CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219209Orig1s000

OTHER REVIEW(S)

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

Date:	1/14/2025
Product Name(s):	Suzetrigine (JOURNAVX)
Application Type/Number(s):	NDA 219209
Sponsor/Applicant:	Vertex Pharmaceuticals Inc.
NEXUS Task Tracking Tool ID #:	2024-9747
Reviewers:	Yan Li, PhD, Epidemiologist Division of Epidemiology II Natasha Pratt, PhD, Master Epidemiologist Division of Epidemiology II
Division Leadership:	Adebola Ajao, PhD, Deputy Director Division of Epidemiology II
Sub-Office Director:	David Moeny, RPh, MPH, Deputy Director Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD, MSPH Office of Pharmacovigilance and Epidemiology

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 219209 is being reviewed for suzetrigine, a selective inhibitor of voltage-gated sodium channel subtype 1.8, for the treatment of moderate to severe acute pain in adults. Suzetrigine represents a new pharmacologic class of non-opioid analgesics and receives the breakthrough therapy designation and the priority review determination. The PDUFA goal date is Jan 30, 2025.

1.2. Describe the Safety Concern

There are safety signals of adverse pregnancy outcomes from animal studies in the drug development program. In rats, suzetrigine increased post-implantation loss and resulted in a lower number of live fetuses at doses of 15 mg/kg/day (2.2 times the maximum recommended human dose [MRHD]). Reduced mean gestation length and increased postnatal pup mortality were observed at ≥ 10 mg/kg (1.6 times MRHD) and increased incidences of fully resorbed litters, fewer live newborn pups, and reductions in pup body weights were observed at 15 mg/kg (2.2 times MRHD). In rabbits, increased post-implantation loss and lower fetal body weight were observed at doses of 200 mg/kg/day (5.9 times MRHD). No malformations were observed when suzetrigine was administered orally to rats and rabbits during the period of organogenesis at doses up to 2.2 times and 5.9 times MRHD, respectively. The clinical relevance of these findings to humans is unclear.

Additional investigational studies demonstrated that suzetrigine affects the estrus cycle in rats and inhibits the rat progesterone receptor, which may contribute to the adverse effects on reproduction.

There is very limited human exposure experience to date. In the clinical development program, one subject was exposed to suzetrigine between gestational weeks 2 to 4 (estimated date of conception: (b) (6) first dose of suzetrigine taken: (b) (6) last dose of suzetrigine taken: (b) (6)) and delivered a healthy infant; no adverse events were reported relating to the pregnancy or delivery. Another subject had a positive urine pregnancy test on the same day when she received the last of dose of suzetrigine (i.e., Study Day 14) but was lost to follow-up.

In light of safety signals observed in animal studies at doses close to MRHD, and the potential widespread use of suzetrigine as a non-opioid analgesic alternative, further collecting pregnancy outcome data to evaluate the potential effects of suzetrigine in humans is essential. Of different adverse outcomes, concerns for spontaneous abortion (post-implantation loss), stillbirths (lower live born pups/fetuses), and neonatal mortality (postnatal pup mortality) were at the moderate level, while concerns for preterm birth (reduced mean gestation length) and small for gestational age (lower pup/fetal body weight) were at the low level. Despite negative animal study findings, there are also needs

to examine other adverse pregnancy outcomes such as major congenital malformations, considering the unclear relevance of animal study findings to humans and suzetrigine's ability to bind the progesterone receptor.

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

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

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

2. REVIEW QUESTIONS

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

- ☐ Specific FDA-approved indication in pregnant individuals exists and exposure is expected.
- ☐ No approved indication in pregnant individuals, but practitioners may use product off-label in pregnant individuals.
- ☒ No approved indication in pregnant individuals, but there is the potential for inadvertent exposure before a pregnancy is recognized.
- ☒ No approved indication in pregnant individuals, but use in individuals of childbearing age is a general concern.

2.2. Regulatory Goal[1]

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

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group

[1] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☒ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☐ Other, please specify:

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

Epidemiologic Domain	Explanation on ARIA insufficiency
☐ Study Population	
☒ Exposures (and Comparators)	Suzetrigine is indicated for acute pain (b) (4) The performance of claims-based algorithms to estimate the gestational age for spontaneous abortions and stillbirths is suboptimal in settings where the precise determination of exposure windows is needed,[2,3,4,5] such as the current setting of acute exposure. Given that the purpose of the PMR is signal refinement, it is necessary to require chart review to precisely define the gestational age to reduce exposure misclassification. ARIA is insufficient due to the lack of access to medical charts.
☒ Outcomes	Neonatal deaths ARIA is insufficient due to the incomplete capture of mortality data outside of the hospital setting in the Sentinel System.
☐ Covariates	
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

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

[2] Moll K, et al. Validating Claims-Based Algorithms Determining Pregnancy Outcomes and Gestational Age Using a Linked Claims-Electronic Medical Record Database. Drug Saf. 2021;44(11):1151-64.
[3] Chomistek AK, et al. Development and Validation of ICD-10-CM-based Algorithms for Date of Last Menstrual Period, Pregnancy Outcomes, and Infant Outcomes. Drug Safety. 2023;46(2):209-22.
[4] Zhu Y, et al. Development and validation of claims-based algorithms for estimating gestational age of spontaneous abortion and termination. Am J Epidemiol. 2024: kwae372.
[5] Naleway AL, et al. Identifying pregnancy episodes, outcomes, and mother–infant pairs in the Vaccine Safety Datalink. Vaccine. 2013;31(27):2898–903.

PMR-1: Collect global data from prospective pregnancy exposure registry/registries, preferably disease-based multiproduct pregnancy registry/registries, using a registry-based cohort study design to compare the maternal, fetal, and infant outcomes of women exposed to Journavx during pregnancy with unexposed comparator population(s). Align the U.S. study protocol with protocol(s) outside the U.S. to reach the target sample size. The registry will identify and record pregnancy complications, spontaneous abortion, stillbirths, neonatal deaths, major and minor congenital malformations, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes should be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

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

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/s/

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

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

Memorandum

Date: January 8, 2025

To: James Yeh, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Rita Joshi, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for JOURNAVX (suzetrigine) tablets, for oral use

NDA: NDA 219209

In response to DAAP's consult request dated June 6, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for JOURNAVX (suzetrigine) tablets, for oral use.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 27, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on January 6, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 10, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LATOYA S TOOMBS
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 6, 2025
To:	Rita Joshi, PharmD Senior Regulatory Health Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** LaToya Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JOURNAVX (suzetrigine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 219209
Applicant:	Vertex Pharmaceuticals Incorporated

1 INTRODUCTION

On May 30, 2024, Vertex Pharmaceuticals Incorporated submitted for the Agency's review an original New Drug Application (NDA) 219209 for JOURNAVX (suzetrigine) tablets. JOURNAVX (suzetrigine) is a New Molecular Entity (NME) with a proposed indication for the treatment of moderate to severe acute pain in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on June 12, 2024 and June 6, 2024, for DMPP and OPDP, respectively, to review the Applicant's proposed Patient Package Insert (PPI) for JOURNAVX (suzetrigine) tablets.

2 MATERIAL REVIEWED

- Draft JOURNAVX (suzetrigine) tablets PPI received on May 30, 2024, revised throughout the review cycle, and received by DMPP and OPDP on December 27, 2024.
- Draft JOURNAVX (suzetrigine) tablets Prescribing Information (PI) received on May 30, 2024, revised throughout the review cycle, and received by DMPP and OPDP on December 27, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

HELEN K YOUNG
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LAURIE J BUONACCORSI
01/06/2025 01:21:46 PM

LASHAWN M GRIFFITHS
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

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

Date of This Review:	December 16, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 219209
Product Name, Dosage Form, and Strength:	Journavx (suzetrigine) tablet, 50 mg
Applicant Name:	Vertex Pharmaceuticals Incorporated (Vertex)
FDA Received Date:	December 10, 2024
TTT ID #:	2024-9749-1
DMEPA 1 Safety Evaluator:	Susan Hakeem, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Vertex Pharmaceuticals Incorporated (Vertex) submitted revised container label and carton labeling received on December 10, 2024 for Journavx. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Journavx (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Vertex Pharmaceuticals Incorporated (Vertex) implemented all of our recommendations and we have no additional recommendations at this time.

[a] Hakeem, S. Label and Labeling Review for Journavx (NDA 219209). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 21. TTT ID: 2024-9749.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON DECEMBER 10, 2024

Container Labels:

Carton Labeling:

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/s/

SUSAN HAKEEM
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VALERIE S VAUGHAN
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: December 9, 2024 **Date consulted:** June 10, 2024

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Division of Anesthesiology, Addiction, and Pain Medicine (DAAP)

Drug: Journavx (suzetrigine)

NDA: 219209

Applicant: Vertex Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of moderate to severe acute pain in adults.

Materials Reviewed:

- DPMH consult request, dated 6/10/2024. DARRTS Reference ID: 5396148.
- Applicant's background package and proposed labeling for NDA 219209, Sequence Number (SN) 0004, dated 5/30/2024.
- Applicant's response to DPMH Information Request (IR) dated 7/11/2024, SN 0015, submitted 7/26/2024.

Consult Request/Question: "DAAP is requesting a DPMH consult to review the new NDA draft labeling and any other aspects of the application that DPMH sees that may require its expertise."

I. INTRODUCTION AND BACKGROUND

On May 30, 2024, the Applicant, Vertex Pharmaceuticals, Inc, submitted a 505(b)(1) New Drug Application (NDA) for a New Molecular Entity (NME), Journavx (suzetrigine), for the treatment of moderate to severe acute pain in adults. DAAP consulted the Division of Pediatrics and Maternal Health (DPMH) on June 10, 2024, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Suzetrigine was granted Fast Track designation on March 5, 2020.
- Suzetrigine was granted Breakthrough Therapy designation on June 30, 2022.
- Suzetrigine has not been approved in any country or region for marketing.

Drug Characteristics[1]

Proposed Drug Class	A sodium channel $Na_v1.8$ blocker
Mechanism of Action	A selective blocker of voltage-gated sodium channel (b) (4) (b) (4) $Na_v1.8$ is (b) (4) expressed in peripheral sensory neurons including dorsal root ganglion neurons, where its role is to transmit pain signals (action potentials). By selectively inhibiting $Na_v1.8$ channels, suzetrigine inhibits transmission of pain signals to the spinal cord and brain.
Proposed dosage form and administration	50 mg tablets (b) (4)
Molecular weight	473.39 g/mol
Mean Effective Half-life	23.6 hours for suzetrigine; 33 hours for M6-SUZ (active metabolite)
% protein bound	99% for suzetrigine; 96% for M6-SUZ (active metabolite)
Proposed Drug-Contraceptive Interactions	Hormonal contraceptives Avoid concomitant use of JOURNAVX with hormonal contraceptives containing progestins other than levonorgestrel and norethindrone. If contraception is desired or needed, alternative contraceptives (such as a combined oral contraceptive containing ethinyl estradiol as the estrogen and levonorgestrel or norethindrone as the progestin, or an intrauterine system) or additional nonhormonal contraceptives

[1] NDA 219209, draft Annotated Labeling, under review by DAAP; Module 2.2 Introduction to Summary, p. 1 and Module 2.4.3, Nonclinical Overview, p.11.

	(such as condoms) should be used during the use of JOURNAVX and for 28 days after discontinuation of JOURNAVX. JOURNAVX did not result in clinically significant changes in the pharmacokinetics of ethinyl estradiol and levonorgestrel when used concomitantly with an oral contraceptive containing ethinyl estradiol and levonorgestrel *[see Clinical Pharmacology (12.3)]*.

Pain Management and Pregnancy

Pregnant individuals experience acute pain resulting from physiologic changes associated with pregnancy, or due to acute non-obstetric causes such as infections or injuries. There is considerable variability in individual pain experience. Severe and persistent pain that is not effectively treated during pregnancy can result in adverse maternal outcomes such as depression and high blood pressure.[2] Regardless of etiology, pain management in pregnant patients is complicated by the physiologic changes in the mother as well as the risk posed to the fetus by both pain and analgesia.[3] Systemic nonopioid and opioid analgesics are the two main categories of commonly used analgesics. Of the nonopioid analgesics, acetaminophen is the preferred medication if drugs are needed to relieve pain during pregnancy.[2] NSAIDS are another option. The relative safety and nature of the risks during pregnancy of NSAIDS depends on the timing of use during pregnancy, the dose, and the specific class of medication. NSAIDs can be used during the first trimester.[2,4] The FDA warns that the use of NSAIDS, both over-the-counter and prescription, around 20 weeks gestation or later may cause fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.[5] In addition, NSAIDS should be avoided in the 3rd trimester due to the additional risk of premature closure of the ductus arteriosus. A short course of opioids can be effective for moderate to severe pain and are generally safe in pregnancy, seeming to result in a low risk for Neonatal Opioid Withdrawal Syndrome (NOWS).[2]
Pain is also common in the immediate postpartum period and includes acute perineal (perineal lacerations), uterine (contractions), and incisional pain, as well as pain from breast engorgement. In the immediate postpartum period, the American College of Obstetricians and Gynecologists (ACOG) recommends using a stepwise multimodal approach to pain management, utilizing a combination of agents with different mechanisms of actions to effectively individualize the

[2] Black, E., et al. Medication Use and Pain Management in Pregnancy: A Critical Review. *Pain Practice* 2019; *19* (8), 875-899.
[3] ACS Trauma Quality Programs Best Practices for Acute Pain Management in Trauma Patients, released November 2020. https://www.facs.org/quality-programs/trauma/quality/best-practices-guidelines. Accessed 7/29/2024.
[4] Shah, Shalini, Banh, Esther T., Koury, Katharine, Bhatia, Gaurav, Nandi, Roneeta, Gulur, Padma, Pain Management in Pregnancy: Multimodal Approaches, Pain Research and Treatment, 2015, 987483, 15 pages, 2015. https://doi.org/10.1155/2015/987483.
[5] US FDA Drug Safety Communication. FDA recommends avoiding use of NSAIDS in pregnancy at 20 weeks or later because they can result in low amniotic fluid. https://www.fda.gov/media/142967/download. Accessed on July 29, 2024.

treatment plan.[6] Acetaminophen and NSAIDS are first-line analgesics for individuals intending to provide breast milk to their infants based on their efficacy in addressing pain and their low concentrations in breast milk.[6] Similar to its use during pregnancy, ACOG recommends limiting postpartum opioid exposure to the lowest, briefest exposure necessary to achieve pain control when NSAIDS and acetaminophen are inadequate, as well as monitoring the mother and breastfed infant for CNS depression.[6]

II. REVIEW

PREGNANCY

Nonclinical Experience

No malformations were observed when suzetrigine was administered orally to rats during the period of organogenesis at doses up to 2.2 times the maximum recommended human dose (MRHD). However, effects on implantation and maintenance of pregnancy were observed. In the rat Fertility and Early Embryonic Development (FEED) and Embryofetal Development (EFD) studies, suzetrigine administration resulted in increased post-implantation loss and lower number of live fetuses at doses of ≥15 mg/kg/day (≥ 2.2-times the maximum recommended human dose (MRHD) based on AUC).[7]

In the Pre- and Postnatal Development (PPND) study in rats, suzetrigine resulted in reduced mean gestation length and increased postnatal pup mortality between birth and Postnatal Day 4 at doses of ≥ 10 mg/kg/day (approximately 1.6 times the steady state MRHD exposure based on AUC) and increased incidences of total resorptions of litters, lower number of live newborn pups, and reductions in pup body weights at doses of 15 mg/kg/day (approximately 2.2 times the MRHD based on AUC). These effects were consistent with the effects observed in the rat EFD studies. There were no adverse effects on postnatal development landmarks, neurotoxicity endpoints or F_1 reproduction at doses up to 15 mg/kg/day.[8]

According to the Applicant's nonclinical overview, in repeat-dose toxicity studies, "oral administration of suzetrigine to female rats for 13 weeks resulted in reproductive system effects (ovarian follicular cysts, pituitary and mammary gland hyperplasia) at ≥100 mg/kg/day (AUC-based safety margin of 15-times the maximum recommended human dose)."[9]

Progesterone receptor (PR) antagonism was determined as the mechanism for these effects. Investigational studies, including paired rat and human PR reporter assays and the (b) (4) functional coactivator recruitment assay, demonstrated that suzetrigine "was a 94x more potent antagonist of rat PR than human PR, providing a plausible explanation for all suzetrigine-related findings in the reproductive system of female rats".[10] Thus, the Applicant concluded that "the findings in rat are not relevant for humans."[11]

No malformations were observed when suzetrigine was administered orally to rabbits during organogenesis at doses up to 5.9 times the MRHD. Increased post-implantation loss and lower mean fetal body weight were observed at 200 mg/kg/day (approximately 5.9 times the MRHD based on AUC). This dose also caused signs of maternal toxicity such as maternal body weight

[6] Pharmacologic Stepwise Multimodal Approach for Postpartum Pain Management. ACOG Clinical Consensus No.1. Obstetrics & Gynecology 138(3): p 507-517, September 2021. | DOI: 10.1097/AOG.0000000000004517.
[7] NDA 219209, Module 2.4, Nonclinical Overview, p. 16 and 35.
[8] NDA 219209, Module 2.6.6.6.3, Toxicology Written Summary, p. 40-43.
[9] NDA 219209, Module 2.7.4, Summary of Clinical Safety, p. 52.
[10] NDA 219209, Module 2.4.6.1, Nonclinical Overview, p. 17.
[11] NDA 219209, Module 2.4.4.5, Nonclinical Overview, p. 16.

loss, decreased food consumption and clinical signs of poor toleration. Fetal morphology (external, visceral, and skeletal) was unaffected at doses up to 200 mg/kg/day.[12]

A Placental Transfer Study was conducted in rats. After oral administration of ^{14}C-SUZ to pregnant rats on Gestation Days 13 and 18, radioactivity was quantifiable in fetal blood and tissues (such as brain, eyes, GI tract, kidney, liver, lungs, muscle, and other sites) up to 48-72 hours post dose, indicating that ^{14}C-SUZ-related radioactivity can cross the placenta.[13]

The nonclinical team reviewed the Applicant's submission and provided the following information:
There were no malformations in either the rat or rabbit. However, there were effects on implantation and maintenance of pregnancy when suzetrigine was administered to rats from the early embryonic stage through organogenesis at doses ≥ 2.2-times the maximum recommended human dose (MRHD) based on AUC. In addition, decreased mean gestational length and increased pup mortality between birth and postnatal day 4 at doses approximately 1.6 times the steady state MRHD exposure based on AUC, and decreased pup body weight from birth to weaning at doses approximately 2.2 times the MRHD based on AUC were observed. Although there were effects seen in the rabbit, these occurred at the same dose that caused signs of maternal toxicity. Lastly, although there were reproductive system effects seen in the female rat during the 13-week repeat dose study, these findings occurred at ≥100 mg/kg/day (AUC-based safety margin of 15-times the maximum recommended human dose). The current indication for suzetrigine is for the treatment of acute pain (b) (4) as such, these findings are not considered pertinent to the current proposed maximum length of usage.

