximal tubule cells over 14 days, similar to the current study time course.⁴¹

Cortical Neurons

iPSC-derived cortical neurons were provided by (b) (4) the CRO conducting the current study.

Reviewer note: Based on the limited provided information, these cells were obtained from a different source than those used in Study HSTOX-7619. No donor information or differentiation procedures were provided for these cells by the Applicant.

Cortical neuron firing rate was measured as described for Study HSTOX-7619. Baseline recordings of spontaneous cell activity were taken prior to drug application on Day 0. Following treatment, electrical recordings were conducted on Days 1, 4, 7, 10, and 14 post-dose.

Kainic acid and nimodipine were used as positive controls for measurement of cortical neuron firing rate. Kainic acid receptors play an integral role in synaptic transmission and neuronal plasticity in the maturation of various neuronal circuits and in the regulation of neuronal excitability.⁴² To capture the corresponding mechanism of potential induction of hyperexcitability and excitotoxicity due to compound administration, kainic acid was tested at a concentration of 1.5 μ M (selected based on a 5-point concentration-response curve, designed using a $C_{\max}$ of 5 μ M, over a 14-day longitudinal study) to evaluate its effects on neuronal activity, based on significantly increased neuronal activity to excitotoxicity observed with a temporal relationship at this concentration.⁴³ Nimodipine is known to have an inhibitory effect on neuronal activity. Nimodipine was tested at a concentration of 10 μ M (selected based on a 5-point concentration-response curve, designed using a $C_{\max}$ of 1 μ M, over a 14-day longitudinal study) as this concentration produced a significant inhibitory effect by Day 4 of treatment.⁴⁴

Metabolism of Tradipitant in the Four-Organ System

Tradipitant and its primary metabolites of interest (M2, M3, and M4) were quantified from medium collected from each four-organ system on Day 14 using HPLC-MS. Medium sample quantification was utilized to determine the free drug concentration and the corresponding tissue accumulation. Similarly, intracellular concentrations of tradipitant and metabolites were quantified on Day 14 following system disassembly and lysis of the four different cell types individually.

⁴¹ Regec AL, Trifillis AL, Trump BF. The effect of gentamicin on human renal proximal tubular cells. *Toxicol Pathol.* 1986;14(2):238-41. doi: 10.1177/019262338601400213. PMID: 2876489.

⁴² Nair JD, Wilkinson KA, Henley JM, Mellor JR. Kainate receptors and synaptic plasticity. *Neuropharmacology.* 2021 Sep 15;196:108540. doi: 10.1016/j.neuropharm.2021.108540. Epub 2021 Mar 30. PMID: 33794245.

⁴³ See Figure 22 in the Appendix of the [study report](#).

⁴⁴ See Figure 23 in the Appendix of the [study report](#).

GLP Compliance

No information on GLP compliance was provided in this study report. Based on the available information,⁴⁵ it appears that this study was not conducted in compliance with US FDA GLP regulations.

Results

Reviewer note: Although not included in the figures below, statistical testing of all treated conditions compared to the vehicle control was provided by the Sponsor. P values can be viewed in the full study report. For the purposes of this review, all p values < 0.05 were considered statistically significant.

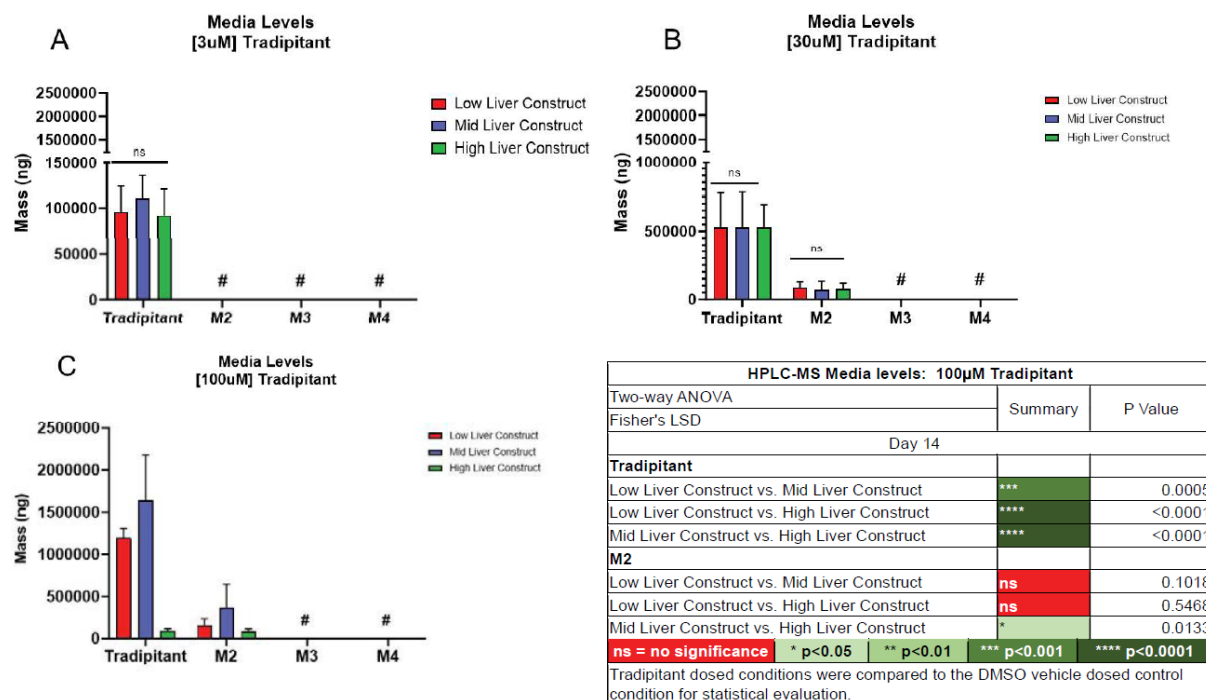
Metabolism of Tradipitant in the Four-Organ System

Following 14 days of treatment with tradipitant at 3 μ M, no difference in the media levels of tradipitant was observed between the low, moderate, and high metabolizer systems. Metabolites M2, M3, and M4 were undetectable at this concentration.

At 30 μ M, no difference in the media levels of tradipitant was observed between the low, moderate, and high metabolizer systems. Tradipitant levels were approximately 5-fold higher at 30 μ M compared to 3 μ M, despite the 10-fold difference in concentration. “Low” levels of metabolite M2 were observed at this concentration, similarly with no difference between the low, moderate, and high metabolizer systems. M3 and M4 were undetectable at this concentration.

At 100 μ M, tradipitant levels were highest in the moderate metabolizer system, followed by the low metabolizer system; levels in the high metabolizer system were notably lower than the other two systems. Tradipitant levels were approximately 2- and 3-fold higher in the low and moderate metabolizer systems at 100 μ M compared to 30 μ M for a 3.3-fold increase in concentration, while levels in the high metabolizer system were lower (a small fraction) at 100 μ M compared to 30 μ M. Levels of M2 were “low” compared to the parent drug but followed a similar pattern in that they were significantly higher in the moderate metabolizer system compared to the high metabolizer system. M3 and M4 were undetectable at this concentration.

⁴⁵ Although the GLP status of this study was not explicitly stated in the study report, (b) (4) previously stated that, in their view, US FDA GLP regulations, “did not apply [to] our organization.”

Figure 37. Quantification of Tradipitant and Its Metabolites in Media from the Four-Organ System (Day 14)

Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

#: not detected.

Figure copied directly from study report (Study HSTOX 2008-002, Figure 17).

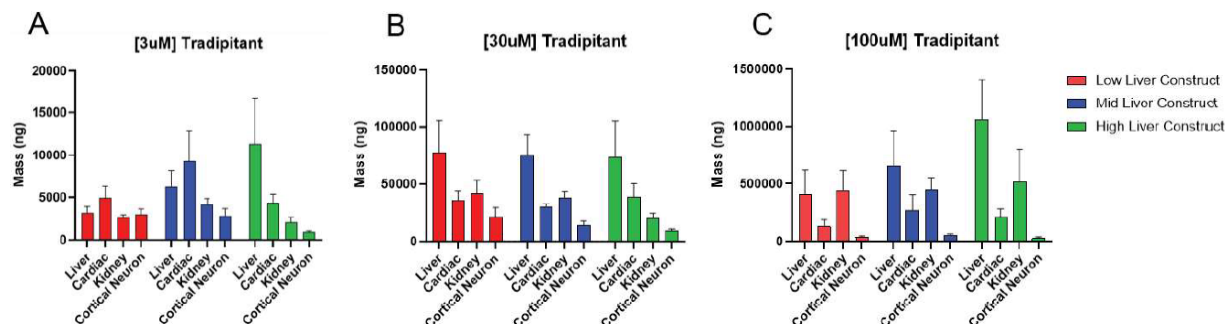
Reviewer note: As stated in the study report, each tissue did not contain the same cellular content and no normalization was included in the methodology. Thus, direct comparisons of mass detected between organ constructs should be interpreted cautiously. However, comparison of relative mass accumulation of different compounds within each construct may be useful.

Following 14 days of treatment with tradipitant at 3 μ M, the tissue level of tradipitant in hepatocytes increased in a stepwise fashion between the low, moderate, and high metabolizer constructs. Cardiomyocyte and renal cell levels of tradipitant were highest in the moderate metabolizer system, with similar levels in the low and high metabolizer systems. Cortical neuron levels of tradipitant were similar in the low and moderate metabolizer systems but lower in the high metabolizer system.

At 30 μ M, tissue levels of tradipitant in hepatocytes and cardiomyocytes were similar among the three different metabolizers. In renal cells and cortical neurons, tradipitant levels were similar in the low and moderate metabolizer systems and somewhat lower in the high metabolizer system.

At 100 μ M, the tissue level of tradipitant in hepatocytes increased in a stepwise fashion between the low, moderate, and high metabolizer constructs. Levels in cardiomyocytes, renal cells, and cortical neurons were similar among the three different metabolizers.

Figure 38. Tissue Accumulation of Tradipitant Following 14 Days of Treatment

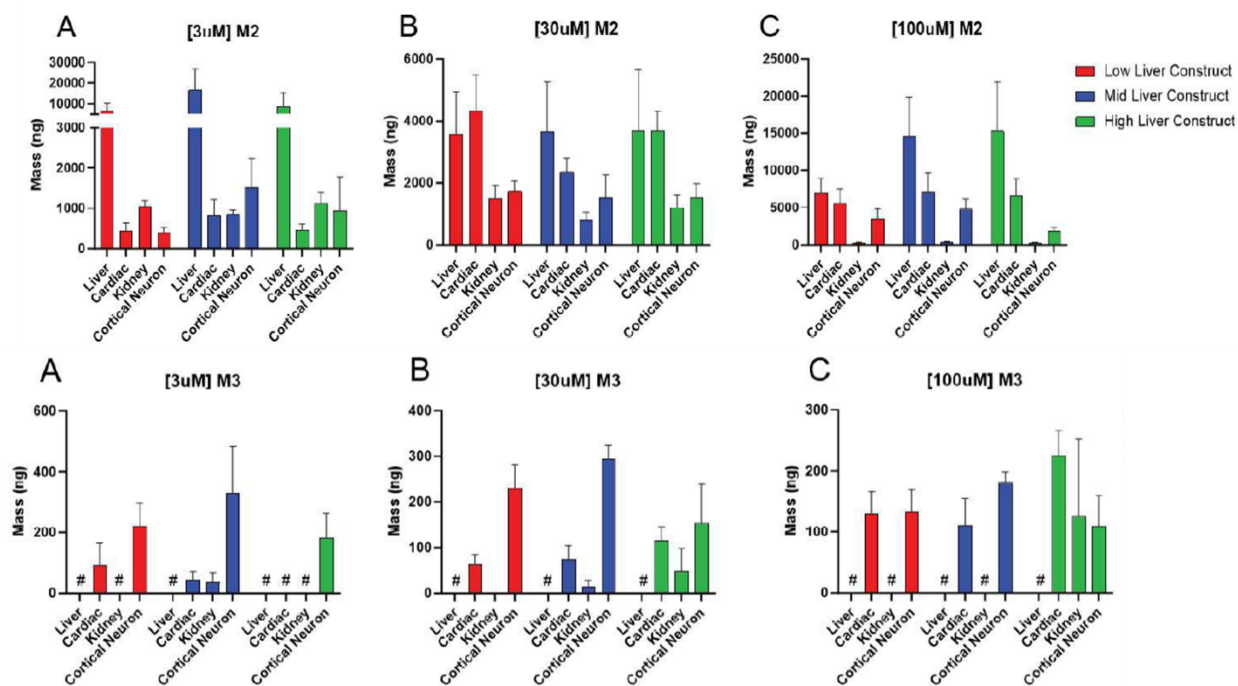


Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure copied directly from study report (Study HSTOX 2008-002, Figure 18).

M2 was detected in all cell types. M3 was found primarily in the cardiac and cortical neuron constructs, with detectable levels in the liver under some conditions. No detectable M4 was reported for any system or condition.

Figure 39. Tissue Accumulation of Metabolites M2 and M3 Following 14 Days of Treatment of Tradipitant



Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figures adapted slightly from study report (Study HSTOX 2008-002, Figures 19 and 20).

While the levels of tradipitant and M2 were generally in proportion among the different metabolizers and experimental conditions (i.e., when higher tradipitant was observed, M2 levels were also generally higher), M3 did not show a similar pattern. M3 was not detected in the liver, despite notable levels of both tradipitant and M2. In contrast, M3 was observed at relatively consistent levels in cortical neurons regardless of the relative levels of tradipitant or M2.

Hepatocytes

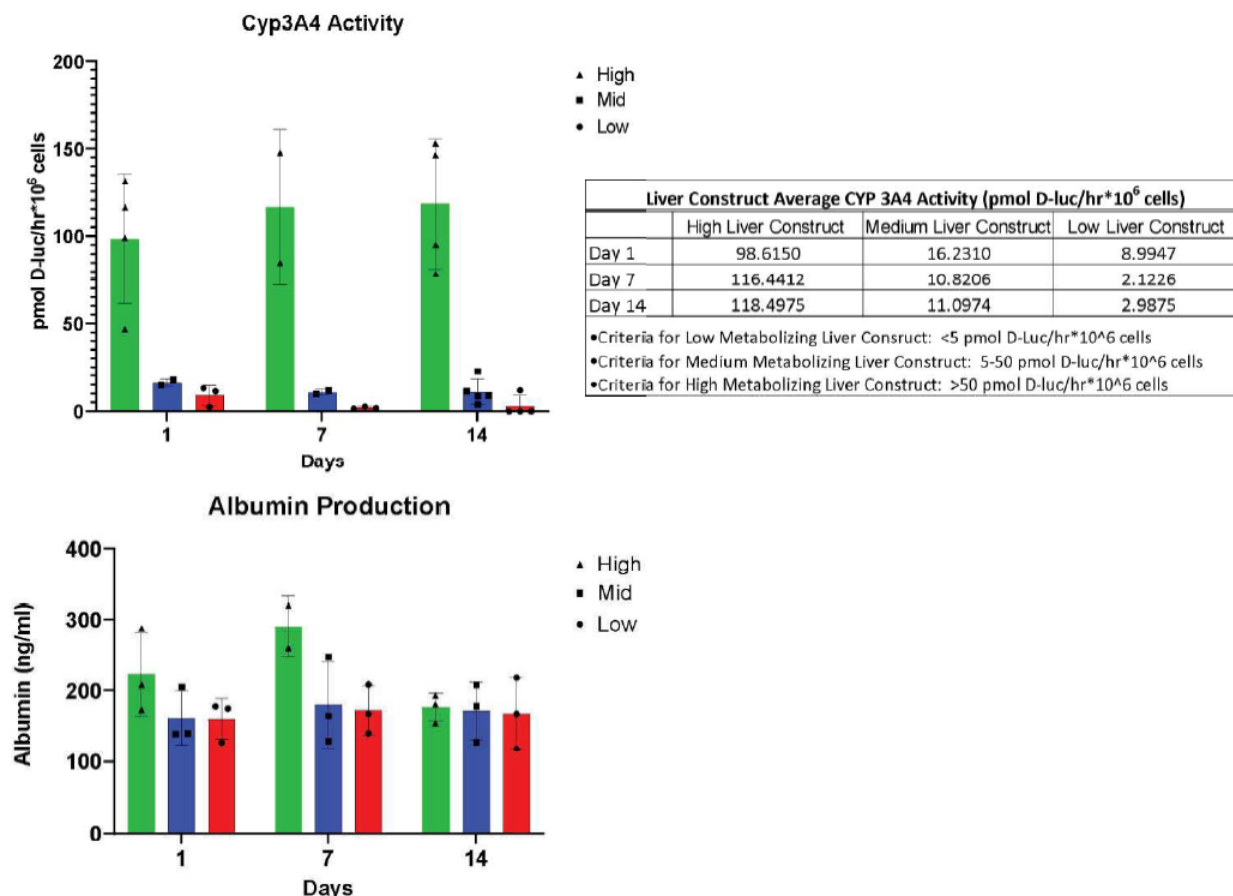
Identification of Donors with High, Moderate, and Low CYP3A4 Levels

Various donor sources were investigated to identify physiological representations of high, moderate, and low metabolizing hepatocytes, based on CYP3A4 activity.

Hepatocytes from (b) (4) were selected as the high metabolizer, and (b) (4) hepatocytes from separate donors were selected as the moderate and low metabolizers for further study.

*Reviewer note: Based on nonclinical and clinical data submitted by the Applicant, CYP3A4 has a role in the metabolism of tradipitant, but it is not the predominant or only pathway responsible (see NDA Integrated Review, Sections 13 and 14, for review of nonclinical and clinical data, respectively). Tradipitant is metabolized to M2 by non-CYP-mediated pathways; to M3 by CYP3A4 (major), CYP2C19 (minor), and CYP2C8 (minor); and to M8 by glucuronidation. M2 and M3 are further metabolized to M4 by CYP-mediated and non-specified pathways, respectively. According to the current study report, previous work (Study HSTOX-2008.001, not submitted to the Agency) demonstrated that the M2 metabolite is “spontaneously generated” and not CYP-dependent. Induction of CYP enzymes was observed following repeated dosing in rats and dogs, and clinically relevant induction of CYP3A is possible but was not definitively demonstrated. Apparent clearance of tradipitant was 33% lower in subjects with the heterozygous CYP3A4*22 allele compared to wild type (CYP3A4*1), and the Applicant suggests that CYP3A4*22 subjects may be at higher risk of adverse events; however, the impact of this finding on human PK was of unclear clinical significance. Additionally, no scientific justification or biological rationale was provided for the criteria used to define a low, moderate, or high CYP3A4 donor, and it is not clear that these criteria were pre-specified. Overall, the available data do not clearly demonstrate that endogenous/baseline CYP3A4 activity has a significant impact on tradipitant metabolism, and the clinical relevance of using donors with three different levels of CYP3A4 activity in this study has not been justified.*

Untreated hepatocytes (in isolated culture, not part of a four-organ system) displayed healthy morphology over 14 days. CYP3A4 activity was maintained over the 14-day study for all three donors; notably, no induction of CYP3A4 activity was observed. No differences in albumin levels were observed between medium and low metabolizer hepatocytes throughout the study. Albumin levels for the high metabolizer hepatocytes were higher compared to other donors on Days 1 and 7; however, by Day 14, albumin levels were similar for all donors.

Figure 40. Identification and Characterization of Low, Moderate, and High CYP3A4 Hepatocytes

Low, Mid, High: hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity). These measurements were obtained using hepatocytes in isolated cultures (i.e., not part of a four-organ system).

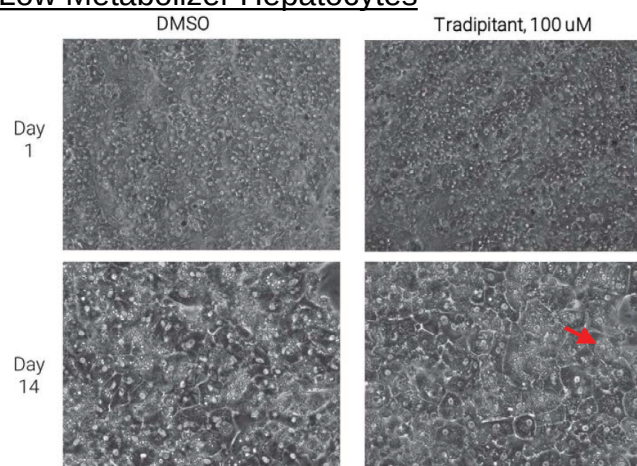
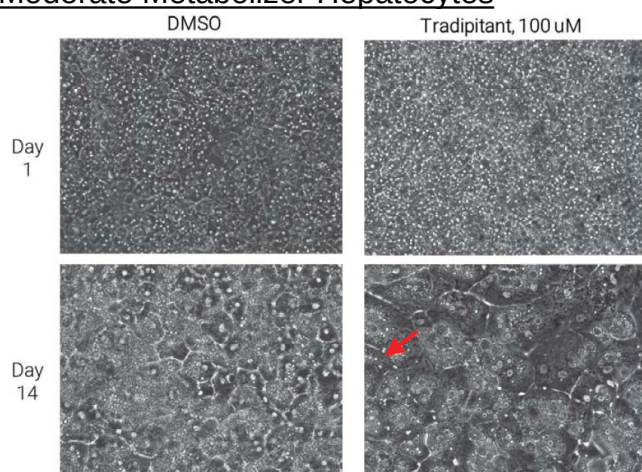
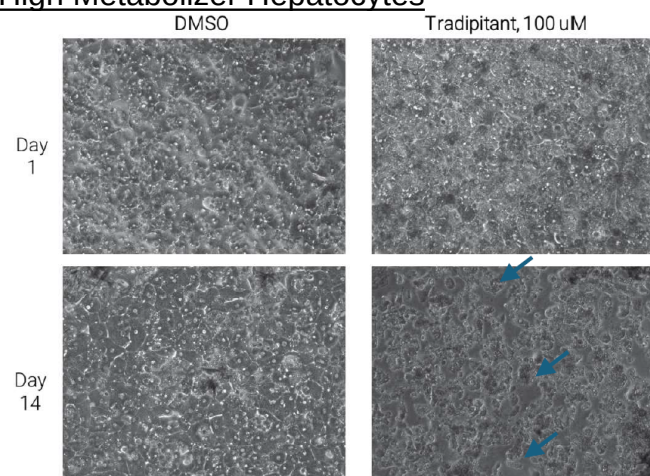
Figure copied directly from study report (Study HSTOX 2008-002, Figure 4).

Effects of Tradipitant on Viability in Hepatocytes from Different Donors

Hepatocytes in isolated culture were monitored over 14 days to assess changes in morphology attributable to parent and metabolite exposure. Observations of excessive vacuole formation or detachment of hepatocytes resulting in an inconsistent monolayer were considered evidence of toxicity.

No morphological evidence of toxicity was observed in low, moderate, or high metabolizer hepatocytes at a tradipitant concentration of 3 μ M during the 14-day study when compared to vehicle control cells. At 100 μ M, vacuoles were observed in low and moderate metabolizer hepatocytes (see red arrows in Figure 41), but these findings were similar to those observed in vehicle controls. However, substantial cell detachment (see blue arrows) was observed in the high metabolizer hepatocytes at Day 14, indicating toxicity with tradipitant treatment. Toxicity under these conditions may be attributable to prolonged exposure to metabolite(s) and/or metabolite byproduct(s) that

were not present or were present at lower levels in the low and moderate metabolizer hepatocytes; however, no direct association was suggested by the Applicant.

Figure 41. Morphology in Hepatocytes Treated with 100 μ M Tradipitant for 14 Days**Low Metabolizer Hepatocytes****Moderate Metabolizer Hepatocytes****High Metabolizer Hepatocytes**

Figures copied directly from study report (Study HSTOX 2008-002, Figures 5-7).

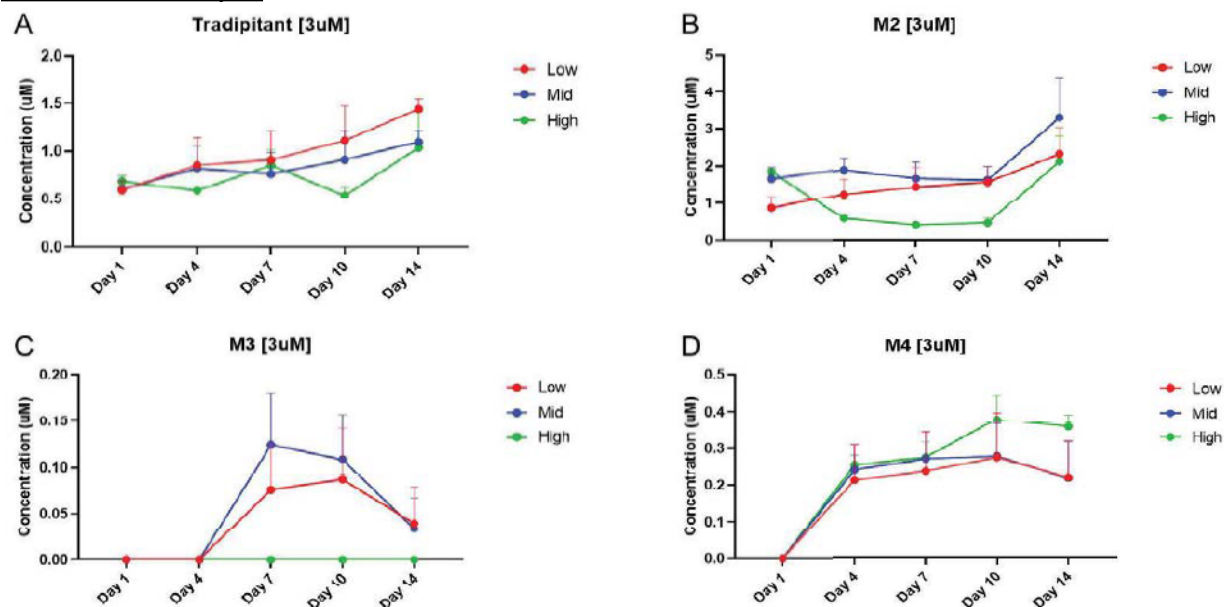
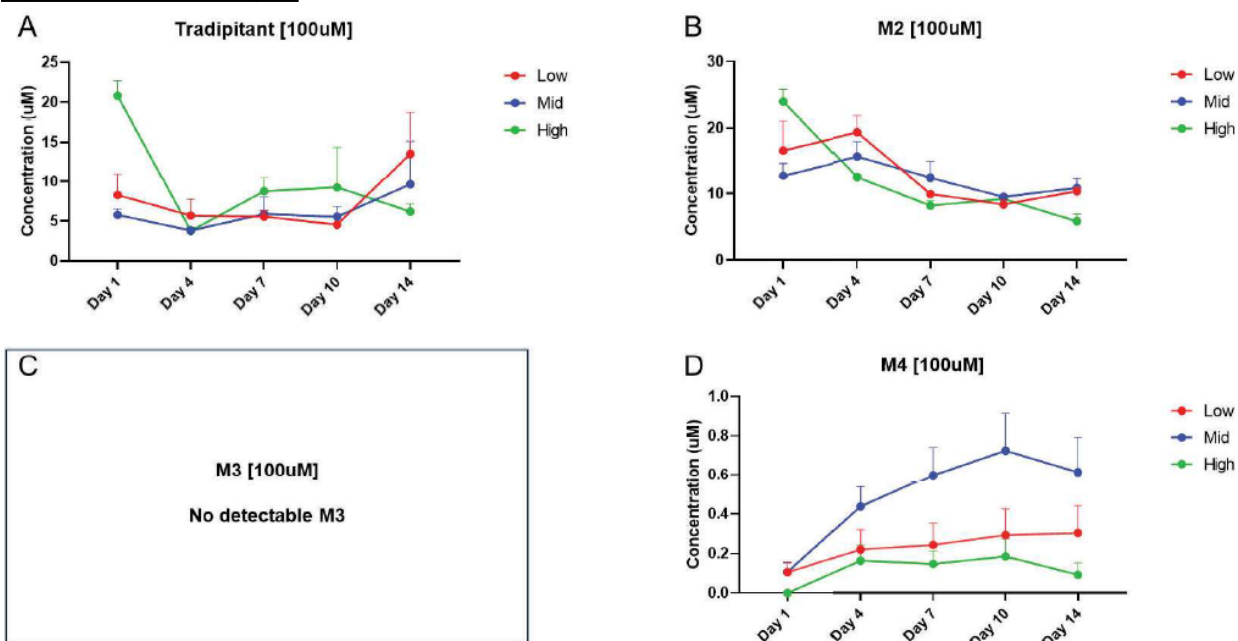
Over the course of 14 days, treatment with tradipitant at 3 μ M resulted in some accumulation of the parent drug and metabolites in hepatocytes from all donors, though variability prevents any firm conclusions of metabolic patterns between the different metabolizing conditions at this concentration. The final concentration of tradipitant on Day 14 was loosely inversely related to the level of CYP3A4 activity, although the absolute differences were small. Production of M2 over the course of the study was highest in the moderate metabolizer hepatocytes, followed by the low and lastly the high metabolizers. Production of M3 was below the limit of detection (not provided) in all donors on Day 1 but detectable thereafter, with the highest levels observed in the moderate metabolizer hepatocytes followed by the low metabolizer hepatocytes; M3 remained undetectable in the high metabolizer hepatocytes throughout the study. Production of M4 was below the limit of detection (not provided) in all hepatocytes on Day 1 but detectable thereafter. M4 levels were similar in the low and moderate metabolizer hepatocytes, while the high metabolizer hepatocytes had similar levels as other donors on Days 4 and 7 but higher levels on Days 10 and 14.

Treatment with tradipitant at 100 μ M resulted in relatively stable levels of parent drug in low and moderate metabolizer hepatocytes over 14 days but lower exposure in high metabolizer hepatocytes on Day 14 compared to Day 1. The final concentration of tradipitant on Day 14 was loosely inversely related to the level of CYP3A4 activity, although the absolute differences were small. Production of M2 decreased over the course of the study, with levels similar among the three different metabolizers on Day 14. Production of M3 was below the limit of detection (not stated) in all donors at all timepoints. Production of M4 was highest in the moderate metabolizer hepatocytes, with lower levels observed in the low and high metabolizers.

Overall, quantified levels of M2 were similar to or higher than tradipitant in all donors. Levels of M3 relative to tradipitant were lower (10% to 20% those of tradipitant at 3 μ M and undetectable at 100 μ M) and were not clearly related to CYP3A4 activity. Levels of M4 relative to tradipitant were highly variable (undetectable to approximately 40% at 3 μ M and undetectable up to approximately 20% at 100 μ M).

Reviewer note: As discussed for Study HSTOX-7619, the drug and metabolite pharmacokinetic profiles measured in this in vitro study are not consistent with human clinical or in vivo animal study data. Following a single dose of 25 mg radiolabeled tradipitant in healthy human volunteers, drug-related exposure measured over 24 hours was 9% parent drug, 4% M2, 5% M3, and 8% M4 (i.e., the parent drug and major identified human metabolites accounted for only 26% of drug-related exposure; see Study H8R-MC-HKAK and 2.4 Nonclinical Overview, pg. 20). In healthy volunteers administered 85 mg tradipitant BID for 12 days, drug-related exposure measured over 24 hours was composed of 50% parent drug, 17% M2, 16% M3, and 17% M4 (see Study VP-VLY-686-1102, pgs. 60-63). Additionally, although data are limited, M2 represented < 1% of drug-related exposure in nonclinical toxicology studies. Due to the differences in in vitro and in vivo metabolism, any findings related to toxicity in this assay may not be biologically relevant to humans. Finally, these results call into question the role and importance of CYP3A4 in the metabolism of tradipitant. As stated

above, CYP3A4 has been identified as the major pathway of metabolism of tradipitant to M3, with little or no additional effects; however, the production of M3 was not highest in the high metabolizer hepatocytes, as would be expected. An alternative explanation could be that increased production of M3 led to further conversion of M3 to M4 (by non-CYP-mediated pathways); however, again, levels of M4 were lowest in the high metabolizer hepatocytes, contrary to that expected. While it is clear that differences in metabolism were present among the three donors in this study, it is not clear what the biologically significant differences were (e.g., differences in baseline or induced activities of other CYP enzymes, differences in non-CYP pathways) or how such differences may be clinically relevant.

Figure 42. Quantification of Tradipitant and Its Metabolites Over 14 Days of Treatment with Tradipitant**Treatment at 3 μ M****Treatment at 100 μ M**

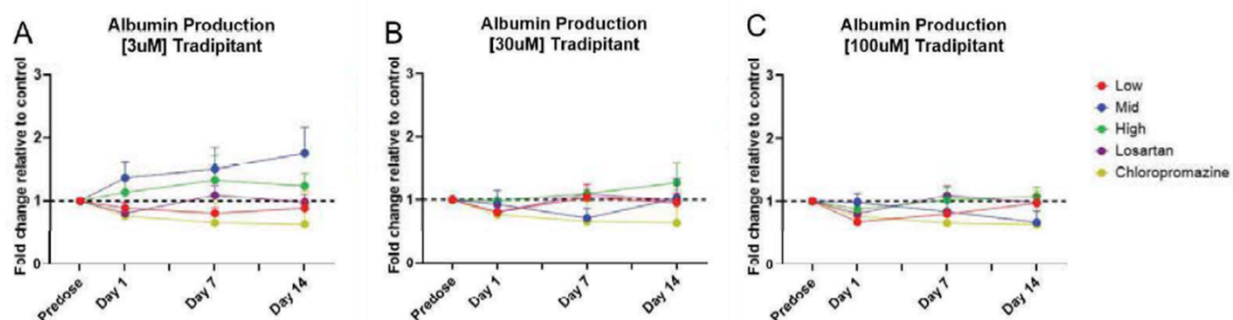
Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figures copied directly from study report (Study HSTOX 2008-002, Figures 8 and 9).

Effects of Tradipitant Treatment on Hepatocytes as Part of the Four-Organ System

No significant effect of tradipitant treatment was observed on albumin production in the four-organ system on Days 1 and 7. On Day 14, significantly increased albumin production was observed at 3 μ M in the moderate metabolizer system only compared to control, with no significant effects observed under other conditions. No significant effects of losartan or chlorpromazine were observed on albumin production at any timepoint.

Figure 43. Albumin Production in the Four-Organ System Over 14 Days of Treatment with Tradipitant



Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure adapted slightly from study report (Study HSTOX 2008-002, Figure 10).

Cardiomyocytes

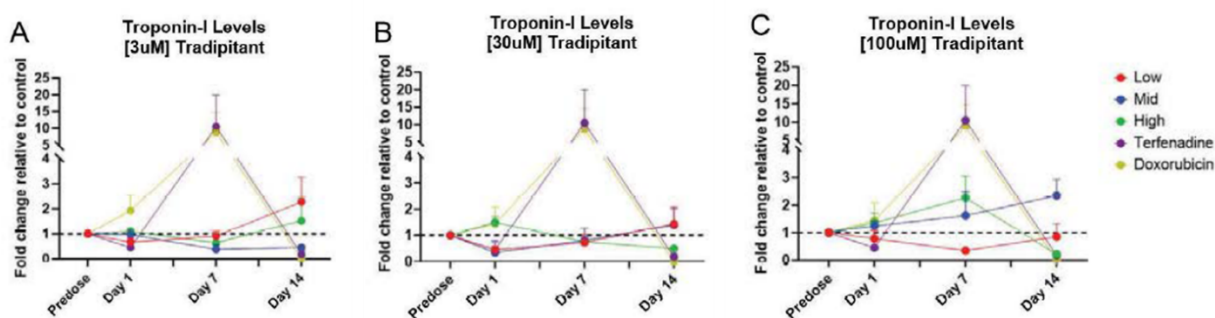
Positive controls terfenadine and doxorubicin produced substantial toxicity over the 14-day study, resulting in non-viable cultures and, thus, limited datasets at later timepoints. Results with these compounds should be interpreted with caution, especially at later timepoints.