The reader is referred to the full nonclinical review by Irene Surh.

> ***Reviewer comment:***
> *DPMH discussed the nonclinical findings with the nonclinical review team. Per the nonclinical review team, the Applicant provided reasonable data to support the conclusion that inhibition of the rat progesterone receptor (PR) is playing a role in these effects. This off-target activity provides a plausible explanation as this pharmacology is involved in the maintenance of pregnancy. However, it is unclear if this is definitively the only mechanism involved. Additionally, the nonclinical team did not find clear evidence that suzetrigine is a significantly more potent antagonist of the rat progesterone receptor compared with the human progesterone receptor and that suzetrigine will not inhibit human PR at a concentration that would be relevant to the current clinical use. As a result, the effects on implantation, maintenance of pregnancy, reduced mean gestational length and increased postnatal pup mortality in rats are of uncertain relevance to humans.*

[12] NDA 219209, Module 2.6.6.6.2.2 Toxicology Written Summary, p. 38.
[13] NDA 219209, Module 2.6.4.4.3, Pharmacokinetics Written Summary, p. 41.

Review of Safety Database

The Applicant reported two subjects with positive pregnancy tests during the clinical development program (study VX22-548-107) as follows:[14]

1) Subject (b) (6) On (b) (6) (Study Day 1), the 36-year-old subject had joint stabilization surgery. The same day, the subject had a negative urine pregnancy test, was enrolled, and received the first dose of suzetrigine 100 mg/50 mg q 12 h. The subject took rescue medications including ibuprofen and acetaminophen. On (b) (6) (Study Day 14), the subject had a negative urine pregnancy test. The subject received their last dose of the study drug the same day. On (b) (6) (Study Day 28), the subject had 2 positive urine pregnancy tests at their Safety Follow-up Visit. On (b) (6) serum-HCG test was positive. The estimated date of conception was (b) (6) with a LMP (b) (6) Follow-up information reported that a (b) (6) g male infant was delivered (b) (6) via elective c-section for frank breech presentation. The surgery was uncomplicated. Mother and infant were discharged home in good condition.
2) Subject (b) (6) One pregnancy occurred in a 30-year-old subject. On (b) (6) (Study Day 1), the subject was enrolled and received the first dose of suzetrigine 100 mg/50 mg q 12 h for the treatment of acute pain in the left upper extremity. The subject had a negative urine pregnancy test the day prior to enrollment. The subject took rescue medications including ibuprofen and acetaminophen. On (b) (6) (Study Day 14), the subject received their last dose of suzetrigine. The same day, the subject had a positive pregnancy test. The subject was lost to follow-up.

Reviewer Comment:
Based on the estimated date of conception for subject (b) (6) it is likely that early pregnancy suzetrigine-exposure occurred. Teratogenic insult at this stage of pregnancy might result in miscarriage, which did not occur. Based on the timing of the positive pregnancy test in relation to the doses of suzetrigine, subject (b) (6) may have been exposed to suzetrigine early in pregnancy as well, however, this subject was lost to follow-up, so this pregnancy outcome is unknown. There are insufficient human pregnancy data from the two pregnancies that occurred during the clinical development program to inform the safety of suzetrigine use in pregnancy.

Review of Literature

Applicant's Review:

The applicant did not provide a review of the literature related to suzetrigine and pregnancy.

DPMH review:

DPMH conducted a search of published human studies in PubMed, using the search term "suzetrigine". No publications were found. DPMH also searched Embase, Micromedex[15], Reprotox[16], TERIS[17], and Shepard's[18]. No information was found.

[14] NDA 219209, SN 0004, Module 5.3.5.2 Study reports of Uncontrolled Clinical Studies, Study Report Body VX22-548-107, p. 37 (12.5.4), Narratives p. 207 and 208 (14.3.3.5).
[15] Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 7/18/2024.
[16] Reprotox Website: www.Reprotox.org. Accessed 7/18/2024.
[17] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/18/2024.
[18] Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 7/18/2024.

Reviewer comment:
There are no publications to inform the safety of suzetrigine use in pregnancy. Suzetrigine is a new molecular entity. It has not been marketed in other countries. Given DPMH's review of the literature did not yield any publications related to suzetrigine and pregnancy, DPMH did not pursue the Applicant's omission of a literature review further.

LACTATION

Nonclinical Experience

Mammary gland lacteal excretion of suzetrigine in rats was demonstrated following a single dose (10 mg/kg) of suzetrigine administered on Day 10 postpartum to lactating rats. Exposure of suzetrigine in rat milk was approximately 2.6-times the value observed in the plasma of the lactating rats (based on AUC).

The reader is referred to the full nonclinical review by Irene Surh.

Reviewer comment:
The presence of suzetrigine in rat milk was demonstrated following a single oral dose of suzetrigine to lactating rats. During the postpartum/nursing phase of the pre- and postnatal development study, adverse effects were observed. As mentioned in the Pregnancy section of this review, postnatal pup mortality (total litter loss) occurred during Lactation Days 0 through 3 and lower mean pup body weights and lower body weight gains occurred during the preweaning period at doses approximately 2.2 times the MRHD based on AUC. The early toxicity seen in the rat pups is most likely due to in utero exposure. However, it is difficult to determine whether the effects seen later in the preweaning period are due to in utero toxicity or lactational exposure.

Review of Safety Database

The Applicant reported that there were no cases of suzetrigine exposure in lactating individuals in the suzetrigine clinical or safety databases.[19]

Review of Literature

Applicant's review:

The Applicant did not provide a review of the literature related to suzetrigine and lactation.

DPMH review:

DPMH conducted a search of published human studies in PubMed, using the search term "suzetrigine". No publications were found.

In addition, DPMH conducted a search for suzetrigine in Micromedex[15], Hale's *Medications and Mothers' Milk*[20], Reprotox[16], the Drugs and Lactation Database (LactMed)[21], and Briggs *Drugs*

[19] NDA 219209, SN 0015, Applicant's response to DPMH IR, dated 7/11/2024, submitted 7/26/2024.
[20] Hale, Thomas W. Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 7/18/2024.
[21] Drugs and Lactation Database (LactMed). Accessed 7/18/2024.

in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk[22]. No information was found.

> ***Reviewer comment:***
> *Suzetrigine is a new molecular entity, has not been marketed in other countries, and there are no publications related to suzetrigine and lactation. Given DPMH's review of the literature did not yield any publications, DPMH did not pursue the Applicant's omission of a literature review further.*
> *There are no human data available to inform labeling of suzetrigine use in lactation. However, because suzetrigine is present in animal milk, it is likely present in human milk. A clinical lactation study is needed; see the Discussion and Conclusions section below for the rationale for this recommendation and details about the recommended clinical lactation study. Until data are available, the labeling should explain the absence of data related to lactation and the need to conduct an individualized benefit-risk assessment for patients who are lactating. See the Labeling Recommendations section for further details.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Suzetrigine was not mutagenic in the bacterial reverse mutation assay (Ames test), or clastogenic in the in vitro micronucleus assay with a human TK6 lymphoblastoid cell line, or in the in vivo rat bone marrow micronucleus assay.

A Fertility and Early Embryonic Development (FEED) study was conducted in rats. Male rats were treated orally with suzetrigine at 3.6, 9.7, and 13.8-times the steady state MRHD exposure based on AUC for a minimum of 28 days prior to mating and through mating, Suzetrigine had no effects on sperm parameters (motility, concentration, or morphology), reproductive performance or uterine parameters (number of implants, viable implants, pre-implantation loss, early resorptions and post-implantation loss) at any dose tested. Female rats were treated orally with suzetrigine at 0.57, 1.6, and 2.2-times the steady state MRHD exposure based on AUC for a minimum of 14 days prior to mating, throughout mating, and through Gestation Day 7. Increased pre-implantation loss was observed at approximately 2.2-times the MRHD based on AUC.

The reader is referred to the full nonclinical review by Irene Surh.

> ***Reviewer comment:***
> *Per the nonclinical review team, in a female fertility study in rats, increased pre-implantation loss was observed at oral suzetrigine doses ≥ 2.2-times the MRHD when administered prior to mating and through Gestation Day 7 in female rats. The relevance to humans is unclear but based on these findings, suzetrigine may impair female fertility.*

Drug-Drug Interaction (DDI)

Based on a DDI study using an oral contraceptive containing levonorgestrel and ethinyl estradiol, that found no clinically relevant effect on the exposures of the oral contraceptive hormones, the Applicant concluded that suzetrigine can be used with oral contraceptives containing ethinyl

[22] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

estradiol, levonorgestrel, or norethindrone.[23] The impact of suzetrigine on progestins that are more sensitive Cytochrome P450 3A substrates are unknown,[24] and thus, the Applicant proposes to include the following statement in labeling subsection 7.2: (b) (4)

> ***Reviewer comment:***
> *Per the Clinical Pharmacology team, norethindrone was not evaluated in the dedicated DDI oral contraceptives study but is added by the Applicant based on the literature comparison of CYP3A sensitivity to levonorgestrel. This addition is acceptable to the Clinical Pharmacology team. The Clinical Pharmacology and the Clinical review teams agree with including a cautionary statement about progestins other than levonorgestrel and norethindrone but the language in labeling will be revised. Clinical Pharmacology also recommends avoiding concomitant use of suzetrigine with hormonal contraceptives containing other progestins or to use an alternative hormonal or nonhormonal contraceptives during coadministration with suzetrigine and for 28 days after the final dose. The 28 days reflects the time for the hepatic enzyme to recover from the effects of suzetrigine.*

The reader is referred to the full Clinical Pharmacology review by Suresh Naraharisetti, PhD.

Review of Safety Database

The Applicant reported that there were no cases reporting effects on male or female fertility from their clinical or safety database.[19]

Review of Literature

Applicant's review:

The Applicant did not provide a review of the literature related to suzetrigine and effects on human fertility.

DPMH review:

DPMH conducted a search of published human studies in PubMed, using the search term "suzetrigine". No publications were found. DPMH also searched Embase, Micromedex[15], Reprotox[16] and TERIS[17]. No information was found.

> ***Reviewer comment:***
> *There are no human data available to inform labeling of suzetrigine and its effects on human fertility. As discussed in both the Pregnancy and Lactation sections of this review, given DPMH's review of the literature did not yield any publications, DPMH did not pursue the Applicant's omission of a literature review further.*

[23] NDA 219209, Module 2.5 Clinical Overview, p. 27.
[24] NDA 219209, Module 2.5 Clinical Overview, p. 30.
[25] NDA 219209, draft Annotated Labeling, under review by DAAP.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Based on the nonclinical data, suzetrigine does not appear to be teratogenic in rats or rabbits. In the rat reproduction studies, there were effects on implantation and maintenance of pregnancy when suzetrigine was administered from the early embryonic stage through organogenesis. In addition, decreased mean gestational length, increased pup mortality between birth and postnatal day 4, and decreased pup body weight from birth to weaning were observed. The inhibition of the rat progesterone receptor (PR) is playing a role in these effects; however, it is unclear if this is the only mechanism involved. Also, the nonclinical review did not find clear evidence that suzetrigine is a significantly more potent antagonist of the rat PR compared with the human PR, and thus, the degree of suzetrigine inhibition of the human PR at a concentration relevant to the proposed clinical use remains uncertain. The effects on implantation, maintenance of pregnancy, reduced mean gestational length and increased postnatal pup mortality in rats identify potential safety concerns for human pregnancy.

Given there are only two case reports of exposure related to pregnancy available from the clinical studies conducted during the drug development of suzetrigine, there are insufficient data on suzetrigine use in pregnancy to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Suzetrigine would be an alternative to opioid treatment of acute pain and its use to treat moderate to severe acute pain in females of reproductive potential is anticipated to be high. As half of US pregnancies are unplanned, it is important to obtain safety information related to any exposure to this new molecular entity in pregnancy. Additionally, as mentioned above, there were findings in the animal reproduction studies in rats, including increased post-implantation loss, lower number of live fetuses and lower number of live newborn pups at approximately 2.2-times the MRHD, and reduced mean gestational length and increased postnatal pup mortality between birth and postnatal day 4 at approximately 1.6-times the MRHD. The animal reproduction studies identify potential pregnancy safety concerns in humans, including miscarriages, pregnancy loss, preterm labor, and preterm births. Collecting pregnancy outcome data is needed to evaluate the potential effects in humans based on the findings in animals. Therefore, DPMH recommends issuing a postmarketing requirement (PMR) for a Pregnancy Exposure Registry Study and a Complementary Pregnancy Study. Because miscarriages are common in females of reproductive potential, occurring in 15% to 20% of all clinically recognized pregnancies[26,27,28], chart review is necessary as part of the claims database complementary study for outcome validation to minimize misattribution of events as drug-related.

[26] Ammon Avalos L, Galindo C, Li DK. A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Res A Clin Mol Teratol. 2012 Jun;94(6):417-23. doi: 10.1002/bdra.23014. Epub 2012 Apr 18. PMID: 22511535.

[27] Quenby, S., et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021 May 1;397(10285):1658-1667. doi: 10.1016/S0140-6736(21)00682-6. Epub 2021 Apr 27. PMID: 33915094.

[28] Genovese HG, McQueen DB. The prevalence of sporadic and recurrent pregnancy loss. Fertil Steril. 2023 Nov;120(5):934-936. doi: 10.1016/j.fertnstert.2023.08.954. Epub 2023 Aug 28. PMID: 37648145.

Lactation

Suzetrigine is present in rat milk. Lactation data for suzetrigine are not currently available for humans. Given suzetrigine is present in animal milk, it is likely to be present in human breast milk. Additionally, suzetrigine is orally bioavailable, has a low molecular weight and has an effective half -life of 33 hours. These physicochemical properties suggest the excretion of suzetrigine into breast milk is likely. However, suzetrigine is highly protein bound so it may transfer less readily. Since the current ACOG guideline recommends limited use of opioids, suzetrigine may serve as an alternative for the management of postpartum pain, especially when the other, available, non-opioid options are not effective enough. Additionally, lactating women may need a non-opioid pain medication for other causes of moderate to severe acute pain. Since suzetrigine use during lactation is anticipated and its physicochemical properties indicate it will likely be transferred into breast milk, DPMH recommends issuing a PMR for a clinical milk-only lactation study. The data obtained from a clinical milk-only lactation study would be helpful in determining whether suzetrigine is present in human breastmilk, and if so, in what amounts. If a clinical milk-only lactation study demonstrates a clinically important amount of suzetrigine in breast milk, further study to examine systemic exposure in the breastfed infant may be needed in the future.