No significant effect of tradipitant treatment was observed on troponin-I levels on Day 1. On Day 7, significantly increased troponin-I was observed with tradipitant at 100 μ M in the high metabolizer system compared to control, but no effects were observed with tradipitant at 100 μ M in the low or moderate metabolizer systems or in any system with tradipitant at 3 or 30 μ M. On Day 14, significantly increased troponin-I was observed with tradipitant at 3 μ M in the low metabolizer system and at 100 μ M in the high metabolizer system, but not for the other conditions. Significantly increased troponin-I was observed with both terfenadine and doxorubicin on Day 7 but not on Day 1 or Day 14, with the latter likely due to the observed high level of cytotoxicity rather than recovery.

Reviewer note: As previously stated, it is not clear which hepatocytes were used for the experiments with positive controls. As terfenadine metabolism to the non-cardiotoxic metabolite fexofenadine is primarily via CYP3A4, it is expected that treatment with terfenadine would have different toxic effects on cardiac function between low, moderate, and high metabolizer systems. As terfenadine did produce cardiac toxicity in this assay, this positive control is generally considered sufficient to demonstrate the

validity of the assay (at least through Day 7, before excessive cytotoxicity was observed). However, demonstrable differences in terfenadine toxicity via troponin-I levels with the different metabolizer systems would have provided additional validation of the differences in CYP3A4 activity between donors and demonstrated that this could result in differences in drug toxicity.

Figure 44. Troponin-I Levels in the Four-Organ System Treated with Tradipitant for 14 Days

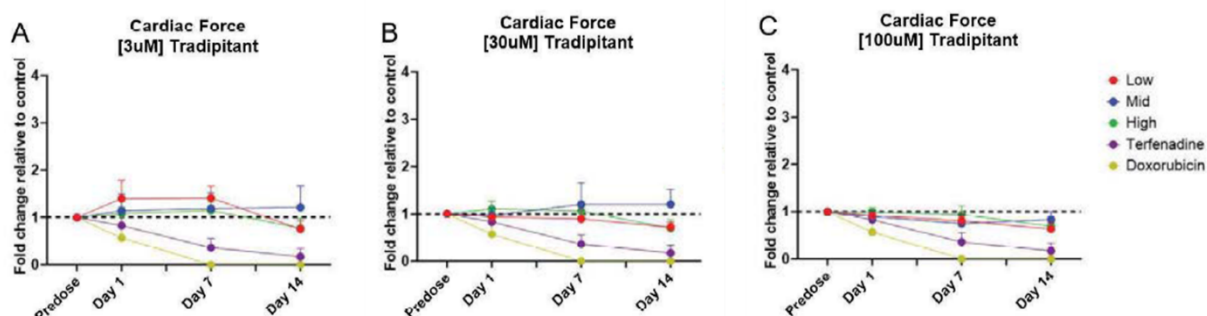


Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 11).

No significant effect of tradipitant treatment was observed on cardiac force on Days 1 or 7. On Day 14, significantly decreased cardiac force was observed with tradipitant at 100 μ M in the low metabolizer system only compared to control, with no effects observed under other conditions. Terfenadine treatment resulted in significantly decreased cardiac force on Days 7 and 14 compared to control. Doxorubicin treatment resulted in significantly decreased cardiac force on Days 1, 7, and 14 compared to control.

Figure 45. Cardiac Force in Cardiomyocytes Treated with Tradipitant for 14 Days



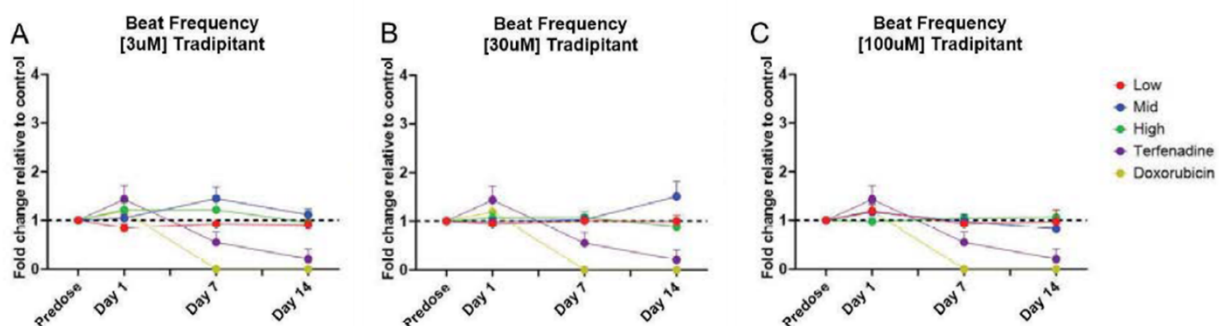
Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 12).

No significant effect of tradipitant treatment was observed on cardiac beat frequency on Day 1. On Day 7, significantly decreased cardiac beat frequency was observed only

with tradipitant at 3 μM in the moderate metabolizer system compared to control, with no effects observed under other conditions. On Day 14, significantly decreased cardiac beat frequency was observed only with tradipitant at 30 μM in the moderate metabolizer system compared to control, with no effects observed under other conditions. Terfenadine treatment resulted in significantly decreased cardiac force on Days 1, 7, and 14 compared to control. Doxorubicin treatment resulted in significantly decreased cardiac force on Days 7 and 14 compared to control.

Figure 46. Cardiac Beat Frequency in Cardiomyocytes Treated with Tradipitant for 14 Days

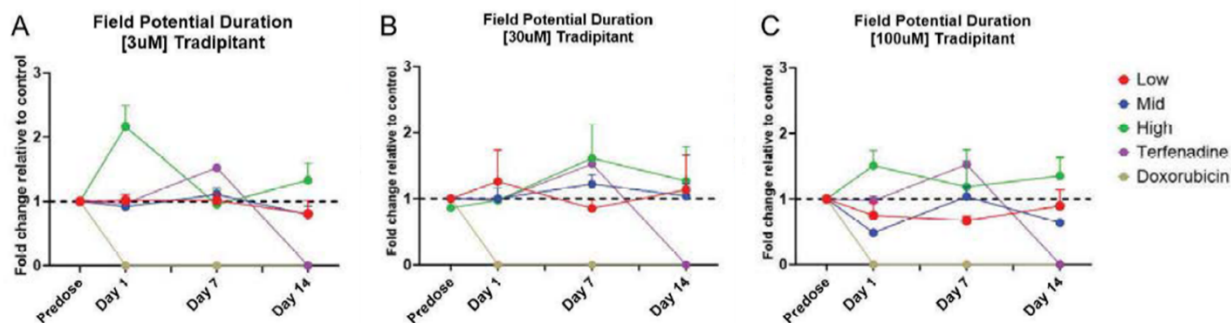


Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 13).

On Day 1, significantly increased FPD was observed with tradipitant at 3 and 100 μM in the high metabolizer system only compared to control, with no effects observed under other conditions. No significant effect of tradipitant treatment as observed on FPD on Days 7 and 14. Terfenadine treatment resulted in significantly increased FPD on Day 7 and decreased FPD on Day 14 compared to control. Doxorubicin treatment resulted in significantly decreased FPD on Days 1, 7, and 14 compared to control.

Figure 47. Field Potential Duration in Cardiomyocytes Treated with Tradipitant for 14 Days



Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

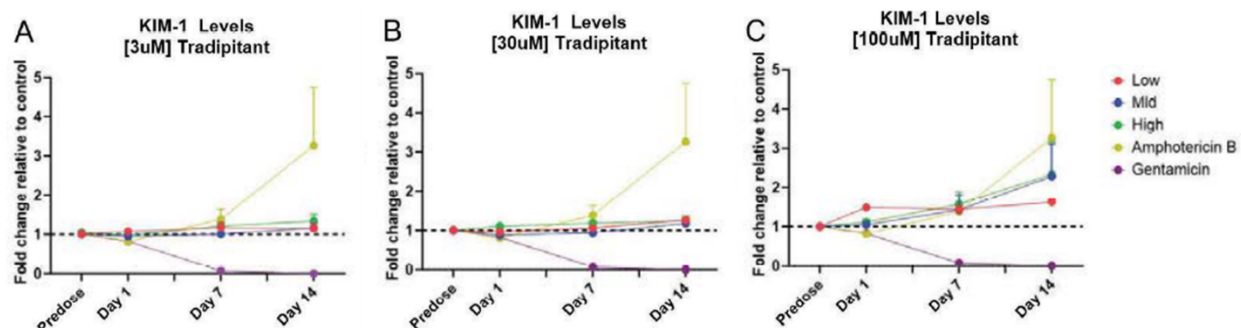
Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 14).

Proximal Tubular Epithelial Cells

No significant effect of tradipitant treatment was observed on KIM-1 release on Day 1. On Day 7, significantly increased KIM-1 was observed only with tradipitant at 3 and 30 μM in the high metabolizer system compared to control, with no effects observed under other conditions. On Day 14, significantly increased KIM-1 was observed with tradipitant at 3 μM in the high metabolizer system, at 30 μM in all systems, and at 100 μM in both the moderate and high metabolizer systems compared to controls. Amphotericin B treatment only resulted in significantly increased KIM-1 on Day 14 compared to control. Gentamicin treatment only resulted in significantly decreased KIM-1 on Day 7 compared to control.

Reviewer note: Based on the limited data provided, it appears that gentamicin treatment produced significant toxicity by Day 7, and thus data from this and later timepoints should be interpreted with caution.

Figure 48. KIM-1 Release in Proximal Tubule Epithelial Cells Treated with Tradipitant for 14 Days

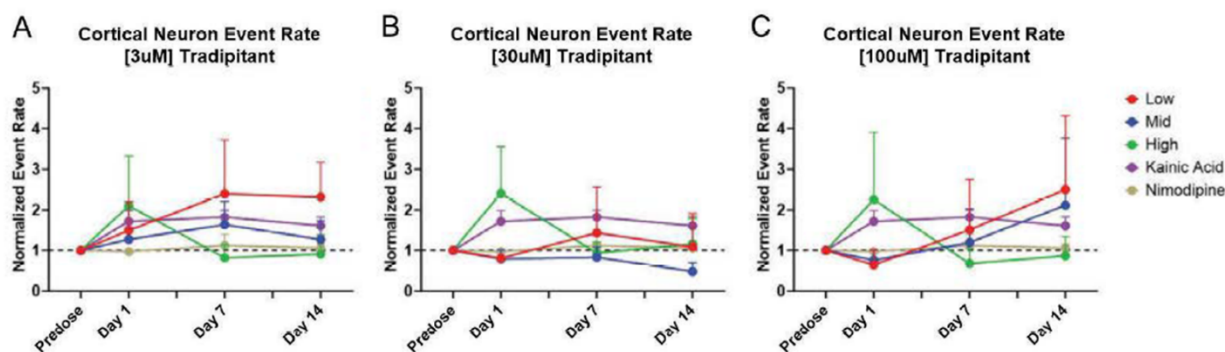


Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 15).

Cortical Neurons

On Day 1, significantly increased cortical firing rate was observed with tradipitant only at 30 μM in the high metabolizer system compared to control, with no effects observed under other conditions. No significant effect of tradipitant treatment was observed on cortical firing rate on Days 7 and 14. Kainic acid treatment resulted in significantly increased cortical firing rate on Days 7 and 14 compared to control. No significant effect of nimodipine treatment was observed on cortical firing rate throughout the study.

Figure 49. Firing Rate in Cortical Neurons Treated with Tradipitant for 14 Days

Low, Mid, High: four-organ system including hepatocytes from low, moderate, and high metabolizers (based on CYP3A4 activity).

Figure slightly adapted from study report (Study HSTOX 2008-002, Figure 16).

11 Other Toxicology Studies

11.1 Toxicology Assessment of Tradipitant and Four Corresponding Metabolites Performed via the TEST, ILab2, and ToxTree Software and augmented by analog searches from the DSSTox, SuperToxic and ACToR databases – 2015-01-30

In Silico Toxicologic Assessment

Methods

Tradipitant and metabolites M2, M3, M4, and M8 were analyzed for potential toxicologic properties using in silico methods. Tools and databases used in this analysis included TEST (Toxicity Estimation Software Tool), ILab2, ToxTree, DSSTox, SuperToxic, and ACToR. Various toxicological properties were assessed, including the potential for acute toxicity (LD₅₀ in rats), mutagenicity, carcinogenicity, developmental toxicity, hERG inhibition, as well as skin and eye irritation.

Results

Tradipitant and its metabolites raised a number of toxicological concerns in the analysis, including potential mutagenicity and inhibition of the hERG channel current. The multiple polarized aryl groups in tradipitant, most notably the 3-pyridinyl group, were flagged as potentially reactive and may result in unexpected toxicological effects. However, the analysis concluded that tradipitant and its metabolites were considered overall to have “a low net toxicity risk.”

Reviewer note: Although this assessment was conducted in 2015, this report was submitted for the first time in the current NDA.⁴⁶ The review team requested the study report,¹ and the report was submitted in response to the IR during the review cycle

⁴⁶ Discussed in Modules 2.4 Nonclinical Overview, 2.6.6 Toxicology Written Summary, and 2.6.7 Toxicology Tabulated Summary.

(SDN 9: March 25, 2025). While the broad in silico analysis conducted here is useful for highlighting potential toxicity risks for further analysis, it is important to confirm (or refute) such risks experimentally. In light of the completed in vitro and in vivo toxicity studies with tradipitant and/or its metabolites, the findings in this report are not considered toxicologically relevant.

11.2 Chemical and structural analysis of tradipitant and its metabolites M2, M3, and M4

[Response to Non-Clinical Information Request dated 01 October 2025](#)

Methods

Updated in silico analyses were conducted by the Applicant to support the safety of metabolites M2, M3, and M4 for this application.^{47,48,49,50} These analyses were intended to assess if and how structural differences in the metabolites might affect their toxicity profile compared to tradipitant. Briefly, these in silico analyses were conducted using a machine learning-assisted workflow developed by xAI's Grok system, an advanced large language model trained on scientific datasets and further validated via the Applicant's in-house Python scripts. Notably, the Applicant's comparative structural prediction data were inferred based on RDKit-computed descriptors and qualitative thresholds aligned with best practices from consensus classifiers, rather than direct execution of these models. It is not clear why the Applicant chose to design a workflow using a large language model and a custom set of molecular descriptors and use information from existing classifier techniques to 'infer' predictions, rather than directly using existing (Q)SAR modeling software. Additionally, insufficient detail was provided on the consensus classifiers used in the analyses to fully define the approach. However, enough information was provided to facilitate review of the findings.

Results

For metabolite M2, no additional reactive groups were identified compared to tradipitant, and no significant differences between tradipitant and M2 were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M2 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. M2 was predicted to have slightly increased risks of hepatotoxicity and cardiotoxicity compared to tradipitant. Metabolite M3 was shown to have structural alerts for oxidative stress, hepatotoxicity, and genotoxicity related to the N-oxide moiety and increased covalent binding risk (e.g., sensitization and hepatotoxicity) related to the alpha, beta-unsaturated ketone moiety that are not present in tradipitant. Compared to tradipitant, M3 had no significant differences predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M3 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. M3 was

⁴⁷ NDA 220152: Information Request. October 1, 2025.

⁴⁸ NDA 220152, SDN 23: October 15, 2025.

⁴⁹ NDA 220152: Information Request. October 20, 2025.

⁵⁰ NDA 220152, SDN 24: October 22, 2025.

predicted to have slightly increased risk of oxidative stress, hepatotoxicity, and cardiotoxicity compared to tradipitant.

For metabolite M4 compared to tradipitant, no significant differences were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization. The potential for tradipitant and M4 to cause nephrotoxicity and neurotoxicity was also considered comparable and low. Compared to tradipitant, M4 was predicted to have slightly increased risk of oxidative stress, hepatotoxicity, and cardiotoxicity. A structural alert was also identified for genotoxicity with M4 based on the N-oxide moiety.

Overall, the updated in silico analyses predicted that metabolites M2, M3, and M4 were unlikely to present additional toxicity concerns compared with tradipitant. The review team acknowledges that this type of computational toxicology analysis is not validated for this intended use. However, in conjunction with the internally conducted (Q)SAR analysis and following consideration of all available data (see discussion in Section 13.3.2.5 of the Integrated Review for this NDA), we generally agree with the Applicant's stated position.

12 Nonclinical Discussion

12.1 Assessment of Nonclinical Data to Support the Safety of Unrestricted, Lifetime Use of Tradipitant

12.1.1 Background of the Nonclinical Program for Tradipitant

A detailed account of the regulatory history of this application is provided in the IRT for NDA 220152. The below discussion is intended to provide the context necessary to understand the scientific and regulatory issues that impacted the nonclinical assessment of this NDA. As such, this background should not be considered exhaustive.

The Applicant submitted NDA 220152 for tradipitant for the acute prevention of vomiting induced by motion in adults on December 30, 2024. Although tradipitant will be used intermittently⁵¹ for this indication, clinical data with tradipitant in Trial 3403 have demonstrated that a subset of individuals are likely to use the product frequently (see IRT Section 7.6.2.1 for a detailed presentation of the clinical data). Additionally, the relatively long half-life of tradipitant and its major human metabolites (28+ hours) supports that even single doses spaced days apart could lead to sustained exposure to and even accumulation of drug-related material. Therefore, long-term nonclinical data are warranted to support the safety of unrestricted use of tradipitant over a lifetime.

Completed repeat-dose toxicity studies with tradipitant include studies of up to 3 months in mice, 6 months in rats, and 3 months in dogs. During clinical development, the review team recommended that the Applicant conduct a chronic (i.e., ≥6-month) toxicity study in a nonrodent species to adequately assess the risk of cumulative toxicity following repeated short-term exposures to tradipitant and, thus, support the safety of tradipitant for the indication of prevention of vomiting induced by motion.⁵² This is in line with recommendations for some other drugs with repeated, short-term exposure (e.g., products for migraine, herpes simplex). At the time of this review, the Applicant has not conducted a chronic toxicity study with tradipitant in a nonrodent species to assess the risk of cumulative toxicity following repeated short-term exposures to tradipitant. Additionally, the Applicant had not provided adequate scientific justification for why such a study is not warranted to support the safety of tradipitant for the current indication.

The initial NDA submission and subsequent nonclinical amendments included reports of 24 nonclinical studies that had not previously been submitted to IND 141315 or cross-referenced from any other IND for tradipitant.⁵³ Seven of these reports were of

⁵¹ Although vomiting induced by motion will resolve after exposure to motion ceases, such episodes are expected to recur once the motion stimulus is reintroduced. Based on clinical knowledge about this indication and the Applicant's protocol for Trial VP-VLY-686-3403 for this intended use, tradipitant is expected to be used repeatedly over a lifetime.

⁵² IND 141315: [Advice Letter](#). February 28, 2023.

(b) (4)

alternative in vitro assays intended to support the safety of tradipitant for the proposed indication. The Applicant did not provide their rationale for the conduct of these studies or otherwise discuss their contribution to the overall nonclinical program in the current NDA. However, the Applicant previously indicated that nonclinical studies using alternative assays were conducted “to help elaborate further on the safety of tradipitant short of conducting a lethal (animal sacrifice required) 9-month dog study.”⁵⁴ Specifically, the Applicant claimed that data derived from these alternative assays, as part of their “totality of evidence” approach, indicate that the recommended chronic nonrodent toxicity study (e.g., a 9-month dog study) is not justified.⁵⁵ The scientific and regulatory utility of these nonclinical studies using NAMs is the focus of this discussion.

12.1.2 Assessment of Alternative Assays to Characterize the Safety of Tradipitant

Liver Models of Toxicity

Liver- and thyroid-related findings were consistently observed in nonclinical species treated with tradipitant. These findings (i.e., increased organ weights, moderate and reversible increases in liver enzymes, and/or minimal to mild hepatocyte and thyroid follicular cell hypertrophy/hyperplasia) were generally considered by the Applicant to be adaptive changes indicative of increased expression of metabolizing enzymes; the Division considers this explanation reasonable. However, foci of inflammatory cells, together with minimal to slight hepatocyte necrosis, were observed in 6/10 mid dose males, 9/10 high dose males, and 3/10 high dose females in the 13-week study in Han Wistar rats (clinical effect margins of 8.5 in males and 85 in females, respectively, relative to the maximum clinical dose of 170 mg/day, based on HED); these findings were considered adverse rather than adaptive. Such findings were not observed in studies in Fisher rats of up to 6 months duration or in studies in dogs of up to 3 months duration, and the potential explanation for the species and strain differences is unknown.

The Applicant conducted five safety pharmacology studies using alternative in vitro assays with the objective of further investigating and/or quantifying the in vitro hepatotoxic potential of tradipitant and to evaluate its underlying toxicity mechanisms.

In the four non-GLP studies using cultured 3D human hepatocytes, significant variability was observed between donors, including variability in the toxicity induced by the positive control (when included) as well as variability in the toxicity observed between studies, even when the same donors were used.⁵⁶ In Studies HPTOX-3550, HPTOX-

(b) (4)

⁵⁶ Three donors were used in both Studies HPTOX-3550 and HPTOX-3610 with inconsistent findings. Following 2 weeks of treatment with tradipitant, toxicity was noted at a notably lower concentration for 2/3 donors (0.350 versus 17.5 µg/mL) and at a higher concentration for the remaining donor (35 µg/mL).

3560, and HPTOX-3540, decreased hepatocyte cell viability was observed following tradipitant treatment for 2 or 4 weeks at concentrations as low as 1.05 µg/mL but more consistently in the range of 3.5-7.0 µg/mL, with no clear concentration- or time-dependent effects reported. Additionally, no primary mechanism for the observed hepatocyte toxicity was identified in these studies, although the potential for tradipitant to induce cholestasis was noted when hepatocyte spheroids were co-cultured with bile acids. In Study HPTOX-3610, hepatocyte toxicity was observed following tradipitant treatment for 2 weeks at concentrations as low as 0.350 µg/mL. Hepatocyte toxicity was also observed with tradipitant metabolites M2 (at concentrations as low as 0.350 µg/mL), M3 (as low as 1.05 µg/mL but more commonly at 10.5 or 35 µg/mL), M4 (as low as 0.350 µg/mL), and M8 (in 2/4 donors only, as low as 0.350 and 10.5 µg/mL, respectively).

In the study using the liver co-culture MPS, qualitative findings of mild to moderate hepatocyte toxicity were noted with tradipitant in all donors at the highest tested concentration (26.3 µM or 15 µg/mL) starting at 72 hours, while no toxicity was observed in LSECs with treatment up to 168 hours (7 days). Qualitative findings of minimal to mild toxicity were also noted sporadically in hepatocytes and LSECs treated with metabolites M2, M3, M4, and/or M8 at the latest timepoint of 168 hours. No clear effects of tradipitant or its metabolites were observed on isolated endpoints representative of liver function and injury including albumin, AST, ALT, ROS generation, CCK-18 protein expression, or miRNA-122 expression. Although four positive controls were used in this study, no explanation was given for their selection. At least one positive control resulted in statistically significant changes for each chosen endpoint. However, thresholds for biologically or clinically significant changes were not pre-specified for each endpoint. Additionally, no potential mechanism for the observed hepatocyte toxicity was identified.

These studies do not rule out the potential for tradipitant and/or its major metabolites to cause liver injury, as previously observed in the 13-week study in Han Wistar rats, and support that the potential risk is not animal-specific (i.e., it can also occur in human cells). As mentioned previously, the stated objective of the submitted studies using cultured 3D human hepatocyte spheroids or human liver co-culture MPS was to quantify the in vitro hepatotoxic potential of tradipitant and to evaluate its underlying toxicity mechanisms; this objective was not achieved. The Applicant did not identify a primary mechanism for potential liver toxicity in these studies. Additionally, the Applicant did not provide any validation to support the clinical relevance of the extent or durability of drug exposure under these study conditions (i.e., how exposure following daily dose administration relates to constant treatment or drug refreshment every few days in culture). Furthermore, although the Applicant referred to the tested concentrations as multiples of the clinical C_{max} , this approach does not clearly define a threshold at which the effects may be expected to be observed clinically. Indeed, IVIVE analyses should have been conducted to determine how the in vitro concentration relates to that observed in humans, as direct comparison of C_{max} and in vitro concentrations

versus 7.0 µg/mL) in Study HPTOX-3610 compared to Study HPTOX-3550. The source of this variability is unknown.

“oversimplifies the complex relationship between in vitro and in vivo drug behavior and can lead to inaccurate conclusions.”⁷ Ultimately, even setting aside the identified limitations, these short-duration experiments (up to 4 weeks in hepatocyte spheroids and 7 days in the liver co-culture chip MPS) are inadequate to inform the potential risk of liver injury with long-term use of tradipitant.

Four-Organ System to Address Potential Multi-Organ Toxicity

The Applicant also conducted two prospective toxicology studies using a “four-organ” MPS comprised of human liver, cardiac, renal, and neuronal cells with the objective of evaluating the safety of tradipitant.

Based on the stated objective, these studies are in vitro nonclinical laboratory studies intended to support the safety and approval of tradipitant under this NDA. These studies were not conducted in compliance with US FDA GLP regulations. The validity and reliability of the results from nonclinical safety studies depend on careful adherence to certain standards for study conduct that help to ensure the quality, integrity, and reliability of the data, establishing confidence in the scientific merit of the study so that accurate interpretation of the results is possible. We do not wholly discount the findings of these studies based on their non-GLP status; however, caution should be applied in the interpretation of findings.

Study HSTOX-7619: 7-Day Study of Tradipitant in the Four-Organ System

According to the Applicant, no effects of tradipitant were observed on selected biomarkers of function for any of the four cell types following repeated treatment with tradipitant for 7 days.

Numerous limitations in study design and conduct preclude its substantive contribution to the long-term safety profile of tradipitant.

- The evaluation of potential toxicity using the four-organ system was limited in scope (i.e., not comprehensive).
 - o The MPS used human-derived cells from the heart, liver, kidney, and brain, a small subset of tissues compared to those present in a whole animal or human. Furthermore, there is no rationale for the specific subset of organs chosen for this study or how an investigation using only these organs can evaluate toxicity within fully integrated physiological systems (i.e., including any effects of metabolism, immune responses, and hormones) to provide a broad, tissue-agnostic assessment of toxicity and to inform safe use of a drug.
 - o Within an individual “organ,” only a single cell type was cultured and exposed to tradipitant. A single cell type only represents a portion of an organ and thus cannot adequately or comprehensively assess potential toxicities within that organ, precluding a recapitulation of full in vivo physiology and pathophysiology. For example:

- Liver cell types: hepatocytes, cholangiocytes, liver natural killer cells, erythroid cells, endothelial cells, hepatic stellate cells, Kupffer cells, neutrophils, T cells, plasma cells.⁵⁷
- Kidney cell types: Podocytes, proximal tubular cells, Ascending Loop of Henle cells, endothelial cells, fibroblasts, macrophages, T cells, plasma cells.⁵⁷
- Heart cell types: Cardiomyocytes, cardiac mitotic cells, endothelial cells, smooth muscle cells, fibroblasts, macrophages, neutrophils, T cells, plasma cells.⁵⁷
- This study evaluated a small number of endpoints (one to three factors per “organ”) that do not provide enough information to evaluate potential toxicity in each tissue.
- The biological relevance of the system and chosen endpoints to characterize the safety of tradipitant was neither justified nor established.
 - Some evaluated endpoints 1) are not considered representative of toxicity (i.e., CYP activity), 2) were used as biomarkers of organ injury despite a lack of validation or clinical acceptance (i.e., KIM-1⁵⁸), and/or 3) were inconsistent with the results of other studies, including the in vitro liver assays described above and the completed toxicity studies in rats and dogs (i.e., CYP activity, hepatocyte viability).
 - No positive controls were used to demonstrate assay validity and potential toxicity in this system using the chosen endpoints.
 - As acknowledged by the Applicant, the metabolism of tradipitant in the four-organ system was significantly different than that observed in humans or in nonclinical species.
 - The statistical methods used for analyses were not included in the study report or provided following an information request.
- The experiment was conducted using a single donor or source for each primary tissue type. Any findings in these assays may reflect the response of an individual donor or cell preparation and may not be predictive of the general population.
- The duration of treatment in this study was only seven days; short-duration experiments do not provide data on the chronic toxicity of the drug.

⁵⁷ The Human Protein Atlas. Version 23.0, 6-19-2023; accessed September 5, 2024.

<https://www.proteinatlas.org/humanproteome/tissue+cell+type>.

⁵⁸ KIM-1 has not been qualified as a stand-alone biomarker of kidney injury for any context of use. Urinary KIM-1 has been qualified as part of a panel of six urinary biomarkers (clusterin, cystatin-C, KIM-1, N-acetyl-beta-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and osteopontin) whose composite measure is used in conjunction with traditional measures to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause renal tubular injury in humans. See <https://www.fda.gov/drugs/biomarker-qualification-program/reviews-qualification-biomarker-clusterin-clu-cystatin-c-cysc-kidney-injury-molecule-1-kim-1-n>. A similar panel of urinary biomarkers (KIM-1, albumin, total protein, β 2-microglobulin, cystatin C, clusterin, and trefoil factor-3) has been qualified for the detection of acute drug-induced nephrotoxicity in rats (in conjunction with traditional clinical chemistry markers and histopathology) in toxicology studies. See <https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=72>. Another biomarker panel including urinary KIM-1 is in the qualification process.

Study HSTOX-2008-002: 14-Day Study of Tradipitant in the Four-Organ System Using Hepatocytes with Different Metabolizer Phenotypes

Evidence of potential toxicity with tradipitant was observed under select conditions at select timepoints in all four cell types tested: hepatocytes (decreased viability), cardiomyocytes (increased troponin-I, decreased cardiac force, increased field potential duration), renal proximal tubular epithelial cells (increased KIM-1 release), and cortical neurons (increased firing rate). The Applicant concluded that “chronic” exposure of tradipitant in the four-organ system yielded only minor adverse effects in all “organ” constructs. When comparing the safety of tradipitant across systems containing either high, moderate, or low metabolic activity (based only on CYP3A4 activity), significant effects could be observed, suggesting that differences in hepatic expression of metabolizing enzymes (e.g., polymorphisms leading to activity of metabolic enzymes that is higher or lower than that seen in the general population) may influence physiological outcomes with tradipitant, including outcomes related to safety.

Numerous limitations in study design and conduct preclude its substantive contribution to the long-term safety profile of tradipitant. In general, these limitations are similar to those identified for Study HSTOX-7619, and, for brevity, only general limitations will be repeated.

- The evaluation of potential toxicity using the four-organ system was limited in scope (i.e., not comprehensive).
- The biological relevance of the system and chosen endpoints to characterize the safety of tradipitant was neither justified nor established.
 - o While two positive controls were used for each assay, the utility of the resulting information was limited. Several of these compounds induced cytotoxicity that was considered significant enough to confound interpretation of the results (i.e., terfenadine, doxorubicin, gentamicin). In other cases, the positive control did not demonstrate the expected toxicity in the context of the four-organ system (i.e., losartan, chlorpromazine, nimodipine).
 - o For each endpoint, no definition of a biologically relevant change was provided. Thus, the toxicological significance of any observed change cannot be reliably determined.
 - o As acknowledged by the Applicant, the metabolism of tradipitant in the four-organ system was not as expected given previous findings in humans and nonclinical species. Although the Applicant suggested possible explanations for these deviations (i.e., metabolite is absorbed into the housing material, the 14-day study was not long enough for complete metabolite detection, non-hepatic metabolism of the compound in the body occurs in organs that were not included in this study, or a potential enzymatic feedback loop inhibited conversion of the parent compound), no evidence for these possibilities was provided, and there was no discussion on how such deviations impact the clinical translatability of the reported findings.
 - o A major focus of this study was the impact of differing liver metabolism on potential toxicity with tradipitant, but this approach was not justified.

- While CYP3A4 is one mechanism of tradipitant metabolism, it is not the only mechanism nor is it the single major pathway.
- No rationale was provided for the categorization of low, moderate, and high metabolizing donors.
- The experimental results did not correspond to the known metabolism of tradipitant (i.e., the high metabolizer had the lowest levels of M3 and M4).
- The experiment was conducted using a single donor or source for each primary tissue type, with the exception of the liver construct. Any findings in this assay for these cell types may reflect the response of an individual donor or cell preparation and may not be predictive of the general population.
- The duration of treatment in this study was only 14 days; short-duration experiments do not provide data on the chronic toxicity of the drug.

12.1.3 Conclusions and Recommendation

As discussed in this document, the Applicant previously⁵⁹ asserted that their “totality of evidence” approach for the nonclinical program, including six (now seven) additional in vitro assays, sufficiently demonstrates the safety of tradipitant and that a chronic toxicity study in a nonrodent species is not justified. The Division thoroughly reviewed these additional in vitro studies and evaluated their scientific and regulatory contribution to the safety profile of tradipitant, taking into account all previously submitted nonclinical data for this drug.

When evaluating novel in vitro assays for use in regulatory decisions, particularly in lieu of a standard nonclinical toxicity study, it is important to determine that such methods employ sound science and are appropriate to inform regulatory decision-making. For the additional assays submitted in the current NDA, necessary considerations for their usability in regulatory decision-making include best practices for in vitro study design and conduct^{60,61,62} and the compliance (or lack thereof) with US FDA GLP regulations. Additionally, to fully characterize the safety of a drug intended for long-term, unrestricted administration in humans, including under conditions of repeated intermittent dosing, any alternative information submitted in lieu of a chronic toxicity study needs to substantively contribute to the understanding of the long-term safety of the drug.

Following review of the provided study reports, only minor limitations were identified in the study design and conduct of the five in vitro liver safety pharmacology studies

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⁶⁰ OECD (2005), Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, OECD Environment, Health and Safety Publications Series on Testing and Assessment, No. 34, OECD Publishing, Paris.

⁶¹ OECD (2018), Guidance Document on Good In Vitro Method Practices (GIVIMP), OECD Series on Testing and Assessment, No. 286, OECD Publishing, Paris.

⁶² Harrill, A., K. Carstens, N. Sipes, A. Lowit, S. Lynn, M. Perron, Pamela Noyes, J. Gordon, S. Fitzpatrick, AND N. Kleinstreuer. Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies- A Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup (VWG) March 2024. NIH, 2024.

(HPTOX-3540, HPTOX-3550, HPTOX-3560, HPTOX-3610, and SRV-0028), generally involving the unclear biological relevance of the reported endpoints and the lack of clinically actionable findings. These studies do not rule out the potential for tradipitant to cause liver injury, as previously identified in the 13-week study in Han Wistar rats; indeed, they provide evidence that the potential for liver injury is not animal-specific and extends to humans. However, the utility of these studies is limited in that they did not achieve their stated objective; that is, the studies failed to identify a primary mechanism by which liver injury may occur, and they did not clearly define a threshold at which the effects may be expected to be observed clinically.