Females and Males of Reproductive Potential

There are no clinical data to inform labeling related to human fertility. Nonclinical data revealed increased pre-implantation loss at oral suzetrigine doses ≥ 2.2-times the MRHD when administered prior to mating and through Gestation Day 7 in female rats. The relevance to humans is unclear but based on these findings, suzetrigine may impair female fertility.

A drug-drug interaction study was performed with an oral combined contraceptive containing ethinyl estradiol and levonorgestrel, and suzetrigine did not have a clinically relevant effect on the exposures of the tested hormones. Norethindrone was not evaluated in the dedicated DDI oral contraceptives study but is added in the proposed labeling by the Applicant based on the literature comparison of CYP3A sensitivity to levonorgestrel. Other progestins were not studied and thus, a recommendation either to avoid concomitant use of suzetrigine with hormonal contraceptives containing other progestins or to use an alternative hormonal or nonhormonal contraceptive during coadministration with suzetrigine and for 28 days after the final dose is warranted in labeling subsection 8.3.

POSTMARKETING REQUIREMENTS (PMR) SUGGESTED LANGUAGE

- **Pregnancy Exposure Registry Study:** Collect global data from prospective pregnancy exposure registry/registries, preferably disease-based multiproduct pregnancy registry/registries, using a registry-based cohort study design to compare the maternal, fetal, and infant outcomes of women with acute pain exposed to Journavx during pregnancy with unexposed comparator population(s). Align the U.S. 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, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes should be assessed throughout pregnancy. Infant

outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

- **Complementary Pregnancy Study:** 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 Journavx during pregnancy compared to appropriate comparator population(s).
- **Lactation Study**: Perform a milk-only lactation study in lactating women who have received suzetrigine to measure concentrations of suzetrigine in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

LABELING RECOMMENDATIONS

DPMH provided labeling recommendations for subsections 8.1, 8.2, 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 11/19/2024. DPMH recommendations are below and reflect the discussions with DAAP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DRUG INTERACTIONS----------

- Hormonal contraceptives: Avoid concomitant use with hormonal contraceptives containing progestins other than levonorgestrel and norethindrone. If contraception is desired or needed, use an alternative or an additional nonhormonal contraceptive method during coadministration and for 28 days after discontinuation of JOURNAVX. (7.2)

FULL PRESCRIBING INFORMATION

7 Drug Interactions

7.2 Effect of JOURNAVX on Other Drugs

Hormonal Contraceptives

Avoid concomitant use of JOURNAVX with hormonal contraceptives containing progestins other than levonorgestrel and norethindrone. If contraception is desired or needed, alternative contraceptives (such as a combined oral contraceptive containing ethinyl estradiol as the estrogen and levonorgestrel or norethindrone as the progestin, or an intrauterine system) or additional nonhormonal contraceptives (such as condoms) should be used during the use of JOURNAVX and for 28 days after discontinuation of JOURNAVX.

JOURNAVX did not result in clinically significant changes in the pharmacokinetics of ethinyl estradiol and levonorgestrel when used concomitantly with an oral contraceptive containing ethinyl estradiol and levonorgestrel *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of JOURNAVX during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies in rats, effects on implantation and maintenance of pregnancy occurred at oral suzetrigine doses of ≥ 2.2-times the maximum recommended human dose (MRHD) when administered during early embryonic development or throughout organogenesis. In a pre- and postnatal development study, reduced mean gestation length and increased postnatal pup mortality were observed at maternal rat exposures of 1.6-times the MRHD and decreased rat pup body weights were observed during the period of birth to weaning at maternal exposures of 2.2-times the MRHD. No malformations were observed when suzetrigine was administered orally to rats and rabbits during the period of organogenesis at doses up to 2.2 and 5.9 times, respectively, the MRHD. The clinical relevance of these findings is unclear.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Suzetrigine was administered orally to pregnant rabbits during the period of organogenesis at 50, 100, and 200 mg/kg/day (approximately 1.6, 3.1, and 5.9 times, respectively, the steady state MRHD exposure based on AUC). Increased post-implantation loss and lower fetal body weight were observed at 200 mg/kg/day, which is a dose that also caused maternal toxicity. No adverse embryofetal effects were observed at doses up to 100 mg/kg.

Suzetrigine was administered orally to pregnant rats during the period of organogenesis at 5, 10, and 15 mg/kg/day (approximately 0.57, 1.6, and 2.2 times the steady state MRHD exposure based on AUC). Increased post-implantation loss and lower number of live fetuses were observed at 15 mg/kg/day. No adverse embryofetal effects were observed at doses up to 10 mg/kg. Placental transfer of suzetrigine was observed in pregnant rats.

In a pre- and post-natal development study, suzetrigine was administered orally to pregnant rats at doses of 5, 10, and 15 mg/kg/day (approximately 0.57, 1.6, and 2.2 times the steady state MRHD exposure based on AUC) from Gestation Day 6 through Lactation Day 20. Reduced mean gestation length and increased postnatal pup mortality between birth and Postnatal Day 4 were observed at ≥ 10 mg/kg and increased incidences of fully resorbed litters, lower live newborn pups, and reductions in pup body weights were observed at 15 mg/kg. No effects on learning and memory or sexual maturation were observed at doses up to15 mg/kg/day.

The effects on implantation, maintenance of pregnancy, reduced mean gestation length, and increased postnatal pup mortality in rats are of uncertain relevance to humans.

8.2 Lactation

Risk Summary

There are no data on the presence of suzetrigine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Suzetrigine is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JOURNAVX and any potential adverse effects on the breastfed infant from JOURNAVX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Avoid concomitant use of JOURNAVX with hormonal contraceptives containing progestins other than levonorgestrel and norethindrone. Advise patients using hormonal contraceptives containing progestins other than levonorgestrel and norethindrone to use an alternative contraceptive method or additional nonhormonal contraceptive during treatment with JOURNAVX and for 28 days after discontinuation of JOURNAVX *[see Drug Interactions (7.2)]*.

Infertility

Based on findings from animal studies, JOURNAVX may impair fertility in females of reproductive potential. In a female fertility study in rats, increased pre-implantation loss was observed at oral suzetrigine doses of ≥ 2.2-times the MRHD when administered prior to mating and through Gestation Day 7. The relevance to humans is unclear *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Drug Interactions

When co-administered with hormonal contraceptives containing a progestin other than levonorgestrel or norethindrone, advise patients to use an alternative contraceptive or additional nonhormonal contraceptive (such as condoms) during treatment with JOURNAVX and for 28 days after discontinuation of JOURNAVX *[see Drug Interactions (7.2)]*.

Infertility

Advise females of reproductive potential that JOURNAVX may impair fertility *[see Use in Specific Populations (8.3)]*.

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

/s/

KERRY R SHAAB
12/10/2024 03:43:41 PM

TAMARA N JOHNSON
12/10/2024 05:09:18 PM

LYNNE P YAO
12/13/2024 07:38:32 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 6, 2024

To: Rigoberto Roca, MD, Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** JOURNAVX (suzetrigine) (company code: VX-548)
Dosages, formulations, routes: 50 mg tablet for oral administration. Dosing regimen is 100 mg loading dose followed by 50 mg q12h (100mg/50 mg q12h)
NDA number: 219209
IND Number: 146185
Indication(s): moderate to severe acute pain in adults
PDUFA Goal Date: 01/30/2025

Materials Reviewed:

Table of Contents

I. SUMMARY

1. Background

This memorandum is in response to a consult request from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) to evaluate abuse-related preclinical and clinical data submitted by Vertex Pharmaceuticals, Inc. (Applicant) under NDA 216158 for JOURNAVX **(**suzetrigine) (code name: VX-548), indicated for the treatment of moderate to severe acute pain in adults. Suzetrigine was granted Fast Track designation on March 5, 2020, and a Breakthrough Therapy designation on June 30, 2022. The Applicant submitted a request for a Rolling Review under IND 146185 which was approved on March 18, 2024, for the NDA to be submitted in three parts. The Applicant submitted a 505(b)(1) application on March 28, 2024, and DAAP consulted CSS to review the abuse-related data submitted in the NDA on June 26, 2024. The current goal date for the NDA is January 30, 2025..

CSS first communicated with the Applicant as part of an end of phase 2 meeting held on July 12, 2022, in which the Applicant was informed of the need to compile and submit the appropriate studies and data outlined in the guidance for industry: *Assessment of Abuse Potential of Drugs* (2017) as part of their NDA. Specifically, the Applicant was asked to clarify the activity of the M6-SUZ metabolite, monitor for abuse related adverse events (AE) in their clinical trials, and conduct an animal physical dependence study. The Applicant conducted the requested studies and provided the requested data which are summarized in this document.

Suzetrigine is a new molecular entity developed for the treatment of moderate to severe acute pain. In vitro binding data indicate that it functions as a selective blocker of voltage gated sodium channels subtype 1.8 ($Na_v1.8$) which are expressed in dorsal root ganglion (DRG) neurons and are involved in the pain signaling pathway. Inhibition of $Na_v1.8$ prevents the transmission of pain to the central nervous system (CNS). Suzetrigine is orally bioavailable and is metabolized into one major circulating active metabolite, M6-SUZ, that accounts for approximately half of its activity. Analysis of behaviors at doses that produced supratherapeutic Cmax levels in rats and nonhuman primates did not produce any CNS mediated effects. As a result, suzetrigine did not produce abuse related behavioral effects in animals. The major treatment emergent adverse events (TEAE) related to abuse and dependence were dizziness and somnolence. With a lack of CNS activity, no animal behaviors indicative of abuse or dependence,

and a lack of significant TEAEs related to abuse or dependence, we conclude that suzetrigine does not have a potential for abuse.

After evaluating the nonclinical and clinical data in the NDA, CSS recommends that suzetrigine not be controlled under any schedule under the CSA. Recommendations for the labeling of JOURNAVX regarding abuse and physical dependence (i.e., Section 9) appear below in the Recommendations section.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 219209 for JOURNAVX (suzetrigine) and concludes that the drug does not have abuse potential and should not be controlled under the CSA. This conclusion is based on the following:

- Suzetrigine is a new molecular entity with a novel mechanism of action proposed for the indication of moderate to severe acute pain.

- In vitro binding and activity studies indicate suzetrigine and its active metabolite, M6-SUZ, function as highly selective $Na_v1.8$ channel blockers. Suzetrigine is also an antagonist at the gamma-aminobutyric acid A ($GABA_A$) receptor, dopamine transporter (DAT), and norepinephrine transporter (NET), however, not at clinically relevant doses. Similarly, M6-SUZ is an antagonist at the $GABA_A$ and Orexin 1 (OX1) receptors, however, not at clinically relevant doses. As a result, suzetrigine does not appear to bind or have activity at neuronal targets associated with having a potential for abuse.

- Behavioral studies using suzetrigine in rats and nonhuman primates produced no CNS mediated behaviors, and no signs associated with abuse potential.

- An analysis of CNS-mediated AEs that can be indicative of abuse liability or physical dependence was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs were dizziness and somnolence. There were no concerning reports of AEs that suggest that suzetrigine has a potential for abuse or physical dependence.

- Based on the data provided above, there is no indication that suzetrigine has a potential for abuse. As a result, the Applicant was not asked to conduct animal or clinical studies to directly assess the abuse potential of suzetrigine.

3. Recommendations

Based on the data provided in NDA 219209, CSS recommends that:

- Suzetrigine not be controlled in any schedule under the CSA

- The Applicant should not include Section 9 Drug Abuse and Dependence in their proposed labeling for JOURNAVX.

II. DISCUSSION

1. Chemistry

1.1 Substance and Product Information

JOURNAVX is formulated as oral tablets that contain 50 mg suzetrigine, the active pharmaceutical ingredient. Each tablet contains the active ingredient ((b) (4)%) plus different amounts of the inactive ingredients ((b) (4)%) (b) (4) The inactive ingredients do not have a known potential for abuse.

Suzetrigine is an off-white powder that has an IPUAC name of 4-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-amido]pyridine-2-carboxamide, a CAS # of 2649467-58-1, and company code names of VX-548, VRT-1737548, and VXc-548. Suzetrigine has four chiral centers, a molecular weight of 476.39 g/mol, is insoluble in water, and is sparingly soluble in organic solvents. Suzetrigine has not been approved for medical use in the U.S. and is not controlled under the CSA.

The circulating active metabolite of suzetrigine, M6-SUZ, is also referenced sometimes by the company code name VRT-1875420.

1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Applicant is not seeking abuse-deterrent labeling and did not conduct manipulation or extraction studies to assess the abuse-deterrent properties of suzetrigine.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

The Applicant conducted several in vitro binding studies to assess the primary and secondary pharmacology of suzetrigine.

The Applicant conducted ten in vitro binding studies to determine the binding affinity and efficacy of suzetrigine and M6-SUZ. The data indicate that suzetrigine is a highly selective blocker of $Na_v1.8$ channels expressed in DRG neurons. Other studies indicate that it also functions as an antagonist to $GABA_A$, DAT, and NET, however, it does so at micromolar concentrations that are not clinically relevant, even at high supratherapeutic doses. Notably, $GABA_A$ antagonists are not associated with having a potential for abuse. Similarly, the metabolite, M6-SUZ, is a highly selective blocker of $Na_v1.8$

channels with approximately one third the efficacy of the parent compound. M6-SUZ also functions as an antagonist of the $GABA_A$ and OX1 receptors, however, it does so at micromolar concentrations that are not clinically relevant. Accordingly, suzetrigine was found to bind significantly to, or have activity at, molecular targets that are known for having a potential for abuse including $GABA_A$, DAT, and NET. However, the binding affinity and IC_{50} for these targets are in the micromolar range. According to clinical study VX21-548-005, single oral doses of 395 mg suzetrigine (4-fold the highest therapeutic dose) produced a C_{max} of 1.1 µg/mL (~2.3 µM) which is significantly below the concentration required for clinically relevant pharmacodynamic affects at these receptors, especially when considering the high protein binding (>98%) of suzetrigine and M6-SUZ in the CNS (Study # P298).

1. Study # P272 was an electrophysiology study conducted to assess the binding and activity of suzetrigine at $Na_v1.8$ sodium channels relative to other ion channels. Dorsal root ganglion or recombinant cell systems (HEK or CHO) were used to measure the currents and specificity of suzetrigine to specific ion channels. Suzetrigine blocked human $Na_v1.8$ with a potency of 0.68 ± 0.16 nM in human DRG neurons, the disease-relevant endogenous target tissue. Furthermore, selective block of $Na_v1.8$ by suzetrigine inhibited action potential firing in human DRG neurons, demonstrating that selective block of $Na_v1.8$ is sufficient to alter neuronal excitability.

2. Study # P272 was an electrophysiology study which also assessed the binding and activity of M6-SUZ (VRT-1875420) at $Na_v1.8$ sodium channels relative to other ion channels. Dorsal root ganglion or recombinant cell systems (HEK or CHO) were used to measure the currents and specificity of suzetrigine to specific ion channels. M6-SUZ blocked human $Na_v1.8$ with a potency of 2.5 ± 0.20 nM in human DRG neurons, the disease-relevant endogenous target tissue. M6-SUZ also demonstrated > 1,400-fold selectivity to $Na_v1.8$ over $Na_v1.2$, $Na_v1.5$, and $Na_v1.7$.

3. Study # S048 was an electrophysiology study to assess the binding and activity of suzetrigine and M6-SUZ (VRT-1875420) at $Na_v1.9$ sodium channels. Activity was assessed using electrophysiological methods in ND7/23 cells expressing human $Na_v1.9$ sodium channels. Suzetrigine and M6-SUZ were found to be antagonistic (IC_{50}) at $Na_v1.9$ sodium channels at concentrations of 22 µM and 38 µM respectively. These concentrations are 31,000-fold and 76,000-fold greater than those for $Na_v1.8$ sodium channels and are not considered clinically relevant at therapeutic doses.

4. Study # VRT-1737548-TX-015 was a (b) (4) study conducted to assess the activity of suzetrigine (10 µM) against a panel of receptors, ion channels, and transporters. According to this study, suzetrigine produced greater than 50% inhibition specific receptor binding at the glucocorticoid (85%) and progesterone (80%) receptors, as well as the adenosine (53%) and norepinephrine transporter (NET) (50%). Suzetrigine did not significantly bind to other molecular targets that are known to be associated with have a potential for abuse (e.g., cannabinoid receptors, opioid receptors, $GABA_A$, glutamatergic and serotonergic receptors).