After review of the four-organ studies (HSTOX-7619 and HSTOX-2008-002), the submitted studies as designed, executed, and reported do not contribute to the assessment of the long-term safety of tradipitant (i.e., for unrestricted use over a lifetime). Limitations of the studies included the narrow scope of toxicity evaluations, unjustified biological relevance of the system and chosen endpoints, lack of compliance with US FDA GLP regulations, and short duration of treatment relative to proposed unrestricted use over a lifetime.

Although CDER is open to alternative approaches to traditional nonclinical toxicity studies to assess risk for clinical use, including the use of in vitro assays such as those employed here, any alternative proposal should be scientifically sound and appropriate to inform regulatory decision-making. The Applicant concluded⁶³ that, “given all the alternatives [they] have done,” a chronic toxicity study in a nonrodent species is not justified. As discussed above, the submitted alternative in vitro assays do not substantially contribute to the characterization of the long-term safety of tradipitant.

We acknowledge that the indication of prevention of vomiting induced by motion will involve repeat intermittent use of tradipitant. However, the Applicant has not submitted data to suggest that the cumulative toxicity of tradipitant will be different whether exposure to tradipitant occurs consecutively or intermittently. As we expect repeat intermittent dosing of tradipitant to continue over a lifetime for this indication, long-term nonclinical toxicity studies (i.e., a 6-month toxicity study in a rodent species and a $\geq$ 6-month toxicity study in a nonrodent species) are the most appropriate⁶⁴ to support the safety of unrestricted use of tradipitant over a lifetime for this indication. Following careful evaluation of the entire nonclinical data package, there remains insufficient nonclinical information to adequately characterize the safety of unrestricted use of tradipitant over a lifetime in humans, and a chronic toxicity study in a nonrodent species is still warranted.

We acknowledge that the clinical trial data suggest that tradipitant is effective at preventing vomiting induced by motion, and clinical safety data with tradipitant are available for up to 90 doses. We also acknowledge that the prescribing information will

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⁶⁴ For drug products clinically used for longer than one month in duration, FDA's scientific standard is that chronic toxicity studies in a rodent and nonrodent species are the best studies to characterize the toxicological safety of those products and support approval.

describe the limitations of the available safety data. However, the lack of adequate nonclinical data to support the unrestricted use of tradipitant over a lifetime is an approvability issue.

12.2 Assessment of Available Data To Support the Safety of Tradipitant Metabolites

Based on the available clinical and nonclinical data, the four major human metabolites of tradipitant, M2, M3, M4, and M8, should be qualified to support the safety of tradipitant for this application. Metabolite M3 is the only metabolite qualified by the levels present in the nonclinical studies, while M2, M4, and M8 were not measured, not present, or present at low levels in animals and therefore not considered qualified for safety using typical approaches. However, M2, M4, and M8 are not likely to produce increased or novel toxicities compared to tradipitant, based on a Weight of Evidence (WoE) analysis including structural evaluations and assessment of known on- and off-target effects of tradipitant and the metabolites. Therefore, the levels of these metabolites were considered qualified for safety based on a comparison of total drug-related exposure (i.e., the sum of tradipitant, M2, M3, M4, and M8) in humans and animals, and there are no unresolved safety concerns regarding the metabolites for this application. Support for this determination is discussed herein.

12.2.1 Background on Nonclinical Characterization of Metabolite Safety

Characterization of the metabolic profile of a drug is an important part of the drug development process. Nonclinical testing, including general toxicity studies, typically focuses on adverse effects as they relate to exposure to the parent drug. However, biotransformation of the parent drug via phase 1 and phase 2 metabolic pathways may result in metabolites that also contribute to toxicity. It is not standard practice for drug metabolites to be evaluated separately in a cross-species safety assessment, but nonclinical assessment may be warranted under certain circumstances. These circumstances are broadly discussed in FDA guidance for industry *Safety Testing of Drug Metabolites, Revision 2* (March 2020).

Three successive considerations are used to determine whether nonclinical qualification of drug metabolites should be conducted to support the safety of a drug.

- (1) To warrant qualification, a metabolite should first be shown to be a *disproportionate metabolite*, meaning that the metabolite is only formed in humans and absent in the animal test species, or, that the metabolite is present at higher levels in humans than in the animal species used in the standard toxicology testing with the parent drug.
- (2) If a disproportionate metabolite is identified, a metabolite should be present at >10% of total drug-related exposure at steady state, typically based on AUC, to warrant further characterization. It is not generally feasible to measure AUC of all metabolites by nonradiolabeled methods, particularly for those drugs that have many metabolites. In these cases, a human mass-balance PK study using a single radiolabeled dose of drug provides a reasonable estimate of human total drug-

related exposure and may be an adequate basis for calculating whether a metabolite exceeds 10%.⁶⁵

- (3) Finally, a disproportionate metabolite that is >10% of total drug-related exposure warrants further evaluation if the levels measured in nonclinical species do not approach human exposure (i.e., are <50% the exposure in humans⁶⁵). The decision tree for this process is shown in [Figure 50](#).

Figure 50. Metabolite Decision Tree Flow Diagram

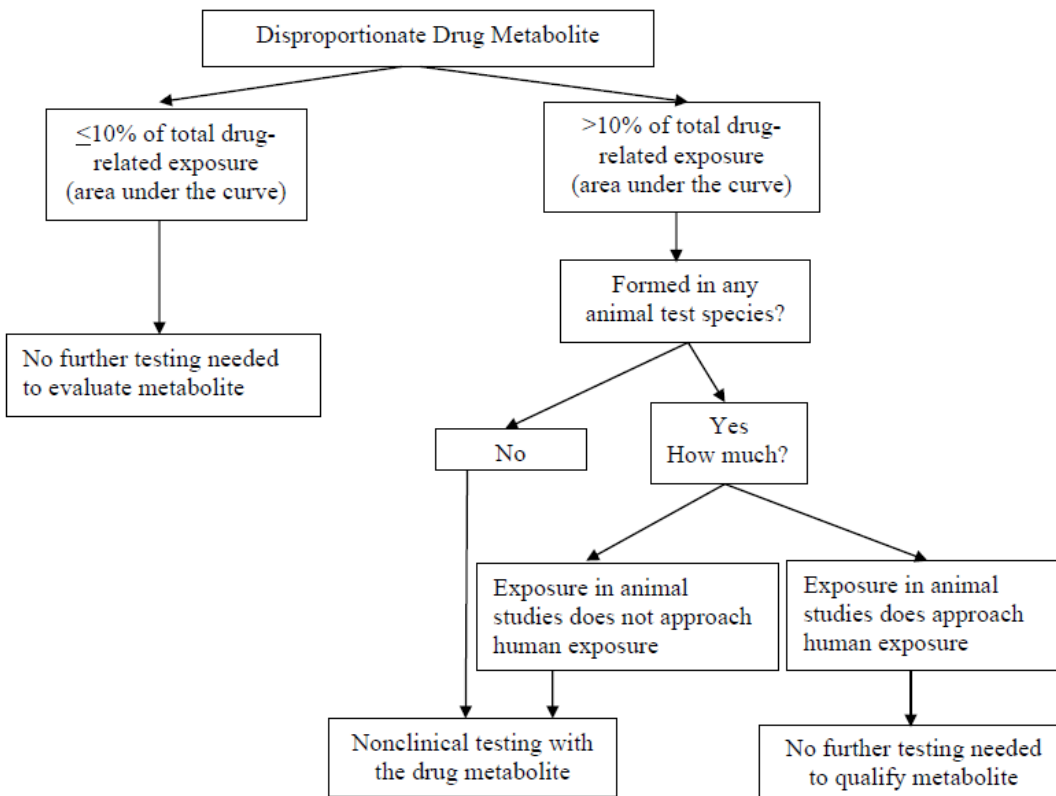


Figure copied directly from FDA guidance for industry M3(R2) Questions and Answers (R2), Appendix A (March 2013).

Sponsors are encouraged to identify any differences in drug metabolism between animals used in nonclinical safety assessments and humans as early as possible during the drug development process, so that appropriate nonclinical studies can be conducted to qualify the safety of these metabolites, if warranted. Such studies should generally be completed prior to the initiation of phase 3 clinical trials and should include a general toxicity study of appropriate duration, in vitro genotoxicity assays (evaluating the potential for both point mutations and chromosomal aberrations), an embryo-fetal development study, and a carcinogenicity study. Unlike the parent drug, in vivo studies conducted in a single species are generally sufficient to support the safety of disproportionate metabolites.

⁶⁵ FDA guidance for industry M3(R2) Questions and Answers (R2), page 5. March 2013.

12.2.2 Timeline of Metabolite Safety as a Review Issue

Metabolite Data Under IND

Eli Lilly, the initial Sponsor for tradipitant, conducted nonclinical and clinical studies to determine the metabolite profile of tradipitant early in the development program, with “four major metabolites being identified (M2, M3, M4, and M8)” in humans.⁶⁶ However, nonclinical data to assess the safety of the four major human metabolites were limited during development, as these metabolites were not prospectively measured in general toxicology studies with tradipitant in Fischer rats (up to 6 months) or in dogs (up to 3 months). Eli Lilly did measure M2, M3, and M4 retrospectively in stored samples from the 3-month study in Fischer rats at the mid dose (150 mg/kg/day) only; however, the amended study report containing toxicokinetic information for these metabolites (Study 1317-105 Amendment 2) was never submitted to any IND for tradipitant. Eli Lilly also conducted and submitted in vitro metabolite profiling using liver microsomes and liver slices, as well as in vivo animal metabolite profiling using plasma, urine, feces, and bile samples.⁶⁷ Based on the findings that tradipitant and the four major metabolites were each <10% of total drug-related exposure⁶⁸ in humans as measured in the single 25 mg dose mass balance study (Trial H8R-MC-HJAK), (b) (4)

(b) (4) indicated that, no additional nonclinical studies of the metabolites were necessary at that time and the planned phase 3 clinical trial with tradipitant under IND (b) (4) was considered safe to proceed.⁶⁹

Vanda Pharmaceuticals (the current Applicant) prospectively measured M2, M3, and M4 in the 13-week repeat-dose toxicity study in Han Wistar rats⁷⁰ (conducted to support dose selection for their carcinogenicity study in rats), the PPND study in rats,⁷¹ the juvenile animal study in rats,⁷¹ as well as the carcinogenicity studies in rats⁷² and transgenic mice⁷¹ submitted under IND. The Applicant also submitted a secondary pharmacology screen (transporters) with M2, M3, and M4 during development.⁷³

⁶⁶ IND 141315, SDN 1: October 2, 2018. Cross-referencing Module 2.6.4 Pharmacokinetics Written Summary, pg. 9, as submitted in IND (b) (4)

⁶⁷ IND 141315, SDN 1: October 2, 2018. Cross-referencing data submitted in IND (b) (4)

⁶⁸ NDA 220152, SDN 22: September 19, 2025 (containing a Meeting Briefing Package previously submitted by Eli Lilly and Company under IND (b) (4) (b) (4) In this submission, Eli Lilly discussed the discrepancies between the observed half-lives of tradipitant (previously named LY68017), M2, M3, and M4 (20 to 30 hours) and that of the total administered radioactivity (113 hours) in human subjects. “These results suggest that circulating metabolite(s) with a long $t_{1/2}$ persist in the plasma,” that “One of these metabolites is evidently M8, which was [...] shown to be the major circulating peak in plasma at 24-hours post-dose,” and that “M8 is believed to represent a substantial portion of the long half-life of radioactivity in plasma.” Based on these comments, it appears that M8, had it been properly measured, may have represented >10 % of drug-related exposure in this study.

⁶⁹ NDA 220152, SDN 22: September 19, 2025 (b) (4) (b) (4) previously recorded under IND (b) (4)

⁷⁰ IND 141315, SDN 1: October 2, 2018. Cross-referencing IND (b) (4) (Study Report located in Appendix B of the Special Protocol Assessment Request).

⁷¹ IND 141315, SDN 11: September 10, 2019.

⁷² IND 141315, SDN 12: November 7, 2019.

⁷³ IND 141315, SDN 1: October 2, 2018. Cross-referencing data submitted in IND (b) (4) (b) (4)

At the time phase 3 trials with tradipitant were initiated, the Applicant's available nonclinical data supported that M2, M4, and M8 were likely to be present at significantly lower levels in rats and dogs compared to humans (i.e., that these were *disproportionate metabolites*).⁷⁴ However, at no point during development were the available clinical pharmacology data sufficient to definitively determine whether any metabolite exceeded the typical threshold of 10% of drug-related exposure at steady state at the proposed clinical doses that would warrant qualification by nonclinical data. Total drug-related exposure at steady state was not evaluated in any clinical study submitted under IND. Although the previously mentioned single-dose human mass-balance PK study was available (Trial H8R-MC-HJAK), this study was considered to have several limitations including:

- The low dose relative to the intended clinical dose (25 mg versus 85 or 170 mg);
- Tradipitant, M2, M3, and M4 only accounted for 26% of total radioactivity, based on AUC;
- Tradipitant itself did not meet the 10% threshold; and
- The AUC of M8 was not reported.

Disregarding the limitations, this study on its face suggested that none of the major human metabolites would meet the typical 10% threshold to warrant further evaluation. Additionally, clinical trials with tradipitant have not exceeded 12 weeks or 90 dosing days for any indication. Therefore, the lingering potential for unqualified metabolites was not considered a safety issue for tradipitant prior to the submission of a marketing application. However, additional data included in the marketing applications for tradipitant led to the concern that the safety of the major human metabolites had not been adequately addressed (see below).

Metabolite Data and Review Under NDA 218489

(b) (4)

⁷⁴ See Module 2.6.4 Pharmacokinetics Written Summary, Table 26, pgs. 43 to 44.

(b) (4)

Metabolite Data and Review Under NDA 220152

No new nonclinical studies, including no new studies with the metabolites, were included in the initial submission for NDA 220152 (December 30, 2024) compared to that submitted under NDA 218489. In addition to the previously submitted clinical pharmacology data, NDA 220152 contained sparse human PK data for tradipitant and its major human metabolites based on Trial 3404 in subjects with a history of motion sickness. The population PK model previously submitted under NDA 218489 was not initially updated with these data, nor was an integrated population PK analysis run to characterize the PK profile of tradipitant and its metabolites in subjects with a history of motion sickness.

Based on the data gaps identified during the review of NDA 218489 and the lack of new information addressing those issues, concerns remained whether the metabolites had been sufficiently characterized and/or qualified based on the available data. In the filing letter, the Applicant was notified of the review team's concerns that human levels of the metabolites were not well-defined and that the safety of the metabolites may not be supported by the submitted nonclinical data.⁸¹ In that letter, the review team requested that the Applicant submit any additional nonclinical data that were available to support the safety of the levels of metabolites M2, M4, and M8 (i.e., the three disproportionate human metabolites). The review team also requested the study of M8 pharmacologic activity that was presumed to be completed but had never been submitted either during the review of NDA 218489 or to the current NDA.

In response to the requests made in the filing letter, the Applicant submitted the M8 activity study as well as a new liver safety pharmacology study with the metabolites (March 25, 2025; SDN 9).

- The M8 activity study demonstrated that M8 has pharmacologic activity at the NK-1 receptor. This information further strengthens (but does not prove) the review team's previous assumption that M2, M3, and M4 are also pharmacologically active. Notably, this study report is dated May 2, 2024, and thus it was available both during the review of NDA 218489 and at the time of the initial submission for NDA 220152.
- The in vitro liver safety pharmacology study using 3D human donor-derived hepatocyte spheroids was similar to those previously conducted with tradipitant and submitted under NDA 218489. Importantly, unlike the previously submitted studies that only tested tradipitant or were limited to qualitative evaluations of hepatotoxicity with the metabolites, this new study included quantitative

⁸¹ NDA 220152: Filing Review Issues Identified Letter. March 14, 2025.

assessments of hepatotoxicity following direct treatment with the metabolites. This study demonstrated that all four major metabolites have the potential to induce hepatotoxicity at concentrations that could reasonably be achieved clinically (with the caveat that proper IVIVE analyses have not been conducted to bridge between in vitro assay concentrations and in vivo drug exposure). This study report is dated January 19, 2025, and thus postdates the review of NDA 218489 as well as the initial submission for NDA 220152.

- Following this submission, the clinical pharmacology team requested that the Applicant update the population PK model and provide simulated PK profiles and parameters for tradipitant and the major human metabolites in subjects with a history of motion sickness under various conditions.⁸² The Applicant agreed to conduct some of the additional analyses.⁸³ Pooled population PK modeling and simulations for tradipitant were provided on June 30, 2025,⁸⁴ while modeling and simulations of the metabolites were provided on July 22, 2025.⁸⁵ While limitations were identified with the modeling and analyses, the findings were generally consistent with those in studies in healthy volunteers. Thus, these analyses increased the review team's confidence in the appropriateness of using the healthy volunteer data to represent the motion sickness population.

Taken together, the new data submitted to NDA 220152 provided confirmation that:

- M8 is pharmacologically active (as, presumably, are M2, M3, and M4);
- All four major metabolites have quantifiable toxicity in an assay using human donor-derived cells. Specifically, these compounds were toxic, evidenced by cell death, to human donor-derived hepatocytes, with findings generally similar to tradipitant itself. As metabolites M2, M4, and M8 are present at much lower levels in the toxicology species compared to humans and have quantifiable toxicity, it is scientifically possible that these metabolites can cause other toxicities that were not adequately captured in the completed animal studies; and
- These metabolites are present at high levels compared to tradipitant itself and at levels that each exceed 10% of the total drug-related exposure in humans as measured in clinical studies (i.e., where total exposure = tradipitant + M2 + M3 + M4 ± M8).

Based on these newly identified factors, the review team concluded that qualification of the levels of the major human metabolites is necessary to support the safety and approval of tradipitant for the prevention of vomiting induced by motion. As such, the adequacy of the nonclinical data to support the safety of the levels of these metabolites was considered a review issue. These concerns were communicated to the Applicant during the Mid-Cycle Meeting held on July 23, 2025.⁸⁶

⁸² NDA 220152: Information Request. April 2, 2025.

⁸³ See NDA 220152, SDN 12: April 16, 2025. See also NDA 220152, SDN 16: June 12, 2025. See also NDA 220152, SDN 19: July 8, 2025.

⁸⁴ NDA 220152, SDN 18: June 30, 2025.

⁸⁵ NDA 220152, SDN 20: July 22, 2025.

⁸⁶ See NDA 220152: Mid-Cycle Agenda (July 21, 2025) and Mid-Cycle Communication (August 22, 2025).

In response to the identified concerns, the Applicant submitted additional information to support the safety of the metabolites. This included a 2006 meeting briefing package that had been submitted under IND (b) (4) but had never been submitted to or referenced by any IND or NDA for tradipitant owned by the Applicant. The meeting briefing package proposed a WoE approach to support that the toxicologic profiles of the metabolites M2, M4, and M8 were not expected to be different than that of tradipitant. The review team requested additional justification for the Applicant's assertion that reduction of the ketone on tradipitant/M3 to form M2/M4 was not expected to be toxicologically significant on October 1, 2025.⁸⁷ The Applicant's response was received on October 15, 2025.⁸⁸ The review team requested clarification on the employed methods⁸⁹ and which the Applicant provided on October 22, 2025.⁹⁰ Additional analyses to determine the scientific appropriateness of this approach were also conducted internally by CDER's Division of Applied Regulatory Science (DARS) Computational Toxicology Consultation Service (CTCS) during this time.

12.2.3 Clinical Characterization of Major Metabolites

The major metabolites of tradipitant were measured in three trials in healthy volunteers and one trial in subjects with a history of motion sickness. Population PK modeling was also conducted to provide further insight into the levels of metabolites expected in subjects with motion sickness using tradipitant. Although these data are not derived from nonclinical studies, understanding the human levels of tradipitant and its metabolites cannot be separated from characterization of their safety in this application. Thus, human PK data for tradipitant and its metabolites, delineated by various parameters (i.e., single and multiple doses in healthy subjects in fed and fasted states, single and multiple doses in subjects with gastroparesis and motion sickness), are presented here as well as in clinical sections of this review, to provide additional context for the nonclinical assessment of the safety of the metabolites.

- At 4 hours following a single dose of 25 mg in a mass balance study with radiolabeled tradipitant in healthy subjects (Trial H8R-MC-HJAK), tradipitant, M2, M3, M4, and M8 accounted for 24%, 11%, 13%, 16%, and 13% of total drug-related radioactivity in the plasma, respectively.⁹¹ The median T_{max} in this trial was 2 hours, with a range of 1 to 8 hours. Based on AUC_{0-inf} , tradipitant, M2, M3, and M4 accounted for approximately 9%, 4%, 5%, and 8% of total drug-related radioactivity in plasma, respectively, while this parameter was not evaluated for M8. Although tradipitant exposure was highly variable, the AUC of M4 was similar to that of tradipitant in 3/5 subjects in this trial.
- Following a single dose of 85 mg in fasted healthy subjects in a food effect study (Trial 1002; [Table 17](#)),⁹² levels of metabolites M2, M3, M4, and M8 were measured at significant levels (33% to 44%) compared to tradipitant itself, based

⁸⁷ NDA 220152: Information Request. October 1, 2025.

⁸⁸ NDA 220152, SDN 23: October 15, 2025.

⁸⁹ NDA 220152: Information Request. October 20, 2025.

⁹⁰ NDA 220152, SDN 24: October 12, 2025.

(b) (4)

⁹² I.e., the sum of AUC values for tradipitant, M2, M3, M4, and M8.

on AUC_{0-inf}. At this dose, tradipitant and the major metabolites each comprised >10% of total drug-related exposure, based on AUC. Similar findings were observed following a single dose of 170 mg in fasted healthy subjects.

Table 17. Tradipitant and Its Major Metabolites Relative to Tradipitant Exposure, Trial 1002

Compound	C _{max} (ng/mL)	AUC _{0-24h} (ng·h/mL)	Tradipitant Exposure		Total Exposure ¹	
			C _{max} %	AUC %	C _{max} %	AUC %
85 mg single dose						
Active compounds	146.7	4756	--	--	--	--
Tradipitant	84.7	1839	--	--	58%	39%
M2	14.2	741	17%	40%	10%	16%
M3	17.1	608	20%	33%	12%	13%
M4	17.4	804	21%	44%	12%	17%
M8	13.3	764	16%	42%	9%	16%
170 mg single dose						
Active compounds	195.7	7558	--	--	--	--
Tradipitant	112	3526	--	--	57%	47%
M2	18.7	803	17%	23%	10%	11%
M3	21.9	835	20%	24%	11%	11%
M4	21.4	1035	19%	29%	11%	14%
M8	21.7	1359	19%	39%	11%	18%

AUC: area under the concentration-time curve; C_{max}: maximum plasma concentration.

¹Where total exposure is the sum of C_{max} or AUC, as appropriate, for tradipitant and the four major human metabolites.

Table created by reviewer, based on data from Trial VP-VLY-686-1002.

- In the same trial (Trial 1002), a large food effect on the levels of the metabolites was observed. Under fed conditions (high fat meal), a single dose of tradipitant at 85 mg resulted in C_{max} values for the metabolites 3.4- to 4.3-fold higher and AUC values 2.4- to 2.7-fold higher than under fasted conditions. Similarly, under fed conditions, a single dose of tradipitant at 170 mg resulted in C_{max} values for the metabolites 5.3- to 6.5-fold higher and AUC values 3.2- to 3.6-fold higher than under fasted conditions.
- Following 12 days of dosing at 85 mg every 12 hours (Q12H) in healthy subjects (Trial 1102; [Table 18](#)),⁹³ metabolites M2, M3, and M4 were measured at 34%, 32%, and 34% that of tradipitant, respectively, based on AUC₀₋₁₂. At this dose, tradipitant and the three metabolites comprised 50%, 17%, 16%, and 17% of total drug-related exposure, based on AUC. M8 was not measured in this trial as the Applicant was unable to synthesize a reference standard at that time.

⁹³ I.e., the sum of AUC values for tradipitant, M2, M3, and M4.

Table 18. Tradipitant and Its Major Metabolites Relative to Tradipitant Exposure, Trial 1102

Compound	C _{max} (ng/mL)	AUC _{0-24h} (ng·h/mL)	Tradipitant Exposure		Total Exposure ¹	
			C _{max} %	AUC %	C _{max} %	AUC %
85 mg Q12H						
Active compounds	630.7	8152	--	--	--	--
Tradipitant	327	4074	--	--	52%	50%
M2	102	1366	31%	34%	16%	17%
M3	97.7	1312	30%	32%	15%	16%
M4	104	1400	32%	34%	16%	17%
M8	NM	NM	--	--	--	--

AUC: area under the concentration-time curve; C_{max}: maximum plasma concentration.

¹ Where total exposure is the sum of C_{max} or AUC, as appropriate, for tradipitant and M2, M3, and M4
 Table created by reviewer, based on data from Trial VP-VLY-686-1102.

- Following a single dose of 170 mg in fasted subjects with motion sickness who had received placebo or tradipitant at 85 or 170 mg within the previous 7 days (Trial 3404; [Table 19](#)), levels of metabolites M2, M3, M4, and M8 were measured at 16%, 17%, 13%, and 12% of tradipitant exposure, respectively, based on the concentration of each at 2 hours postdose.⁹⁴ (Note: *T_{max}* was reported to occur at 1.5, 4.0, 3.0, 4.0, and 30 hours postdose for tradipitant, M2, M3, M4, and M8, respectively, following a single dose of 170 mg to fasted healthy volunteers in Trial 1002. As PK was only measured in Trial 3404 through 2 hours postdose, C_{max} and AUC values for tradipitant and its major metabolites were not available for comparison. Thus, these data may underpredict exposure to metabolites relative to tradipitant and should be interpreted with caution.)

⁹⁴ Based on data from Trial VP-VLY-686-3404. See NDA 220152, SDN 11: April 16, 2025.

Table 19. Tradipitant and Its Major Metabolites Relative to Tradipitant Exposure, Trial 3404

Compound	C _{2h} ¹ (ng/mL)	%Tradipitant Exposure
Tradipitant	165.2	--
M2	26.8	16%
M3	28.4	17%
M4	21.0	13%
M8	19.1	12%

AUC: area under the concentration-time curve; C_{max}: maximum plasma concentration; C_{2h}: concentration measured 2 hours postdose; PK: pharmacokinetic; T_{max}: time to maximum concentration.

¹ Concentrations were measured at 2 hours postdose. T_{max} was reported to occur at 1.5, 4, 3, 4, and 30 hours postdose for tradipitant, M2, M3, M4, and M8, respectively, following a single dose of 170 mg to fasted healthy volunteers in Trial VP-VLY-686-1002. As pharmacokinetic samples were only taken through 2 hours postdose in Trial VP-VLY-686-3404, C_{max} and AUC values were not available for comparison in this trial.

Table created by reviewer, based on data from Trial VP-VLY-686-3404.

- In NDA 218489 for tradipitant for the treatment of gastroparesis, the Applicant provided (b) (4) 95

In the current NDA 220152, the Applicant provided updated population PK modeling and analyses as requested by the clinical pharmacology team. Numerous limitations of the provided information were identified by the Applicant and confirmed by the review team, including, but not limited to:

- (1) Parameter estimates were considered not reliable as the models did not converge properly.
- (2) Dosing history was unreliable due to imprecise time of doses and subject noncompliance.
- (3) The tradipitant modeling did not recapitulate the food effect previously observed in Trial 1002.

Given these limitations, the PK parameters for subjects with motion sickness were considered unreliable, as determined by simulating Trials 3404 and 3403 using the updated population PK model. However, the results of the modeling and analysis supported that PK parameters were expected to be similar between healthy volunteers and subjects with motion sickness. Thus, the parameters of Trial 1002 were considered most appropriate for assessing the safety of single doses of tradipitant, including the safety of the levels of the metabolites,⁹⁶ whereas PK parameters from Trial 1102, which

(b) (4)

⁹⁶ This is in agreement with the Applicant's assessment. See NDA 220152, SDN 20: July 22, 2025. Tradipitant Pooled Population Pharmacokinetic Analysis, page 126.

involved dosing of tradipitant in healthy subjects at 85 mg BID for 12 days, were deemed most appropriate for assessing the safety of tradipitant and the metabolites at steady state. See Section 14 of the NDA Integrated Review for a full discussion of the submitted population PK modeling and analyses.

Overall, data directly measuring the levels of metabolites M2, M3, M4, and M8 in subjects with motion sickness are limited. However, based on assessment of all available information, including the updated population PK modeling and analyses, the data from Trials 1002 and 1102 are considered adequate to represent the levels of metabolites expected in subjects with motion sickness.

12.2.4 Nonclinical Characterization of Major Metabolites

Nonclinical Qualification of M3

Although definitive activity assays have not been conducted, metabolite M3 is presumed to be pharmacologically active based on its ability to inhibit ligand binding at the NK-1 receptor $\geq 99.0\%$ at $10\mu\text{M}$ and with similar potency compared to tradipitant (reported⁹⁷ IC_{50} of 0.38nM , compared to the tradipitant IC_{50} of 0.40nM in a concurrent study). The Applicant attempted to address the in vivo safety of M3 by retroactively measuring it in the 13-week repeat-dose toxicity study in Fischer rats (mid dose only) and prospectively measuring it in the 13-week repeat-dose toxicity study in Han Wistar rats as well as in carcinogenicity (mice and rats), reproductive toxicity (rats only), and juvenile animal (rats) studies; metabolites were not measured in any submitted nonrodent study.

M3 was generally observed in rats⁹⁸ at exposures similar to or exceeding that expected in humans⁹⁹ under both single-dose and steady-state conditions ([Table 20](#)). Therefore, the levels of M3 are qualified for safety and no additional studies are warranted with this metabolite. Data from an in vitro liver safety pharmacology study using human donor-derived hepatocyte spheroids and a study using a human liver co-culture MPS (treatment with M3 directly) resulted in quantitative and qualitative effects on hepatocyte viability, respectively. These studies support that M3 has a human-relevant risk for liver toxicity.

⁹⁷ These values were reported by the Applicant in Module 2.6.2 Pharmacology Written Summary (based on Studies AB28300-1190601, AB28300-1190602, AB28300-1190603, and AB28300-1190604). However, IC_{50} values for M2, M3, and M4 were not stated in these study reports.

⁹⁸ Based on Studies 1317-105 Amendment 2 and TAJ0035.

⁹⁹ Following a dose of 170 mg/day (85 mg Q12H) for 12 days in healthy volunteers; based on Trial VP-VLY-686-1102, pgs. 60 to 63.

Table 20. Nonclinical Qualification of M3

Tradipitant Dose	Duration	M3 AUC ₀₋₂₄ (ng·h/mL) ¹		Ratio Rat:Human ²
		Human	Rat	
85 mg	Single dose	608	5170	8.5
170 mg	Single dose	835	5170	6.2
170 mg/day	Steady state	1312	2240	1.7

AUC: area under the concentration-time curve; Q12H: every 12 hours.

¹ AUC values were adjusted for differences in dosing intervals, when appropriate, to cover the entire 24-hour period.

² An animal:human ratio ≥ 0.5 is sufficient to qualify the safety of the metabolites.

Table created by reviewer, based on Trial VP-VLY-686-1002 (single-dose data), Trial VP-VLY-686-1102 (steady-state data from subjects administered 85 mg Q12H for 12 days), and Study TAJ0035 (single-dose and 13-week values in female Han Wistar rats, i.e., the strain and sex with highest exposure).

Nonclinical Qualification of M2

Although definitive activity assays have not been conducted, metabolite M2 is presumed to be pharmacologically active based on its ability to inhibit binding at the NK-1 receptor $\geq 99.0\%$ at $10\mu\text{M}$ and with similar potency compared to tradipitant (reported⁹⁷ IC₅₀ value of 1.55nM , compared to the tradipitant IC₅₀ of 0.40nM in a concurrent study¹⁰⁰). The Applicant attempted to address the in vivo safety of M2 by retroactively measuring it in the 13-week repeat-dose toxicity study in Fischer rats (mid dose only) and prospectively measuring it in the 13-week repeat-dose toxicity study in Han Wistar rats as well as in carcinogenicity (mice and rats), reproductive toxicity (PPND in rats only), and juvenile animal (rats) studies; metabolites were not measured in any submitted nonrodent study. In general toxicity and carcinogenicity studies in rats,^{98,101} M2 was observed at lower levels compared to the single-dose¹⁰² or steady-state⁹⁹ levels in humans, such that under no condition was at least 50% of human M2 exposure achieved in animals. Findings in mice¹⁰³ were similar. Thus, the levels of M2 are not qualified for safety.

¹⁰⁰ Based on data from Study AB28300-1190604, conducted in 2015.

¹⁰¹ Based on Study WR43WF.

¹⁰² Following a single dose of 85 or 170 mg/day in healthy volunteers; based on Trial VP-VLY-686-1002, Pharmacokinetic Report pgs. 21 to 38.

¹⁰³ Based on Study XW56GT.

Table 21. Nonclinical Qualification of M2

Tradipitant Dose	Duration	M2 AUC ₀₋₂₄ (ng·h/mL) ¹			Ratio ²	
		Human	Rat	Mouse	Rat:Human	Mouse:Human
85 mg	Single dose	741	143	n/a	0.19	n/a
170 mg	Single dose	803	143	n/a	0.18	n/a
170 mg/day	Steady state	1366	17.56	54.7	0.01	0.04

AUC: area under the concentration-time curve; Q12H: every 12 hours.

¹ AUC values were adjusted for differences in dosing intervals, when appropriate, to cover the entire 24-hour period.

² An animal:human ratio <0.5 (i.e., animal exposure <50% of human exposure) is insufficient to qualify the safety of the metabolites.

Table created by reviewer, based on Trial VP-VLY-686-1002 (single-dose data), Trial VP-VLY-686-1102 (steady-state data from subjects administered 85 mg Q12H for 12 days), and Study TAJ0035 (single-dose and 13-week values in female Han Wistar rats, i.e., the strain and sex with highest exposure).

M2 was further evaluated in one in vitro liver safety pharmacology study using human donor-derived hepatocyte spheroids and one study using a human liver co-culture MPS (treatment with M2 directly). In these studies, direct treatment with M2 resulted in qualitative (liver co-culture MPS) and quantitative (hepatocyte spheroids) effects on hepatocyte viability. These studies support that M2 has a human-relevant risk for liver toxicity. Additionally, M2 was evaluated in a four-organ MPS (treatment with tradipitant resulting in substantial metabolism to M2 in one study but limited metabolism to M2 in the second study) in which changes in the chosen endpoints (i.e., potential signals of toxicity) were observed in all organs under certain experimental conditions; the specific contribution of M2 to these toxicities could not be determined.

Based on the available information, metabolite M2 is (1) a major human metabolite; (2) essentially not present in rats and not measured in dogs or another nonrodent species; and (3) presumed to be pharmacologically active given similar IC₅₀ value to tradipitant for inhibition of binding at the NK-1 receptor. Additionally, there is a potential for toxicity with this metabolite in human tissues (e.g., the liver). Therefore, the levels of M2 in humans are not qualified for safety based on the available in vivo nonclinical data, and additional safety assessments are warranted.