5. Study # VRT-1875420-TX-001 was a (b) (4) study conducted to assess the activity of a human active circulating metabolite of suzetrigine, M6-SUZ (10 µM), against a panel of receptors, ion channels, and transporters. According to this study, M6-SUZ produced greater than 50% inhibition specific receptor binding at the Orexin 1 receptor (59%) and progesterone receptor (62%).

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6. Study # VX-548-TX-017; VRT-1875420-TX-002 was conducted to determine the binding affinity of suzetrigine and its active metabolite, M6-SUZ, to a panel of receptors. Both substances were tested at 10 µM with binding calculated as a % inhibition of the binding of a radioactively labeled ligand specific to that target.
    a. Suzetrigine – bound significantly to the glucocorticoid receptor (93%) and to the GABA gated chloride channel (52%).
    b. M6-SUZ – bound significantly to the glucocorticoid receptor (63%) and to the orexin 1 receptor (66%).

7. Study # VRT-1737548-TX-016 was conducted to assess the cellular activity of suzetrigine at specific receptors or transporters. The data are presented in Table 1 below.

Table 1: Off-Target Binding Affinity and Activity of Suzetrigine

Drug Concentration (µM)	**Target**	**% Inhibition**	**K_i (µM)**	**IC_{50} (µM)**
3	Glucocorticoid Receptor	55	1.15	2.39
1	Progesterone Receptor	68	0.32	0.39
10	$GABA_A$ Channel	52	13	11
10	Adenosine Transporter	50	3.01	8.8
10	Dopamine Transporter (DAT)	65	3.75	4.72
10	Norepinephrine Transporter (NET)	55	5.71	5.76

According to the data in Table 1, suzetrigine binds significantly to five different off-target receptors or transporters. However, only two of the these, the dopamine transporter (DAT) and NET are known to be associated with abuse liability. That being said, suzetrigine has low affinity for both of these transporters, 3.75 µM for DAT and 5.71 µM for NET, coupled with a high IC 50, 4.72 µM for DAT and 5.76 µM for NET. As a result, it is unlikely that clinically relevant doses are achieved in the CNS to produce pharmacodynamic effects.

8. Study # TW04-0012354-Q02 was conducted to assess the cellular activity of M6-SUZ at specific receptors or transporters. According to this study, M6-SUZ was only found to bind to, and have activity at, the progesterone receptor (K_i = 3.3 µM, IC_{50} = 3.91 µM). The progesterone receptor is not known for having abuse liability and is therefore not a concern for abuse related purposes.

9. Study # 100064117 was conducted to assess the cellular activity of M6-SUZ at specific receptors or transporters. According to this study, M6-SUZ was found to bind to, and have activity at, the orexin 1 receptor (IC_{50} = 2.7 µM). Dual orexin receptor antagonists are currently associated with having a potential for abuse and are controlled in schedule IV under the CSA. However, the high concentration necessary for efficacy at this receptor are not clinically relevant, especially when considering the high protein binding (>98%) of suzetrigine in the CNS (Study # P298).

10. Study # 100063774 was conducted to determine the binding affinity and activity of suzetrigine and M6-SUZ

a. Suzetrigine – bound significantly to the $GABA_A$ gated chloride channel (K_i = 13 µM and IC_{50} = 11 µM).
b. M6-SUZ – bound significantly to the glucocorticoid receptor (K_i = 4.9 µM and IC_{50} = 2.5 µM) and to the orexin 1 receptor (K_i = 2.0 µM and IC_{50} = 1.8 µM).

2.2 Nonclinical Absorption, Distribution, Metabolism, Elimination (ADME)

Absorption

Suzetrigine is highly orally bioavailable in rats and non-human primates. As a result, these species were used in nonclinical safety and behavioral studies, some of which are outlined below. The pharmacokinetics of single oral doses of suzetrigine and its major circulating human and non-human primate metabolite, SUZ6, are presented in Tables 2 through 6 below.

Distribution

Study # C20089 was a mass balance study conducted to assess the tissue distribution of ^{14}C-suzetrigine in male rats after oral administration (10 mg/kg). Suzetrigine was widely distributed within 2-4 hours after dosing and was eliminated from the tissues within 72 to 169 hours. The whole brain radioactivity PK parameters from this study were: C_{max} of 0.856 µg equiv/g, t_{max} of 1 hour, and half-life of 2.1 hours. These data indicate that suzetrigine does penetrate the blood brain barrier and enter the CNS within one hour of oral dosing.

The Sponsor conducted Study # P298 to assess the in vitro binding of suzetrigine and M6-SUZ to proteins in monkey plasma, cerebral spinal fluid (CSF), brain, spinal cord, and dorsal root ganglion. This study determined the amount of free drug and metabolite after 1 µM was incubated in each fluid. The average suzetrigine free fraction in monkey plasma, CSF, brain, spinal cord, and DRG was 0.0141, 0.967, 0.00548, 0.00435 and 0.00397 respectively. The average M6-SUZ free fraction in monkey plasma, CSF, brain, spinal cord, and DRG was 0.0550, 0.840, 0.0144, 0.00542 and 0.0110 respectively. These data indicate that suzetrigine and M6-SUZ protein binding in monkey brain, spinal cord and DRG was higher (≥99% and ≥98%, respectively) than that of CSF which was low (≤4% and ≤16%, respectively). These data determined that although suzetrigine does penetrate the blood brain barrier, much of it appears to be protein bound.

Metabolism

The metabolism of ^{14}C-SUZ in rats was assessed in plasma, urine, bile, and feces following single oral administration of drug at 10 mg/kg or IV administration at 3 mg/kg. In rats, the majority of suzetrigine was metabolized to M3-SUZ which was excreted in the feces through oxidative metabolism (Study # Q262).

Since rats did not produce the M6-SUZ metabolite to the same extent as humans, non-human primate metabolism studies were also carried out (Study #s S001 and 8471426). The metabolic profiles of ^{14}C-SUZ in plasma, bile, feces, and urine following single oral administration of 15 mg/kg (100 µCi/kg) or IV administration of 2.5 mg/kg (100 µCi/kg) $_{14}$C-SUZ to male monkeys were characterized. Metabolite

profiling by LC-radioactivity detection showed that SUZ, M6-SUZ, and M12-SUZ accounted for 36.1%, 27.6% and 14.0% of the total radioactive peak area in plasma upon a single oral administration. Similar to rats, the major pathway of metabolic clearance was through oxidative metabolism.

Excretion

Although it differs to varying degrees rats, monkeys, and humans excrete metabolized suzetrigine mainly through feces and then urine.

2.3 Animal Behavioral Studies

CNS behavioral effects

The Applicant conducted Study # VRT-1737548-TX-012 to assess the toxicity and toxicokinetic effects of suzetrigine in male and female cynomolgus monkeys. A functional observational battery (FOB) was also conducted as part of this study to assess the CNS effects of suzetrigine. Animals were administered single oral doses of suzetrigine at doses of 0, 20, 50, or 100 mg/kg/day for a total of 28-days. According to the study report, there were no observations related to suzetrigine that were related to body weight, ophthalmoscopic, electrocardiographic, functional observational battery examinations, hematology, coagulation, clinical chemistry, urinalysis, urine chemistry, mean terminal body weights, organ weights, macroscopic or microscopic pathology parameters from males or females treated at doses up to 100 mg/kg/day.

The FOB for this study was conducted on day-2 and assessed CNS mediated effects such as activity level, salivation, tremors, convulsions, stereotypic behavior, pupil response, response to stimuli, ataxia, and more. According to the data, there were no statistically relevant changes in the parameters measured in the FOB. Based on these results, it was concluded that the no-observed-effect-level (NOEL) for acute effects on the nervous system was the high dose of 100 mg/kg/day and the no-observed-adverse-effect-level (NOAEL) for 28 days of suzetrigine administration was 100 mg/kg/day.

The PK parameters of suzetrigine and M6-SUZ in cynomolgus monkeys are presented in Table 2 and Table 3 below. According to the data, the mean C_{max} and exposure of suzetrigine and its M6 metabolite increased in an approximately dose proportionate manner. The exposure of the M6 metabolite was several fold higher than that of the parent, depending on dose. This could play an important role in the overall clinical activity of suzetrigine, as the M6 metabolite has a very similar in vitro binding and activity profile as indicated in section 2.1 of this review.

Table 2: PK Parameters of Suzetrigine After Single Oral Doses in Cynomolgus Monkeys

Dose	**C_{max} (µg/mL)**	**T_{max} (hr)**	**AUC_{0-24} (hr·µg/mL)**
20	1.27	2	9.12
50	3.36	4	27.5
100	5.35	4	53.9

Table 3: PK Parameters of M6-SUZ After Single Oral Doses Suzetrigine in Cynomolgus Monkeys

Dose	**C_{max} (µg/mL)**	**T_{max} (hr)**	**AUC_{0-24} (hr·µg/mL)**
20	2.43	4	22
50	6.58	4	69.2
100	10.8	8	127

Repeat Dose Toxicity Studies

The Applicant assessed the toxicity of suzetrigine in eight repeat dose toxicity studies, four of these studies were conducted on Sprague Dawley rats and four were on Cynomolgus monkeys. As indicated in Table 4, rats were orally (i.e., gavage) administered suzetrigine with daily doses ranging from 5 to 1000 mg/kg for females and 150 to 1000 mg/kg for males. These studies include assessments of drug induced behavioral and clinical effects, some of which may be a signal of abuse liability (e.g., locomotor activation, sedation, scratching, digging, and straub tail). The results of these studies indicated that there were no abuse related behaviors or clinical effects observed in rats. Since rats do not metabolize suzetrigine in a similar manner as humans, nonhuman primates were also used in order to investigate the effects of suzetrigine and its major circulating active metabolite, M6-SUZ.

Suzetrigine was orally administered to cynomolgus monkeys at doses ranging from 10 to 150 mg/kg. Study # VRT-17377548-TX-012 contained a FOB which is discussed in the *CNS Behavioral Effects* section above. The other studies included assessments of drug induced behavioral and clinical effects, some of which may be a signal of abuse liability (e.g., locomotor activation, sedation, scratching, digging, and straub tail). The results of these studies indicated that there were no abuse related behaviors or clinical effects observed in monkeys.

Table 4: List of Repeat Dose Toxicity Studies Conducted for Suzetrigine

Study #	**Species**	**Dose** (mg/kg/day)	**Administration**	**Length of Study**	**Behaviors**
VRT-1737548-TX-003	SD rat (female)	30, 100, 300	oral gavage	7-days	no unusual behaviors. NOAEL = 300 mg/kg
VRT-1737548-TX-011	SD rat	F: 10, 30, 300 M: 200, 600, 1000	oral gavage	28-days	no unusual behaviors. NOAEL = 300 mg/kg for female and 1000 mg/kg for male rats.
VX-548-TX-001	SD rat	F: 10, 100, 1000 M: 200, 600, 1000	oral gavage	91-days	no unusual behaviors. NOAEL = 10 mg/kg for female and 1000 mg/kg for male rats.
VX-548-TX-010	SD rat	F: 5, 10, 50 M: 150, 400, 1000	oral gavage	26-week with 13-week recovery	no unusual behaviors. NOAEL = 10 mg/kg for female and 1000 mg/kg for male rats.
VRT-1737548-TX-006	Cynomolgus monkey	10, 30, 100	oral gavage	9-days (3-days/dose)	no unusual behaviors.

VRT-1737548-TX-012 + FOB	Cynomolgus monkey	20, 50, 100	oral gavage	28-days	no CNS mediated behaviors. NOAEL = 100 mg/kg
VX-548-TX-002	Cynomolgus monkey	20, 50, 150	oral gavage	13-weeks	no unusual behaviors. NOAEL = 150 mg/kg
VX-548-TX-011	Cynomolgus monkey	25, 50, 150	oral gavage	39-weeks with a 6-week recovery	no unusual behaviors. NOAEL = 150 mg/kg

NOAEL = no observable adverse effect level; SD = Sprague-Dawley

Conclusion

The Applicant conducted several studies in both rats and nonhuman primates that assessed behaviors after single and multiple oral doses of suzetrigine. The dose ranges used in these studies produced C_{max} levels of suzetrigine (100 mg/kg) in monkeys that were approximately 10-fold higher than that produced by the highest proposed therapeutic dose in humans (100 mg), and an exposure (AUC) approximately 3-fold higher. Under the studies and conditions tested, the animals did not elicit any CNS mediated behaviors that are indicative of abuse potential.

2.4 Tolerance and Physical Dependence Studies in Animals

The Sponsor conducted Study # VX-548-TX-020 to assess the physical dependence liability of suzetrigine in female Sprague Dawley rats after 30-days of repeated administration. Rats received single oral doses of 30, 300, and 1000 mg/kg/day suzetrigine for 30-consecutive days, plus one control group of animals that received placebo and a positive control group that received morphine. Morphine was administered in escalating doses over the first 2 weeks starting at 20 mg/kg/dose (40 mg/kg/day) and then fixed doses of morphine (150 mg/kg/dose; 300 mg/kg/day) were administered over the last 2 weeks of the study. Administration of drug or placebo was ceased on day-30 and all animals were monitored for signs of a withdrawal syndrome during the drug free period.

The placebo control group did not produce any signs or signals of a withdrawal syndrome. The positive control group (i.e., morphine) expressed a mild to moderate withdrawal syndrome indicative of opioid withdrawal. There were no physiological or behavioral signs of a withdrawal syndrome following abrupt discontinuation of any dose of suzetrigine.

The doses animals received in this study produced a C_{max} range from 7- to 62-fold that produced in humans by the highest therapeutic dose (Table 7). However, rats do not produce the M6-SUZ metabolite to the same extent as humans and nonhuman primates. This resulted in a lower concentration of the metabolite in the rat and may lead to a decrease in the overall effect of suzetrigine. That being said, the concentrations used in this study were 2- to 6.7-fold higher than that produced in humans by the highest therapeutic dose (Table 7) and therefore well within recommended testing parameters for the purposes of behavioral testing.

Table 5: PK Parameters of Single Oral Doses of Suzetrigine in Rats

Dose	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (hr·µg/mL)
30	3.64	24	54.5
300	10.3	12	163
1000	32.5	12	524

Table 6: PK Parameters of M6-SUZ After Single Oral Doses of Suzetrigine in Rats

Dose	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (hr·µg/mL)
30	0.78	24	6.62
300	1.14	12	15.4
1000	2.36	12	29

3. Clinical Studies

3.1 Clinical Pharmacokinetics

The clinical pharmacokinetics of a substance play an important role in its pharmacodynamic effects and abuse potential. This section focuses solely on those aspects of clinical pharmacokinetic parameters that are relevant to abuse liability. A complete review of the clinical pharmacokinetics of suzetrigine was conducted by the clinical pharmacology reviewers. This section will focus on the clinical PK of suzetrigine as it relates to single oral low and high doses in healthy adult subjects and whether the PK was influenced by other factors such as the administration of high- or low-fat diets.

The Sponsor conducted several clinical PK studies: 11 in healthy subjects, two in special populations (e.g., renal impairment), and four studies in subjects with acute pain (Summary of Clinical Pharmacology, Section 1.3, Table 3). The currently proposed dosing regimen for acute pain is 100 mg for the first dose (loading dose), followed every 12-hours with a 50 mg dose (100 mg/50 mg q12h). In humans, suzetrigine is oxidatively metabolized by CYP3A into M6-SUZ which is the only major active circulating metabolite. Exposure of M6-SUZ is approximately 3-fold higher than that of suzetrigine, however, it is 3.7-fold less potent at $Na_V1.8$. According to the Applicant, the PK parameters of suzetrigine were not significantly affected by mild hepatic impairment or moderate renal impairment.

The Applicant combined data from multiple phase 1 clinical studies (study #s 001, 005, and 011) to assess the PK parameters of single oral doses of suzetrigine ranging from 7.5 to 395 mg (Summary of Clinical Pharmacology Studies, Section 3.1.5.1.2, Table 8). These studies measured the PK parameters of suzetrigine and the M6-SUZ active metabolite. According to the data presented in Table 7 and Table 8, single oral doses of suzetrigine in the fasted state increased drug exposure ($AUC_{0-\infty}$) in a dose proportional manner up to doses of 115 mg. However, the C_{max} of suzetrigine and M6-SUZ increased less than dose proportionally across all of the tested doses.

Table 7: PK Parameters of Suzetrigine After Single Oral Doses Were Administered to Fasted Healthy Adult Subjects

Study	Dose (mg)	Analyte	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg·h/mL)	t_{max} (h)	t1/2 (h)
001	7.5	SUZ	0.66	0.99	1	47.6
	22.5	SUZ	0.19	3.29	1.03	48.1
	45	SUZ	0.29	6.7	1.26	43.5
	65	SUZ	0.4	8.6	2	43.8
005	90	SUZ	0.47	12.4	2.75	54.9
011	100	SUZ	0.52	16.5	3	55.3
005	115	SUZ	0.62	19.7	2.5	59.8
005	395	SUZ	1.11	31.1	3.5	35.8

Table 8: PK Parameters of M6-SUZ After Single Oral Doses of Suzetrigine Were Administered to Fasted Healthy Adult Subjects

Study	Dose (mg)	Analyte	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg·h/mL)	t_{max} (h)	t1/2 (h)
001	7.5	M6-SUZ	0.03	2.86	3.25	62.6
	22.5	M6-SUZ	0.11	9.92	2.5	58.6
	45	M6-SUZ	0.22	20.9	5.04	53.2
	65	M6-SUZ	0.26	25	5.5	52.8
005	90	M6-SUZ	0.32	31.1	5	59.5
011	100	M6-SUZ	0.35	38.9	10	62.6
005	115	M6-SUZ	0.37	50.7	7	76.7
005	395	M6-SUZ	1.05	105	24	44.1

The PK parameters of the proposed dosing strategy (100mg/50mg q12h) for suzetrigine were evaluated in phase 2 studies (Study #s 101, 102, 104, and 105) and are summarized in Module 2.7.2, Summary of Clinical Pharmacology Studies, Table 12, on page 50. These studies were conducted in subjects with acute pain and indicated that this dosing regimen produces PK parameters that are not significantly different from those of the single oral 100 mg dosing of suzetrigine presented in Table 7 and Table 8 above, even after 2-days of dosing.

The effect of food as a high-fat meal on the PK parameters of suzetrigine were assessed in Study # 011. This study determined that food does not have a significant effect on the C_{max} or AUC of suzetrigine. However, the rate of absorption of suzetrigine was significantly affected as the T_{max} increased from 3 hours to 5 hours with a high fat meal compared to fasted conditions. With regards to abuse liability, a drug with an extended T_{max} and a similar C_{max} typically correlates with a reduction in abuse liability as it decreases the exposure of the drug at the earlier time points, as is the case here. As a result, administration of suzetrigine with food is not expected to increase the overall abuse liability of the drug.

3.2 Human Abuse Potential Studies

The Applicant was not required to conduct a human abuse potential study to assess the abuse liability of suzetrigine.

3.3 Adverse Event Profile Through all Phases of Development

Abuse-Related Adverse Events in Clinical Studies Conducted by the Applicant

The Applicant analyzed abuse related adverse events from all clinical studies. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and MedDRA system organ class (SOC) and preferred term (PT). The analysis was performed based on a customized MEdDRA Query comprising approximately 200 screening PTs. The assessment included 14 phase 1 studies with a total of 590 subjects who received suzetrigine, four phase 2 studies with a total of 174 subjects who received suzetrigine and, two phase 3 studies with a total of 874 subjects that received suzetrigine. Overall, the studies did not produce a concern regarding the type, or number of PTs, and these data do not indicate that suzetrigine has a potential for abuse or physical dependence.

Phase 1 Studies

The Sponsor conducted 14 Phase 1 studies which are listed in Table 9. These studies were conducted in healthy adult (generally 18 to 55) female and male subjects who were given either single or multiple doses of suzetrigine. The doses of suzetrigine ranged from 5 mg to 395 mg in single and multiple dose regimens, some of which also used different loading doses as the Applicant investigated an appropriate efficacious dose. In some of the studies, other drugs were administered in order to determine drug-drug interactions including: midazolam, levonorgestrel and ethinyl estradiol tablets, itraconazole, digoxin, omeprazole, rifampin, and moxifloxacin. These drugs did not alter the treatment related abuse related adverse events reported in phase 1 studies. An analysis of the treatment emergent adverse events related to abuse from the following studies is presented below.

Table 9: Listing of Phase 1 Studies Analyzed for Abuse or Dependence Related Treatment Emergent Adverse Events

Study ID (Period)	Phase	Design	# of Subjects	Drug dose range	Population	Single or multiple dose
VX19-548-001	1	Randomized, double-blind, placebo controlled	40	7.5, 22.5, 45, or 65 mg	Healthy adults	Single
VX20-548-002	1	Randomized, double-blind, placebo controlled, 2-parts	36	Part 1: 5, 15, or 65 mg qd5 Part 2: 45 mg qd or 40 mg	Healthy adults	Single
VX21-548-004	1	Open label, fixed sequence, DDI	22/23	70 mg	Healthy females	Multiple 16-days

Study ID (Period)	Phase	Design	# of Subjects	Drug dose range	Population	Single or multiple dose
VX21-548-005	1	Randomized, double-blind, placebo controlled	Part 1: 50 Part 2: 30	Part 1: 90, 115, 171, 256, 395 mg Part 2: 90 qd, 115/57.5 mg q12h, 178 mg	Healthy adults	SAD and MAD
VX21-548-006	1	Open label, mass balance	8	20 mg or 80 mg	Healthy adults	Single
VX21-548-007	1	Open label, matched, parallel group	37	50 mg q12h 20 mg q12h	Healthy Adults	Multiple 14-days
VX21-548-008	1	Open label, 2-period, fixed sequence, crossover, DDI	37	50 mg q12h	Healthy Adults	Multiple 18-days
VX21-548-009	1	Randomized, double blind, placebo and active controlled, parallel with nested crossover	36+18=54	200 mg	Healthy adults	Multiple 7-days
VX21-548-010	1	Open label, 2-period, fixed sequence, crossover	37	50 mg q12h	Healthy adults	Multiple 18-days
VX21-548-011	1	Randomized, open label, 3-period cross-over	24	Single doses of 100 mg SUZ	Healthy adults	Single
VX22-548-013	1	Open label, fixed sequence, DDI	15+16=31	100 mg	Healthy adults	Single
VX22-548-014	1	Open label, matched, parallel group	38	50, 100 mg	Healthy adults	Single
VX22-548-016	1	Randomized, open label, 3-period cross-over	24+25+24 = 73	Single doses of 100 mg SUZ	Healthy adults	Single
VX23-548-017	1	Open Label, randomized, crossover	72	70 mg	Healthy Subjects	Single

According to Table 10, the most prevalent abuse related adverse events in phase 1 studies were Dizziness 14 (2.37%), Somnolence 7 (1.19%), and Depressed mood 3 (0.51%). These adverse events are common and are not concerning regarding the abuse liability of suzetrigine.

A more concerning abuse related AE was reported in study # VX20-548-002. A 34-year-old white male subject that received a 15 mg dose of suzetrigine reported euphoric mood. The Applicant determined that this was possibly related to the study drug and the subject fully recovered from the reported effect. The report of this preferred term is considered an anomaly since there is only one report of euphoric mood at a low dose of 15 mg out of 590 individuals who took the drug in phase 1 studies.

Table 10: Abuse Related Adverse Events Reported in Phase 1 Studies, # (%)

Preferred Term	N (%)
Aggression	1 (0.17)
Brain fog	1 (0.17)
Depressed mood	3 (0.51)
Dizziness	14 (2.37)
Euphoric mood	1 (0.17)
Feeling of relaxation	1 (0.17)
Illusion	1 (0.17)
Irritability	2 (0.34)
Lethargy	2 (0.34)
Somnolence	7 (1.19)

Phase 2 and 3 Studies

The Applicant conducted four phase 2 studies and three phase 3 studies. Generally, the phase 2 studies were safety and efficacy studies conducted in a randomized, double-blind, placebo controlled, multi-dose design that were 48-hours in duration. The phase 3 studies were also safety and efficacy studies that were conducted using a randomized, double-blind, placebo and positive control design. The subjects in these studies suffered from moderate to severe pain from one of the following issues depending on the study: bunionectomy, abdominoplasty, diabetic peripheral neuropathy, painful lumbosacral radiculopathy, or after an ambulatory surgical procedure. The number of subjects that received treatments in phase 2 and phase 3 studies were: placebo = 574, hydrocodone/acetaminophen (HB/APAP dosed orally 5 mg/ 325 mg q6h) = 1015, and suzetrigine = 1010. The abuse related AEs from phase 2 and phase 3 studies were analyzed and pooled into Table 11. The highest number of abuse related AEs reported in these studies for suzetrigine were dizziness 41 (4.1%) and somnolence 2 (0.2%). As can be seen in Table 11, these numbers are similar to the placebo control group and to the HB/APAP group supporting that suzetrigine did not produce a concerning number of abuse related AEs in these studies.

Table 11: Pooled Abuse Related Adverse Events Reported in Phase 2 and Phase 3 Studies, # (%)

Preferred Term	Placebo	HB/APAP	Suzetrigine
Dizziness	43 (7.5)	56 (5.5)	41 (4.1)
Somnolence	2 (0.3)	2 (0.2)	2 (0.2)
Dissociation	0	0	1 (0.1)
Feeling Jittery	0	0	1 (0.1)
Brain Fog	0	1 (0.1)	0

Adverse Events from Drug Discontinuation

The measurement of TEAEs after drug discontinuation can be an indication as to whether a drug produced a withdrawal syndrome and may produce physical dependence. In this case, the Applicant monitored for TEAEs that worsened or started 48 hours after the first dose of study drug (for subjects who completed treatment) or after the decision to stop dosing (for subject discontinuation).

Phase 1 Studies

Out of 14 phase 1 studies there were 418 subjects who were monitored for signs of dependence post administration of suzetrigine. Understanding that the majority of these subjects received single oral doses of drug, begs the question of the relevance of this assessment understanding that the effects of physical dependence are typically seen after discontinuation of repeated doses. As a result, the phase 1 studies that administered multiple days of suzetrigine to healthy adult subjects were analyzed as well. The pooled data containing all AEs related to dependence from phase 1 studies are presented in Table 12.

Table 12: Pooled Assessment of Adverse Events from Phase 1 Studies After Treatment Discontinuation (# (%))

Preferred Term	**# (%)**
Dizziness	5 (1.2)
Somnolence	3 (0.72)
Depressed mood	1 (0.24)
Lethargy	2 (0.48)

The phase 1 studies that used multiple days of oral dosing of suzetrigine were: VX20-548-002 (14-days), VX21-548-009 (7-days), and VX21-548-010 (18-days) and had a combined number of 109 healthy subjects that received suzetrigine. The AEs related to dependence post administration of suzetrigine from these three phase 1 studies were dizziness 2 (1.83%) and depressed mood 1 (0.92%).

Phase 2 and 3 Studies

According to the Applicant, all AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). Similar to above, the number of subjects that received treatments in phase 2 and phase 3 studies were: placebo = 574, hydrocodone/acetaminophen (HB/APAP dosed orally 5 mg/ 325 mg q6h) = 1015, and suzetrigine = 1010. Phase 2 studies 101 and 102 were conducted over 48 hours, and studies 103 and 109 were conducted over 12 weeks. Phase 3 studies 104 and 105 were conducted over 48 hours and study 107 was up to 14-days. Notably, AEs from studies 103 and 109 were not separated out because those study reports were not provided by the Sponsor as they are part of another development program. The phase 2 studies had variable dosing regimens and the phase 3 studies used the proposed therapeutic dosing regimen of 100 mg/50 mg q12h suzetrigine. The dependence related AEs from phase 2 and phase 3 studies were analyzed and pooled into Table 13 below. These data clearly demonstrate that suzetrigine produced a similar dependence AE profile to placebo under the tested conditions. If suzetrigine is used for chronic dosing, or under different dosing conditions, the data would need to be reevaluated for that dosing regimen.

Table 13: Pooled Assessment of Adverse Events from Phase 2 and Phase 3 Studies After Treatment Discontinuation, (# (%))

Preferred Term	Placebo	HB/APAP	Suzetrigine
Dizziness	13 (2.3)	8 (0.8)	10 (1.0)
Somnolence	1 (0.2)	0	0

Conclusion

In conclusion, the abuse and dependence related TEAEs from all phase 1, 2, and 3 studies that were reported in clinical studies conducted by the Applicant suggest that suzetrigine did not produce abuse or dependence related affects under the tested conditions. Suzetrigine was administered to a total of 1,600 subjects at doses between 5 mg and 396 mg in both single and multiple oral dosing regimens. CSS does recommend that TEAEs be monitored for dependence if suzetrigine is investigated for chronic use, cessation of dosing after a long dosing period my produce a withdrawal syndrome compared to the short timeframes used in the clinical studies under this NDA.

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

There were no reports of misuse, abuse, or diversion of suzetrigine in clinical trials. However, there was one report of accidental overdose that led to discontinuation from a study. According to the case narrative, the subject had neck pain (acute cervical pain due to fall). On (b) (6) the subject was enrolled and received the first dose of suzetrigine 100 mg/50 mg q12h at 11:45. On the same day (Study Day 1), the subject had an AE of mild accidental overdose. The subject took two tablets of SUZ for 11 succeeding doses from (b) (6) at 22:47 through (b) (6) at 00:42. The overdose was discovered at the subject's clinic visit on (b) (6) On the same day, the subject's vital signs included BP 158/85 mm Hg, other vital signs were within normal limits.

4. Regulatory Issues and Assessment

There are no regulatory issues regarding the abuse potential of suzetrigine. Suzetrigine does not have abuse liability and will not be required to be controlled under the CSA.

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Clinical Inspection Summary (CIS)

Date	11/27/2024
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	James Yeh, M.D., Medical Officer Tanya Brescia-Oddo, M.D., Team Leader Rigoberto Roca, M.D., Division Director Rita Joshi, Regulatory Project Manager Division of Anesthesiology, Addiction, and Pain (DAAP) Office of Neuroscience, Office of New Drugs
Application	NDA 219209
Applicant	VERTEX PHARMACEUTICALS, INC.
Drug	Suzetrigine (Journavx®)
NME or Original NDA	Yes
Proposed Indication	Management of moderate to severe acute pain
Consult Date	07/15/2024
CIS Goal Date	12/12/2024
Review Clock	Priority Review
Action Goal Date	01/30/2025
PDUFA Due Date	01/30/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators (CIs) were inspected for each of the two pivotal Studies VX22-548-104 and VX22-548-105 in support of this original NDA review: (1) Dr. Louise Taber (Phoenix, AZ); (2) Dr. Todd Bertoch (Salt Lake City, UT); and (3) Dr. Jessica McCoun (Atlanta, GA). The data from the inspected CI sites appear to be acceptable in support of the proposed indication according to the inspection reports.

II. BACKGROUND

Vertex Pharmaceuticals, Inc. (Vertex) seeks the marketing approval of suzetrigine in the United States (US) for the management of moderate to severe acute pain in adults. Suzetrigine was granted Fast Track (2020) and Breakthrough Therapy (2022) designations.

Currently available options for pain management are often limited by poor efficacy and high rates of adverse events (AEs). Nonsteroidal anti-inflammatory drugs (NSAIDs) pose gastrointestinal (including hepatic), hematologic, and renal toxicity risks. Analgesia using opioids is limited by serious safety concerns, including (epidemic) abuse potential.

The voltage-gated sodium channel (VGSC) in the neuron has been shown to be important in pain signaling. Inhibitors of VGSC are not (expected to be) associated with the side effects often seen with opioids and other commonly used analgesics. Suzetrigine (VX-548, study code name) is a VGSC inhibitor identified in early clinical studies as a new promising analgesic. This original NDA 219209 is supported by two pivotal studies identified for on-site audit at Good Clinical Practice (GCP) inspections, Studies VX22-548-104 and VX22-548-105. The major study features examined for GCP-compliant protocol adherence are outlined below for each study.

Study VX22-548-104: A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Suzetrigine for Acute Pain After a Bunionectomy

This randomized, double-blind, placebo-controlled study was conducted over 14 months (2022-23) in 1075 subjects randomized at 21 sites in the US. The primary study objective was to evaluate the efficacy of suzetrigine in managing acute post-operative pain following bunionectomy.