Nonclinical Qualification of M4

Although definitive activity assays have not been conducted, metabolite M4 is presumed to be pharmacologically active based on its ability to inhibit binding at the NK-1 receptor ≥99.0% at 10μM and with similar potency compared to tradipitant (reported⁹⁷ IC₅₀ value of 2.23nM, compared to the tradipitant IC₅₀ of 0.40nM in a concurrent study¹⁰⁰). The Applicant attempted to address the in vivo safety of M4 by retroactively measuring it in the 13-week repeat-dose toxicity study in Fischer rats (mid dose only) and prospectively measuring it in the 13-week repeat-dose toxicity study in Han Wistar rats as well as in carcinogenicity (mice and rats), reproductive toxicity (PPND in rats only), and juvenile animal (rats) studies; metabolites were not measured in any submitted nonrodent study.

Following repeated dosing in general toxicity and carcinogenicity studies in rats and mice,^{98,101,103} M4 was generally not detected. In the single instance where it was quantifiable (female Fisher rats treated with tradipitant for 3 months at 150 mg/kg/day), M4 was present at $\leq 1\%$ of the human AUC under the various clinical exposure scenarios. Thus, the levels of M4 are not qualified for safety.

Table 22. Nonclinical Qualification of M4

Tradipitant Dose	Duration	M4 AUC ₀₋₂₄ (ng·h/mL) ¹		Ratio Rat:Human ²
		Human	Rat	
85 mg	Single dose	741	7.96	≤ 0.01
170 mg	Single dose	803		
170 mg/day	Steady state	1366		

AUC: area under the concentration-time curve; Q12H: every 12 hours.

¹ AUC values were adjusted for differences in dosing intervals, when appropriate, to cover the entire 24-hour period

² An animal:human ratio < 0.5 (i.e., animal exposure $< 50\%$ of human exposure) is insufficient to qualify the safety of the metabolites

Table created by reviewer, based on Trial VP-VLY-686-1002 (single-dose data), Trial VP-VLY-686-1102 (steady-state data from subjects administered 85 mg Q12H for 12 days), and Study TAJ0035 (single-dose and 13-week values in female Han Wistar rats, i.e., the strain and sex with highest exposure).

M4 was further evaluated in one in vitro liver safety pharmacology study using human donor-derived hepatocytes and one study using a human liver co-culture MPS (treatment with M4 directly). In these studies, direct treatment with M4 resulted in qualitative (liver co-culture MPS) and quantitative (hepatocyte spheroids) effects on hepatocyte viability. Thus, these studies support that M4 has a human-relevant risk for liver toxicity. Additionally, M4 was evaluated in a four-organ MPS (treatment with tradipitant resulting in highly variable metabolism to M4, with concentrations ranging from undetectable up to 40% of the tradipitant concentration) in which changes in the chosen endpoints (i.e., potential signals of toxicity) were observed in all organs under certain experimental conditions; the specific contribution of M4 to these toxicities could not be determined.

Based on the available information, metabolite M4 is (1) a major human metabolite, (2) essentially not present in rats and not measured in dogs or another nonrodent species, and (3) presumed to be pharmacologically active given similar IC₅₀ value to tradipitant for inhibition of binding at the NK-1 receptor. Additionally, there is a potential for toxicity with this metabolite in human tissues (e.g., the liver). Therefore, the levels of M4 in humans are not qualified for safety based on the available in vivo nonclinical data, and additional safety assessments are warranted.

Nonclinical Qualification of M8

Metabolite M8 is a direct N-glucuronide conjugate of tradipitant that was detected in liver slices from human and nonhuman primate but not in those from rat and dog (i.e., the species used in tradipitant general toxicity studies). Plasma levels of M8 were not

evaluated in any in vivo nonclinical study with tradipitant during clinical development, as the Applicant assumed that M8 was not formed in rats and dogs following administration of tradipitant. However, M8 was “seen at significant levels in humans.”¹⁰⁴

“Phase 2 conjugation reactions [e.g., glucuronidation] generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation.”¹⁰⁵ Indeed, the Applicant initially stated in NDA 218489 and reiterated in the current NDA that “M8 [...] is a direct glucuronide conjugate and therefore was considered of lesser concern.”¹⁰⁶ However, M8 was shown to inhibit binding to the NK-1 receptor by 99.3% at 10 μ M, with an IC₅₀ of 0.49nM (compared to an IC₅₀ of 3.3nM for tradipitant in the same study).¹⁰⁷ In the current NDA,¹⁰⁸ the Applicant further demonstrated that M8 inhibits substance P-induced calcium release in vitro, similarly to tradipitant, with reported IC₅₀ values of 6.3 and 0.63nM, respectively. The C_{max} values for M8 following a single dose of tradipitant of 85 or 170 mg in fasted healthy volunteers were 13.3 and 21.7 ng/mL, respectively,¹⁰⁹ or approximately 2.7- and 4.4-fold the IC₅₀ for substance P-induced calcium release. Thus, M8 is a pharmacologically active metabolite, and this activity is relevant at the proposed clinical doses.

As previously stated, M8 has not been measured in any in vivo nonclinical toxicity study with tradipitant. M8 was evaluated in one in vitro liver safety pharmacology studies using human donor-derived hepatocytes and one study using a human liver co-culture MPS (treatment with M8 directly). In these studies, direct treatment with M8 resulted in qualitative (liver co-culture MPS) and quantitative (hepatocyte spheroids) effects on hepatocyte viability. Thus, these studies support that M8 has a human-relevant risk for liver toxicity. M8 was not measured in the studies using the four-organ MPS.

Based on the available information, metabolite M8 is (1) a major human metabolite, (2) not expected to be produced in nonclinical species (and was not measured in these studies), and (3) has pharmacologic activity at the proposed clinical doses. Therefore, the levels of M8 in humans are not qualified for safety based on the available in vivo nonclinical data, and additional safety assessments are warranted.

12.2.5 Qualification of Metabolite Safety based on Total Drug-Related Exposure

Eli Lilly previously argued that no further nonclinical evaluation of metabolites M2, M4, and M8 was necessary based on a WoE assessment of the nonclinical and clinical data available at that time. Their primary argument was that each metabolite did not meet the

¹⁰⁴ See Module 2.6.4 Pharmacokinetics Written Summary, pg. 9.

¹⁰⁵ FDA guidance for industry *Safety Testing of Drug Metabolites Revision 2* (March 2020).

¹⁰⁶ See Module 2.6.4 Pharmacokinetics Written Summary, pg. 9.

(b) (4)

¹⁰⁸ These data were submitted during the review of NDA 220152 (SDN 9: March 25, 2025), in response to the Division's Information Request (March 14, 2025).

¹⁰⁹ Based on data from Trial VP-VLY-686-1002. No multidose or steady-state PK data are available for M8 in either healthy volunteers or subjects with vomiting induced by motion.

threshold of 10% of drug-related material¹¹⁰ in the single-dose mass balance study. As a secondary point, Eli Lilly argued that no idiosyncratic toxicity was expected with these metabolites based on their structural changes compared to tradipitant, and that the on-target safety of the metabolites was adequately covered by the completed nonclinical studies in rats and dogs based on the pharmacological similarities between tradipitant and the metabolites (i.e., similar binding affinities for the NK-1 receptor). As stated previously, it was agreed at the time of the 2006 meeting request (under IND (b) (4)) that no further nonclinical evaluation of these metabolites was necessary, although the merits of specific arguments were not formally reviewed.^{68,69}

We first note that the initial draft guidance for industry Safety Testing of Drug Metabolites, as referenced by Eli Lilly in their submission, was published in 2005. Since then, the Agency's thinking about what defines a concerning human metabolite has evolved, in part due to technological advances to detect, identify, and characterize metabolites. As reflected in the most recent FDA guidance on safety testing of drug metabolites (March 2020), the Agency considers drug metabolites to be a potential safety concern when they (1) are shown to be disproportionate metabolites and (2) present in humans "at greater than 10 percent of total drug-related exposure at steady state [unless there is some justification for a different measure of exposure]." The current thinking of the Agency now supersedes the early, draft recommendation cited by Eli Lilly.

Despite these revisions, the level of the metabolite in humans (i.e., whether it meets the 10% threshold necessitating nonclinical qualification) remains a primary consideration, although, as stated in the guidance, "other metabolites also can elicit safety concern."¹¹¹ Based on the points discussed previously (i.e., pharmacologic relevance, toxicologic relevance, and relative abundance of the metabolites), we do not agree that the safety of the metabolites has been adequately addressed simply because they do not appear to meet the 10% threshold following a single 25 mg dose (i.e., a dose much lower than proposed for the current indication) in the mass balance study. In other words, based on the currently available information (i.e., including numerous studies not available at the time of Eli Lilly's analysis), we do not inherently agree with the 2006 determination that no additional nonclinical information is warranted to support the safety of the metabolites for the prevention of vomiting induced by motion. Rather, M2, M4, and M8 are disproportionate human metabolites that are not qualified for safety based on the available in vivo nonclinical data. Notably, both Eli Lilly and the current Applicant agree

¹¹⁰ At the time of Eli Lilly's submission (2006), the published guidance for industry "Safety Testing of Drug Metabolites" was in a draft stage (publication June 2005). "This guidance defines major metabolites primarily as those identified in human plasma that account for greater than 10 percent of drug related material (administered dose or systemic exposure whichever is less) and that were not present at sufficient levels to permit adequate evaluation during standard nonclinical animal studies." Note that, in this draft guidance, the term "major metabolite" was used instead of the currently accepted "disproportionate metabolite." Similarly, "drug related material" has been replaced with "total drug-related exposure at steady state" in the current guidance. Numerous other changes have been made since 2005 to reflect FDA's evolving understanding of metabolite safety. The principles of the most recent version of the guidance, published in March 2020, serve as the basis for the current review.

¹¹¹ FDA guidance for industry *Safety Testing of Drug Metabolites Revision 2* (March 2020), footnote 12.

that the levels of M2, M4, and M8 are significantly lower in animals compared to humans, such that the animal levels do not support safety on their own.

As suggested by Eli Lilly, a WoE assessment (i.e., an integrated assessment of all available nonclinical and clinical data) may support the conclusion that the unqualified metabolites are expected to have similar toxicological profiles to tradipitant. Specifically, it was suggested that the structural changes to these metabolites compared to tradipitant are not toxicologically significant and would not result in potential differences in toxicity profiles that have not been characterized by the completed studies, despite the fact that the metabolites themselves were not present at adequate levels in animals. If indeed the WoE supports the toxicological equivalence of tradipitant and its metabolites, the available data may allow the review team 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.

The review team notes that the WoE in 2006 was inadequate to support the conclusion that the unqualified metabolites were expected to have toxicological profiles similar to tradipitant. Additional studies conducted in recent years by the current Applicant are pivotal to considering a WoE approach and included primary pharmacology (binding and/or functional activity), secondary pharmacology, liver safety pharmacology, in vitro distribution (protein binding), and in vitro genotoxicity studies with the metabolites, as well as population PK modeling supporting the relevance of healthy volunteer PK parameters for the motion sickness population and in silico analyses using various tools and databases.

It is not expected that the unique use of this WoE approach will set a general precedent for the qualification of metabolites, as each situation must be evaluated on its own merits based on the totality of data and information. Although in silico analyses are highly valuable in certain situations, they are unlikely to routinely address safety concerns in lieu of typical in vivo toxicity studies.

Weight-of-Evidence Assessment of M2

Tradipitant is metabolized to M2 by reduction of the di-aryl ketone (see [Figure 51](#)). Eli Lilly stated that, "There are no known structural alerts for idiosyncratic toxicity associated with this [metabolic] pathway and the World Health Organization Expert Committee on Food Additives classifies simple alcohols as Class I substances, having a low order of oral toxicity." Additionally, M2 "maintained pharmacological activity similar to [tradipitant]."¹¹² We do not agree with the stated conclusion based on these arguments. First, the metabolic enzyme(s) responsible for the formation of M2 from tradipitant was and is still unknown; thus, it cannot be determined whether an unknown pathway is expected to form toxic metabolites. Secondly, the cited WHO report is taken out of context and presents a safety assessment of food additives that is not relevant for

¹¹² NDA 220152, SDN 22: September 19, 2025 (containing a Meeting Briefing Package previously submitted by Eli Lilly and Company under IND (b) (4)

the safety assessment of a drug such as tradipitant or its metabolites. M2 is not a “naturally occurring simple [...] alcohol,” or a flavoring substance with “a long history of human experience in [...] consumption from traditional foods,” nor does it have “organoleptic and gustatory properties” limiting its use (e.g., to <1 mg/person/day).¹¹³ Thus, the safety assessment in the cited WHO report is not applicable to tradipitant or its metabolites, and it does not support the assertion that M2 is expected to have “a low order of oral toxicity.”¹¹²

Figure 51. Metabolism of Tradipitant to M2

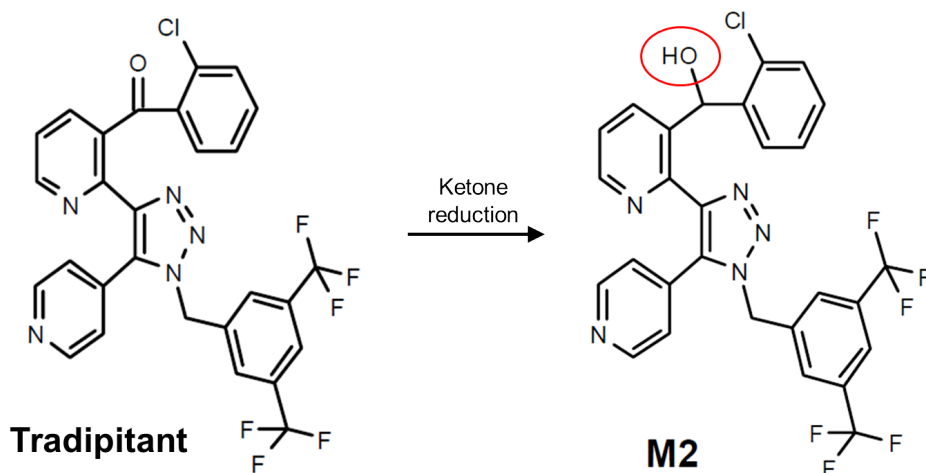


Figure created by reviewer, based on Study ADME Report 01, Figure 1.

In the context of the current application, the scientific appropriateness for qualification of M2 based on total drug-related exposure was determined using a WoE approach. The WoE included assessment of the structural differences, pharmacological on-target activity (including pharmacodynamics), and off-target activity of M2 compared to tradipitant and relied on all available information for both compounds (i.e., including data that was not available in 2006).

Structural Assessment

To assess the potential toxicological significance of the ketone reduction, a (Q)SAR analysis was performed by CDER's Division of Applied Regulatory Science (DARS) Computational Toxicology Consultation Service (CTCS) to generate predictions of the hepatobiliary toxicity of M2 compared to tradipitant and to identify new structural alerts related to the ketone reduction.¹¹⁴ Briefly, tradipitant and M2 were evaluated with a battery of statistical- and expert rule-based hepatotoxicity (Q)SAR models. The battery utilized statistical (Q)SAR software platforms from Leadscape Model Applier (LMA) and

¹¹³ World Health Organization, 1996, Toxicological Evaluation of Certain Food Additives and Contaminants. The 44th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series 35, accessed 2025, <https://www.inchem.org/documents/jecfa/jecmono/v35je21.htm>.

¹¹⁴ NDA 220152: Hepatobiliary Toxicity (Q)SAR analysis and Chemical Structural Similarity Search for Metabolites of Tradipitant. CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service. October 31, 2025.

CASE Ultra (CU) that contained models for liver damage, liver enzyme abnormalities, cholestasis, bile duct disorders, and gall bladder disorders. The battery also included the expert rule-based software, Derek Nexus, which utilized a set of 64 hepatotoxicity structural alerts. Structural similarity searches were conducted using Leadscape Enterprise and Lhasa Limited's Vitic toxicity database to identify drug substances that contain an alcohol in a similar chemical environment to M2 to serve as comparators. Additionally, a search of the published literature was conducted. Similarity and substructure-based searches were focused on capturing some variant of the di-aryl secondary alcohol group. An additional search was conducted across the drug class of NK-1 receptor antagonists for any structurally similar drug substances containing the di-aryl secondary alcohol.

The results of the in silico hepatobiliary toxicity models overall suggested no new concerns related to the ketone reduction in M2 compared to the parent drug, tradipitant. Most predictions for hepatobiliary toxicity with M2 exhibited the same or lower positive prediction probabilities compared to tradipitant. An increase in the signaling strength with the CU cholestasis model for M2 was considered nonspecific and therefore dismissed. An increase in the signaling strength with LMA's liver damage model with M2 compared to tradipitant was considered to represent the loss of the phenone-like carbonyl group, identified by the model as a mitigating (negative contributing) feature in the parent molecule; this effect was not mirrored in the results from the CU model and was therefore considered not toxicologically significant.

No structural alerts were identified for M2 using the Derek Nexus expert rule-based model.

No structurally relevant comparator compounds were identified containing a ketone or a secondary alcohol in the same chemical environment as tradipitant or M2, respectively, precluding an assessment of systemic toxicity based on data with comparator drugs. CTCS searched broadly for substructures that had the ketone/alcohol flanked by two aryl rings (not just specifically one phenyl and one pyridine ring, as featured in tradipitant) but were unable to find any compounds with this moiety. CTCS also looked for globally similar (whole molecule similarity) compounds to tradipitant and M2 and did not find sufficiently similar analogs with available toxicity data. Additionally, other members of the class of NK-1 receptor antagonists did not yield any useful analogs, as the shared substructural regions of the other class members with tradipitant are in the bis-trifluoromethylphenyl region, not the substructures of interest.

Overall, the results of the CDER CTCS (Q)SAR analyses support that no enhanced or unanticipated toxicities are expected with M2 compared to tradipitant based on the ketone reduction.

The Applicant conducted their own assessment of the potential toxicological significance of the ketone reduction in parallel with the CDER analyses.^{47,48,49,50} Briefly, these in silico (computational) analyses were conducted using a machine learning-assisted workflow developed by xAI's Grok system, an advanced large language model

trained on scientific datasets. This workflow, validated via the Applicant's in-house Python scripts, leveraged RDKit version 2024.03.5 for substructure matching and molecular property calculations, infers qualitative thresholds and probability estimates for toxicity endpoints from RDKit-computed molecular descriptors (e.g., LogP, TPSA, HBD, HBA). It draws on established rules and patterns synthesized from peer-reviewed literature, (Q)SAR tool manuals (e.g., OECD QSAR Toolbox, Tox21), and manuscripts describing consensus classifiers such as CORAL, OCHEM, and Balanced Random Forest (BRF). These include profilers such as DNA binding by OASIS v1.5, Protein binding by OASIS v1.5, and Carcinogenicity alerts by ISS v2.0, with attributes like mechanistic domains and SMARTS-based pattern recognition.

Notably, the Applicant's comparative computational prediction data were inferred based on RDKit-computed descriptors and qualitative thresholds aligned with best practices from consensus classifiers, rather than direct execution of (Q)SAR models. It is not clear why the Applicant chose to design a workflow using a large language model and a custom set of molecular descriptors and use information from existing classifier techniques to 'infer' predictions, rather than directly using existing (Q)SAR modeling software. Several times it is mentioned that this workflow is using 'established' rules, patterns, and model performance metrics from peer-reviewed literature, but no literature was cited. Validation statistics and training set attributes of these consensus models were requested but not provided.

In the Applicant's analyses, no additional reactive groups were identified in M2 compared to tradipitant. No significant differences between tradipitant and M2 were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization; in general, these predictions are consistent with completed in vitro studies with M2 and tradipitant and/or in vivo nonclinical studies with tradipitant. The potential for tradipitant and M2 to cause nephrotoxicity and neurotoxicity were also considered comparable and low. Compared to tradipitant, M2 was predicted to have slightly increased risk of hepatotoxicity (increased oxidation potential, potential drug-induced liver injury [DILI] alerts) and cardiotoxicity (increased hERG affinity, with predicted $IC_{50} > 5\mu M$ or approximately 29-fold the clinical $C_{max,ss}$). Despite the slight increase in risk presented by these analyses, the potential liver toxicity of M2 is considered to be consistent with tradipitant based on the CDER (Q)SAR analyses and findings in the completed in vitro liver safety pharmacology studies. The potential for M2-related cardiotoxicity due to hERG channel binding, while not directly assessed in nonclinical studies, has been assessed in completed clinical studies (with no risk identified, although the high-exposure scenario has not been addressed) and will be further assessed in a clinical TQT study (b) (4)

Overall, the Applicant's overall predictions are consistent with available data and with CDER's internal analyses supporting that M2 is unlikely to pose additional toxicity concerns over tradipitant based on structural differences.

Pharmacologic, Pharmacokinetic, and Toxicologic Comparisons

Although M2 was not adequately qualified based on in vivo nonclinical studies, as described above, a number of other studies provide additional information on the expected on- and off-target effects of this metabolite (see Table 23).

Based on available data, tradipitant and M2 are expected to have similar pharmacologic (i.e., on-target) activity. Both tradipitant and M2 inhibited ligand binding at the NK-1 receptor $\geq 99\%$ at $10\mu\text{M}$, with similar IC_{50} values of 0.40 and 1.55nM, respectively, in studies conducted concurrently. A functional pharmacology assay was not conducted with M2.

The predicted off-target effects of tradipitant and M2 were generally similar based on a typical in vitro secondary pharmacology assay using a panel of 189 receptors, channels, and transporters. However, M2 did show significant (i.e., $>50\%$) inhibition of the human $\text{ER}\alpha$ at the tested concentration of $10\mu\text{M}$ (approximately 58 times the $\text{C}_{\text{max,ss}}$ of M2), while tradipitant did not. Even acknowledging the large potential food effect on M2 (C_{max} 4-fold higher than that observed under fasted conditions, based on Trial 1002), the risk of M2 significantly inhibiting ligand binding to $\text{ER}\alpha$ is considered low at the proposed clinical dose. Thus, no clinically relevant differences in off-target binding are expected between tradipitant and M2, based on the secondary pharmacology screen.

In general, reduction of a ketone group to an alcohol can result in alterations in drug pharmacokinetics, including changes in half-life and altered tissue distribution.¹¹⁵ However, notable differences in elimination half-life ($t_{1/2}$) and T_{max} between tradipitant and M2 were not observed ($t_{1/2}$: 28.2 versus 43.7 hours; T_{max} : 1.5 versus 4.0 hours).¹¹⁶ Protein plasma binding was high for both tradipitant and M2. Reduction of the di-aryl ketone is not expected to significantly alter the lipophilicity of tradipitant, and thus no significant differences are expected in tissue distribution. Therefore, based on available evidence, the pharmacokinetics of tradipitant and M2 are not expected to be significantly different.

Tradipitant significantly inhibited transporters BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K in vitro, with IC_{50} values in the micromolar range. Metabolite M2 similarly inhibited OATP1B1 and MATE1, with no effect on the other evaluated transporters. Tradipitant was a poor substrate for P-gp, while M2 was not a substrate for P-gp or BCRP.

In liver safety pharmacology studies using 3D human hepatocyte spheroids, treatment with either tradipitant or M2 resulted in quantitative, biologically significant decreases in hepatocyte viability at concentrations as low as $0.350\mu\text{g/mL}$ (approximately 1.1 and 3.4 times the clinical $\text{C}_{\text{max,ss}}$ values for tradipitant and M2, respectively). In a liver safety pharmacology study using a liver co-culture MPS, tradipitant resulted in qualitative,

¹¹⁵ This is in agreement with the Applicant's analysis that states, "The ketone reduction pathway is commonly used for human drugs and typically results in simple alcohols that have a chemical profile similar to the parent, although less lipophilic and less likely to cross membranes and accumulate." See NDA 220152, SDN 23: October 15, 2025. Response to Non-Clinical Information Request, page 6.

¹¹⁶ Based on data from Trial VP-VLY-686-1002 following a single dose of 170 mg under fasted conditions.

time- and concentration-dependent, minimal to moderate findings of hepatocyte toxicity over the concentration range of 0.772-15 µg/mL. Treatment with M2 at 1.5 µg/mL, but not a lower concentration, produced sporadic findings of minimal to mild hepatocyte toxicity. Based on these studies, and given that the plasma concentration of M2 in humans is expected to be approximately 20% to 40% that of tradipitant,¹¹⁷ M2 is expected to have a similar or less severe risk of hepatocyte toxicity compared to tradipitant at the clinical dose.

Although the four-organ MPS studies in general did not elicit interpretable results, they did not provide any data demonstrating that M2 is likely to have increased or novel toxicities compared to tradipitant.

Finally, both tradipitant and M2 were negative for genotoxicity in the Ames assay and the in vitro chromosomal aberration assay in human lymphocytes.

Although M2 was not adequately evaluated in general toxicity studies with tradipitant, the WoE supports that tradipitant and M2 are expected to have similar toxicological profiles. Therefore, it is considered scientifically acceptable to qualify the safety of M2 based on total drug-related exposure to tradipitant and its active metabolites.

¹¹⁷ Based on data from Trial VP-VLY-686-1002 and Trial VP-VLY-686-1102.

Table 23. Comparison of Nonclinical Findings With Tradipitant and M2

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M2
Primary pharmacology	Inhibited binding to NK1R $\geq 99\%$ at $10\mu\text{M}$; $\text{IC}_{50}=0.40\text{nM}$	Inhibited binding to NK1R $\geq 99.3\%$ at $10\mu\text{M}$; $\text{IC}_{50}=1.55\text{nM}$
Secondary pharmacology	- Significantly inhibited ($10\mu\text{M}$): - Rat benzothiazepine L-type calcium channels: 65% - Rat dihydropyridine L-type calcium channels 63% - Rat GABA_A TBOB chloride channel: 62%	- Significantly inhibited ($10\mu\text{M}$): - Rat benzothiazepine L-type calcium channel: 52% - Rat GABA_A TBOB chloride channel: 53% Human estrogen receptor alpha: 64%
Pharmacokinetics ¹	T_{max} (hours): 1.5 $t_{1/2}$ (hours): 28.2 - Protein binding (human): $\geq 99.9\%$ - Significantly inhibited transporters BCRP, OATP1B1 ($\text{IC}_{50}=2.83\mu\text{M}$), OATP1B3, MATE1 ($\text{IC}_{50}=3.20\mu\text{M}$), and MATE2-K in vitro	T_{max} (hours): 4.0 $t_{1/2}$ (hours): 29.5 - Protein binding (human): $>99.7\%$ - Significantly inhibited transporters OATP1B1 ($\text{IC}_{50}=2.06\mu\text{M}$) and MATE1 ($\text{IC}_{50}=2.89\mu\text{M}$)
General toxicity	- Notable findings included: - Body weight loss or decreased body weight gain (dogs) - Adaptive changes in the liver and/or thyroid related to induction of CYP enzymes (rats and dogs) - Adverse changes in liver including dose-dependent hepatocyte hypertrophy and foci of inflammatory cells with hepatocyte necrosis (HW rats only)	Levels were too low to be informative

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M2
Other toxicity evaluations	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (15 µg/mL) • Four-organ system: no evidence of toxicity at 7 days; sporadic evidence of toxicity in all organs at 14 days	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: inconsistent, qualitative findings of hepatocyte toxicity (1.4 µg/mL) • Four-organ system: no evidence of toxicity at 7 days (high media concentration of M2); sporadic evidence of toxicity in all organs at 14 days (low media concentration and tissue exposure to M2)
Genotoxicity	• Negative in: – Ames assay – In vitro chromosomal aberration assay in human lymphocytes – In vivo micronucleus assay in mice	• Negative in: – Ames assay – In vitro chromosomal aberration assay in human lymphocytes

BCRP: breast cancer resistance protein; CYP: cytochrome P450; HW: Han Wistar; IC₅₀: half-maximal inhibitory concentration; MATE: multidrug and toxin extrusion protein; MPS: microphysiological system; N/A: not applicable; NK1R: neurokinin 1 receptor; OAT: organic anion transporter; P-gp: P-glycoprotein; t_{1/2}: half-life; TBOB: tert-butylbicycloorthobenzoate; T_{max}: time to maximum concentration.

Bold text highlights potentially increased or novel toxicities with a metabolite compared to tradipitant.

¹ Human T_{max} and t_{1/2} data derived from Trial VP-VLY-686-1002 following a single dose of 170 mg under fasted conditions.

Table created by reviewer, based on Applicant's provided data (see Sections 13.1 and 13.2 of the NDA Integrated Review for summaries of all nonclinical studies).

Weight-of-Evidence Assessment of M4

Tradipitant is metabolized to M4 by both reduction of the di-aryl ketone (i.e., in the same way tradipitant is metabolized to M2) and N-oxidation of the mono-substituted pyridine ring (i.e., in the same way tradipitant is metabolized to M3); thus, M4 can be formed by secondary metabolism of either M2 or M3. As such, a WoE assessment of M4 includes not only evaluations of M4 itself, but also evidence generated with M2 and M3.

Figure 52. Metabolism of Tradipitant to M4

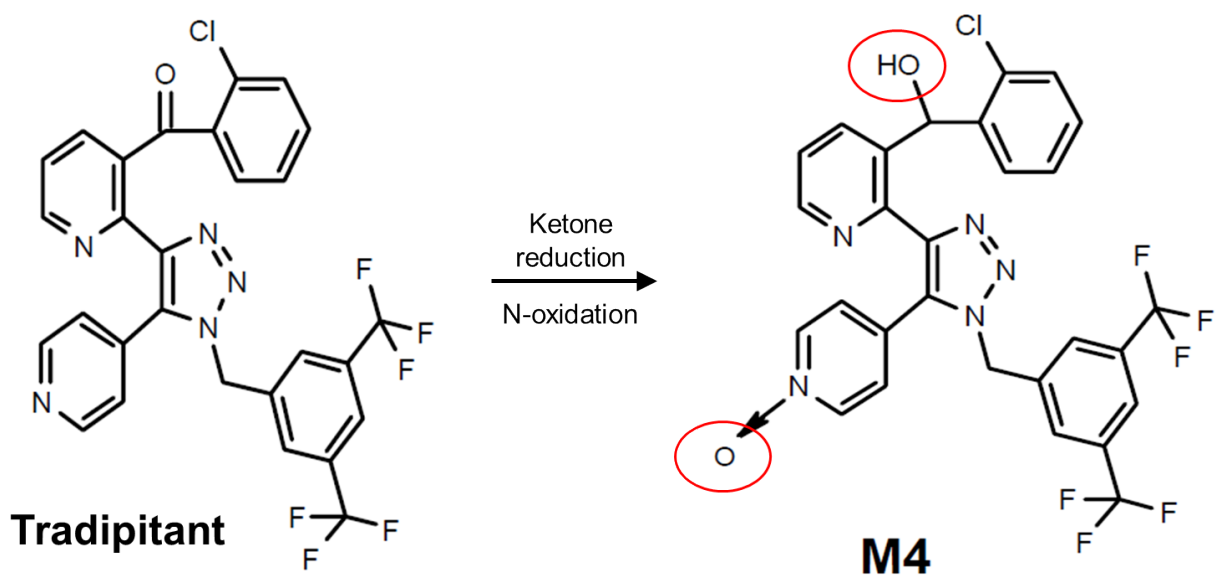


Figure created by reviewer, based on Study ADME Report 01, Figure 1.

In the context of the current application, the scientific appropriateness of a WoE approach for qualification of M4 based on total drug-related exposure was determined by assessing its structural differences, pharmacological on-target activity, and off-target activity compared to tradipitant. This WoE assessment relied on all available information for tradipitant, M2, M3, and M4 (i.e., including data that was not available in 2006).

Structural Assessment

As with M2, a (Q)SAR analysis was performed by the CDER CTCS to generate predictions of the hepatobiliary toxicity of M4 compared to tradipitant and to identify new structural alerts related to the ketone reduction.¹¹⁴ The results of the hepatobiliary toxicity models overall suggested no new concerns related to the ketone reduction, as most predictions with M4 exhibited the same or lower positive prediction probabilities as compared to the parent drug, tradipitant. An increase in the signaling strength with LMA's liver damage model with M4 was considered to represent the loss of the phenone-like carbonyl group, identified by the model as a mitigating (negative contributing) feature in tradipitant; this effect was not mirrored in the results from the CU model and was therefore considered not toxicologically significant. No structural alerts were identified for M4 using the Derek Nexus expert rule-based model. As with M2, no structurally relevant comparator compounds were identified containing a ketone or a

secondary alcohol in the same chemical environment as tradipitant or M4, respectively, precluding an assessment of toxicity using data with comparator drugs. Overall, the results of the CDER (Q)SAR analyses support that no enhanced or unanticipated toxicities are expected with M4 compared to tradipitant based on the ketone reduction.

As described above for M2, the Applicant conducted their own assessment of the potential toxicological significance of both the N-oxidation and ketone reduction using comparative computational prediction data inferred based on RDKit-computed descriptors and qualitative thresholds aligned with best practices from consensus classifiers (e.g., CORAL, OCHEM, BRF), rather than direct execution of these models.^{47,48,49,50} No significant differences between tradipitant and M4 were predicted for PK parameters, acute toxicity, mutagenicity, carcinogenicity, aquatic toxicity, or skin sensitization; in general, these predictions are consistent with completed in vitro and/or in vivo nonclinical studies. The potential for tradipitant and M4 to cause nephrotoxicity and neurotoxicity were also considered comparable and low. Compared to tradipitant, M4 was predicted to have slightly increased risk of oxidative stress (structural alert based on the N-oxide), hepatotoxicity (with potential DILI alerts) and cardiotoxicity (increased hERG affinity, with predicted $IC_{50} > 5\mu M$ or approximately 29-fold the clinical $C_{max,ss}$). Despite the slight increase in risk presented by these analyses, the potential liver toxicity of M4 is considered to be consistent with tradipitant based on the CDER (Q)SAR analysis and findings in the completed in vitro liver safety pharmacology studies. The potential for M4-related cardiotoxicity due to hERG channel binding, while not directly assessed in nonclinical studies, has been assessed in completed clinical studies with no risk identified, although the high-exposure scenario has not been addressed, and will be further assessed in a clinical TQT study (b) (4)

Although a structural alert for genotoxicity was identified based on the N-oxide, both M3 and M4 were demonstrated to be negative for genotoxicity in the Ames assay and an in vitro chromosomal aberration assay in human lymphocytes.

Notably, the combination of the ketone reduction and N-oxidation was not predicted to have additive or synergistic effects in any of the Applicant's computational analyses; rather, the predicted effects of these two modifications were either distinct or offsetting. Thus, for all parameters, toxicity related to M4 (combination of the two individual modifications) was predicted to be the same or less than that of M2 or M3 (each with one modification compared to tradipitant) and similar to tradipitant.

Overall, the Applicants predictions are consistent with available data and with CDER's internal analyses supporting that M4 is unlikely to pose additional toxicity concerns over tradipitant based on structural differences. Any residual uncertainty regarding the risk of toxicity due to the N-oxide modification are sufficiently addressed by data generated from the completed repeat-dose toxicity studies in rats in which the levels of M3 (also containing this modification) were adequately qualified for safety.

Pharmacologic, Pharmacokinetic, and Toxicologic Comparisons

Although M4 was not adequately characterized in vivo in nonclinical studies, as described above, a number of other studies provide additional information on the expected on- and off-target effects of this metabolite (see Table 24).

Based on available data, tradipitant and M4 are expected to have similar pharmacologic (i.e., on-target) activity. Both tradipitant and M4 inhibited ligand binding at the NK-1 receptor $\geq 99\%$ at $10\mu\text{M}$, with similar IC_{50} values of 0.40 and 2.23nM, respectively, in studies conducted concurrently. A functional pharmacology assay was not conducted with M4.

M4 did not demonstrate significant off-target effects based on a typical in vitro secondary pharmacology assay using a panel of 189 receptors, channels, and transporters. This suggests a similar or lower potential for off-target effects with M4 compared to tradipitant.

Notable pharmacokinetic differences between tradipitant and M4 were not observed ($t_{1/2}$: 28.2 versus 28.6 hours; T_{max} : 1.5 versus 4.0 hours). Protein plasma binding was high for both tradipitant and M4. As with M2, the ketone reduction is not expected to significantly alter the polarity of tradipitant, and thus no significant differences are expected in tissue distribution. Therefore, based on available evidence, the pharmacokinetics of tradipitant and M4 are not expected to be significantly different.¹¹⁸ While tradipitant significantly inhibited transporters BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K in vitro, with IC_{50} values in the micromolar range, M4 did not significantly inhibit any tested transporter. Tradipitant was a poor substrate for P-gp, while M4 was a strong substrate of P-gp and weak substrate of BCRP (similar to M3). In liver safety pharmacology studies using 3D human hepatocyte spheroids, treatment with either tradipitant or M4 resulted in quantitative, biologically significant decreases in hepatocyte viability at concentrations as low as $0.350\mu\text{g/mL}$ (approximately 1.1 and 3.4 times the clinical $C_{\text{max,ss}}$ values for tradipitant and M4, respectively). In a liver safety pharmacology study using a liver co-culture MPS, tradipitant resulted in qualitative, time- and concentration-dependent, minimal to moderate findings of hepatocyte toxicity over the concentration range of $0.772\text{--}15\mu\text{g/mL}$, while treatment with M4 at concentrations up to $1.5\mu\text{g/mL}$ had no effects. Based on these studies, and given that the plasma concentration of M4 in humans is expected to be approximately 30% to 40% that of tradipitant,¹¹⁷ M4 is expected to have similar or less severe risk of hepatocyte toxicity compared to tradipitant at the clinical dose.

¹¹⁸ This is in agreement with the Applicant's analysis that states, "The ketone reduction pathway is commonly used for human drugs and typically results in simple alcohols that have a chemical profile similar to the parent, although less lipophilic and less likely to cross membranes and accumulate. The N-oxide modifications make the drug less lipophilic and easier to excrete. These metabolic pathways operate at approximately equal rates and as such, all 4 major metabolites are roughly of equal concentrations in the plasma." See NDA 220152, SDN 23: Response to Non-Clinical Information Request, page 6. October 15, 2025.

In general, the four-organ MPS studies did not elicit interpretable results. Additionally, the levels of M4 were low such that any findings (or lack of findings) in these studies could not be attributed to M4.

Finally, both tradipitant and M4 were negative for genotoxicity in the Ames assay and the in vitro chromosomal aberration assay in human lymphocytes.

In addition to the lack of additional concerns identified with M4 itself compared to tradipitant, both of the individual metabolic changes (i.e., ketone reduction and N-oxidation) are considered not concerning based on available data. As described above, the WoE assessment supports that the ketone reduction on M2 compared to tradipitant is not expected to be toxicologically significant. Furthermore, the safety of the level of M3 was qualified based on in vivo nonclinical studies. Finally, data support that the ketone reduction and N-oxidation modifications are independent structural changes, and no risk of additive or synergistic effects of these modifications was identified. As M4 is expected to be present in humans at similar levels compared to M2 and M3, these findings further support that the metabolism of tradipitant to M4 is expected to be of limited toxicological significance.

Although M4 was not adequately evaluated in general toxicity studies with tradipitant, the WoE supports that tradipitant and M4 are expected to have similar toxicological profiles. Therefore, it is considered scientifically acceptable to qualify the safety of M4 based on total drug-related exposure to tradipitant and its active metabolites.

Table 24. Comparison of Nonclinical Findings With Tradipitant and M4

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M4
Primary pharmacology	Inhibited binding to NK-1R $\geq 99\%$ at $10\mu\text{M}$; $\text{IC}_{50}=0.40\text{nM}$	Inhibited binding to NK-1R 100% at $10\mu\text{M}$; $\text{IC}_{50}=2.23\text{nM}$
Secondary pharmacology	- Significantly inhibited ($10\mu\text{M}$): - Rat benzothiazepine L-type calcium channels: 65% - Rat dihydropyridine L-type calcium channels 63% - Rat GABA_A TBOB chloride channel: 62%	No significant off-target binding observed
Pharmacokinetics ¹	T_{max} (hours): 1.5 $t_{1/2}$ (hours): 28.2 - Protein binding (human): $\geq 99.9\%$ - Significantly inhibited transporters BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K in vitro; not a substrate of P-gp or BCRP	T_{max} (hours): 4.0 $t_{1/2}$ (hours): 28.6 - Protein binding (human): $>95.4\%$ - No significant inhibition of transporters in vitro; substrate of P-gp and BCRP
General toxicity	- Notable findings included: - Body weight loss or decreased body weight gain (dogs) - Adaptive changes in the liver and/or thyroid related to induction of CYP enzymes (rats and dogs) - Adverse changes in liver including dose-dependent hepatocyte hypertrophy and foci of inflammatory cells with hepatocyte necrosis (HW rats only)	Levels were too low to be informative

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M4
Other toxicity evaluations	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 1.05/0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (15 µg/mL) • Four-organ system: no evidence of toxicity at 7 days; sporadic evidence of toxicity in all organs at 14 days	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: no toxicity observed • Four-organ system: levels were too low to be informative
Genotoxicity	• Negative in: – Ames assay – In vitro chromosomal aberration assay in human lymphocytes – In vivo micronucleus assay in mice	• Negative in: – Ames assay – In vitro chromosomal aberration assay in human lymphocytes

BCRP: breast cancer resistance protein; CYP: cytochrome P450; HW: Han Wistar; IC₅₀: half-maximal inhibitory concentration; MATE: multidrug and toxin extrusion protein; MPS: microphysiological system; N/A: not applicable; NK1R: neurokinin 1 receptor; OAT: organic anion transporter; P-gp: P-glycoprotein; t_{1/2}: half-life; TBOB: tert-butylbicycloorthobenzoate; T_{max}: time to maximum concentration.

¹ Human T_{max} and t_{1/2} data derived from Trial VP-VLY-686-1002 following a single dose of 170 mg under fasted conditions.

Table created by reviewer, based on Applicant's provided data (see Sections 13.1 and 13.2 of the NDA Integrated Review for summaries of all nonclinical studies).

Weight-of-Evidence Assessment of M8

As discussed above, tradipitant is metabolized to M8 via direct N-glucuronide of the mono-substituted pyridine ring. Both tradipitant and M8 inhibited ligand binding at the NK-1 $\geq 99\%$ at $10\mu\text{M}$, with similar IC_{50} values of 3.3 and 0.49nM , respectively, in the same study. In an in vitro functional assay, tradipitant and M8 inhibited substance P-mediated calcium release with IC_{50} values of 0.63 and 6.3nM , respectively.

Figure 53. Metabolism of Tradipitant to M8

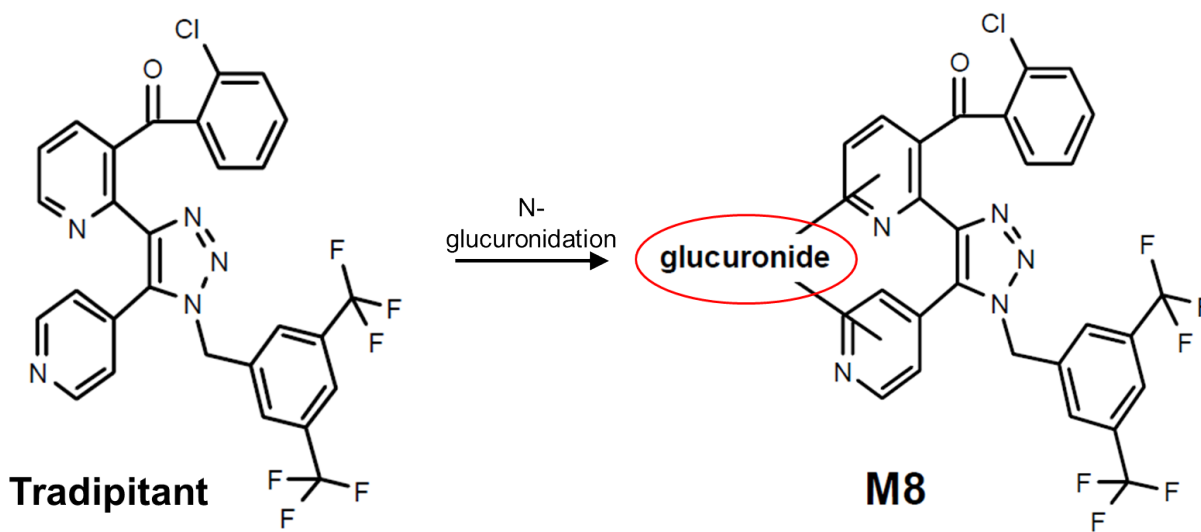


Figure created by reviewer, based on Study ADME Report 01, Figure 1

Although M8 was not adequately characterized in vivo in nonclinical studies, as described above, a number of other studies provide additional information on the expected on- and off-target effects of this metabolite (see Table 25). M8 did not demonstrate significant off-target effects based on a typical in vitro secondary pharmacology assay using a panel of 43 receptors, channels, and transporters (including the benzothiazepine L-type calcium channel, dihydropyridine L-type calcium channel, $\text{ER}\alpha$, and GABA_A TBOB chloride channel). This suggests a similar or lower potential for off-target effects with M8 compared to tradipitant.

M8 has altered pharmacokinetic properties compared to tradipitant, including slightly increased $t_{1/2}$ and notably later T_{max} ($t_{1/2}$: 28.2 hours for tradipitant versus 31.4 hours for M8; T_{max} : 1.5 versus 30 hours). Glucuronidation is expected to increase polarity of a metabolite and, thus, water solubility, decreasing the ability of that metabolite to cross membranes. This results in increased plasma circulation and decreased distribution of a metabolite (M8) to tissues compared to a parent drug (tradipitant). Thus, the differences in pharmacokinetic parameters between tradipitant and M8 are consistent with the expected effects of glucuronidation.

In liver safety pharmacology studies using 3D human hepatocyte spheroids, treatment with tradipitant consistently resulted in quantitative, biologically significant decreases in

hepatocyte viability at concentrations as low as 0.350 µg/mL, while treatment with M8 had biologically significant effects in only 2/4 donors (at 0.350 and 10.5 µg/mL, respectively). In a liver safety pharmacology study using a liver co-culture MPS, tradipitant resulted in qualitative, time- and concentration-dependent, minimal to moderate findings of hepatocyte toxicity over the concentration range of 0.772 to 15 µg/mL. Treatment with M8 at approximately 700 µg/mL, but not a lower concentration, produced minimal to mild hepatocyte toxicity. Based on these studies, M8 is expected to have similar or less severe risk of hepatocyte toxicity compared to tradipitant at the clinical dose.

M8 was not evaluated in the four-organ MPS studies. M8 was also not evaluated in genotoxicity assays; however, N-glucuronides themselves are typically not expected to be genotoxic in the absence of a reactive acyl group.

Although M8 was not adequately evaluated in general toxicity studies with tradipitant, the WoE supports that M8 is expected to remain primarily in the plasma and have similar or reduced toxicity compared to tradipitant. Therefore, it is considered scientifically acceptable to qualify the safety of M8 based on total drug-related exposure to tradipitant and its active metabolites.

Table 25. Comparison of Nonclinical Findings With Tradipitant and M8

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M8
Primary pharmacology	• Inhibited binding to NK1R $\geq 99\%$ at $10\mu\text{M}$; $\text{IC}_{50}=3.3\text{nM}$ • Inhibited substance P-mediated calcium release $\text{IC}_{50}=0.63\text{nM}$	• Inhibited binding to NK1R 99.3% at $10\mu\text{M}$; $\text{IC}_{50}=0.49\text{nM}$ • Inhibited substance P-mediated calcium release $\text{IC}_{50}=6.3\text{nM}$
Secondary pharmacology	• Significantly inhibited ($10\mu\text{M}$): – Rat benzothiazepine L-type calcium channel: 65% – Rat dihydropyridine L-type calcium channel: 63% – Rat GABA_A TBOB chloride channel: 62%	• No significant off-target binding observed
Pharmacokinetics ¹	• T_{max} (hours): 1.5 • $t_{1/2}$ (hours): 28.2 • Protein binding (human): $\geq 99.9\%$ • Significantly inhibited transporters BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K in vitro; not a substrate of P-gp or BCRP	• T_{max} (hours): 30 • $t_{1/2}$ (hours): 31.4 • Protein binding (human): not determined • Effects on transporters not determined
General toxicity	• Notable findings included: – Body weight loss or decreased body weight gain (dogs) – Adaptive changes in the liver and/or thyroid related to induction of CYP enzymes (rats and dogs) – Adverse changes in liver including dose-dependent hepatocyte hypertrophy and foci of inflammatory cells with hepatocyte necrosis (HW rats only)	• Levels not assessed and thus not informative

Nonclinical Data	Nonclinical Findings	
	Tradipitant	M8
Other toxicity evaluations	• 3D human hepatocyte spheroids: quantitatively decreased cell viability (as low as 1.05/0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (15 µg/mL) • Four-organ system: no evidence of toxicity at 7 days; sporadic evidence of toxicity in all organs at 14 days	• 3D human hepatocyte spheroids: inconsistent, quantitatively decreased cell viability (as low as 0.350 µg/mL) • Liver co-culture MPS: qualitative findings of hepatocyte toxicity (≥0.04 µg/mL) • Four-organ system: M8 not measured in these studies
Genotoxicity	• Negative in: – Ames assay – In vitro chromosomal aberration assay in human lymphocytes – In vivo micronucleus assay in mice	• Not tested

BCRP: breast cancer resistance protein; CYP: cytochrome P450; HW: Han Wistar; IC₅₀: half-maximal inhibitory concentration; MATE: multidrug and toxin extrusion protein; MPS: microphysiological system; N/A: not applicable; NK1R: neurokinin 1 receptor; OAT: organic anion transporter; P-gp: P-glycoprotein; t_{1/2}: half-life; TBOB: tert-butylbicycloorthobenzoate; T_{max}: time to maximum concentration.

¹ Human T_{max} and t_{1/2} data derived from Trial VP-VLY-686-1002 following a single dose of 170 mg under fasted conditions.

Table created by reviewer, based on Applicant's provided data (see Sections 13.1 and 13.2 of the NDA Integrated Review for summaries of all nonclinical studies).

Qualification of Metabolite Safety Based on Total Drug-Related Exposure

Although the individual levels of M2, M4, and M8 are considered not qualified based on the completed repeat-dose toxicity studies, the WoE supports that these metabolites are expected to have similar toxicological profiles compared to tradipitant. As such, it is considered appropriate to qualify these metabolites based on total drug-related exposure in animals (i.e., rats) compared to humans.

Total tradipitant-related drug exposure in rats included measurement of tradipitant, M2, M3, and M4; M8 was not measured in these studies as it was not expected to be formed in rodent species. Based on these measurements, total drug-related exposure (i.e., AUC_{0-24}) in rats was 42,613 ng·h/mL following a single dose and 12,400 ng·h/mL following repeated dosing.

In humans following a single dose of tradipitant at 85 or 170 mg, total tradipitant-related drug exposure included measurement of tradipitant, M2, M3, M4, and M8. This resulted in total drug-related exposure (AUC_{0-24}) of 4,756 and 7,558 ng·h/mL, respectively.¹¹⁹ Using the previously stated rat data, this provides exposure margins following a single dose of tradipitant at 85 or 170 mg of 9.0 and 5.6, respectively. Thus, the safety of the levels of metabolites M2, M4, and M8 following these single doses are considered qualified based on total drug-related exposure.

At steady state, following 12 days of dosing at 85 mg BID, total tradipitant-related drug exposure included measurement of tradipitant, M2, M3, and M4; M8 was not measured. This resulted in total drug-related exposure (AUC_{0-24}) at steady state of 8,152 ng·h/mL.¹²⁰ Using the previously stated rat data, this provides an exposure margin of 1.5. It is noted that the data from Trial 1102 were derived from BID dosing and reported as AUC_{0-12} , then those values were doubled to approximate AUC_{0-24} . Although this conservative approach likely overestimates AUC_{0-24} following once daily dosing, this is considered appropriate given the additional uncertainties in the clinical PK data discussed previously. On the other hand, based on the lack of M8 data at steady state, the human AUC_{0-24} is considered an underestimate of total drug-related exposure. Including M8 in this value could conservatively be estimated to double the total steady-

¹¹⁹ The total drug-related exposure (AUC) reported here was determined by summing the reported AUC values of tradipitant, M2, M3, M4, and M8 in humans administered tradipitant as a single dose of 85 or 170 mg in Trial 1002. It is acknowledged that this calculated total includes some uncertainty versus calculating the total of all analytes for each pharmacokinetic timepoint and deriving the total AUC from those values, due to the extrapolation of the terminal phase. However, data were not available at the time of this review to enable the precise calculation of total drug-related exposure. The uncertainty or slight inaccuracy associated with the current approach is not expected to affect the overall safety determination.

¹²⁰ The total drug-related exposure (AUC) reported here was determined by summing the reported AUC values of tradipitant, M2, M3, and M4 in humans administered tradipitant at 85 mg twice daily for 12 days in Trial 1102. It is acknowledged that this calculated total includes some uncertainty versus calculating the total of all analytes for each pharmacokinetic timepoint and deriving the total AUC from those values, due to the extrapolation of the terminal phase. However, data were not available at the time of this review to enable the precise calculation of total drug-related exposure. The uncertainty or slight inaccuracy associated with the current approach is not expected to affect the overall safety determination.

state AUC (although, more likely, it would be closer to 1.5 times the reported value based on available data). This would provide an exposure margin of $1.5 \div 2 = 0.75$. This exposure margin is considered acceptable to qualify the levels of metabolites M2, M4, and M8 at steady state based on total drug-related exposure in the context of this development program.

Table 26. Qualification of Metabolites Based on Total Drug-Related Exposure

Tradipitant Dose	Duration	Total AUC ₀₋₂₄ (ng·h/mL) ¹		Ratio Rat:Human
		Human	Rat	
85 mg	Single dose	4756	42613	9.0
170 mg	Single dose	7558	42613	5.6
170 mg/day	Steady state	8152	12400	1.5 (0.76) ²

AUC: area under the concentration-time curve; Q12H: every 12 hours.

¹ AUC values were adjusted for differences in dosing intervals, when appropriate, to cover the entire 24-hour period.

² To account for the absence of M8 in the human AUC value, an additional factor of 2 was applied to the ratio. This is considered a conservative approach to ensuring that the total drug-related exposure in humans at steady state is not significantly underrepresented.

Table created by reviewer, based on data from Trial VP-VLY-686-1002 (single-dose data), Trial VP-VLY-686-1102 (steady-state data from subjects administered 85 mg Q12H for 12 days), Study TAJ0035 (single dose and 13-week values in female Han Wistar rats, i.e., the strain and sex with highest exposure).

12.2.6 Conclusions and Recommendation

As discussed, the Applicant has identified four major human metabolites of tradipitant: M2, M3, M4, and M8. Prior to submission of NDA 220152, because of limited clinical pharmacology data, it could not be determined if these metabolites individually represent $\geq 10\%$ of total drug-related exposure at steady state, although tradipitant itself did not seem to meet this threshold.¹²¹ However, based on all data available at the time of this review, it was determined that adequate nonclinical assessment of these metabolites is warranted to support the safety of tradipitant for its intended clinical use. Based on the available data, three of the four major human metabolites (i.e., M2, M4, and M8) are present at disproportionately higher levels in humans compared to species used in the nonclinical toxicology studies and therefore had not been qualified based on in vivo data. However, using a WoE approach for M2, M4, and M8, taking into consideration data from a (Q)SAR analysis as well as primary pharmacology, secondary pharmacology, pharmacokinetic, general toxicity, special toxicity, and genotoxicity studies with each metabolite and/or tradipitant, the review team has determined that each metabolite is expected to have a similar toxicological profile to that of tradipitant, and no potential for increased or novel toxicities was identified. Therefore, it was considered acceptable to qualify the safety of these metabolites based on total drug-related exposure rather than on an individual basis.

¹²¹As previously discussed, tradipitant accounted for approximately 9% of total drug-related radioactivity in the plasma, based on AUC_{0-inf}, following a single dose of 25 mg in a mass balance study (Trial H8R-MC-HJAK). Total drug-related exposure at steady state was not evaluated in any clinical study.

Based on total tradipitant-related drug exposure, the levels of M2, M4, and M8 are considered qualified under both the single-dose and steady-state scenarios for the prevention of vomiting induced by motion. However, as the nonclinical data supporting the safety of unrestricted use of tradipitant over a lifetime are considered inadequate, the safety of the metabolites is likewise not considered to be adequately supported by nonclinical data for unrestricted use of tradipitant over a lifetime.

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Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 220152
Link to EDR	EDR NDA220152 ¹
Submission Date	12/30/2024
Submission Type	Original submission, Standard review
Brand Name	NEREUS
Generic Name	Tradipitant
Dosage Form and Strength	Capsules, 85 mg
Route of Administration	Oral
Proposed Indication	Acute prevention of vomiting induced by motion in adults
Applicant	Vanda Pharmaceuticals
Associated IND	IND 141315
OCP Review Team	Sanjida Mahjabeen, Ph.D. (Clinical Pharmacology) Shen Li, Ph.D. (Clinical Pharmacology TL) Hongshan Li, Ph.D. (Pharmacometrics) Vishnu Sharma, Ph.D. (Pharmacometrics TL)
OCP Final Signatory	Chandahas G Sahajwalla, Ph.D.

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the multidisciplinary integrated review. The OCP's review is based on the information currently in the administrative record. If we must review information that is subsequently added to the administrative record, we will update our part of the multidisciplinary integrated review accordingly.

¹ [docubridge://open/&Host=docubridge-cder.fda.gov&Id=Dabc37696a273469b92aa96ab5e12d9ab&Current=1](https://open.&Host=docubridge-cder.fda.gov&Id=Dabc37696a273469b92aa96ab5e12d9ab&Current=1)

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Appendix 14.2. Individual Study Review

By: Sanjida Mahjabeen, Ph.D.; Shen Li, Ph.D.

1. Individual PK Study Review

1.1 Trial H8R-EW-HJAC

Title

Single oral dose-escalating study to assess the safety and pharmacokinetics of LY686017 in healthy subjects.

Study Design

This was a single-center, subject-blind, crossover, randomized, placebo-controlled, dose-escalating study in healthy male subjects. Subjects received LY686017 dosing under fasted conditions according to the following treatment sequence (Table 1). The washout duration between periods within subjects was at least 9 days.

Table 1. Treatment Sequence, Study H8R-EW HJAC

	Study Period 1	Study Period 2	Study Period 3
Group 1	Placebo (n=3)	30 mg (n=3)	200 mg (n=3)
	1 mg (n=3)	Placebo (n=3)	200 mg (n=3)
	1 mg (n=3)	30 mg (n=3)	Placebo (n=3)
Group 2	Placebo (n=3)	50 mg (n=3)	400 mg (n=3)
	3 mg (n=3)	Placebo (n=3)	400 mg (n=3)
	3 mg (n=3)	50 mg (n=3)	Placebo (n=3)
Group 3	Placebo (n=3)	100 mg (n=3)	800 mg (n=3)
	10 mg (n=3)	Placebo (n=3)	800 mg (n=3)
	10 mg (n=3)	100 mg (n=3)	Placebo (n=3)

Source: Table HJAC.9.2. of Study H8R-EW-HJAC CSR

Abbreviations: CSR, clinical study report; n, number of subjects in treatment group

Formulation

1 mg, 10 mg, 100 mg capsules.

Results

Tradipitant exposure [AUC_{0-inf} and C_{max}] was nonlinear with dose over the evaluated dose range. With a 16-fold increase in dose from 50 mg to 800 mg, AUC_{0-inf} increased by 3-fold and C_{max} increased by 4-fold (Table 2). The less than dose-proportional increase in the systemic exposure may at least partially due to the low solubility of tradipitant.

Table 2. Plasma PK Parameters Following Oral Single-Dose Administration of LY686017

Dose (mg)	Geometric Mean (%CV) (N _{PK} =6)						
	C _{max} (ng/mL)	t _{max} ^a (h)	AUC(0-t _{last}) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	t _{1/2} ^b (h)	CL/F (L/h)	V _{ss} /F (L)
1	8.20 (26.9)	0.53 (0.50-2.00)	30.4 (66.0)	35.2 (61.0)	11.0 (4.78-20.0)	28.4 (61.0)	321 (50.6)
3	18.5 (20.8)	1.50 (0.50-2.00)	112 (50.4)	122 (46.3)	17.7 (11.1-23.3)	24.7 (46.3)	430 (27.7)
10	25.8 (17.4)	2.00 (1.00-2.00)	306 (20.6)	338 (27.6)	19.7 (12.6-30.0)	29.6 (27.6)	841 (15.1)
30 ^c	99.3 (62.6)	1.00 (0.50-2.00)	1360 (55.6)	1530 (55.2)	21.2 (14.3-34.1)	19.6 (55.2)	631 (60.6)
50	63.1 (41.6)	1.00 (1.00-3.02)	1280 (40.6)	1370 (43.8)	16.4 (11.5-26.1)	36.5 (43.8)	1040 (36.6)
100	69.0 (52.9)	1.50 (1.00-5.00)	1810 (29.5)	2390 ^d (51.0)	24.1 ^d (16.7-66.4)	41.9 ^d (51.0)	1720 ^d (47.1)
200	92.9 (29.3)	3.00 (1.00-6.00)	2190 (32.8)	2370 (36.3)	17.0 (11.1-28.2)	84.4 (36.3)	2430 (30.5)
400	91.9 (39.1)	1.50 (1.00-2.00)	2370 (42.9)	3320 ^c (70.3)	28.3 ^c (12.8-96.5)	120 ^c (70.3)	5420 ^c (42.5)
800	277 (41.0)	1.00 (1.00-4.00)	4150 (29.2)	4620 ^c (41.7)	20.4 ^c (12.9-41.0)	173 ^c (41.7)	5050 ^c (38.9)

Source: Table HJAC.14.20 through to Table HJAC.14.28

Abbreviations: AUC(0-t_{last}) = area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration; AUC(0-∞) = area under the plasma concentration-time curve from time zero to infinite time; CL/F = apparent clearance; C_{max} = maximum observed plasma concentration; N_{PK} = number of subjects included in the pharmacokinetic analysis; t_{1/2} = apparent terminal elimination half-life; t_{max} = observed sampling time of C_{max}; V_{ss}/F = apparent volume of distribution at steady-state.

^aMedian (range)

^bGeometric mean (range)

^cN_{PK} = 5

^dN_{PK} = 4

Source: Table HJAC.11.1. in clinical study report H8R-EW HJAC
Abbreviations: CV, coefficient of variation

1.2 Trial H8R-EW-HJAD

Title

Part A: A multiple-dose safety, pharmacokinetic, and pharmacodynamic study of LY686017 in healthy male subjects.

Part B: A PET imaging study with carbon-11 GR205171 to determine occupancy of cerebral neurokinin-1 receptors by LY686017 in healthy subjects.

Study Design

This was a two-part, single-center, multiple-dose, dose-escalation study in healthy male subjects.

Part A

Each subject was randomized to receive either LY686017 (n=6) or matching placebo (n=6) for 28 consecutive days.

Table 3. Study Design, Study H8R-EW-HJAD

Study Day	LY686017 Daily Dose ^a
Day 1 - Day 7	1 mg
Day 8 - Day 14	10 mg
Day 15 - Day 21	30 mg
Day 22 - Day 28	100 mg

Source: protocol

^a In Part A, 6 subjects were randomised to received placebo throughout the entire 28-day dosing period (see [Section 9.1.2](#)).

Source: Table HJAD.9.1 of Study H8R-EW-HJAD CSR

Abbreviation: CSR, clinical study report

Part B

Four groups of two subjects were enrolled sequentially. All subjects received LY686017, there was no placebo control. In addition, each subject was scheduled to undergo three PET scans for receptor occupancy assessment.

Table 4. Summary of Timing of PET Scans, Study H8R-EW-HJAD Part B

Group	Subject Number	PET Scan						
		Baseline	24 hours (approx.) after 7 days dosing				48 hours (approx.) after 7 days dosing	72 hours (approx.) after 7 days dosing
		Predose	1 mg	10 mg	30 mg	100 mg	100 mg	100 mg
1	3, 4	X	X	X				
2	5, 6	X	X			X		
3	1	X				X ^a	X	
	2	X					X	X
4	7 ^b , 8	X		X	X			

Source: filenote dated 08 March 2004; [Section 14.3.1, Listing 1.2](#).

^a This PET scan could not be performed because of scan failure due to scanner console problem (only one data point lost due to technical failure).

^b Subject ^(b)₍₆₎ received his final PET scan after an extra day of dosing with 30 mg (see [Section 9.8.1](#)).

Source: Table HJAD.9.2 of Study H8R-EW-HJAD CSR

Abbreviations: approx., approximately; CSR, clinical study report; PET, positron emission tomography

Formulation

1 mg, 10 mg, 100 mg capsules.

Results

As presented in Table 5, $C_{\max,ss}$ and $AUC_{\tau,ss}$ increased less than proportionally with the increasing dose.

Table 5. PK Parameters of LY686017 Following Oral Administration of LY686017, Study H8R-EWHJAD

Pharmacokinetic Parameter	Geometric Mean (%CV) [N _{PK} =14]			
	1 mg Day 7	10 mg ^a Day 14	30 mg Day 21	100 mg Day 28
$C_{\max,ss}$ (ng/mL)	7.88 (38.7)	32.9 (36.7)	89.4 (39.9)	97.6 (33.2)
$C_{\text{trough},ss}$ (ng/mL)	0.663 (55.4)	9.41 (56.4)	31.8 (58.1)	48.0 (63.1)
$t_{\max,ss}$ (h) ^b	1.00 (0.50-2.00)	1.00 (0.50-4.00)	1.00 (0.50-4.00)	2.00 (0.50-6.00)
$AUC_{\tau,ss}$ (ng·h/mL)	41.4 (38.6)	336 (42.4)	991 (51.9)	1300 (48.5)
$C_{av,ss}$ (ng/mL)	1.72 (38.6)	14.0 (42.4)	41.3 (51.8)	54.2 (48.5)
$t_{1/2}$ (h)	NA	NA	NA	25.4 (30.6) ^c
R_A	1.41 (19.4)	NA	NA	NA
CL_{ss}/F (L/h)	24.2 (38.6)	29.7 (42.4)	30.3 (51.9)	77.2 (53.1)

Source: Appendix 14.2, Table HJAD.14.1 through to Table HJAD.14.5

Abbreviations: CV = coefficient of variation; N_{PK} = number of subjects included in the PK analysis;

$C_{\max,ss}$ = maximum observed concentration during a dosing interval at steady-state;

$C_{\text{trough},ss}$ = concentration observed 24 hours postdose at steady-state conditions; $t_{\max,ss}$ = time of maximum observed concentration during a dosing interval at steady-state; $AUC_{\tau,ss}$ = area under the concentration versus time curve during one dosing interval at steady-state; $C_{av,ss}$ = average drug concentration under steady-state conditions during multiple dosing; $t_{1/2}$ = half-life associated with the terminal rate constant (λ_z) in non compartmental analysis; R_A = accumulation ratio; CL_{ss}/F = apparent total body clearance at steady-state after extravascular administration; NA = not applicable.

^a N_{PK} = 11.

^bMedian (range).

^cIncludes pharmacokinetic data obtained post Day 28; N_{PK} = 10.

Source: Table HJAD.11.1. of Study H8R-EW-HJAD CSR

Abbreviations: CSR, clinical study report; PK, pharmacokinetic

Receptor Occupancy Assessment

Receptor occupancy increased with dose in the frontal cortex and the maximum occupancy in the frontal cortex (93% ±4) was determined 24 hours after the last 100 mg dose on Day 28.

However, the clinical relevance of this receptor occupancy assessment is unclear.

1.3 Trial 1002 (Food effect study)

Title

A four-period, two-way crossover open-label study evaluating the pharmacokinetics of a single dose of tradipitant in healthy participants.

Study Design

This was an open-label, four-period, two-way crossover study to evaluate the pharmacokinetics of a single dose of the capsule formulation of tradipitant in healthy subjects in a fed and fasted state. The washout period (at least 11 days) is acceptable given the reported the elimination half-life ($t_{1/2}$) up to 31.6 hours.

- Subjects in Cohort 1 received each of the following treatments:
 - Single dose of 170-mg tradipitant by two 85 mg capsules, fasted
 - Single dose of 170-mg tradipitant by two 85 mg capsules + high fat/high calorie meal
- Subjects in Cohort 2 received each of the following treatments:
 - Single dose of 85-mg tradipitant, fasted
 - Single dose of 85-mg tradipitant + high fat/high calorie meal

Based on the response to the information request dated January 5, 2024, all subjects fasted overnight (10 hours) before dosing on Day 1. For the fed condition, a high-calorie, high-fat meal was eaten 30 minutes or less prior to administration of study medication and finished prior to dosing. The high-calorie, high-fat meal contained the following: 2 eggs cooked in butter, 2 pieces of buttered toast, 2 strips of bacon, 4 oz. of hash browns, and a cup of whole milk. In both conditions, an additional meal was provided 4 hours following dosing.

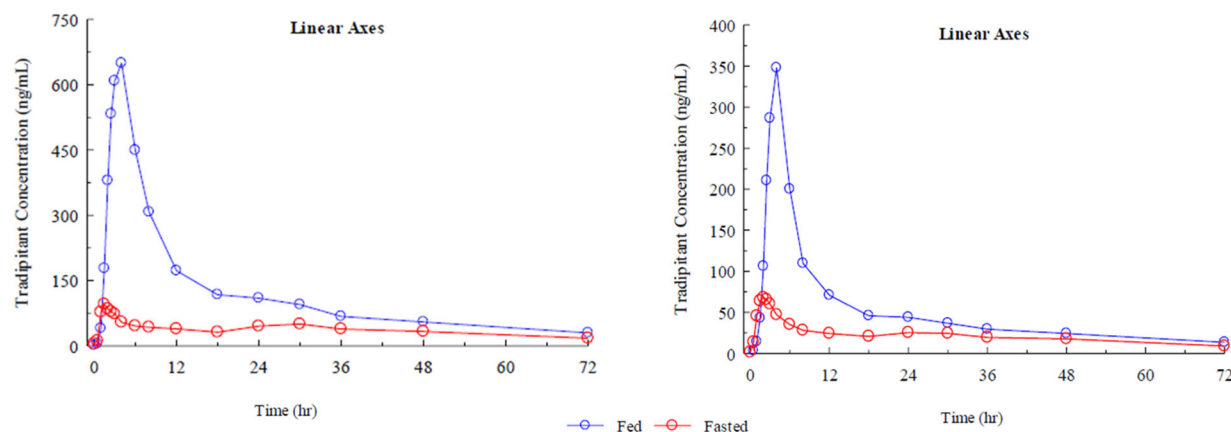
Formulation

85 mg capsule.