Subject Selection

- Adults (18- 80 years old) scheduled for unilateral bunionectomy with distal first metatarsal osteotomy and internal fixation under regional anesthesia (Mayo and popliteal sciatic block)
- Moderate or severe pain on Verbal Rating Scale (VRS) AND Numeric Pain Rating Scale (NPRS) score ≥ 4 following bunionectomy, within 9 hours after reversing the popliteal sciatic nerve block
- *Exclusion for:* prior bunionectomy or other foot surgery on the index foot; body mass index outside 18 to 40 kg/m2 range; and any condition that may complicate study participation or confound the study results (CI judgment)

Treatment Groups and Regimen

A popliteal sciatic nerve block was induced after surgery by local (continuous) intravenous (IV) anesthetic infusion and maintained until the eligible subject was randomized into one of three treatment groups (2/2/1 ratio), stratified by CI site and baseline NPRS score (< 8 or ≥ 8):

- *Group 1: Test medication:* oral suzetrigine, 100 mg first dose then 50 mg every 12 hours (Q12H) alternating with placebo (overall suzetrigine/placebo dosing every 6 hours (Q6H)
- *Group 2: Opioid active control:* oral hydrocodone bitartrate in combination with acetaminophen (HB/APAP), 5/325 mg Q6H
- *Group 3: Placebo control:* placebo matching in appearance, given orally Q6H

The study medication was to be administered within 25 minutes after randomization, and thereafter within 45 minutes of the scheduled dose. Non-study analgesics given were:

- *Rescue medication:* Ibuprofen (400 mg, oral) was permitted Q6H as needed for rescue for pain relief, starting any time after the first dose of the study medication through 48 hours thereafter.
- *Following nerve block removal:* All medications with analgesic properties were prohibited for 5 half-lives or two days (whichever is longer), except as permitted for peri-operative pain control or ibuprofen rescue. Ice packs were not permitted.

Subjects reported NPRS at baseline, for 48 hours after the first dose of the study medication, and immediately before any ibuprofen rescue dosing.

Study Procedures, Assessments, and Analyses

- Primary Endpoint (suzetrigine relative to placebo): time-weighted Sum of Pain Intensity Difference (SPID) measured using NPRS from 0 to 48 hours (SPID-48)
- Key Secondary Endpoints: (1) SPID-48 for suzetrigine relative to HB/APAP; (2) time to ≥ 2-point reduction in NPRS from baseline relative to placebo

Study VX22-548-105: A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Suzetrigine for Acute Pain After an Abdominoplasty

This randomized, double-blinded, placebo-controlled study was conducted over 11 months (concurrently with the bunionectomy study, 2022-23) in 1118 subjects enrolled and randomized at 12 CI sites in the US. The primary study objective was to evaluate the efficacy of suzetrigine in managing acute post-operative pain following abdominoplasty.

The overall study design was nearly identical to that of the bunionectomy study (VX22-548-104), with the following major differences in subject selection inherent to the population to be studied.

Subject Selection

- Subjects scheduled for standard *abdominoplasty* that includes a horizontal incision, umbilical dissection and relocation, and rectus fascia plication
- *Exclusion for:* expected procedure duration ≤ 3 hours; prior abdominoplasty; or vertical supra-umbilical incision or collateral procedures (e.g., liposuction)

III. INSPECTION RESULTS

1. Louise Taber, M.D.

15601 North 28th Avenue, Suite 100
Phoenix, AZ 85053

Inspection Dates: 09/23 – 26, 2024

- Protocol VX22-548-104, Site 059: 137 subjects were screened, 56 were enrolled, and 42 completed the study (14 withdrew/discontinued; lack of efficacy).
- Protocol VX22-548-105, Site 059: 162 subjects were screened, 80 were enrolled, and 53 completed the study (26 withdrew/discontinued; lack of efficacy; 1 lost to follow up).

Protocols VX22-548-104 and VX22-548-105

The study audit included protocol adherence, Institutional Review Board (IRB) oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for efficacy evaluations and AE monitoring. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, protocol deviations (PDs), and use of non-study (concomitant) medications.

No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

2. Jessica McCoun, M.D.

501 Fairburn Road, South West
Atlanta, GA 30331

Inspection Dates: 09/30 - 10/04, 2024

- Protocol VX22-548-104, Site 059: 110 subjects were screened, 66 were enrolled, and 59 completed the study (6 withdrew/discontinued for lack of efficacy; 1 lost to follow up).
- Protocol VX22-548-105, Site 059: 188 subjects were screened, 152 were enrolled, and 139 completed the study (13 withdrew/discontinued; lack of efficacy).

Protocols VX22-548-104 and VX22-548-105

The study audit included protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for efficacy evaluations and AE monitoring. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study (concomitant) medications.

No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

3. Todd Bertoch, M.D.

650 East 4500 South
Salt Lake City, UT 84107

Inspection Dates: 09/23 – 27, 2024

- Protocol VX22-548-104, Site 018: 265 subjects were screened, 136 were enrolled, and all 136 completed the study.

  GCP deficiency observation: Enrollment of one subject on buprenorphine (partial opioid agonist), in violation of Exclusion Criterion 14 which prohibited chronic opioid use within 30 days of enrollment (isolated finding)

- Protocol VX22-548-105, Site 018: 307 subjects were screened, 190 were enrolled, and 190 completed the study.

  GCP deficiency observation: Enrollment of one subject with QTcF of 456 msec on baseline electrocardiogram (ECG), in violation of Exclusion Criterion 29 which specified exclusion for QTcF > 450 msec (non-exclusion override not documented, isolated finding; the subject's safety did not appear to have been impacted)

Protocols VX22-548-104 and VX22-548-105

The study audit included protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for efficacy evaluations and AE reporting. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study (concomitant) medications.

The observed GCP deficiencies (failing to meet protocol-specified exclusion criteria) appeared minor, isolated, and unlikely to have an impact on data quality or subject safety. Significant GCP deficiencies were otherwise not observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

{See appended electronic signature page}

John Lee, M.D., Primary Reviewer
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Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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DAAP / Team Leader / Tanya Brescia-Oddo
DAAP / Clinical Reviewer / James Yeh
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OSI / DCCE / GCPAB Program Analyst / Loreto-Corazon Lim

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LABEL AND LABELING REVIEW

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

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

Date of This Review:	October 21, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 219209
Product Name, Dosage Form, and Strength:	Journavx (suzetrigine) tablet, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Vertex Pharmaceuticals Incorporated (Vertex)
FDA Received Date:	March 28, 2024, May 30, 2024 and July 23, 2024
TTT ID #:	2024-9749
DMEPA 1 Safety Evaluator:	Susan Hakeem, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Journavx (suzetrigine) tablet, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Journavx Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Journavx (suzetrigine) is a proposed 505(b)(1) application submitted on March 28, 2024.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219209.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Journavx Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) in Section 4 and for Vertex Pharmaceuticals Incorporated (Vertex) in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented in the *Dosage and Administration* section, the dosing instructions lack clarity on the number of hours between the first and second doses.	Failure to provide clarity on the number of hours between the first and second doses may result in dosing errors.	We recommend providing clarity on the number of hours between the first and second doses. For example, revise to: (b) (4) See *Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format (January 2023).*[a]
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosing instructions lack clarity on the number of hours between the first and second doses.	Failure to provide clarity on the number of hours between the first and second doses may result in dosing errors.	We recommend providing clarity on the number of hours between the first and second doses. For example, revise to: (b) (4) See *Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and*

[a] Draft Guidance for Industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2023). Available from: https://www.fda.gov/media/72142/download. When final, this guidance will represent FDA's current thinking on this topic.

Table 2. Identified Issues and Recommendations for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Biological Products-Content and Format (January 2023).[a]
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	A description of the dosage form is not provided (e.g., shape).	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(17)(iii).	Provide a description of identifying characteristics of the tablets (e.g., capsule-shaped) in accordance with 21 CFR 201.57(c)(17)(iii).
Patient Information			
1.	As currently presented in the *How should I take JOURNAVX?* section, the dosing instructions lack clarity on the number of hours between the first and second doses.	Failure to provide clarity on the number of hours between the first and second doses may result in dosing errors.	We recommend providing clarity on the number of hours between the first and second doses. For example, revise to: (b) (4)

5 RECOMMENDATIONS FOR VERTEX PHARMACEUTICALS INCORPORATED (VERTEX)

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (Vertex) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the format for the expiration date is not defined on the 30-count container label and 100-count container label and carton labeling.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (Vertex) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*[b]
2.	The propriety name is presented in different font colors.	We typically reserve highlighting a portion of the name as a strategy to mitigate name confusion.	We recommend you consider changing the font color of the proprietary name to appear in one color on the container labels, carton labeling, and sample carton and wallet.
3.	The placeholder for the 2-D matrix barcode portion of the product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-	Clarify the intended location of the 2-D matrix barcode. Additionally, ensure that the 2-D matrix barcode is not in close proximity to the other barcodes, (e.g., part number barcode) to enhance scannability.

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (Vertex) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	
Carton Labeling			
1.	As currently presented, the 100-count blister carton labeling states, "For in-institution use only."	For additional clarity.	Consider revising "For in-institution use only" to "For institutional use only".
Blister backing			
1.	As currently presented, (b) (4)	(b) (4)	We recommend removing the (b) (4) Additionally, please clarify if the 'MM' of the expiration date format, YYYY-MM, will be presented in all numerical characters.
Sample wallet			
1.	The sample wallet does not clearly indicate that the sample is intended to cover the "initial" 48 hours of treatment.	Dosing errors could occur, for example, inadvertently redosing at 2 tablets (100 mg) after initial start and in instances where the	We recommend including on the principal display panel of the sample wallet and wallet carton, a clarifying statement, for example:

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (Vertex)
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		patient has not missed two or more doses, if multiple samples are received by the patient.	"Sample covers initial 48 hours of treatment" Additionally, we recommend revising the statement, (b) (4) which is located on the inside of the wallet to "Sample covers initial 48 hours of treatment."
2.	As currently presented on the principal display panel, it is not immediately clear what the designated strength is per blister unit (i.e., 50 mg per tablet).	Failure to clearly express the product strength "50 mg per tablet" may lead to misinterpretation that all 5 tablets equal 50 mg.	We recommend revising the strength statement "50 mg" to state "50 mg per tablet" to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card.
3.	The dosing instructions lack clarity on the number of hours between the first and second doses.	Failure to provide clarity on the number of hours between the first and second doses may result in dosing errors.	We recommend providing clarity on the number of hours between the first and second doses. For example, revise to: (b) (4) Furthermore, because patients could receive more than one sample, we recommend revising the statement (b) (4) to "Sample covers initial 48 hours of treatment".
4.	As currently presented, the dose statement (b) (4)	The (b) (4) may lead to misinterpretation (b) (4)	We recommend revising the dose statement (b) (4) to "one 50 mg tablet" to avoid

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (Vertex) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	could be misinterpreted (b) (4)	(b) (4)	misinterpretation (b) (4) Additionally, although (b) (4) the statement, (b) (4) for consistency we also recommend removing (b) (4) (b) (4)
Sample Carton			
1.	As currently presented on the principal display panel, it is not immediately clear what the designated strength is per blister unit (i.e., 50 mg is per tablet).	Failure to clearly express the product strength "50 mg per tablet" may lead to misinterpretation that all 5 tablets equal 50 mg.	We recommend revising the strength statement "50 mg" to state "50 mg per tablet" to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Journavx received on March 28, 2024 from Vertex.

Table 4. Relevant Product Information for Journavx	
Initial Approval Date	N/A
Active Ingredient	suzetrigine
Indication	JOURNAVX is (b) (4) indicated for the treatment of moderate to severe acute pain in adults.
Dosage Form	tablet
Strength	50 mg
Route of Administration	Oral
Dose and Frequency	Two 50 mg tablets (100 mg) followed by one 50 mg tablet every 12 hours; maximum daily dose is 150 mg on day 1, followed by 100 mg per day, in divided doses, thereafter.
How Supplied	JOURNAVX (suzetrigine) tablets are supplied as blue, film-coated tablets containing 50 mg of suzetrigine. Each tablet is debossed with the characters "VX50" on one side and plain on the other, and is packaged as follows: • 30-count bottle NDC 51167-548-30 • 100-count bottle NDC 51167-548-31 • 100-count Hospital Unit Dose Carton (10 blister cards, each containing 10 tablets) NDC 51167-548-34 • 25-count Physician Sample Carton (5 wallets, each containing 5 tablets) NDC 5116-548-25
Storage	Store at 68°F – 77°F (20°C – 25°C); excursions permitted to 59°F – 86°F (15°C – 30°C) [see USP Controlled Room Temperature]
Container Closure	(b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Journavx labels and labeling submitted by Vertex Pharmaceuticals Incorporated (Vertex).

- Prescribing Information and Patient Information received on July 23, 2024, available from \\CDSESUB1\EVSPROD\nda219209\0013\m1\us\draft-labeling-text-suzetrigine-tc.pdf.
- Container labels received on May 30, 2024
- Carton labeling received on May 30, 2024
- Professional Sample Blistercards received on May 30, 2024
- Professional Sample Carton Labeling received on May 30, 2024

B.2 Container Labels and Carton Labeling Images

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

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219209
Submission Number	4
Submission Date	5/30/2024
Date Consult Received	6/6/2024
Drug Name	Suzetrigine (VX-548) tablets
Indication	Treatment of moderate to severe acute pain
Therapeutic Dose	100 mg loading dose followed by 50 mg q12h
Clinical Division	DNP
Protocol Review	link

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

This review responds to your consult dated 6/6/2024 regarding the Applicant's QTc interval evaluation report. We reviewed the following materials:

- Previous IRT review under IND 146185 dated 09/04/2020, 09/14/2022, 12/01/2022, 05/11/2023, 12/04/2023, 01/31/2024 in DARRTS;
- Previous DCN review under IND 146185 dated 01/17/2023 in DARRTS;
- Cardiac safety report of TQT study VX21-548-009 (IND146185 / SN0173; link);
- Clinical study report of TQT study VX21-548-009 (NDA219209 / SN0004; link);
- Updated cardiac safety report of study VX21-548-005 (IND146185 / SN0173; link);
- Proposed label (NDA219209 / SN0004; link);
- Investigator's brochure (IND146185 / SN0077; link);
- QT evaluation checklist (NDA219209 / SN0004; link); and
- Highlights of clinical pharmacology and cardiac safety (IND146185 / SN0173; link).

1 SUMMARY

VX-548 did not prolong the QTcF interval in this thorough QT (TQT) assessment study as described in the ICH E14 guidance – see Table 1 for overall results.

The clinical study VX21-548-009 was a randomized, double-blind, placebo- and active-controlled parallel with nested crossover, multiple-dose ECG study evaluating the effect of VX-548 on the QT/QTc interval in healthy subjects. The highest dose studied was 200 mg QD for 7 days (from Day 4 to Day 10), which covers the maximum anticipated high exposure (Cmax) scenario when VX-548 is administered to subjects with severe hepatic impairment by 1.2-fold for VX-548 and 0.9-fold for M6-548.

Data were analyzed using exposure-response analysis as primary analysis, which do not suggest that VX-548 is associated with significant QTc prolongation (refer to section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in by-time analysis (refer to section 4.3) and categorical analysis (section 4.4). Assay sensitivity was established based on the concentration-QTc analysis of 400 mg oral moxifloxacin.

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The high clinical exposure scenario for VX-548 and M6-548 is expected in subjects with severe hepatic impairment. The predicted mean ratios for Cmax for subjects with severe hepatic impairment relative to healthy volunteers based on a PBPK model (Report S313) are 1.7 and 1.6, respectively (section 3.1).
• The highest dose of 200 mg QD on Day 6 and Day 10 of oral tablets covers the high clinical exposure scenario by 1.2 for VX-548 and 0.9 for M6-548, respectively.

<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>200 mg QD Day 6</td><td>1251.7 ng/mL</td><td>-0.70</td><td>(-3.83, 2.42)</td></tr>
<tr><td>ΔΔQTcF</td><td>200 mg QD Day 10</td><td>1163.8 ng/mL</td><td>0.66</td><td>(-3.75, 2.44)</td></tr>
</table>
</td></tr>
<tr><td>In vitro and In vivo findings</td><td>Integrated nonclinical risk assessment was not performed.</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY APPLICANT

We agree that based on the thorough QT study (clinical study VX21-548-009), VX-548 is not associated with significant QTc prolongation up to 2-times exposure of the maximum recommended dose.

1.2 COMMENTS TO THE REVIEW DIVISION

None.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 4 (link) from the CS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At 2 times exposure of the maximum recommended dose, clinically significant QTc prolongation was not observed. (b) (4) [redacted]

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

VX-548 (JOURNAVX, Suzetrigine, SUZ, VRT-1737548, oral tablet) is a selective NaV1.8 sodium channel inhibitor indicated for the treatment of moderate to severe acute pain in adults. The recommended dose is 100 mg followed by 50 mg every 12 hours (q12h) [redacted] (b) (4) taking with or without food [redacted] (b) (4)

The CS-IRT has been consulted multiple times for this product. Review dated 12/04/2023 provided a complete summary of most consults. Below is a high-level summary of relevant reviews to the thorough QT (TQT) study:

12/01/2022: We reviewed the synopsis of the TQT study VX21-548-009 and noted insufficient information about the proposed CQT analysis.