PK Results

Geometric mean plasma concentration-time profiles for tradipitant and metabolites are presented in Figure 1, Figure 2, and Figure 3, respectively. Concomitant high fat meal significantly increased the systemic exposure to tradipitant and its 4 metabolites (Table 6, Table 9, and Table 10).

Figure 1. Geometric Mean Plasma Concentration-Time Profiles of Tradipitant After Oral Administration of 170 mg (Left Panel) or 85 mg (Right Panel) of Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Trial 1002



Source: Figures 1 and 2 of Trial VP-VLY-686-1002 Pharmacokinetic Report

Table 6. Summary of PK Parameters for Tradipitant After Single Administration of 85 mg and 170 mg of Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Trial 1002

PK Parameters ¹	Tradipitant 85 mg		Tradipitant 170 mg	
	Fasted	Fed	Fasted	Fed
C _{max} (ng/mL)	84.7 [39.7]	401 [36.9]	112 [74.1]	774 [29.6]
T _{max} (hr)	2.0 [1.0–8.0]	4.0 [1.5–6.0]	1.5 [1.0–3.0]	4.0 [2.0–8.0]
AUC _{0-t} (hr·ng/mL)	1,649 [47.3]	3,862 [41.7]	2,793 [49.4]	9,153 [41.2]
AUC _{0-inf} (hr·ng/mL)	1,839 [58.1]	4,516 [51.9]	3,526 [53.0]	10,374 [51.4]
t _{1/2} (hr)	31.6 [39.0]	31.0 [29.0]	28.2 [30.1]	27.2 [37.1]

Source: Tables 2 and 4 of Trial VP-VLY-686-1002 Pharmacokinetic Report

¹ Geometric mean [geometric %CV] except T_{max} for which the median [range] are reported.

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the concentration-time curve from time zero to time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; t_{1/2}, elimination half-life; T_{max}, time to maximum concentration

Table 7. Statistical Analysis of Food Effect on Tradipitant After Oral Administration of 170 mg of Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Trial 1002

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV(%)	Power* (%)
	Fed	Fasted	Estimate	90% Confidence Interval		
C _{max}	777.82	110.51	703.87	546.99 → 905.75	40.4	67.5
AUC(0-t)	9,178.34	2,796.44	328.21	276.02 → 390.27	27.2	61.2
AUC(inf)	10,402.26	2,725.23	381.70	238.29 → 611.42	32.9	87.9

Source: Table 3 of Trial VP-VLY-686-1002 Pharmacokinetic Report

* Power to detect a 20% difference at α=0.05.

Based on analysis of natural log-transformed pharmacokinetic parameters.

Abbreviations: AUC(inf), area under the concentration-time curve from time zero to infinity; AUC(0-t), area under the concentration-time curve from time zero to time t; C_{max}, maximum plasma concentration; CV, coefficient of variation

Table 8. Statistical Analysis of Food Effect on Tradipitant After Oral Administration of 85 mg of Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Trial 1002

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV(%)	Power* (%)
	Fed	Fasted	Estimate	90% Confidence Interval		
C _{max}	401.00	84.67	473.59	408.09 → 549.60	24.2	65.6
AUC(0-t)	3,861.87	1,648.91	234.21	192.66 → 284.71	32.1	61.2
AUC(inf)	4,702.37	1,787.46	263.08	201.12 → 344.12	30.6	72.7

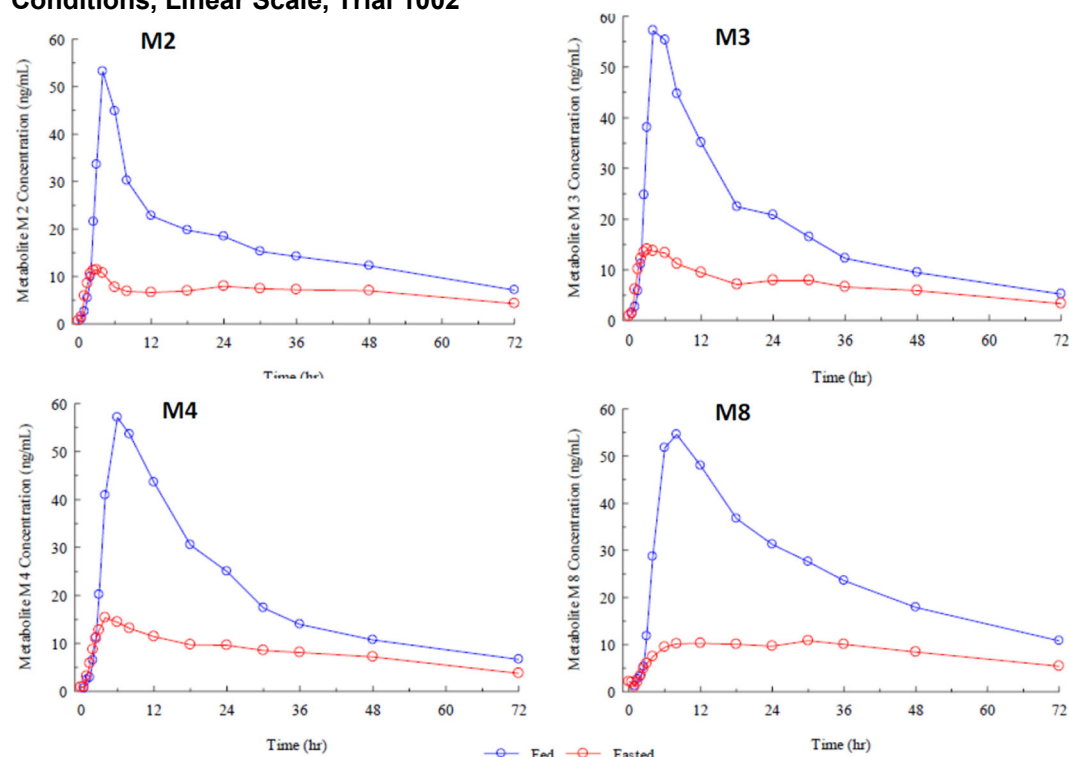
Source: Table 5 of Trial VP-VLY-686-1002 Pharmacokinetic Report

* Power to detect a 20% difference at $\alpha=0.05$.

Based on analysis of natural log-transformed pharmacokinetic parameters.

Abbreviations: AUC(inf), area under the concentration-time curve from time zero to infinity; AUC(0-t), area under the concentration-time curve from time zero to time t; C_{max}, maximum plasma concentration; CV, coefficient of variation

Figure 2. Geometric Mean Plasma Concentration-Time Profiles of Metabolites M2, M3, M4, and M8 After Single-Dose Administration of 85-mg Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Linear Scale, Trial 1002



Source: Adapted from Figures 4, 6, 8, 10 of Trial VP-VLY-686-1002 Pharmacokinetic Report

Abbreviation: M, metabolite

Table 9. PK Parameters of Tradipitant Metabolites After Single-Dose Administration of 85-mg Tradipitant Under Fasted and Fed Conditions in Healthy Subjects, Trial 1002

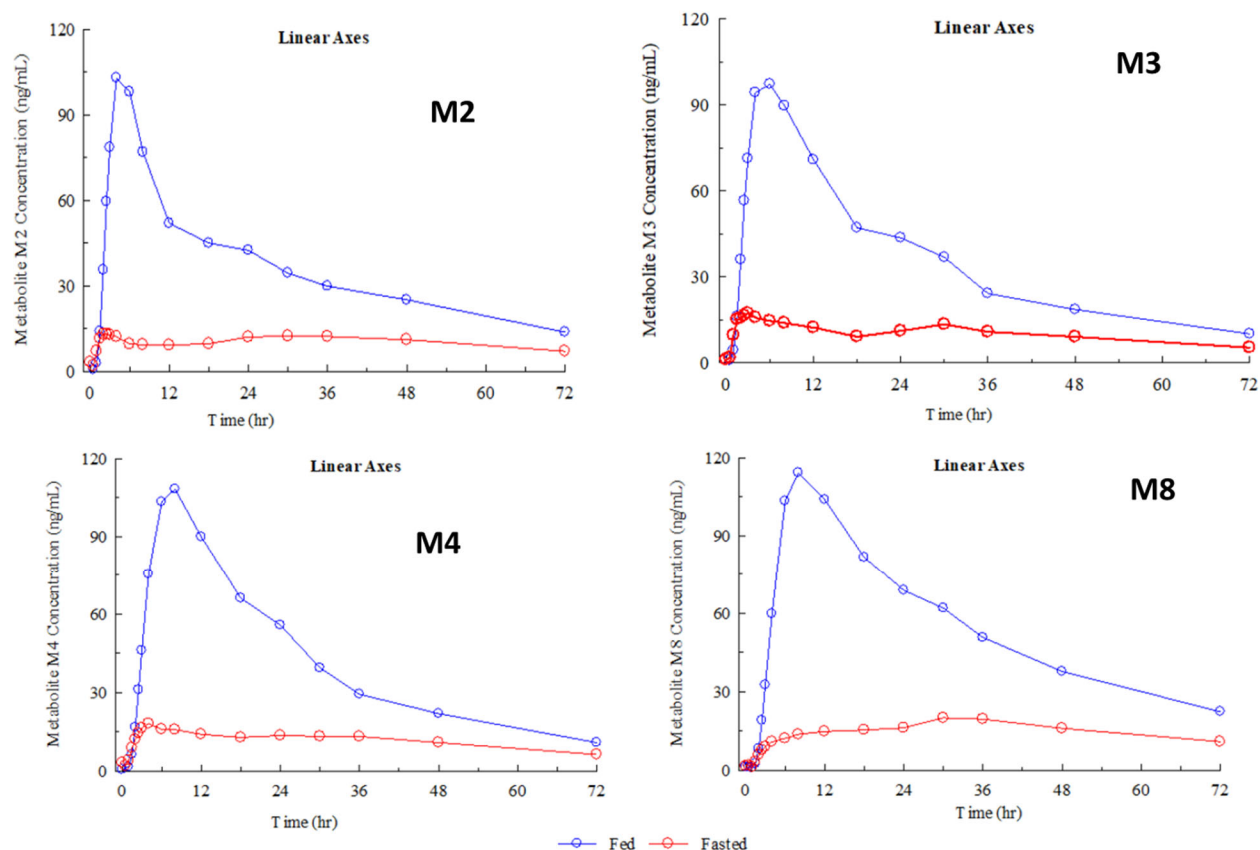
Metabolites	C _{max} (ng/mL)*		AUC _{inf} (hr·ng/mL)*		T _{max} (hr)		t _{1/2} (hr)*	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
M2	14.2 [55.8]	57.7 [49.7]	741 [92.9]	1553 [73.2]	4.0 [1.5-48]	4.0 [2.0-6.0]	43.7 [56.3]	35.8 [37.0]
M3	17.1 [35.1]	63.5 [21.3]	608 [56.4]	1567 [45.2]	3.0 [1.5-12]	4.0 [2.0-6.0]	30.2 [35.2]	28.0 [26.5]
M4	17.4 [46.5]	59.0 [23.3]	804 [74.3]	1752 [63.6]	4.1 [3.0-36]	6.0 [4.0-8.0]	32.4 [50.2]	26.9 [22.3]
M8	13.3 [51.0]	56.9 [23.7]	764 [62.2]	2276 [52.1]	15 [6.0-48]	8.0 [4.0-12]	36.3 [58.3]	30.3 [43.2]

Source: Tables 8, 12, 16, 20 of Trial VP-VLY-686-1002 Pharmacokinetic Report

* Geometric mean [geometric %CV] except T_{max} for which the median [range] are reported.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; M, metabolite; PK, pharmacokinetic; t_{1/2}, elimination half-life; T_{max}, time to maximum concentration

Figure 3. Geometric Mean Plasma Concentration-Time Profiles of Metabolites M2, M3, M4, and M8 After Single-Dose Administration of 170-mg Tradipitant to Healthy Subjects Under Fed and Fasted Conditions, Linear Scale, Trial 1002



Source: Adapted from Figures 3, 5, 7, 9 of Trial VP-VLY-686-1002 Pharmacokinetic Report

Abbreviation: M, metabolite

Table 10. PK Parameters of Tradipitant Metabolites After Single-Dose Administration of 170-mg Tradipitant Under Fasted and Fed Conditions in Healthy Subjects, Trial 1002

Metabolites	C _{max} (ng/mL)*		AUC _{inf} (hr·ng/mL)*		T _{max} (hr)		t _{1/2} (hr)*	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
M2	18.7 [67.6]	121 [33.9]	803 [61.8]	3522 [48.2]	4.0 [1.5-48]	4.0 [2.5-8.0]	29.5 [14.7]	31.4 [36.1]
M3	21.9 [52.2]	114 [17.1]	835 [62.5]	3589 [41.2]	3.0 [1.0-48]	4.0 [3.0-8.0]	25.7 [32.4]	27.5 [47.2]
M4	21.4 [54.0]	116 [16.7]	1035 [62.7]	3627 [61.3]	4.0 [3.0-48]	6.0 [4.0-12]	28.6 [39.7]	23.1 [47.2]
M8	21.7 [57.4]	120 [21.0]	1359 [67.8]	5415 [72.2]	30 [8.0-72]	8.0 [6.0-12]	31.4 [30.9]	31.1 [53.3]

Source: Tables 6, 10, 14, 18 of Trial VP-VLY-686-1002 Pharmacokinetic Report

* Geometric mean [geometric %CV] except T_{max} for which the median [range] are reported.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; M, metabolite; PK, pharmacokinetic; t_{1/2}, elimination half-life; T_{max}, time to maximum concentration

1.4 Trial H8R-MC-HJAK (Mass Balance Study)

Title

Clinical pharmacology study report: disposition after oral administration of ¹⁴C-labeled NK-1 Antagonist II (LY686017)

Study Design

Six healthy male subjects received a single oral dose of 10 mL of polyethylene glycol 400 solution containing a total of 25 mg of LY686017 (approximately 100 µCi of LY686017-¹⁴C) on Day 1. Five subjects completed the study. One subject discontinued after screening visit due to a personal reason.

Results

The Cumulative Excretion of Radioactivity

Following a single 25 mg (100 µCi) oral dose of LY686017-¹⁴C, the mean total recovery of radioactivity was approximately 88% (80.11% in feces and 7.14% in urine) of the dose recovered within 312 hours postdose (13 days). 85% of radioactivity was recovered by 168 hours postdose.

The unchanged parent drug was not detected in urine and minimum in feces. LY686017 did not appear to distribute consistently into red blood cells. The mean percentage of radioactivity in red blood cells was approximately 20% at 0.5 hours postdose but were either minimal or less than zero after 1 hour.

Table 11. Mean $\pm$ SEM Cumulative Percentages of Dose Excreted in Five Healthy Subjects Following a Single 25 mg (100 μ Ci) Oral Dose of LY686017- 14 C, Study H8R-MC-HJAK

Time interval (hours)	Feces ^a	Toilet Paper ^b	Urine ^c	Breath ^d	Cumulative Total Recovery
0-1	-	-	-	0.01 $\pm$ 0.00	0.01 $\pm$ 0.00
0-4	-	-	-	0.02 $\pm$ 0.00	0.02 $\pm$ 0.00
0-6	-	-	2.35 $\pm$ 0.14	0.02 $\pm$ 0.00	2.36 $\pm$ 0.14
0-8	-	-	2.35 $\pm$ 0.14	0.02 $\pm$ 0.00	2.37 $\pm$ 0.14
0-12	-	-	3.99 $\pm$ 0.21	0.02 $\pm$ 0.00	4.02 $\pm$ 0.21
0-24	7.42 $\pm$ 2.53	0.05 $\pm$ 0.02	4.99 $\pm$ 0.26	0.02 $\pm$ 0.00	12.48 $\pm$ 2.73
0-48	31.18 $\pm$ 8.96	0.22 $\pm$ 0.07	6.04 $\pm$ 0.30	0.02 $\pm$ 0.00	37.47 $\pm$ 9.10
0-72	57.52 $\pm$ 7.83	0.38 $\pm$ 0.09	6.53 $\pm$ 0.33	0.02 $\pm$ 0.00	64.44 $\pm$ 7.74
0-96	68.67 $\pm$ 4.48	0.43 $\pm$ 0.10	6.81 $\pm$ 0.36	0.02 $\pm$ 0.00	75.94 $\pm$ 4.38
0-120	74.17 $\pm$ 2.31	0.46 $\pm$ 0.10	6.96 $\pm$ 0.38	0.02 $\pm$ 0.00	81.62 $\pm$ 2.13
0-144	75.94 $\pm$ 2.38	0.47 $\pm$ 0.10	7.06 $\pm$ 0.40	0.02 $\pm$ 0.00	83.49 $\pm$ 2.17
0-168	77.45 $\pm$ 1.84	0.47 $\pm$ 0.10	7.13 $\pm$ 0.41	0.02 $\pm$ 0.00	85.06 $\pm$ 1.59
0-192	78.41 $\pm$ 1.77	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	86.04 $\pm$ 1.52
0-216	79.14 $\pm$ 1.74	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	86.77 $\pm$ 1.50
0-240	79.46 $\pm$ 1.70	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	87.09 $\pm$ 1.47
0-264	79.69 $\pm$ 1.67	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	87.32 $\pm$ 1.44
0-288	79.88 $\pm$ 1.74	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	87.51 $\pm$ 1.50
0-312	80.11 $\pm$ 1.71	0.47 $\pm$ 0.10	7.14 $\pm$ 0.42	0.02 $\pm$ 0.00	87.75 $\pm$ 1.48

Source: Table HJAK.7.2. in H8R-MC-HJAK Study Report

^a Feces samples collected on the first day are reported in the 0-to-24-hour row. The last fecal sample collection for Subject (b) (6) was at 288 hours, whereas the remaining subjects provided samples through the end of the study at 312 hours.

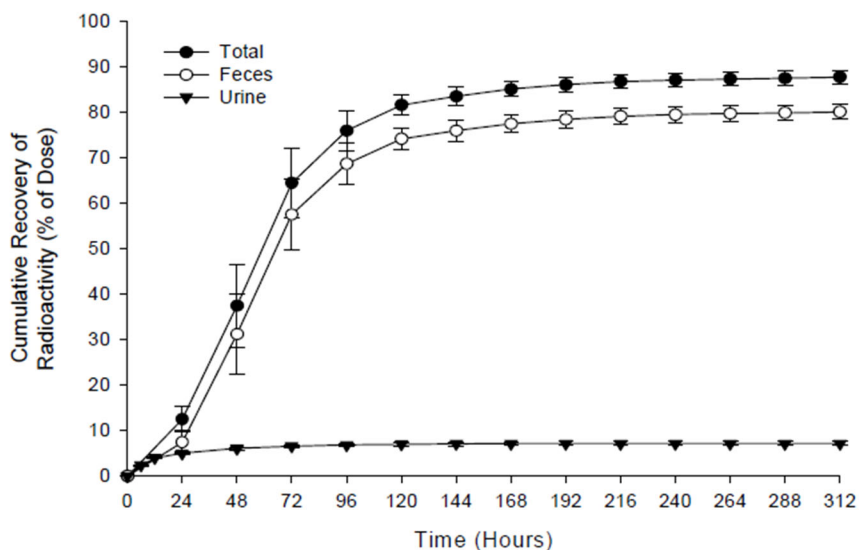
^b Residual radioactivity in toilet paper was only calculated from fecal samples collected up to 144 hours.

^c Urine samples were collected from all subjects from 0 to 6 hours, 6 to 12 hours, 12 to 24 hours, and at 24-hour intervals until collection ceased at 168 hours for Subjects (b) (6) and at 192 hours for Subject (b) (6).

^d Breath samples were collected at 1, 4, 8, 12, and 24 hours.

Abbreviation: SEM, standard error of the mean

Figure 4. Mean $\pm$ SEM Cumulative Percentages of Dose Excreted Following the Administration of a Single 25 mg (100 μ Ci) Oral Dose of LY686017- 14 C in Healthy Subjects, Study H8R-MC-HJAK



Abbreviations: SEM = standard error of the mean.

Source: Figure HJAK.7.1. of H8R-MC-HJAK Study Report

Abbreviation: SEM, standard error of the mean

Plasma Pharmacokinetics and Total Radioactivity in Plasma

Metabolite profiling in plasma samples was conducted in samples collected up to 24 hours postdose.

During the first 24 hours after dosing, tradipitant, M2, M3, M4, and M8 were detected as the main identified entities in plasma samples based on radio chromatogram. Metabolite profiling in plasma samples based on radioactivity was not conducted for plasma samples collected after 24 hours. Pharmacokinetics of LY686017 (tradipitant), M2, M3, and M4 but not M8 was further characterized using a liquid chromatographic separation with tandem mass spectrometry (LC-MS/MS) to estimate AUC_{0-inf}. Based on AUC_{0-inf} assessed using a validated LC-MS/MS Method LY686017, M2, M3, and M4 accounted for approximately 9%, 4%, 5%, and 8% of radioactivity, respectively. Compared to mean $t_{1/2}$ ranged from 20 to 30 hours for LY686017, M2, M3, and M4, the mean $t_{1/2}$ of radioactivity was 113 hours, indicating that the $t_{1/2}$ of radioactivity is likely comprised of nonmonitored metabolite(s) with a substantially longer $t_{1/2}$.

Of note, in Trial 1002, the mean half-life of M8 was 36.3 hours and it was 31.6 hours for tradipitant.

Table 12. Plasma PK Parameters of LY686017, Metabolites, and Radioactivity Following a Single 25 mg (100 µCi) Oral Dose of LY686017-¹⁴C, Study H8R-MC-HJAK

Parameter	Geometric Mean (%CV)				
	LY686017 [N=5]	M2 (2081070) [N=5]	M3 (2195411) [N=5]	M4 (2329249) [N=5]	Radioactivity [N=5]
C_{max}^a [ng/mL]	63.3 (75.4)	12.6 (36.8)	12.7 (61.1)	19.5 (26.1)	157 (36.0)
t_{max}^b [h]	1.00 (1.00)	3.00 (1.00-3.00)	2.00 (1.00-4.05)	4.00 (3.00-4.05)	2.00 (1.00-2.00)
$t_{1/2}$ [h]	25.7 (27.3)	29.6 (19.8)	20.0 (48.6)	24.8 (57.0)	113 (33.0)
$AUC(0-\infty)^c$ [ng•h/mL]	520 (94.4)	199 (66.9)	289 (97.8)	425 (63.9)	5500 (37.7)
$AUC(0-t_{max})$ / Radioactivity	0.458 (34.8)	NC	NC	NC	NC
$AUC(0-\infty)$ / Radioactivity	0.0944 (51.2)	0.0362 (39.3)	0.0525 (52.4)	0.0772 (26.7)	NA

Source: Table HJAK.7.3. of Study H8R-MC-HJAK CSR

^a Radioactivity units are ng-equiv/mL.

^b Median (range) reported.

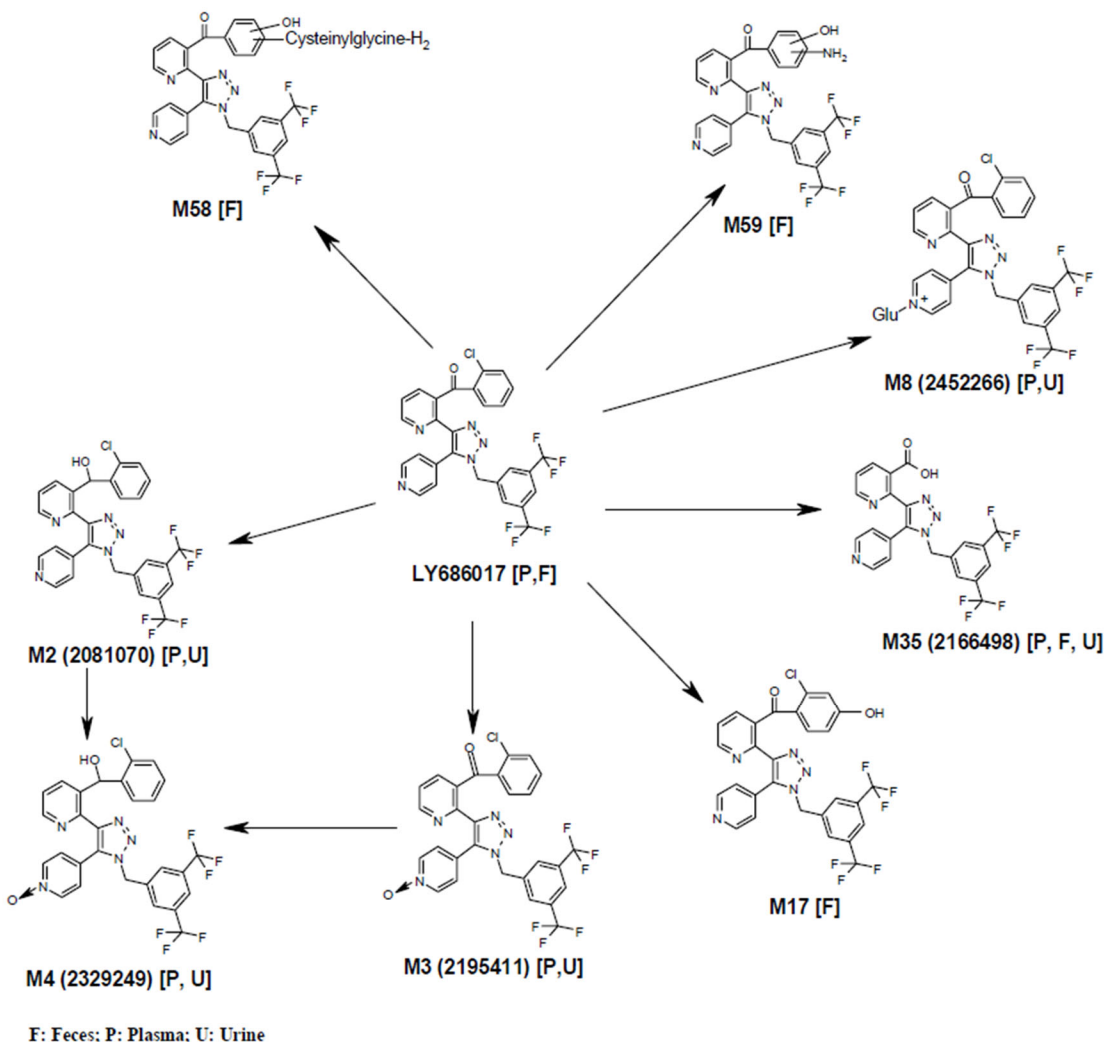
^c Radioactivity units are ng-equiv•h/mL.

Abbreviations: $AUC(0-T_{max})$, area under the concentration curve up to T_{max} of LY686017; $AUC(0-\infty)$, area under the concentration-time curve to time infinity; C_{max} , maximal concentration; CSR, clinical study report; CV, coefficient of variation; M, metabolite; N, number of subjects included in the PK analysis; NA, not applicable; NC, not calculated; PK, pharmacokinetic; T_{max} , time to maximal concentration; $t_{1/2}$, elimination half-life

Metabolic Profile of LY686017

Multiple metabolic pathways were identified and the major pathways (>5% of the dose) included ketone reduction (M2 and M4), N-oxidation (M3 and M4) and N-glucuronidation at the monosubstituted pyridine ring (M8). The chiral metabolites (M2 and M4) were observed in plasma and/or urine as racemic mixtures. Metabolites M17, M35, M58, and M59 were the major components excreted in feces. Metabolite M60 was the major urinary metabolite, but it accounted for <2% of the dose.

Figure 5. Proposed Major Metabolic Pathways of LY686017-¹⁴C in Healthy Subjects, Study H8R-MC-HJAK



Source: Figure HJAK.7.2. of Study H8R-MC-HJAK CSR

Note: The Applicant noted in the submission that M2 was inadvertently mislabeled as present in Plasma (P) and Urine (U) and should have been labeled as present in Plasma (P) and Feces (F).

Abbreviations: CSR, clinical study report; M, metabolite

Metabolites in Feces

Ten metabolites that were common to all five subjects were detected by radioactivity and identified by mass spectrometry in the fecal extracts. Metabolites M17, M35, M58, and M59 were the major parent-related components in feces, accounting for 9%, 9%, 9%, and 6% of the dose in the selected fecal samples, respectively. Each of the other metabolites accounted for <5% of the dose in the selected fecal samples. Together, the identified metabolites in the selected fecal samples accounted for 44.1% of the dose. A series of minor metabolites that were detected by radioactivity but not identified constituted a total of approximately 11% of the dose in the selected fecal samples.

Metabolites in Urine

Ten radiolabeled metabolites that were common to all 5 subjects were detected. M60 (glycine conjugate of chlorobenzoic acid, Compound 29263) was the major urinary metabolite, which accounted for 1.12% of the dose in the selected urine samples. Each of the other urinary metabolites accounted for <1% of the dose in the selected samples. Together, identified metabolites in the selected urine samples accounted for 4.05% of the dose. Parent compound was not found in detectable amounts in the urine.

1.5 Trial 1102 (Drug Interaction Study With Midazolam)

Title

An open-label, single-sequence study to assess the effect of multiple doses of tradipitant on cytochrome P450 3A4 using midazolam as a substrate in healthy subjects

Study Design

This was an open-label, single-sequence, 20-day, inpatient study. The dosing schedule is as shown in Table 13. Midazolam oral solution was administered at 10 mg dose between 07:00 and 09:00. Tradipitant was administered between 07:00 and 09:00 for the morning dosing and between 19:00 and 21:00 for the evening dosing. When the drugs were coadministered (Day 16), subjects were administered tradipitant first and then midazolam.

Dosing

Based on the response to the information request dated January 5, 2024, subjects fasted for at least 8 hours prior to the morning drug administration. When confined, subjects received a light breakfast, standard lunch, standard dinner, and a light snack in the evening. No other food was taken at any time during confinement (20 days). Meals were served at 9:00, 13:00, and 20:00. Both the morning and evening doses of tradipitant were provided without food, prior to the breakfast and dinner services respectively.

Table 13. Dosing Schedule, Trial 1102

	Treatment Period 1		Treatment Period 2		Treatment Period 3
Day(s)	D1	D2	D3	D4-15	D16
Treatment	MDZ (10 mg) Single dose	No drug	tradipitant (85 mg) Single dose	tradipitant (85 mg) Q12H dosing	MDZ (10 mg) + tradipitant (85 mg) Single dose

Source: Table 9.1.1 of Trial VP-VLY-686-1102 CSR

Abbreviations: CSR, clinical study report; D, day; MDZ, Midazolam; Q12H, every 12 hours

Results

Following administration of tradipitant doses of 85 mg Q12H for 12 days, when midazolam was coadministered with tradipitant, midazolam and 1-hydroxymidazolam exposure ($C_{\max}$ and AUC) increased up to 16% as compared to when midazolam was administered alone (Table 14).

After administration of tradipitant doses of 85 mg Q12H for 12 days, the accumulation ratios for tradipitant and its metabolites, based on AUC_{0-12} , ranged from 4.6 to 9.3 (Table 16). The metabolite-to-parent ratio, based on AUC_{0-12} on Day 16, ranged from 0.31 to 0.33 for all 3 metabolites (M2, M3, and M4). Based on C_{trough} comparison and analysis, it is inconclusive regarding whether the steady state of tradipitant was reached after 85 mg BID from Days 4 to 16 in healthy subjects due to the lack of additional PK samples after Day 16.

Midazolam and Metabolite Pharmacokinetics

Table 14. Statistical Comparison of PK Parameters for Midazolam After Oral Administration of 10 mg of Midazolam on Study Day 1 (Alone) and Then on Study Day 16 After Tradipitant 85 mg Q12H on Study Days 4 Through 16 to Healthy Subjects, Trial 1102

Pharmacokinetics Parameters	Least square geometric means		Geometric mean ratio (%)		Within Subject CV (%)
	Midazolam + Tradipitant	Midazolam alone	Estimate	90% Confidence interval	
$C_{\max}$	138.50	130.50	106.13	92.05 → 122.36	29.37
$AUC_{(0-t)}$	344.26	303.63	113.38	103.59 → 124.10	18.40
$AUC_{(0-\infty)}$	367.32	317.37	115.74	105.56 → 126.89	17.87

Source: Table 11.4.1.2 of Trial VP-VLY-686-1102 CSR

Abbreviations: $AUC_{(0-\infty)}$, area under the concentration-time curve from time zero to infinity; $AUC_{(0-t)}$, area under the concentration-time curve from time zero to time t; $C_{\max}$, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; PK, pharmacokinetic; Q12H, every 12 hours

Table 15. Statistical Comparison of PK Parameters for 1-OH Midazolam After Oral Administration of 10 mg of Midazolam on Study Day 1 (Alone) and Then on Study Day 16 After Tradipitant 85 mg Q12H on Study Days 4 Through 16 to Healthy Subjects, Trial 1102

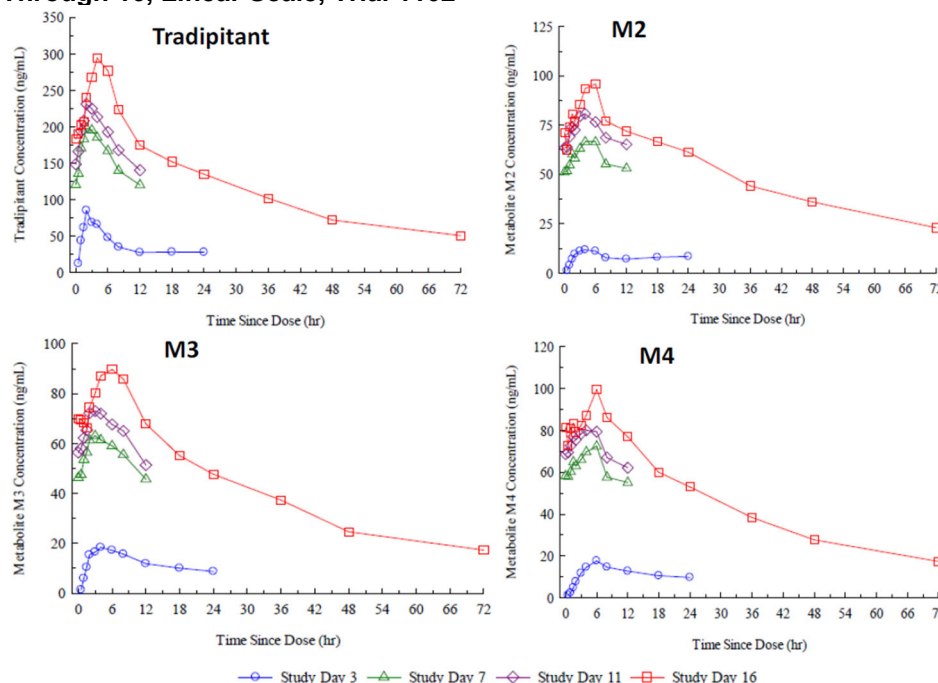
Pharmacokinetics Parameters	Least square geometric means		Geometric mean ratio (%)		Within Subject CV (%)
	Midazolam + Tradipitant	Midazolam alone	Estimate	90% Confidence interval	
$C_{\max}$	117.34	124.16	94.51	84.90 → 105.21	18.05
$AUC_{(0-t)}$	138.50	130.50	106.13	92.05 → 122.36	29.37
$AUC_{(0-\infty)}$	344.26	303.63	113.38	103.59 → 124.10	18.40

Source: Table 11.4.1.4 of Trial VP-VLY-686-1102 CSR

Abbreviations: $AUC_{(0-\infty)}$, area under the concentration-time curve from time zero to infinity; $AUC_{(0-t)}$, area under the concentration-time curve from time zero to time t; $C_{\max}$, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; 1-OH, 1-hydroxide; PK, pharmacokinetic; Q12H, every 12 hours

Tradipitant and Its Metabolites Pharmacokinetics

Figure 6. Geometric Mean Plasma Concentration-Time Profiles of Tradipitant and Its Metabolites After Oral Administration of 85 mg of Tradipitant on Day 3 and Then 85 mg Q12H on Days 4 Through 16, Linear Scale, Trial 1102



Source: Adapted from Figures 11.4.1.3, 11.4.1.4, 11.4.1.5, and 11.4.1.6 of Trial VP-VLY-686-1102 CSR
Abbreviations: CSR, clinical study report; M, metabolite; Q12H, every 12 hours

Table 16. PK Parameters (Geometric Mean [Geometric %CV]) of Tradipitant and Its Metabolites After 85 mg Q12H Administration in Healthy Subjects, Trial 1102

Tradipitant/ Metabolite	First Dose (Day 3) (N=24)		Day 16 (N=24)		Accumulation Ratio (Day 16/Day 3)	
	C _{max} (ng/mL)	AUC ₍₀₋₁₂₎ (ng·h/mL)	C _{max} (ng/mL)	AUC ₍₀₋₁₂₎ (ng·h/mL)	C _{max} (ng/mL)	AUC ₍₀₋₁₂₎ (ng·h/mL)
Tradipitant	98.3 (59)	445 (61.9)	327 (42.4)	2037 (43.4)	3.3	4.6
M2	13.6 (65.4)	73.5 (59.3)	102 (54)	683 (55.3)	7.5	9.3
M3	20.9 (59.8)	118 (54.8)	97.7 (31)	656 (34.6)	4.7	5.6
M4	18 (51.5)	95 (45.1)	104 (47.3)	700 (51.3)	5.5	7.4

Source: Tables 11.4.1.5, 11.4.1.6, 11.4.1.7, and 11.4.1.8 of Trial VP-VLY-686-1102 CSR)

Abbreviations: AUC₍₀₋₁₂₎, area under the concentration-time curve from time 0 to 12 hours postdose; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; M, metabolite; N, number of subjects; PK, pharmacokinetic; Q12H, every 12 hours

Table 17. Trough Concentration Comparison After Oral Administration of 85 mg of Tradipitant, Trial 1102

Time point	N	Least-Square Geometric means	Helmert Contrast of ratio (90% CI) [p-value] ^a
Day 3, Hour 12	24	27.6	0.19 (0.17, 0.21) [<0.0001]
Day 7, Hour 0	24	120.7	0.80 (0.72, 0.87) [<0.0001]
Day 7, Hour 12	24	120.2	0.75 (0.68, 0.82) [<0.0001]
Day 11, Hour 0	24	148.7	0.90 (0.82, 0.99) [0.08]
Day 11, Hour 12	24	140.5	-
Day 16, Hour 0	24	183.5	-
Day 16, Hour 12	24	174.6	

Source: Table 11.4.1.9 of Trial VP-VLY-686-1102 CSR

Abbreviations: CI, confidence interval; CSR, clinical study report; N, number of subjects included in the analysis

Metabolite M8 of tradipitant was not measured in this study. The Applicant was unable to synthesize a reference standard for the analysis of this metabolite preventing the measurement of M8 metabolite levels in plasma.