05/11/2023: We reviewed the protocol of the TQT study and found the study design and analysis plan acceptable.

12/04/2023: We reviewed the report of study 005 and considered it could be used as a substitute for a TQT study together with the nonclinical data.

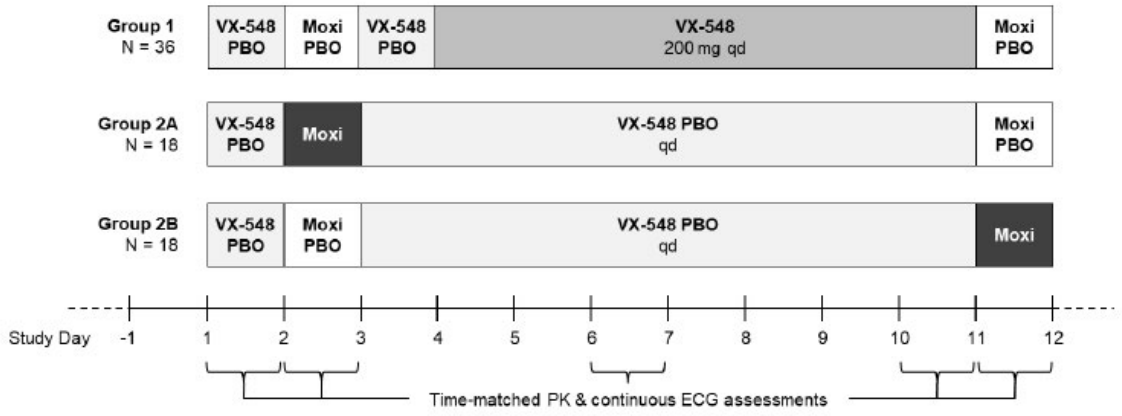
01/31/2024: Dataset of study 005 was submitted. We decided to wait for the TQT study to come in instead of reviewing data of 005.

DCN was also consulted about concerns of arrhythmic risk with inhibition of NaV1.8 and/or NaV1.5. DCN responded that all drugs that inhibit NaV1.5 are proarrhythmic and that the proarrhythmic profile of NaV1.8 blockers is unknown (01/17/2023).

In this submission, Applicant submitted updated cardiac safety report and dataset for the TQT study # 009 in healthy subjects. It was a randomized, double-blind, placebo- and active-controlled parallel with nested cross-over study. The highest dose was 200 mg QD

for 7 days (Day 4 to Day 10). Concentration-QTc analysis is the primary analysis. Three models were explored: the full model with both analytes of VX-548 and M6-548 (Model A), and individual models with VX-548 alone (Model B) and with M6-548 alone (Model C). The prediction results from other models (Models A and C) were similar to those from Model B and thus Model B (VX-548 only) was selected as the final model. The analysis to show assay sensitivity was based on the concentration-QTc analysis of the effect on ΔQTcF of 400 mg oral moxifloxacin versus placebo. See Appendix in previous review (05/11/2023) for details.

Figure 1. Study Design of VX21-548-009



Moxi: moxifloxacin; N: total sample size; PBO: placebo; PK: pharmacokinetics; qd: once daily
Notes: To maintain the blind, matching placebo will be administered, as applicable, so that all subjects receive the same number of tablets or capsules.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety (link).

Median Tmax of VX-548 is 3 hours and terminal half-life is 55 hours following 100- and 50-mg single doses under fasted condition respectively.

VX-548 is primarily metabolized through CYP3A4 with minimal unchanged VX-548 and M6-548 (major metabolite) excreted in urine (below limit of quantification). VX-548 and M6-548 exhibited dose proportionality in the evaluated range of 5 to 65 mg. The mean (%CV) accumulation ratio is estimated to be 3.37 (30.2%) for VX-548 and 4.49 (30.6%) for M6-548 respectively.

The clinical therapeutic dose is 100 mg loading dose followed by 50 mg q12h, oral tablets and the high clinical exposure scenario is predicted in subjects with severe hepatic impairment where the mean ratio of Cmax is increased 1.72 and 1.57-fold for VX-548 and M6-548 respectively in severe hepatic impairment subjects relative to healthy volunteers based on a PBPK model.

Also, a single 20 mg dose of VX-548 co-administered with 200 mg itraconazole at steady state (strong CYP3A inhibitor) resulted in a 1.47-fold increase in Cmax and a 31.7% decrease in M6-548 Cmax.

Food has minimal impact on the exposures of VX-548 as Cmax increased only by 4%, whereas the absorption was slower under fed conditions; fed Tmax was 5 hours compared

to 3 hours fasted at a dose of 100 mg. The Cmax ratio of highest dose of 200 mg QD on Day 6 in QTc assessment, when compared to Cmax after high clinical exposure scenario, when administered in subjects with severe hepatic impairment resulted in the ratio of 1.2 and 0.91 for VX-548 and M6-548 respectively as given in Table 2.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	100 mg loading dose followed by 50 mg q12h, oral tablets	0.623 µg/mL ($C_{max,ss}$) for VX-548 and 1.52 µg/mL for M6-548, predicted
Sponsor's High clinical exposure scenario	1.7 and 1.57-fold increase for VX-548 and M6-548 with severe hepatic impairment	1.07 µg/mL for VX-548 2.4 µg/mL for M6-548
Highest dose in QT assessment	200 mg QD on Day 3, oral tablets	1.27 µg/mL for VX-548 (Day 6) and 2.19 µg/mL for M6-548 (Day 10)
C_{max} Ratio	1.2 for VX-548 high clinical exposure 0.91 for M6-548 clinical exposure	

3.1.2 Nonclinical Safety Pharmacology Assessments

A GLP in vitro hERG study (VRT-1737548-TX-014) tested the effect of VX-548 on hERG current at doses of 0, 1, 3, 10, and 30 µM. At 30 µM, the mean percent inhibition of hERG current was 55.2%. IC50 was 22.9 µM. Terfenadine was used as positive control. At 60 nM, the mean hERG inhibition was 85.9%.

A GLP in vitro hERG study (VRT-1875420-TX-003) tested the effect of M6-548 on hERG current at doses of 0 and 10 µM. At 10 µM, the mean percent inhibition of hERG current was 8.6%. IC50 >10 µM. Ondansetron was used as positive control. At 0.5 uM and 5 uM, the mean hERG inhibition was 25.4% and 76.5% respectively.

A GLP single oral dose CV/respiratory study in telemetered male monkeys tested the effect of VX-548 at doses of 0, 20, 50, or 100 mg/kg in a Latin square design (n = 4). There were no VX-548-related changes in body temperature, blood pressure, pulse pressure, heart rate, or ECG intervals. NOEL was 100 mg/kg. Margin from NOEL to the predicted steady state free concentration was 15-fold for VX-548 and 14-fold for M6-548.

ECGs were also collected at Tmax in 28-day,13-week, and 39-week repeat-dose monkey studies. There were no VX-548-related changes in qualitative or quantitative ECG parameters on Day 28 (100 mg/kg/day), Day 91 or Week 39 (150 mg/kg/day) at highest doses tested.

***Reviewer's comment**: The hERG safety margin of VX-548 (MW: 473.4 g/mol; IC50 = 22.9 µM) over free (unbound 0.012) high clinical exposure (1.06 µg/mL) is 852-fold. For M6-548, assuming hill coefficient to be 1, the projected IC50 is 106 µM (inhibition at 10 µM is 8.6%). The hERG safety margin (MW: 489.39 g/mol) over free (unbound 0.041) clinical exposure (1.52 µg/mL) is 835-fold.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for VX-548 was based on exposure-response analysis, please see section 3.2.3 for additional details.

Applicant presented by-time analysis results for all intervals.

Reviewer's comment: *FDA analysis results are similar to the applicant's analysis results. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was demonstrated by the moxifloxacin in both C-QTc relationship. The slope of the relationship was positive and statistically significant (0.0049 ms per ng/mL [90% CI: 0.00261, 0.00721; P = 0.0007]), and the lower bound of the 2-sided 90% CI of the predicted QT effect (15.25 ms [90% CI: 11.07, 19.44]) at the geometric mean peak moxifloxacin concentration (2141.1 ng/mL) was above 5 ms.

Reviewer's comment: *Moxifloxacin produced the expected modest QTcF increase. Assay sensitivity was established both by the by-time analysis and exposure response analysis.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the Applicant's analysis results. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The Applicant used the model recommended in the white paper, using a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched VX-548 plasma concentration as an explanatory variable, centered baseline QTcF as an additional covariate, treatment (active = 1 or placebo = 0) and time as fixed effects, and a random intercept and random slope per subject. Applicant model predicted effects on ΔΔQTcF at the geometric mean Cmax were -0.70 ms (90% CI: -3.83, 2.42) and 0.66 ms (90% CI: -3.75, 2.44) at the geometric mean Cmax of VX-548 on Day 6 (1251.7 ng/mL) and on Day 10 (1163.8 ng/mL), respectively. The geometric mean Cmax values were calculated only for subjects with PK and QTcF data available. The results of the applicant's analysis show an absence of significant QTc prolongation.

Reviewer's comment: *The overall results of the reviewer analysis on ΔΔQTcF at the geometric mean Cmax after once daily doses of 200 mg on Day 6 and Day 10 are comparable to the Applicant predicted values.*

3.2.4 Safety Analysis

In the TQT study 009, there was no death, SAEs, severe AEs, or AE leading to treatment discontinuation. There was no cardiac disorder AEs. The most common AEs (≥2 subjects in any treatment group) were nausea, dizziness, headache, dermatitis contact, and diarrhea. The incidence of AEs that were considered related or possibly related to study drug was similar between the VX-548 and placebo/moxifloxacin treatment groups. There were no

clinically meaningful findings in laboratory results, ECG parameters, or vital signs assessments. One subject in the 200 mg dose group (1/36, 3%) had a syncope event (Grade 2).

A total of 874 subjects with pain after bunionectomy or abdominoplasty have received at least 1 dose of VX-548 in a total of 2 completed placebo- and active-controlled phase 3 studies. In study 104, subjects with pain after bunionectomy were randomized 2:2:1 and received VX-548 100 mg (loading dose)/50 mg q12h (3 maintenance doses) (n = 426), HB/APAP q6h (n = 431), and placebo (n = 216). In study 105, subjects with pain after bunionectomy were randomized 2:2:1 and received VX-548 100 mg/50 mg q12h (3 doses) (n = 448), HB/APAP q6h (n = 448), and placebo (n = 251).

Out of the cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths), 7 events of syncope and 1 event of QT prolongation were reported in study 104 and 105, in the VX-548 group. The incidence of syncope events in the VX-548 100 mg/50 mg q12h was similar to that in HB/APAP and placebo groups (0.8%, 1.0%, and 1.1% respectively). Most syncope events were likely related to surgery and perioperative volume shifts in the pooled Phase 3 studies. Only 1 subject (0.1%) in the pooled phase 3 studies had a mild AE of ECG QT prolonged that was considered possibly related to VX-548. This subject had a single, isolated QTcF on 1 ECG, which resolved without intervention. Comparatively, 2 subjects (0.2%) in the HB/APAP group had a QTcF interval increase >60 msec.

Reviewer's comment: *The incidence of cardiac safety events per ICH E14 was similar in the VX-548 group in the completed phase 3 trials comparing with active control or placebo.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 0).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to subject and treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

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

The data for this study came from a nested crossover design. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and average baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

4.3.1 QTc

Figure 2 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 3.

Figure 2: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

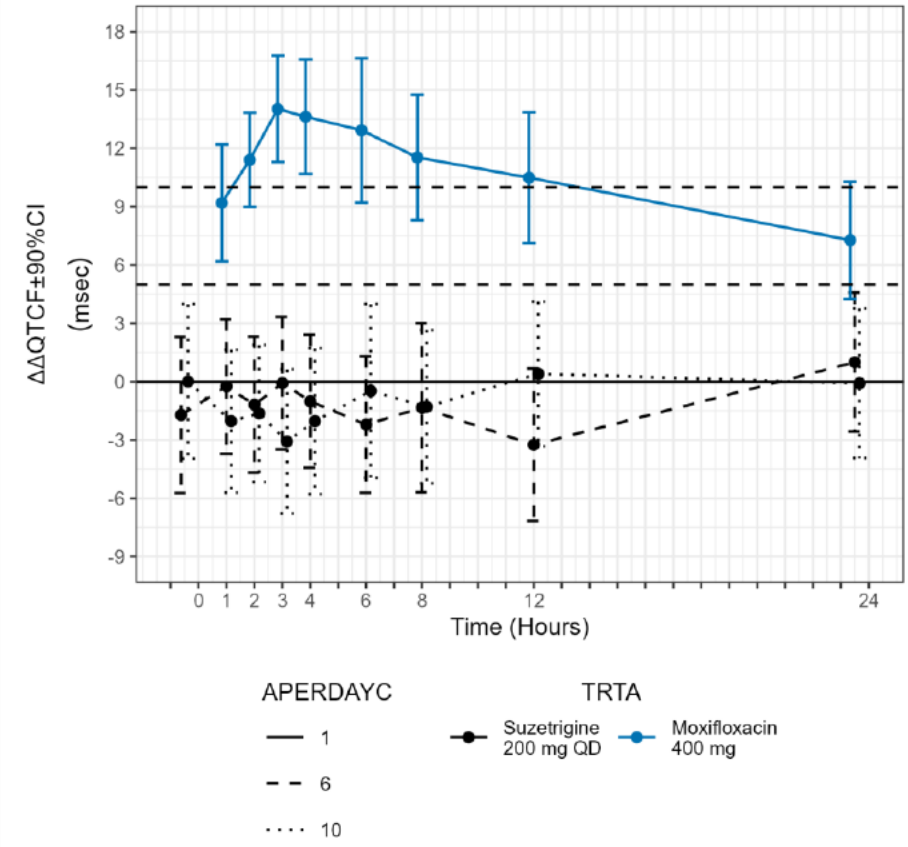


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Suzetrigine 200 mg QD	6	32 / 32	23.5	1.0	(-2.6 to 4.6)
Suzetrigine 200 mg QD	10	34 / 35	12.0	0.4	(-3.3 to 4.1)

4.3.1.1 Assay Sensitivity

The statistical reviewer used a linear mixed model to analyze the moxifloxacin effect by-time for each biomarker. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and a time-matched baseline as a covariate. The model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period. The time-course of changes in ΔΔQTcF is shown in Figure 2 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

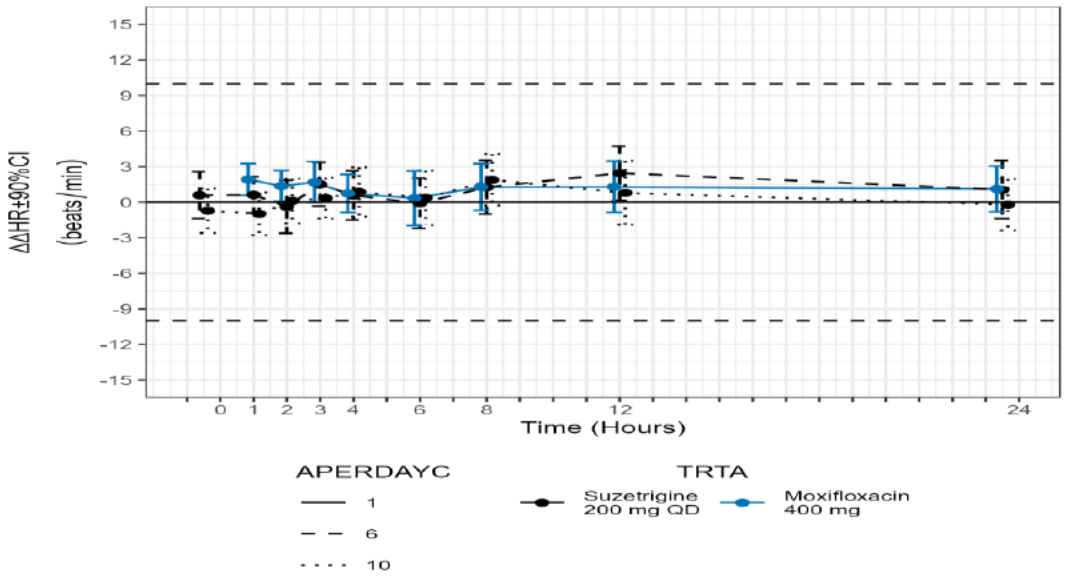
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	36 / 36	3.0	14.0	(11.3 to 16.8)	(10.2 to 17.9)

4.3.2 HR

Figure **3** displays the time profile of ΔΔHR for different treatment groups.