1.6 Trial H8R-MC-HJAP (Interaction Study With ethanol)

Title

A multiple dose, fixed sequence, two-period crossover, LY686017-ethanol Interaction study in healthy volunteers.

Study Design

This was a randomized, double-blind, multiple-dose, two-way cross-over study in healthy subjects. Briefly, the study consisted of two treatment periods with a washout period of at least 7 days. In each period, subjects received LY686017 at 50 mg once daily or placebo for 7 days. On Day 6 subjects also received a drink of orange juice 1 hour after dosing. On Day 7 subjects received a drink of orange juice containing alcohol 1 hour after dosing.

Results

While the Applicant reported the systemic exposure of LY686017 was slightly increased when 50 mg LY686017 was administered 1 hour prior to consumption of orange juice containing ethanol (20% w/v). To note, the Applicant is proposing 85 mg or 170 mg single dose for current indication which is for the acute prevention of vomiting induced by motion. Hence the applicability of this study results to the currently proposed dose levels is unclear because the tradipitant dose was lower and the formulation used in this study was different from the proposed to-be-marketed formulation.

1.7 Trial 1301 (Gastric emptying study)

Title

A single center, randomized, double-blind, placebo-controlled study to evaluate the effects of tradipitant on satiation, gastric volume, gastric accommodation and gastric emptying in healthy volunteers

Study Design

This was a randomized, double-blind, placebo-controlled study conducted in 24 healthy subjects. Briefly, subjects received tradipitant 85 mg BID for 9 consecutive days. On Day 7, gastric emptying was measured by scintigraphy. On Day 8, satiation with a nutrient drink test was measured. On Day 9, gastric accommodation was measured using single photon emission computed tomography. At the end of each visit (Days 7 to 9), blood samples were also obtained 2 hours postdose for PK assessment.

Results

The gastric emptying time and postprandial gastric volume measures were overall similar between tradipitant, and placebo and no statistically significant differences were reported. The clinical relevance of this study to support current indication is unclear.

1.8 Trial 3404 (Phase 3 efficacy study in subjects with history of motion sickness)

Title

A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in participants affected by motion sickness during travel

Study Design

This was a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of a single oral dose of tradipitant 85 mg or 170 mg in subjects who had a history of motion sickness on prior vehicle travel and met inclusion criteria at screening visit (Visit 1, Day 1). Subjects were randomly assigned to one of three following treatment groups stratified by port and received single dose in efficacy assessment period at Visit 2 (Day 2):

- 85-mg tradipitant (n=104)
- 170-mg tradipitant (n=106)
- Placebo (n=106)

Subjects were administered their assigned medication approximately 60 minutes prior to the start of the vehicle travel assessment. There were 20 individual vehicle travel assessments ranging approximately from 123 to 245 minutes in duration. Subjects had the option to undergo a PK

assessment at Visit 3 (Day 7 following the dosing at Visit 2). Subjects who agreed were administered a single oral dose of tradipitant 170 mg. Briefly, subjects received the first dose on Day 2 and subsequently an optional dose for PK assessment was administered on Day 7 (i.e., 6 days after the first dose). Blood samples were collected for PK assessment at specified time intervals, including at baseline (predose), and 1 and 2 hours following dosing.

Results

Among 316 study subjects, 171 subjects agreed on the optional PK assessment dosing. Among these 171 subjects, 61 subjects received placebo, 55 subjects received 85 mg and 55 subjects received 170 mg single dose of tradipitant at Visit 2 (Day 2). The sparse PK data obtained from the optional PK assessment period at Visit 3 was grouped by treatment at Visit 2 in Table 18.

Table 18. Mean Tradipitant and Metabolite Concentration Following Oral Single Dose of 170-mg Tradipitant During Optional PK Assessment Period

Treatment on Visit 2	Analyte	Predose Mean (SD); ng/mL	1 hr Postdose Mean (SD); ng/mL	2 hr Postdose Mean (SD); ng/mL
Placebo (n=61)	Tradipitant	1.01 (0.057)	125.18 (212.215)	174.72 (140.412)
	M2	0.5 (00)	11.93 (14.98)	22.86 (19.91)
	M3	0.5	14.84 (11.5)	27.83 (18.88)
	M4	0.5 (0)	6.06 (5.44)	17.1 (11.38)
	M8	0.5	1.96 (1.544)	11.96 (10.54)
Tradipitant 85 mg (n=55)	Tradipitant	14.68 (15.47)	140.31 (93.95)	172.09 (139.81)
	M2	6 (5.9)	18.3 (13.301)	29.44 (26.32)
	M3	4.92 (5.27)	19.24 (11.6)	28.88 (15.7)
	M4	5.72 (6.8)	11.76 (8.827)	22.06 (13.4)
	M8	13.11 (15.58)	14.64 (15.02)	23.12 (17.56)
Tradipitant 170 mg (n=55)	Tradipitant	23.12 (31.46)	135.41 (89.92)	147.84 (85.094)
	M2	10.53 (11.46)	21.3 (16.81)	28.61 (18.72)
	M3	6.98 (8.14)	21.06 (11.81)	28.59 (13.5)
	M4	9.16 (10.94)	15.22 (12.43)	24.31 (14.41)
	M8	13.67 (16.29)	15.54 (16.63)	22.75 (18.04)

Source: Reviewer's analysis based on the PK data (PC.xpt) provided by the Applicant in response to Clinical Pharmacology Information request issued on April 2, 2025 (Response Date: April 17, 2025)
Abbreviations: M, metabolite; PK, pharmacokinetic; SD, standard deviation

The subjects who received 85-mg and 170-mg dose during efficacy evaluation period (i.e., at Visit 2) had higher predose concentration of tradipitant at Visit 3 compared to the subjects who received placebo at Visit 2.

Appendix 14.5. Pharmacometrics

By: Hongshan Li, Ph.D.; Vishnu Sharma, Ph.D.

2. Pharmacometrics Assessment

2.1 Executive Summary

The Applicant's initial population pharmacokinetic (PPK) analysis (submitted on December 30, 2024) included no PK data from subjects with motion sickness. An information request (IR) was sent on April 2, 2025, requesting the Applicant conduct additional PPK modeling and simulation analysis incorporating the PK data for tradipitant and its metabolites (M2, M3, M4, and M8) in subjects with motion sickness obtained from Trial 3404 and 3403 (if available). In response to the IR, an updated PPK report was submitted on July 22, 2025, based on pooled tradipitant and metabolite concentration data from 7 trials (1002, 1102, 1301, 2301, 3301, 3403, and 3404). Key highlights of the PPK models are described below:

- The Applicant's NONMEM executions finished with unsuccessful minimization, probably due to the over-parameterization of the models. However, the PPK analysis generally captured the concentration data reasonably well and the predicted tradipitant and metabolite exposures appear generally reasonable.
- The observed PK exposures of tradipitant and metabolites of Trial 3403 are higher than other trials (including Trial 3404, another trial in motion sickness). Per the Applicant, these differences may reflect the small number of postdose samples obtained in each trial and the short interval of these samples relative to dosing.
- In addition, each dosing amount was derived via averaging the total dosing micrograms over a period of time for subjects with poor compliance (as low as 46.4%) added uncertainty to the PPK modeling and simulation analysis. It might be rational to exclude PK data from subjects with confirmed low-compliance in the PPK analysis. The FDA reviewer's independent PPK analysis of tradipitant suggested one-compartmental model could also be used to describe the PK data (with low-compliance subject and Trial 1002 excluded). However, this model also under-predicted the elevated concentrations observed in Trial 3403.

2.2 The Applicant's Population PK Analysis

2.2.1 Background

The Applicant originally submitted PPK analysis was based on 4126 PK samples collected from 520 subjects in 5 trials (1002, 1102, 1301, 2301, and 3301), without any PK data from subjects with motion sickness. In response to FDA information request for tradipitant and metabolite simulations under fed versus fasted conditions dated April 2, 2025, an updated PPK report for motion sickness was submitted on July 22, 2025, based pooled PK data from 7 trials (1002,

1102, 1301, 2301, 3301, 3403, and 3404). The pharmacometrics review of PPK analysis is performed mainly based on the version submitted on July 22, 2025.

2.2.2 Objective

The objective of this analysis was to develop and validate population pharmacokinetic models to describe exposure of tradipitant and four metabolites (M2, M3, M4, and M8) in subjects with a history of motion sickness. This analysis included the evaluation of the potential effect of intrinsic factors, including body size, age, [REDACTED], and organ function.

2.2.4 Data

A pooled analysis on 5616 tradipitant plasma concentration (ranged 0.5 to 1510 ng/mL) samples of 1206 subjects from 7 trials (1002, 1102, 1301, 2301, 3301, 3403, and 3404) with orally administered tradipitant was conducted. The trial designs and population descriptions are briefly described below:

Trial 1002

This was a two-way crossover open label PK trial of a single dose of tradipitant in healthy subjects to evaluate the food effect and PK linearity. Subjects received either one or two 85-mg tradipitant capsules under fasted conditions or fed conditions. The continuous variables and categorical variables of Trial 1002 are listed in Table 19 and Table 20, respectively.

Table 19. Continuous Variables of Subjects (N=31), Trial 1002

Variable	Mean	SD	Median	Min	Max
Age (years)	37.52	8.95	38	22	55
Weight (kg)	85.48	14.91	86.8	54.9	113.9
Height (cm)	175.26	10.47	176	152	197
BMI (kg/m ²)	27.81	4.19	28.3	20.2	36.5
BSA (m ²)	2.03	0.22	2.076	1.586	2.428
Lean body mass (kg)	56.66	8.66	58.3	38.6	72.6
ALT (IU)	21.52	9.86	20	5	48
AST (IU)	20.29	5.8	19	9	33
Alkaline phosphate (IU)	62	17.76	64	33	103
Total bilirubin (mg/dL)	0.48	0.17	0.5	0.2	0.9
Serum creatinine (mg/dL)	0.99	0.19	0.95	0.71	1.4
CrCL (Cockcroft_Gault, mL/min)	117.77	27.73	120.9	75	171.1
MDRD GFR (mL/min/1.73 m ²)	57.79	9.75	58.4	42.08	77.51
CKD-EPI GFR (mL/min/1.73 m ²)	88.73	15.5	90.69	63.29	115.29
Modified MDRD GFR (mL/min)	67.99	14.16	65.73	45.49	98.74
Modified CKD-EPI GFR (mL/min)	104.32	21.88	100.85	69.15	147.51

Source: Table 7 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL; creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 20. Categorical Variables of Subjects (N=31), Trial 1002

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	18	58.1
	2	Female	13	41.9
Race	1	White	30	96.8
	2	African American	1	3.2
Elderly (>65)	0	No	31	100
	-1	Missing	31	100
Ethnicity	1	Not Hispanic	0	0
	2	Hispanic	0	0

Source: Table 8 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: PPK, population pharmacokinetic

Trial 1102

This was an open-label, single sequence trial to assess the effect of multiple doses of tradipitant on cytochrome P450 3A4 using midazolam as a substrate in healthy subjects. A single oral dose of 10 mg midazolam was administered alone on Day 1, followed by tradipitant 85 mg once daily on Days 3 to 15, followed by coadministration of single oral doses of tradipitant 85 mg and midazolam 10 mg on Day 16. The continuous variables and categorical variables of Trial 1102 are listed in Table 21 and Table 22, respectively.

Table 21. Continuous Variables of Subjects (N=24), Trial 1102

Variable	Mean	SD	Median	Min	Max
Age (years)	40	10.94	42	21	55
Weight (kg)	69.09	11.98	69.45	51.8	97.1
Height (cm)	168.83	7.4	169	156	182
BMI (kg/m ²)	24.06	2.559	24.2	19.5	30
BSA (m ²)	1.8	0.191	1.81	1.53	2.2
Lean body mass (kg)	49	7.408	48.4	37.8	63.4
ALT (IU)	34.17	9.234	33.5	21	52
AST (IU)	23.67	4.842	22	17	35
Alkaline phosphate (IU)	64.83	14.963	64.5	37	86
Total bilirubin (mg/dL)	0.7	0.27	0.68	0.33	1.44
Serum creatinine (mg/dL)	0.79	0.12	0.75	0.63	1.05
CrCL (Cockcroft_Gault, mL/min)	112.44	17.16	110.3	83.4	157.5
MDRD GFR (mL/min/1.73 m ²)	71.6	8.89	70.97	54.74	89.85
CKD-EPI GFR (mL/min/1.73 m ²)	106.99	12.18	104.3	80.27	127.34
Modified MDRD GFR (mL/min)	74.02	10.09	72.47	57.47	102.8
Modified CKD-EPI GFR (mL/min)	110.31	11.11	111.18	89.51	134.06

Source: Table 9 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL, creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 22. Categorical Variables of Subjects (N=24), Trial 1102

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	12	50
	2	Female	12	50
Race	1	White	22	91.7
	6	Other	2	8.3
Elderly (>65)	0	No	24	100
Ethnicity	1	Not Hispanic	22	91.7
	2	Hispanic	2	8.3

Source: Table 10 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: PPK, population pharmacokinetic

Trial 1301

This was a randomized, double-blind, placebo-controlled trial to evaluate the effect of tradipitant on satiation, gastric volume, gastric accommodation, and gastric emptying in healthy subjects.

The continuous variables and categorical variables of Trial 1301 are listed in Table 23 and Table 24, respectively.

Table 23. Continuous Variables of Subjects (N=11), Trial 1301

Variable	Mean	SD	Median	Min	Max
Age (years)	33.64	10.03	28	24	49
Weight (kg)	68.36	9.32	69.9	47.8	81.9
Height (cm)	168.14	8.88	172.7	153.7	177.7
BMI (kg/m ²)	24.13	2.41	24.07	19.34	27.21
BSA (m ²)	1.78	0.16	1.814	1.445	1.987
Lean body mass (kg)	48.56	7.03	51.2	36.6	56.2
ALT (IU)	22.82	12.39	21	9	43
AST (IU)	21.46	2.73	22	16	26
Alkaline phosphate (IU)	71.36	27.15	61	31	118
Total bilirubin (mg/dL)	0.46	0.18	0.4	0.2	0.9
Serum creatinine (mg/dL)	0.92	0.14	0.86	0.76	1.1
CrCL (Cockcroft_Gault, mL/min)	103.65	20.95	101.3	75.1	148
MDRD GFR (mL/min/1.73 m ²)	63.33	10.81	61.06	47.55	83.1
CKD-EPI GFR (mL/min/1.73 m ²)	97.06	15.65	93.96	72.39	121.44
Modified MDRD GFR (mL/min)	65.37	13.2	63.52	45.95	92.66
Modified CKD-EPI GFR (mL/min)	100.02	18.3	98	69.97	135.41

Source: Table 11 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL; creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 24. Categorical Variables of Subjects (N=11), Trial 1301

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	6	54.5
	2	Female	5	45.5
Race	1	White	5	45.5
	3	Asian	3	27.3
	6	Other	3	27.3
Elderly	0	No	11	100
Ethnicity	-1	Missing	11	100

Source: Table 12 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: PPK, population pharmacokinetic

Trial 2301

This was a randomized, double-blind, placebo-controlled trial to assess the effect of tradipitant in relieving symptoms of gastroparesis. The continuous variables and categorical variables of Trial 2301 are listed in Table 25 and Table 26, respectively.

Table 25. Continuous Variables of Subjects (N=75), Trial 2301

Variable	Mean	SD	Median	Min	Max
Age (years)	45.19	13.29	46	18	72
Weight (kg)	80.85	18.15	81.8	43.1	138.1
Height (cm)	164.33	9.31	163	140	191
BMI (kg/m ²)	29.89	5.91	30.3	17	39.4
BSA (m ²)	1.91	0.25	1.93	1.38	2.71
Lean body mass (kg)	49.6	8.17	49.4	33.9	80.6
ALT (IU)	20.96	12.76	17	6	63
AST (IU)	19.56	8.13	17	8	45
Alkaline phosphate (IU)	71.07	22.89	69	23	118
Total bilirubin (mg/dL)	0.46	0.21	0.41	0.2	1.21
Serum creatinine (mg/dL)	0.8	0.22	0.77	0.46	1.64
CrCL (Cockcroft_Gault, mL/min)	120.78	37.9	120	42	248.9
MDRD GFR (mL/min/1.73 m ²)	64.96	18.4	65.17	30.96	127.74
CKD-EPI GFR (mL/min/1.73 m ²)	94.13	22.38	99.24	43.16	135.07
Modified MDRD GFR (mL/min)	71.11	20.05	71.99	30.08	128.48
Modified CKD-EPI GFR (mL/min)	103.22	25.54	106.92	41.94	167.87

Source: Table 13 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL, creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 26. Categorical Variables of Subjects (N=75), Trial 2301

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	8	10.7
	2	Female	67	89.3
Race	1	White	64	85.3
	2	African American	9	12
	3	Asian	1	1.3
	4	Native Hawaiian/Other Pacific Islander	1	1.3
Elderly	0	No	69	92
	1	Yes	6	8
Ethnicity	1	No	64	85.3
	2	Yes	11	14.7
CYP3A4	-1	Missing	3	4
	1	Wild-Type	66	88
	2	*22 allele Heterozygous	5	6.7
	3	*22 allele Homozygous	1	1.3

Source: Table 14 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

Trial 3301

This was a randomized, double-blind, placebo-controlled trial to assess the efficacy of tradipitant in relieving symptoms of gastroparesis. Subjects received tradipitant 85 mg BID were included in the PPK analysis. The continuous variables and categorical variables of Trial 3301 are listed in Table 27 and Table 28, respectively.

Table 27. Continuous Variables of Subjects (N=380), Trial 3301

Variable	Mean	SD	Median	Min	Max
Age (years)	50.14	12.95	52	18	76
Weight (kg)	85.1	17.89	85.5	44.5	136.9
Height (cm)	166.05	9.31	165	145	198
BMI (kg/m ²)	30.78	5.56	31.09	17.55	41.13
BSA (m ²)	1.97	0.24	1.99	1.36	2.66
Lean body mass (kg)	51.98	8.74	51.45	32.6	78.3
ALT (IU)	22.33	14.84	17.5	2.5	105
AST (IU)	20.84	9.09	19	7	71
Alkaline phosphate (IU)	85.12	28.46	81	26	238
Total bilirubin (mg/dL)	0.36	0.21	0.305	0.075	1.81
Serum creatinine (mg/dL)	0.77	0.27	0.7	0.2	2.2
CrCL (Cockcroft_Gault, mL/min)	133.06	49.95	125.1	40.3	398.6
MDRD GFR (mL/min/1.73 m ²)	71.89	26.27	67.79	22.93	301.69
CKD-EPI GFR (mL/min/1.73 m ²)	96.2	22.55	99.19	31.84	171.25
Modified MDRD GFR (mL/min)	81.34	29.37	76.75	25.23	293.5
Modified CKD-EPI GFR (mL/min)	109.01	26.8	111.2	36.34	180.36

Source: Table 15 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL; creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 28. Categorical Variables of Subjects (N=380), Trial 3301

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	88	23.2
	2	Female	292	76.8
Race	1	White	309	81.3
	2	African American	62	16.3
	3	Asian	1	0.3
	4	American Indian/Alaskan Native	4	1.1
	5	Native Hawaiian/Other Pacific Islander	1	0.3
	6	Other	3	0.8
Elderly	0	No	333	87.6
	1	Yes	47	12.4
Ethnicity	-1	Missing	1	0.3
	1	Not Hispanic	287	75.5
	2	Hispanic	92	24.2
CYP3A4	-1	Missing	28	7.4
	1	*22 allele heterozygous	330	86.8
	2	*22 allele homozygous	22	5.8
Etiology	1	Diabetes Mellitus	183	48.2
	2	Idiopathic	197	51.8

Source: Table 16 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

Trial 3403

This is an ongoing open-label trial to investigate the safety and efficacy of tradipitant in subjects affected by motion sickness during travel. Subjects were randomized to 85-mg or 170-mg tradipitant in a 1:1 ratio and were given a maximum 3-month supply of tradipitant 85-mg or 170-mg tradipitant. PK samples were collected at 1- and 2-hours following dosing during the PK visit. The continuous variables and categorical variables of Trial 3403 are listed in Table 29 and Table 30, respectively.

Table 29. Continuous Variables of Subjects (N=515), Trial 3403

Variable	Mean	SD	Median	Min	Max
Age (years)	47.95	13.91	49	18	75
Weight (kg)	78.88	17.98	76.2	45.8	135
Height (cm)	168.67	9.54	167.6	147	196
BMI (kg/m ²)	27.58	5.15	26.93	18.34	41.59
BSA (m ²)	1.91	0.25	1.892	1.381	2.637
Lean body mass (kg)	51.45	9.2	50.3	33	77.7
ALT (IU)	20.63	12.76	17	5	109
AST (IU)	21.1	7.67	19	8	85
Alkaline phosphate (IU)	74.35	23.19	70	17	185
Total bilirubin (mg/dL)	0.45	0.23	0.39	0.15	1.81
Serum creatinine (mg/dL)	0.8	0.23	0.8	0.4	3.6
CrCL (Cockcroft_Gault, mL/min)	117.22	34.47	112.25	25.1	240.8
MDRD GFR (mL/min/1.73 m ²)	67.56	16.03	65.64	10.94	141.02
CKD-EPI GFR (mL/min/1.73 m ²)	96.48	18.14	97.85	15.99	142.2
Modified MDRD GFR (mL/min)	74.25	18.41	72.23	11.58	147.83
Modified CKD-EPI GFR (mL/min)	106.07	21.91	105.81	16.92	164.85

Source: Table 17 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL, creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 30. Categorical Variables of Subjects (N=515), Trial 3403

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	171	33.2
	2	Female	344	66.8
Race	1	White	431	83.7
	2	African American	30	5.8
	3	Asian	42	8.2
	4	American Indian/Alaskan Native	1	0.2
	5	Native Hawaiian/Other Pacific Islander	2	0.4
	6	Other	9	1.7
Elderly	0	No	448	87
	1	Yes	67	13
Ethnicity	1	Not Hispanic	469	91.1
	2	Hispanic	46	8.9
	-1	Missing	223	43.3
CYP3A4	1	Wild-Type	264	51.3
	2	*22 allele Heterozygous	28	5.4

Source: Table 18 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

Trial 3404

This was a randomized, double-blind, placebo-controlled trial to investigate the efficacy of tradipitant in subjects affected by motion sickness during travel. Subjects were randomized in a 1:1:1 ratio to take tradipitant 85 mg, 170 mg, or placebo approximately 60 minutes prior to boat travel. Subjects returned for an EOS visit within 7 days of Visit 2. PK samples were collected at 1- and 2-hours following dosing during the PK visit from whom agreed to the optional PK assessment. The continuous variables and categorical variables of Trial 3404 are listed in Table 31 and Table 32, respectively.

Table 31. Continuous Variables of Subjects (N=170), Trial 3404

Variable	Mean	SD	Median	Min	Max
Age (years)	47.28	14.33	49	18	75
Weight (kg)	80.48	17.33	78.45	47.6	128.2
Height (cm)	171.04	9.94	172	149.9	199
BMI (kg/m ²)	27.34	4.47	26.9	19.01	39.9
BSA (m ²)	1.95	0.25	1.93	1.41	2.587
Lean body mass (kg)	53.24	9.38	52.55	33.5	76.3
ALT (IU)	24.27	14.12	20	7	75
AST (IU)	24.29	11.54	22	9	112
Alkaline phosphate (IU)	71.08	18.43	68	34	123
Total bilirubin (mg/dL)	0.52	0.33	0.4	0.2	2.1
Serum creatinine (mg/dL)	0.84	0.17	0.825	0.45	1.36
CrCL (Cockcroft_Gault, mL/min)	115.21	30.72	112.05	50.6	214
MDRD GFR (mL/min/1.73 m ²)	65.02	12.72	64.35	28.78	108.43
CKD-EPI GFR (mL/min/1.73m ²)	94.85	16.23	95.11	40.29	135.1
Modified MDRD GFR (mL/min)	72.9	15.76	72.03	33.3	126.31
Modified CKD-EPI GFR (mL/min)	106.25	20.21	105.92	46.63	155.56

Source: Table 19 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL; creatinine clearance; GFR, glomerular filtration rate; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 32. Categorical Variables of Subjects (N=170), Trial 3404

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	78	45.9
	2	Female	92	54.1
Race	1	White	140	82.4
	2	African American	7	4.1
	3	Asian	15	8.8
	5	American Indian/Alaskan Native	1	0.6
	6	Native Hawaiian/Other Pacific Islander	2	1.2
	99	Other	5	2.9
Elderly	0	No	150	88.2
	1	Yes	20	11.8
Ethnicity	1	No	145	85.3
	2	Yes	25	14.7
CYP3A4	-1	Missing	88	51.8
	1	Wild-Type	78	45.9
	2	*22 allele Heterozygous	4	2.4

Source: Table 20 of Applicant's PPK report submitted on July 22, 2025

Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

Table 33. Summary of PK Data Included in the PPK Analysis for Tradipitant

Study	1002	1102	1301	2301	3301	3403	3404	All
N_Subjects	31	24	11	75	380	515	170	1206*
N_Sample	980	1103	33	139	1865	1047	449	5616*

Source: FDA reviewer's analysis and Tables 5 and 9 of Applicant PPK report submitted on June 30, 2025

* The sum of the counts for individual studies in 1217. However, 11 subjects crossed over between VP-VLY-686-3404 and VP-VLY-686-3403, yielding 1206 unique subjects in the analysis. The dataset included two subjects for whom there were no samples > assay LOQ, one in VP-VLY-686-2301, the other in VP-VLY-686-3301.

Abbreviations: LOQ, limit of quantification; N, number; PK, pharmacokinetic; PPK, population pharmacokinetic

2.2.5 Methods

A linear two-compartment PK model with elimination from the central compartment was adopted. To accommodate large secondary peaks in the fasted sessions of the food effect study,

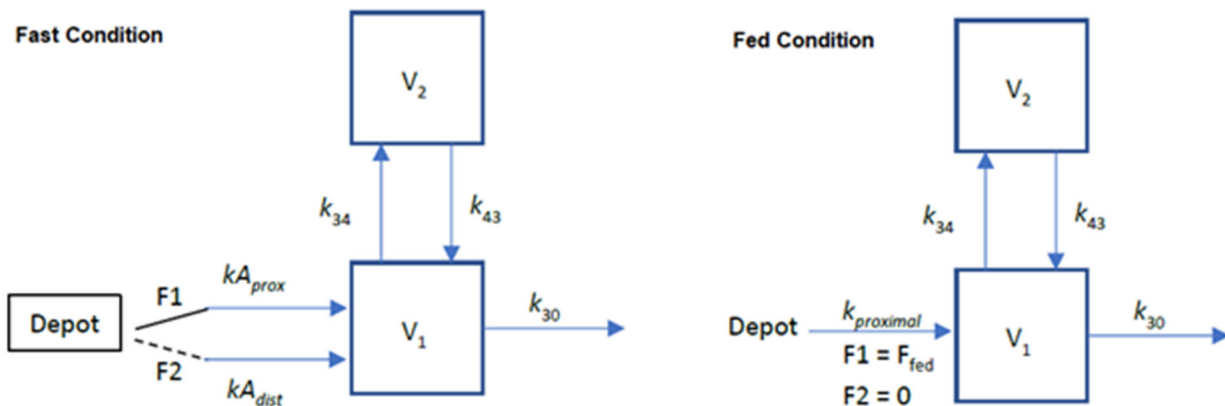
the model included two absorption compartments for that session with the dose apportioned between the two. Parameters were added to the model to accommodate differences in PK characteristics between studies. Post hoc fits for each study showed minimal bias. Post hoc parameters were then used to simulate concentration profiles for each subject. Exposure metrics in two trials (Trials 3403, Trials 3404) were calculated for each subject, then summarized by trial and presented graphically and in tables and text. First order conditional estimation with Eta-Sigma interaction was performed using the nonlinear mixed-effects modeling program NONMEM, Version 7.5.1 or later (ICON Development Solutions, Ellicott City, MD). (b) (4)

was used for file management and creation of graphics. Estimates for population mean parameters (typical values), between-subject variability, residual variability and, if possible, standard errors of the parameters were obtained.

Using NONMEM's ADVAN5, a model was developed for Trial 1002 that addressed the secondary peaks as well as differences between the fasted and fed sessions (Figure 7). For the fasted condition, the dose is partitioned between the proximal absorption (F1) and distant absorption (F2) with $F1 + F2$ equals 1. For the fed sessions, the entire dose, scaled by F_{fed} , is delivered to the central compartment. Distant absorption exists but is ignored because bioavailability to that compartment (F2) equals 0.

The lower limit of quantitation (LOQ) was 1.00 ng/mL for tradipitant and 0.500 ng/mL for metabolites. Predose samples with concentrations below the LOQ (BQL) were assigned a value of 0 and excluded from the analysis. Postdose BQL samples >15 days after the final dose were also excluded from the analysis. The remaining postdose BQL values were assigned a concentration of $LOQ/2$ and included in the analysis.

Figure 7. Structural Model for Tradipitant for Trial 1002 for Food Effect

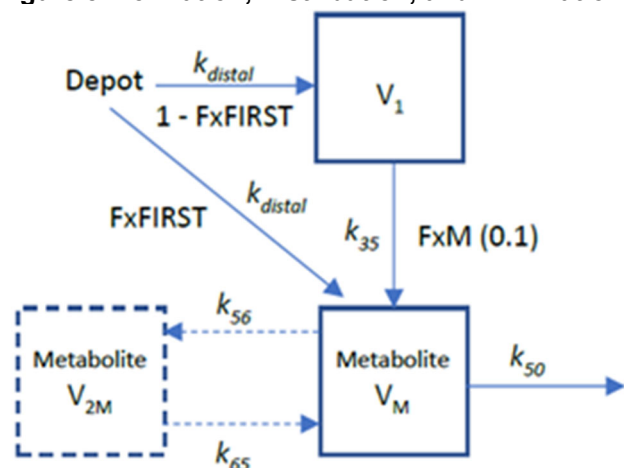


Source: Figures 6 and 7 of Applicant PPK report submitted on June 30, 2025
Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

In the remaining 6 trials, although subjects were instructed to take the drug on an "empty stomach," closer to fasted condition, the fed model (right panel of Figure 7) was applied with one difference: $F1=1$ (not $F1 = F_{fed}$) and $F2=0$. Conversion of tradipitant to each metabolite was described by a first-order process from the central compartment of the parent (Figure 8). Datasets

for metabolites included post hoc (individual) parameters for tradipitant obtained from the optimal model. Formation of metabolites is driven by the central compartment concentration. The fraction of tradipitant converted to each metabolite is fixed arbitrarily to 0.1 (described below). Distribution of metabolite to a peripheral compartment (dashed lines) is optional.

Figure 8. Formation, Distribution, and Elimination of Metabolites of Tradipitant



Source: Figure 9 of Applicant PPK report submitted on June 30, 2025
Abbreviations: CYP, cytochrome P450; PPK, population pharmacokinetic

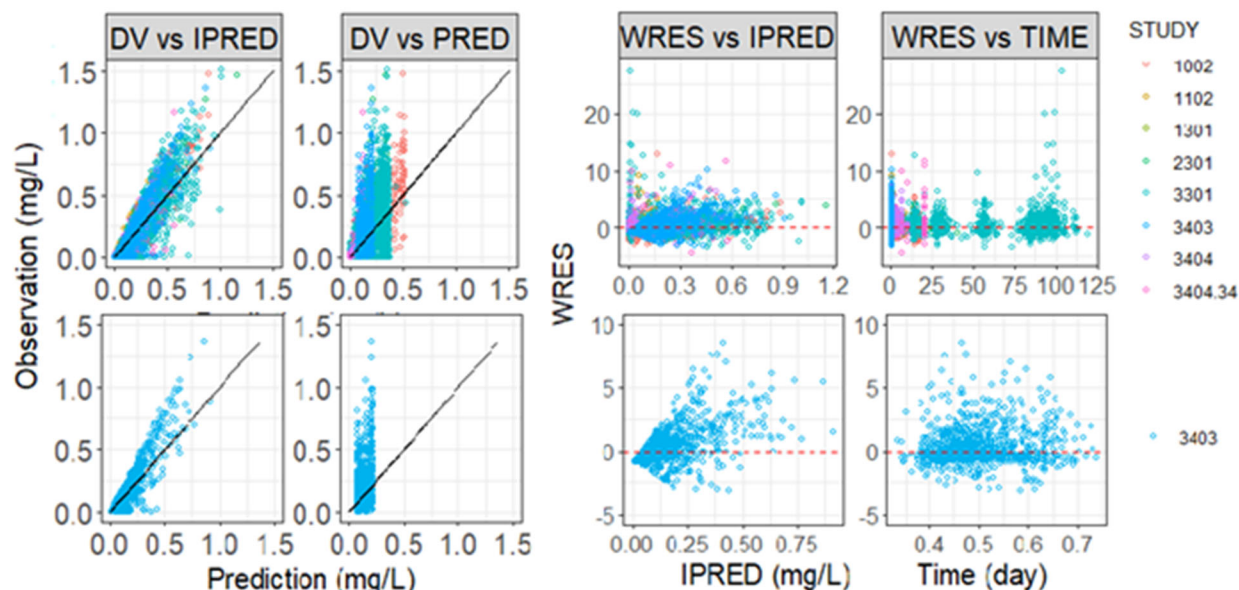
Metabolites were modeled independently, assuming no interaction between their formation, no conversion between metabolites, and unidirectional formation of metabolite. Formation of each metabolite was assumed to be a first-order process in which input to the metabolite central compartment was driven by the central compartment (plasma) concentration of tradipitant. Two rate constants describe irreversible movement of tradipitant from its central compartment, one accounting for elimination, the other for conversion to metabolite. where FxFIRST is the fraction of the dose directed to the metabolite central compartment and (1 - FxFIRST) is the fraction of the dose directed to the tradipitant central compartment.

2.2.6 Results

Tradipitant

A two-compartment model with first-order elimination, first-order absorption, and an absorption lag fit the data well. In the food effect study (Trial 1002), dense sampling revealed two peaks in the fasted session (but not in the high-fat session). This was addressed with a model that included two depots with different absorption rates. However, sampling in the other studies was more limited and allowed only for a single absorption compartment. The estimates of the parameters of the final PPK model for tradipitant parent are listed in Table 34 with no standard error available for any parameters probably due to over-parameterization. Based on the final model of tradipitant, the simulated Day 1 and Day 40 tradipitant exposures under fasted and fed conditions are listed in Table 35.

Figure 9. Goodness-of-Fit Plots for Applicant's Final Tradipitant PPK Model (Control-250617-154011) With Upper Panels for the Whole Dataset and the Lower Panels for Trial 3403 Only



Source: Generated by FDA based on submitted output table of Applicant's final PPK model located at //CDSESUB1/evsprod/NDA220152/0021/m5/datasets/vp-vly-686-1002-1102-1301-2301-3301-3404-3403/listings/allrecords-250617-154011.csv
Abbreviations: CWRES, conditional weighted residuals; DV, observations; IPRED, individual predictions; PPK, population pharmacokinetic

Table 34: Parameter Estimates of the Applicant's Final Tradipitant PPK Model

Parameter	Definition	Value	Comment
CL (mL/day)	01	715.613	FIX
V1 (mL)	02	255.267	FIX
CLD (mL/day)	03	787.112	FIX
V2 (mL)	04	579.182	FIX
Ka_proxi_fasted (1/d)	05	39.7821	FIX
Tlag_proxi_fasted (day)	06	0.0176067	FIX
Ka_distal_fasted (1/day)	07	0.344468	FIX
Tlag_distal_fasted (day)	08	0.297136	FIX
Ka_proxi_fed (1/day)	09	10.7342	FIX
Tlag_proxi_fed (day)	010	0.0205396	FIX
F1_from_proxi	011	0.256519	FIX
F_relative_high_fat	012	1.57354	FIX
factor_CYP_on_CL	013	1	FIX (effect off)
Study1102_on_Ka_proxi_fasted	014	0.264974	FIX
Study1102_on_CL	015	1	FIX (effect off)
Study1102_on_CLD	016	6.79631	FIX
Study1102_on_V2	017	2.61731	FIX
Study1301_on_CL	018	2.4076	Estimated
Study1301_on_F1	019	1.0268	Estimated
Study2301_on_CL	020	0.41687	Estimated

Study2301_on_F1	021	0.52224	Estimated
Study3301_on_Ka_proxi_fasted	022	0.554025	FIX
Study3301_on_CL	023	0.929698	FIX
Study3301_on_V1	024	0.823568	FIX
Study3301_on_CLD	025	2.17477	FIX
Study3301_on_V2	026	1.50057	FIX
Study3404_on_CL	027	1.1849	Estimated
Study3404_on_V1	028	3.9693	Estimated
Study3404_on_CLD	028	3.9693	Mistaken
Study3404_on_V2	030	1	FIX (effect off)
Study3404_on_F1	031	1	FIX (effect off)
Study3404_on_Ka_proxi_fasted	032	0.58337	Estimated
Study3404_on_ALAG_proxi_fasted	033	0	FIX (effect off)
Study3403_on_CL	034	1.7991	Estimated
Study3403_on_V1	035	0.43515	Estimated
Study3403_on_CLD	036	1	FIX (effect off)
Study3403_on_V2	037	1	FIX (effect off)
Study3403_on_F1	038	1	FIX (effect off)
Study3403_on_Ka_proxi_fasted---TH39	039	0.098445	Estimated
Study3403_on_ALAG_proxi_fasted	040	0	FIX (effect off)
AGE_on_CL	041	1	FIX (effect off)
BMI_on_CL	042	1	FIX (effect off)
Compliance_on_CL	043	1	FIX (not used)
CL IIV% for MS subjects	η1	76	Estimated
V1 IIV% for MS subjects	η2	61.4	Estimated
CLD IIV% for MS subjects	η3	149.4	Estimated
V2 IIV% for MS subjects	η4	136.1	Estimated
Ka_proxi_fasted IIV% for MS subjects	η5	3.3	Estimated
Tlag_proxi_fasted IIV% for MS subjects	η6	645.3	Estimated
Ka_distal_fasted IIV% for all subjects	η7	80.2	Estimated
Tlag_distal_fasted IIV% for all subjects	η8	0.4	Estimated
Ka_proxi_fed IIV% for all subjects	η9	57.2	Estimated
Tlag_proxi_fed IIV% for all subjects	η10	74.8	Estimated
Bioavailability Logit IIV% for all subjects	η11	69.6	Estimated
CL IIV% for subjects excluding MS	η12	65.3	Estimated
V1 IIV% for subjects excluding MS	η13	41	Estimated
CLD IIV% for subjects excluding MS	η14	141.4	Estimated
V2 IIV% for subjects excluding MS	η15	49.2	Estimated
Ka_proxi_fasted IIV% for subjects excluding MS	η16	77.7	Estimated

Tlag_proxi_fasted IIV% for subjects excluding MS	η_{17}	4.5	Estimated
Proportion error for Study 1002 (%)	ϵ_1	27.8	Estimated
Additive error for Study 1002 (ng/mL)	ϵ_2	5.4	Estimated
Proportion error for Studies 3403 and 3404 (%)	ϵ_3	44.6	Estimated
Additive error for Studies 3403 and 3404 (ng/mL)	ϵ_4	1.3	Estimated
Proportion error for other studies (%)	ϵ_5	38.9	Estimated
Additive error for other studies (ng/mL)	ϵ_6	0.3	Estimated

Source: FDA reviewer-generated based on Tradipitant Appendix 1 of Applicant's PPK Report Submitted on July 22, 2025.

Note: Minimization terminated due to rounding errors (Error =134) with number of significant digits unreportable, and no standard error was obtained in the output file.

Abbreviations: CL, clearance; CLD, distribution clearance; CYP, cytochrome P450; F1, bioavailability; IIV, interindividual variability; Ka, absorption rate constant; MS, motion sickness; PPK, population pharmacokinetic; Tlag, lag time; V1, apparent volume of the central or plasma compartment in a two-compartment model; V2, Apparent volume of the peripheral compartment in a two-compartment model

Table 35. Simulated Tradipitant Exposures by Applicant's Final PPK Model of Tradipitant Parent

Study	Day	85 mg QD		85 mg BID		170 mg QD	
		3403	3404	3403	3404	3403	3404
C _{max} (ng/mL)	Fasted Day 1	136.76 (110.11)	74.62 (52.76)	175.43 (135.21)	120.73 (84.82)	273.52 (220.23)	149.23 (105.51)
	Fed Day 1	408.31 (314.45)	101.72 (74.39)	437.28 (324.97)	173.02 (124)	816.61 (628.89)	203.45 (148.79)
	Fasted Day 40	159.93 (115.17)	162.56 (103.87)	212.96 (142.11)	278.16 (182.29)	319.86 (230.34)	325.11 (207.73)
	Fed Day 40	436.36 (317.07)	238.05 (155.42)	484.11 (329)	419.84 (278.75)	872.73 (634.14)	476.1 (310.84)
	Fasted Day 1	62.72 (47.9)	51.11 (36.61)	110.28 (86.34)	80.98 (58.29)	125.43 (95.8)	102.22 (73.22)
	Fed Day 1	103.43 (77.83)	76.25 (54.76)	195.04 (151.99)	117.36 (84.5)	206.86 (155.65)	152.49 (109.52)
	Fasted Day 40	79.07 (50.74)	124.3 (84.06)	158.14 (101.48)	248.6 (168.13)	158.14 (101.48)	248.6 (168.13)
	Fed Day 40	124.18 (79.69)	195.66 (132.31)	248.35 (159.38)	391.33 (264.63)	248.35 (159.38)	391.33 (264.63)

Source: FDA reviewer-generated-based on Tables 31-34 of Applicant PPK report submitted on July 22, 2025

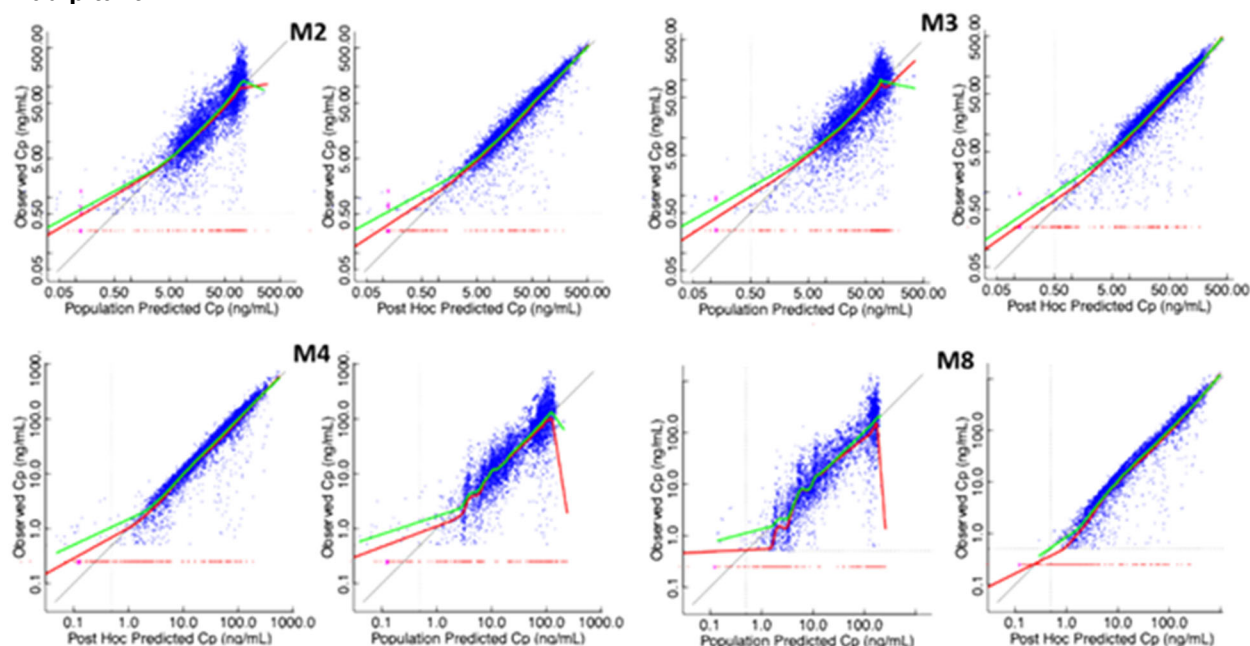
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PPK, population pharmacokinetic; QD, once daily

Tradipitant Metabolites

Each metabolite was modeled separately, and it was assumed that there was no interaction or inter-conversion between metabolites. A two-compartment model with first-order elimination fit the data well. Input to each metabolite was the plasma concentration of tradipitant.

Pharmacokinetic parameters differed between trials. Results, including exposure metrics, are included in the body of this report. Of note, simulated values for metabolite M8 exposures were predicted poorly for Trial 3403, most likely because only two samples were obtained both at early time points, with the second sample showing consistent higher concentrations compared to the first. Based on the final models of tradipitant metabolites, the simulated Day 1 and Day 40 tradipitant exposures under fasted and fed conditions are listed in Table 36, Table 37, Table 38, and Table 39 for M2, M3, M4, and M8, respectively.

Figure 10. Goodness-of-Fit Plots for Applicant's Final PPK Models for the Four Metabolites of Tradipitant



Source: Figures 23, 35, 48 and 58 of Applicant's PPK Report Submitted on July 22, 2025

Abbreviations: M, metabolite; PPK, population pharmacokinetic

Table 36. Simulated Tradipitant M2 Exposures by Applicant's Final PPK Model of M2

Study	Day	85 mg QD		85 mg BID		170 mg QD	
		3403	3404	3403	3404	3403	3404
C_{max} (ng/mL)	Fasted Day 1	15.94 (13.39)	25.79 (25.29)	20.44 (16.46)	46.82 (45.28)	31.88 (26.78)	51.58 (50.58)
	Fed Day 1	47.54 (38.22)	39.63 (38.91)	50.91 (39.53)	72.24 (69.9)	95.08 (76.45)	79.26 (77.82)
	Fasted Day 40	18.64 (14.06)	66.07 (56.16)	24.81 (17.4)	121.6 (103.61)	37.27 (28.12)	132.14 (112.33)
	Fed Day 40	50.8 (38.62)	102.41 (87.28)	56.36 (40.16)	189.68 (161.89)	101.61 (77.24)	204.81 (174.55)
AUC (ng*d/mL)	Fasted Day 1	7.31 (5.84)	20.89 (20.08)	12.85 (10.5)	30.54 (29.15)	14.62 (11.67)	41.78 (40.16)
	Fed Day 1	12.07 (9.51)	30.6 (29.41)	22.76 (18.54)	43.03 (41)	24.15 (19.01)	61.19 (58.82)
	Fasted Day 40	9.22 (6.23)	58.81 (50.36)	18.44 (12.46)	117.62 (100.72)	18.44 (12.46)	117.62 (100.72)
	Fed Day 40	14.49 (9.8)	92.54 (79.25)	28.98 (19.6)	185.08 (158.49)	28.98 (19.6)	185.08 (158.49)

Source: FDA reviewer-generated based on the Applicant PPK report submitted on July 22, 2025

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max} , maximum plasma concentration; M, metabolite; PPK, population pharmacokinetic; QD, once daily

Table 37. Simulated Tradipitant M3 Exposures by Applicant's Final PPK Model of M3

Study	Day	85 mg QD		85 mg BID		170 mg QD	
		3403	3404	3403	3404	3403	3404
C _{max} (ng/mL)	Fasted Day 1	21.45 (17.93)	12.5 (7.34)	27.57 (22.1)	20.17 (11.68)	42.89 (35.86)	24.99 (14.68)
	Fed Day 1	62.89 (50)	16.97 (10.3)	67.51 (51.76)	28.84 (17.05)	125.78 (99.99)	33.93 (20.59)
	Fasted Day 40	25.12 (18.86)	27.41 (14.52)	33.53 (23.42)	46.9 (25.68)	50.24 (37.72)	54.81 (29.04)
	Fed Day 40	67.34 (50.56)	40.09 (21.77)	74.94 (52.67)	70.75 (39.35)	134.67 (101.12)	80.18 (43.54)
AUC (ng*d/mL)	Fasted Day 1	9.97 (7.98)	8.51 (5.03)	17.42 (14.21)	13.49 (8.01)	19.93 (15.95)	17.03 (10.06)
	Fed Day 1	16.49 (13.04)	12.7 (7.52)	31 (25.28)	19.55 (11.62)	32.98 (26.07)	25.4 (15.05)
	Fasted Day 40	12.6 (8.58)	20.94 (11.92)	25.21 (17.17)	41.89 (23.84)	25.21 (17.17)	41.89 (23.84)
	Fed Day 40	19.82 (13.51)	32.97 (18.76)	39.63 (27.01)	65.94 (37.52)	39.63 (27.01)	65.94 (37.52)

Source: FDA reviewer-generated based on Tables 46-49 of Applicant PPK report submitted on July 22, 2025

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; M, metabolite; PPK, population pharmacokinetic; QD, once daily

Table 38. Simulated Tradipitant M4 Exposures by Applicant's Final PPK Model of M4

Study	Day	85 mg QD		85 mg BID		170 mg QD	
		3403	3404	3403	3404	3403	3404
C _{max} (ng/mL)	Fasted Day 1	42.45 (25.4)	20.98 (12.61)	70.09 (35.56)	37.5 (22.54)	84.9 (50.8)	41.96 (25.23)
	Fed Day 1	89 (59.33)	31.98 (19.4)	130.79 (69.53)	57.37 (34.29)	178.01 (118.66)	63.96 (38.8)
	Fasted Day 40	67.1 (24.16)	55.63 (35.91)	114.4 (33.18)	102.26 (69.54)	134.2 (48.33)	111.25 (71.83)
	Fed Day 40	124.98 (53.98)	86.04 (56.31)	192.39 (60.94)	159.39 (109.22)	249.96 (107.97)	172.08 (112.62)
AUC (ng*d/mL)	Fasted Day 1	30.59 (15.51)	16.29 (9.37)	45.31 (24.85)	23.8 (13.34)	61.18 (31.03)	32.58 (18.75)
	Fed Day 1	54.24 (26.28)	23.83 (13.61)	86.15 (46.19)	33.52 (18.68)	108.49 (52.56)	47.66 (27.21)
	Fasted Day 40	54.19 (14.59)	49.36 (34.48)	108.37 (29.18)	98.72 (68.95)	108.37 (29.18)	98.72 (68.95)
	Fed Day 40	85.26 (22.95)	77.67 (54.25)	170.53 (45.91)	155.34 (108.5)	170.53 (45.91)	155.34 (108.5)

Source: FDA reviewer-generated based on Tables 52-55 of Applicant PPK report submitted on July 22, 2025

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; M, metabolite; PPK, population pharmacokinetic; QD, once daily

Table 39. Simulated Tradipitant M8 Exposures by Applicant's Final PPK Model of M8

Study	Day	85 mg QD		85 mg BID		170 mg QD	
		3403	3404	3403	3404	3403	3404
C _{max} (ng/mL)	Fasted Day 1	59.22 (57.83)	19.14 (10.01)	104.15 (104.31)	34.69 (17.63)	118.44 (115.66)	38.28 (20.02)
	Fed Day 1	97.9 (94.16)	29.62 (15.39)	184.57 (183.73)	52.56 (26.77)	195.8 (188.33)	59.24 (30.77)
	Fasted Day 40	2981 (2505)	67.81 (48.39)	5941 (4997)	130.93 (96.37)	5962 (5010)	135.61 (96.78)
	Fed Day 40	4698.2 (3945)	106.14 (76.14)	9376 (7884)	205.37 (151.63)	9396.4 (7891)	212.28 (152.28)
AUC (ng*d/mL)	Fasted Day 1	38.99 (39.5)	13.98 (7.2)	51.28 (52.16)	19.13 (10.01)	77.98 (79.0)	27.97 (14.41)
	Fed Day 1	73.96 (74.6)	20.02 (10.39)	101.39 (102.91)	26.44 (13.91)	147.91 (149.2)	40.03 (20.77)
	Fasted Day 40	2954 (2484)	64.64 (48.15)	5870 (4938)	129.27 (96.31)	5908 (4969)	129.27 (96.31)
	Fed Day 40	4665 (3923)	101.71 (75.77)	9271 (7798)	203.42 (151.54)	9330 (7847)	203.42 (151.54)

Source: FDA reviewer-generated based on Tables 59-62 of Applicant PPK report submitted on July 22, 2025

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; M, metabolite; PPK, population pharmacokinetic; QD, once daily

The Applicant acknowledged that the exposure metrics for metabolite M8 in Trial 3403 should be considered with extreme caution because the sampling regimen in that trial likely led to meaningless estimates. For tradipitant and other metabolites, differences in the exposure metrics for both tradipitant and metabolites between Trial 3403 and Trial 3404 were unexpected because both trials were conducted in similar populations. These differences may reflect the small number of postdose samples obtained in each trial and the short interval of these samples relative to the dose.

As a result of these limitations and given that the general population of patients experiencing motion sickness is not expected to have significantly different drug exposure (C_{max}, AUC) compared to healthy subjects, the pharmacokinetic results from healthy subjects tested in fasted and fed conditions in a controlled clinic environment (Trial 1002) should be considered as more representative than those from Trial 3403 and Trial 3404.

2.3 Reviewer's Population PK Sensitivity Analysis

2.3.1 Background

The Applicant's final PPK model did not converge properly and terminated due to rounding error with NO. OF SIG. DIGITS UNREPORTABLE (as stated in the "lst" file of the final model on Page 143 of the PPK report).

2.3.2 Objective

To conduct sensitivity analysis to identify a stable PPK model with minimization successful and with covariance of each parameter reported.

2.3.3 Data and Methods

Applicant's final model for tradipitant used dataset "rawdata-250617-154011.csv" with total 5616 records of 1206 subjects from 7 trials. FDA reviewer's analysis used the same dataset excluding compliance <97.5% and >102.5% and exclude Trial 1002 where the PK behavior appears different from other trials, result dataset is named as "fda02.csv" with 3531 records of 915 subjects from 6 trials. NONMEM 7.5 and R 4.3.3 were used. The population values of continuous and categorical variables of the revised dataset are listed in Table 40 and Table 41, respectively. General 1, 2, and 3 compartmental models were applied to the data to select a base structural model, and covariates were applied the base model.

Table 40. Continuous Variables of Subjects (N=915), Trials 1102, 1301, 2301, 3301, 3403, and 3404

Variable	Mean	SD	Median	Min	Max
Age (years)	47.8	14	49	18	75
Weight (kg)	79.9	17.9	77.7	45.8	138.1
Height (cm)	168.4	9.8	167.6	140	199
BMI (kg/m ²)	31.6	5.3	28.1	17.6	41.6
BSA (m ²)	1.9	0.3	1.9	1.4	2.7
Lean body mass (kg)	57.9	9.1	51.7	33	80.6
ALT (IU)	22	13.7	18	2.5	109
AST (IU)	21.7	8.6	20	8	112
ALKP (IU)	75.1	23.6	71	17	238
Total bilirubin (mg/dL)	0.5	0.3	0.4	0.1	2.1
Serum creatinine (mg/dL)	0.8	0.2	0.8	0.2	3.6
CrCLCG (mL/min)	101.8	33.1	96.3	21.3	338.8
eGFR(MDRD) (mL/min/1.73 m ²)	68.1	18.9	65.8	10.9	301.7
eGFR(CKD.EPI) (mL/min/1.73 m ²)	96.4	19	97.9	16	171.3
Modified eGFR(MDRD) (mL/min)	75.3	21.5	72.5	11.6	293.5
Modified eGFR.EPI (mL/min)	106.6	23	107.2	16.9	180.4
GFRCG (mL/min)	119.8	38.9	113.3	25.1	398.6
Compliance%	99.8	0.6	100	97.6	102.5

Source: FDA reviewer's analysis

Abbreviations: ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GFRCG, glomerular filtration rate Cockcroft-Gault; max, maximum; MDRD, modification of diet in renal disease; min, minimum; PPK, population pharmacokinetic; SD, standard deviation

Table 41. Categorical Variables of Subjects (N=915), Trials 1102, 1301, 2301, 3301, 3403, and 3404

Variable	Value	Descriptor	Count	Percentage
Sex	1	Male	311	34.0
	2	Female	604	66.0
Race	1	White	756	82.6
	2	African American	68	7.4
	3	Asian	62	6.8
	4	American Indian/Alaskan Native	4	0.4
	5	Native Hawaiian/Other Pacific Islander	3	0.3
	6	Other	22	2.5
Elderly	0	No	333	87.6
	1	Yes	47	12.4
Ethnicity	-1	Missing	11	1.2
	1	Not Hispanic	774	84.6
	2	Hispanic	130	14.2

Variable	Value	Descriptor	Count	Percentage
CYP3A4	-1	Missing	355	38.8
	1	*22 allele Heterozygous	516	56.4
	2	*22 allele Homozygous	44	4.8
Etiology	-1	Missing	720	78.7
	1	Diabetes Mellitus	100	10.9
	2	Idiopathic	95	10.4

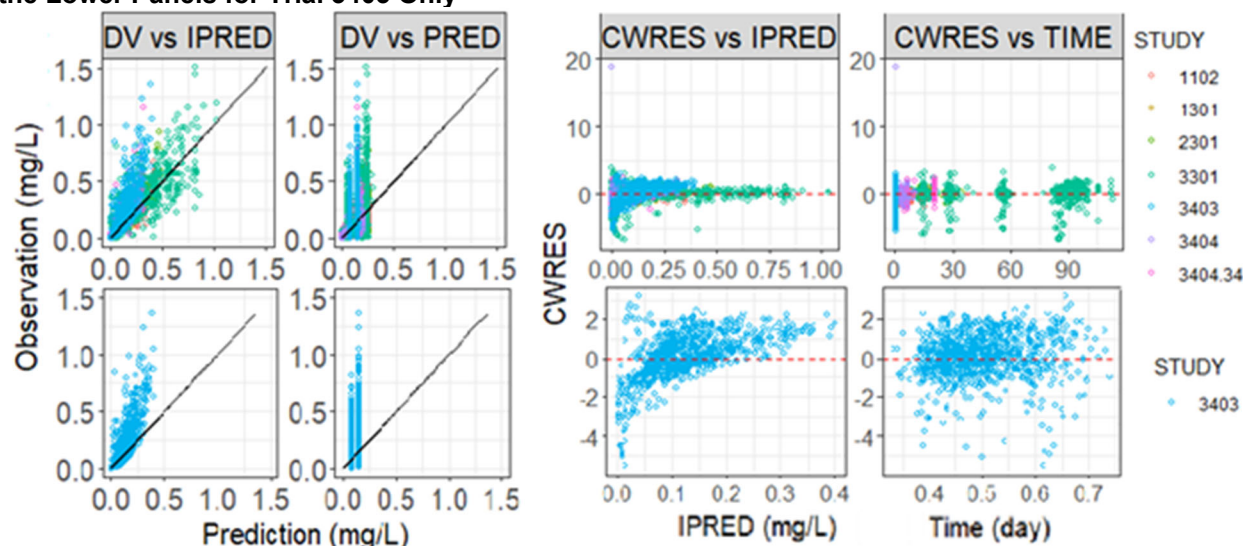
Source: FDA reviewer's analysis

Abbreviations: CYP, cytochrome P450; N, number; PPK, population pharmacokinetic

2.3.4 Results

The one compartment model (ADVAN2 TRANS2, with CL and V were different between motion sickness studies and other studies) was chosen as the structure model for the stability demonstrated on “fda02.csv” and covariance was available. Although the two compartmental model (ADVAN4 TRANS4) completed the run on “fda02.csv” with minimization successful, about 90% runs of the bootstrap terminated due to rounding error. The 3-compartmental model didn't finish the run due to numerical difficulty. To address under-prediction issue of high concentrations, other models, such as Michaelis Menten model, absorption overflow model (when drug amount in the absorption site is greater than an amount, the overflow portion follows a different absorption rate) were tested but not successful. For the 1-compt structure model selected, while ethnicity was identified as statistically significant covariate of some parameters, the effect size was very small and not meaningful for implementation, so the base model was identified as the final model. The goodness-of-fit of the final model is shown in Figure 11.

Figure 11. Goodness-of-Fit Plots for FDA PPK Model With Upper Panels for the Whole Dataset and the Lower Panels for Trial 3403 Only



Source: FDA reviewer's analysis

Abbreviations: CWRES, conditional weighted residuals; DV, observations; IPRED, individual predictions; PPK, population pharmacokinetic

Table 42. FDA Model Parameter Estimates of Subjects (N=915, Dataset = fda02.csv), Trials 1102, 1301, 2301, 3301, 3403, and 3404

Parameter (Unit)	Estimate	RSE (%)	95% CI Low	95% CI High
CL_motion-sickness (mL/day)	730	8.6	607	853
V_motion-sickness (mL)	1520	10.5	1206	1834
CL_other (mL/day)	596	5.5	532	660
V_other (mL)	1060	3.2	993	1127
KA (1/d)	174	30.9	68.6	279
Absorption Tlag1 (d)	0.02 (Fix)	--	--	--
W for error	0.755	9.5	0.614	0.896
IIV_CL_motion-sickness (%)	118	11.9	90.4	146
IIV_VL_motion-sickness (%)	114	17.3	75.4	153
IIV_CL_other (%)	51.8	15.4	36.2	67.4
IIV_VL_other (%)	54.9	9.4	44.8	65
IIV_KA (%)	185	13.8	135	235
IIV_AbsorptionTlag1 (%)	Fixed as 0			

Source: FDA reviewer's analysis

Abbreviations: CI, confidence interval; CL, clearance; IIV, interindividual variability; Ka, absorption rate constant; N, number; RSE, relative standard error; Tlag, lag time

Based on FDA's final model, the simulated Day 1 and Day 7 tradipitant exposure are listed in Table 43.

Table 43. Simulated Day 1 and Day 7 Tradipitant Exposure Based on FDA's Model

Exposure	Trial	N	QD 85 mg		BID 85 mg		QD 170 mg	
			Mean	SD	Mean	SD	Mean	SD
C _{max} (ng/mL) on Day 1	1102	24	55	19	97	33	110	37
	1301	11	57	11	102	20	114	23
	2301	34	72	22	128	40	143	44
	3301	161	79	51	142	92	158	102
	3403	515	90	36	158	62	181	73
	3404	159	72	22	127	38	144	44
	3404.34	11	89	34	155	60	177	67
	All	915	83	38	147	65	166	75
C _{max} (ng/mL) on Day 7	1102	24	133	46	235	83	265	91
	1301	11	146	30	261	53	291	59
	2301	34	184	59	330	106	368	117
	3301	161	207	137	372	249	413	275
	3403	515	203	70	356	119	405	141
	3404	159	166	48	293	84	332	96
	3404.34	11	202	96	356	176	404	191
	All	915	194	84	343	149	388	169
AUC _{0-24h} (ng*day/mL) on Day 1	1102	24	42	14	66	22	85	28
	1301	11	45	9	70	14	90	18
	2301	34	57	18	88	27	113	35
	3301	161	63	41	97	63	126	82
	3403	515	69	26	106	41	137	52
	3404	159	55	16	86	26	111	33
	3404.34	11	68	26	105	40	135	52
	All	915	64	28	99	44	128	56
AUC _{0-24h} (ng*day/mL) on Day 7	1102	24	596	207	1145	396	1192	413
	1301	11	657	134	1263	257	1315	268
	2301	34	831	265	1596	508	1663	529
	3301	161	938	624	1801	1197	1877	1249
	3403	515	920	306	1771	591	1840	612
	3404	159	754	214	1451	411	1508	427
	3404.34	11	920	433	1769	829	1840	867
	All	915	879	376	1692	724	1759	753

Source: FDA reviewer's analysis

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; N, number; QD, once daily; SD, standard deviation

Based on FDA's model, the simulated Day 1 and Day 7 tradipitant exposure are listed in Table 44.

Table 44. Simulated Day 1 and Day 7 Tradipitant Exposures Based on the Applicant's Final Model With θ_{29} Correctly Implemented

Exposure	Trial	N	QD 85 mg		BID 85 mg		QD 170 mg	
			Mean	SD	Mean	SD	Mean	SD
C _{max} (ng/mL) on Day 1	1002	31	178	133	234	339	357	266
	1102	24	85	39	128	154	170	78
	1301	11	216	27	194	227	433	54
	2301	75	136	16	182	183	272	33
	3301	380	182	61	224	243	365	123
	3403	515	139	113	188	278	277	227
	3404	159	71	44	122	169	142	88
	All	1206	144	94	191	250	288	188
C _{max} (ng/mL) on Day 7	1002	31	242	193	330	444	484	386
	1102	24	151	53	234	162	302	107
	1301	11	229	32	292	277	458	64
	2301	75	225	48	341	222	449	97
	3301	380	271	84	397	316	541	167
	3403	515	191	128	307	364	383	257
	3404	159	145	78	248	215	289	157
	All	1206	214	116	331	331	428	231
AUC _{0-24h} (ng*day/mL) on Day 1	1002	31	70	59	190	213	140	119
	1102	24	41	18	111	92	81	37
	1301	11	43	9	104	74	87	19
	2301	75	56	11	149	90	112	22
	3301	380	64	24	166	117	127	48
	3403	515	79	57	188	197	159	115
	3404	159	49	31	125	121	98	62
	All	1206	68	45	168	159	135	89
AUC _{0-24h} (ng*day/mL) on Day 7	1002	31	745	674	1449	1363	1490	1349
	1102	24	540	190	1053	506	1080	380
	1301	11	352	86	686	157	704	172
	2301	75	727	233	1422	618	1454	466
	3301	380	789	340	1528	754	1578	680
	3403	515	757	453	1468	889	1513	907
	3404	159	629	356	1218	784	1258	712
	All	1206	743	409	1441	839	1487	819

Source: FDA reviewer's analysis

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; N, number; QD, once daily; SD, standard deviation

Within motion sickness population, the observed and predicted tradipitant and metabolite exposure in Trial 3403 is significantly higher than that of Trial 3404, and the Applicant attributed this to random variability by stating the following on Page 22 of the PPK report submitted on July 22, 2025: "Exposure metrics for metabolite M8 in study VP-VLY-686-3403 should be considered with extreme caution because the sampling regimen in that study likely led to meaningless estimates. For tradipitant and other metabolites, differences in the exposure metrics for both tradipitant and metabolites between VP-VLY-686-3403 and VP-VLY-686-3404 were unexpected because both studies were conducted in similar populations. These differences may

reflect the small number of postdose samples obtained in each study and the short interval of these samples relative to the dose. As a result of these limitations and given that the population of patients experiencing motion sickness is not expected to result significantly different drug exposure (C_{max} , AUC) compared to healthy volunteers, the pharmacokinetic results from healthy volunteers tested in fasted and fed conditions in a controlled clinic environment (VP-VLY-686-1002) should be considered as more representative than those from VP-VLY-686-3403 and VP-VLY-686-3404.”

2.4 Exposure-Response Analysis

No exposure-response analysis has been submitted for motion sickness indication.

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/

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