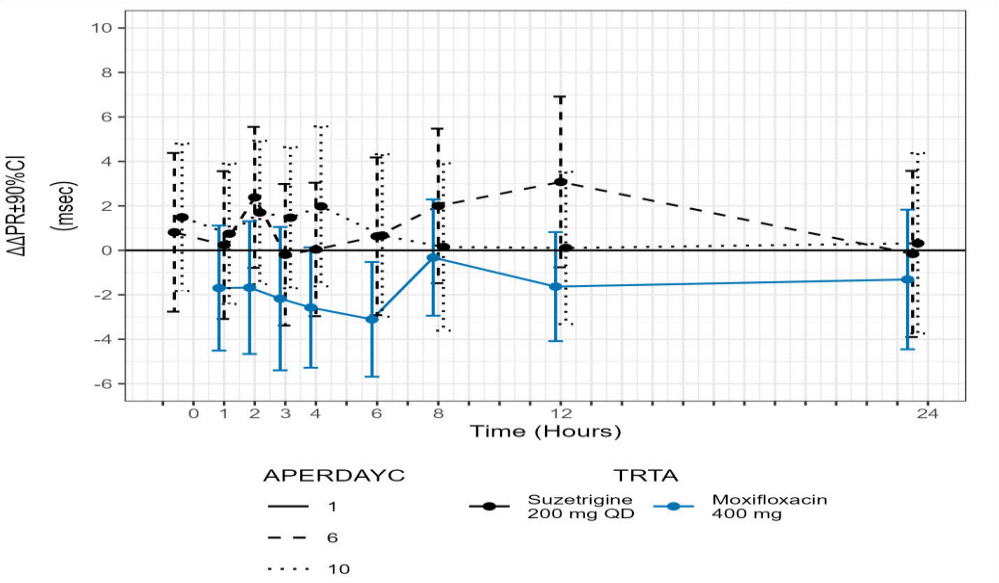
Figure 3: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 4 displays the time profile of ΔΔPR for different treatment groups.

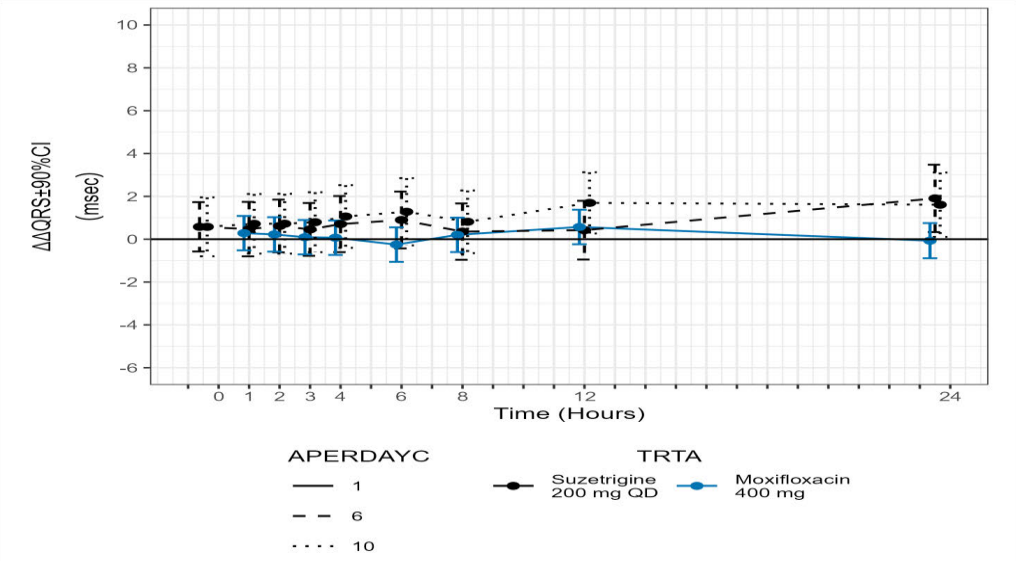
Figure 4: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 5 displays the time profile of ΔΔQRS for different treatment groups.

Figure 5: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

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

4.4.1 QTc

None of the subjects experienced QTcF values of >500 msec or ΔQTcF >60 msec for suzetrigine 200 mg QD.

4.4.2 HR

None of the subjects experienced HR >100 beats/min for suzetrigine 200 mg QD.

4.4.3 PR

None of the subjects experienced PR >220 msec for suzetrigine 200 mg QD.

4.4.4 QRS

None of the subjects experienced QRS >120 msec for suzetrigine 200 mg QD.

4.5 EXPOSURE-RESPONSE ANALYSIS

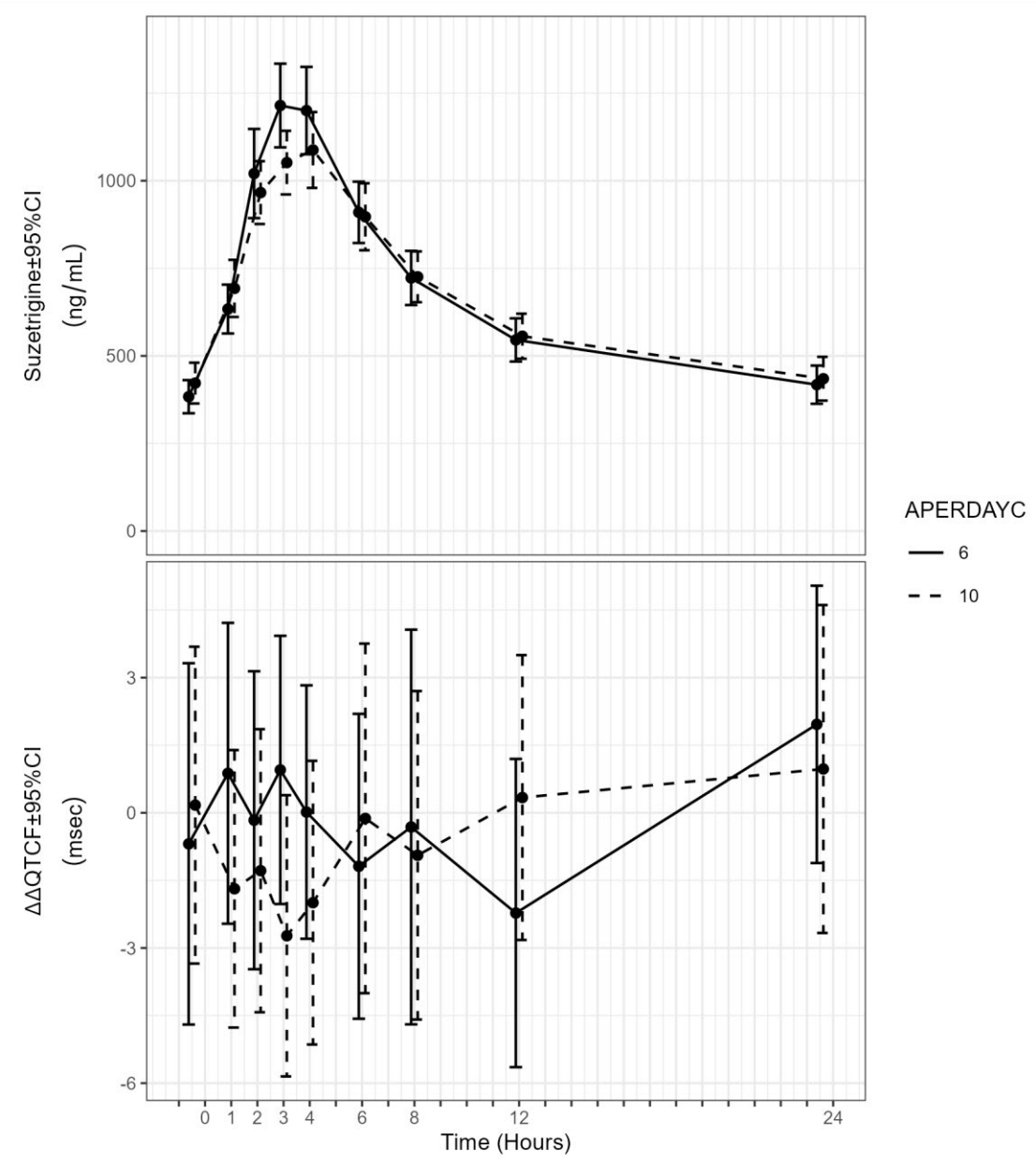
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. A total of thirty-two (32) subjects had adequate pharmacokinetic data which contributed to the suzetrigine pharmacokinetic analysis and constitute the pharmacokinetic analysis population. No subjects were excluded from the analysis.

4.5.1 QTc

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

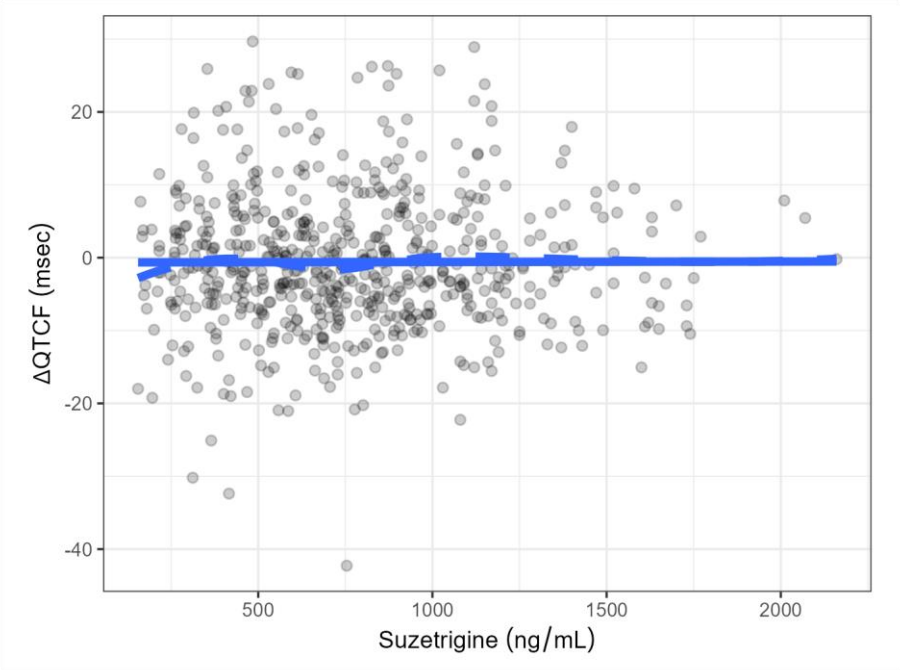
Figure 3 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Since the maximum ΔΔHR changes are < 10 beats/min and therefore Fridericia method was used for heart rate QT correction. Figure 6 offers an evaluation of the relationship between time-course of drug concentration (top) and ΔΔQTcF (bottom), with no appearance of significant hysteresis. Figure 7 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 2

Figure 7: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 8. Predictions from the concentration-QTcF model are provided in Table 5. The overall results of the reviewer analysis were comparable with the sponsor predicted values.

Figure 8: Goodness-of-fit Plot for QTcF

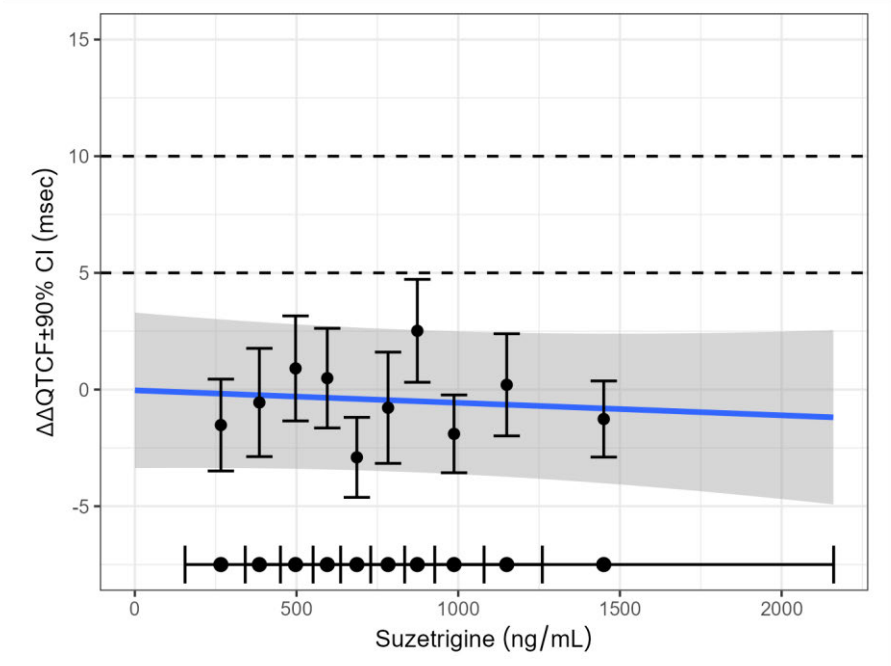


Table 5: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Suzetrigine (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Suzetrigine 200 mg QD	10	1,163.8	-0.7	(-3.8 to 2.4)
Suzetrigine 200 mg QD	6	1,251.7	-0.7	(-3.8 to 2.4)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and ΔΔQTcF is shown in Figure 9. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 10 and the predicted QTcF at the geometric mean Cmax is listed in Table 6.

Figure 9: Time-course of Moxifloxacin Concentration (top) and QTcF (bottom)

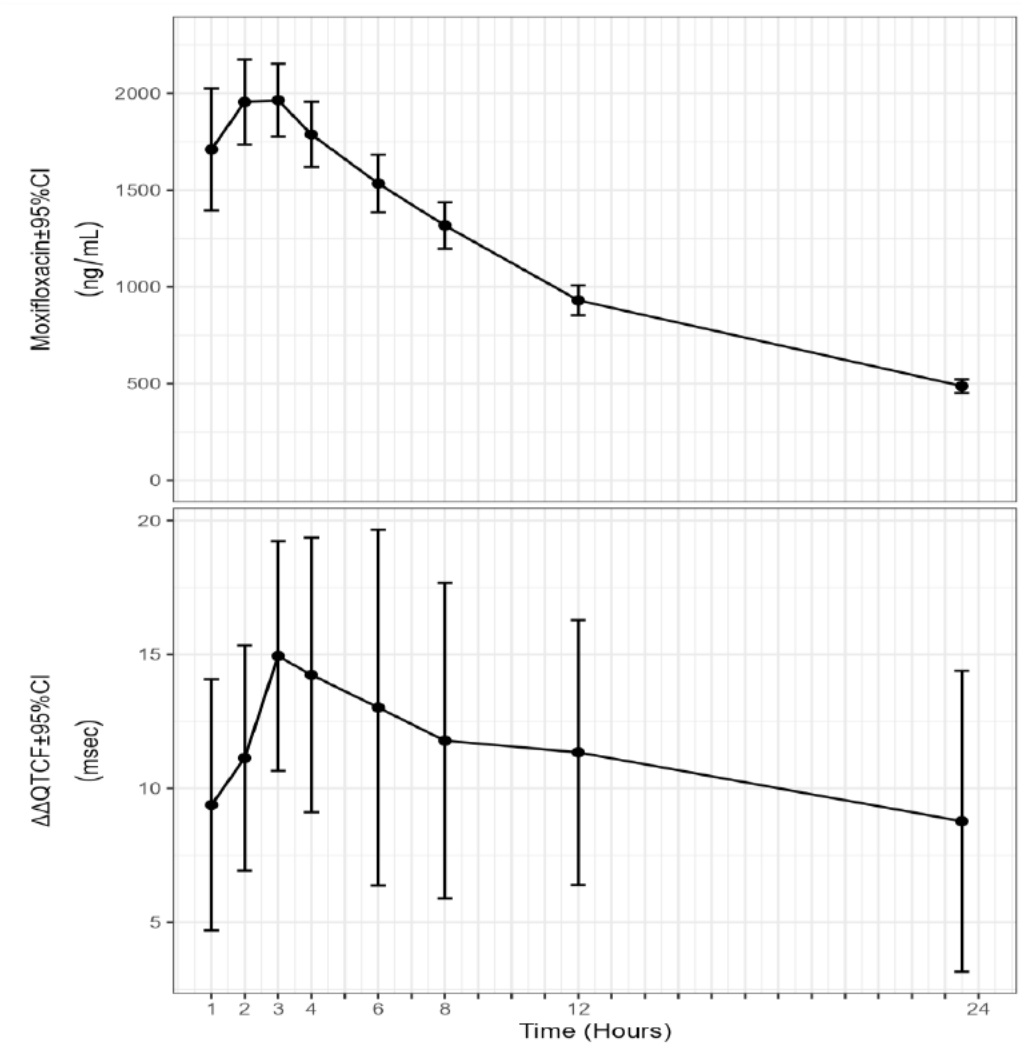


Figure 10: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin

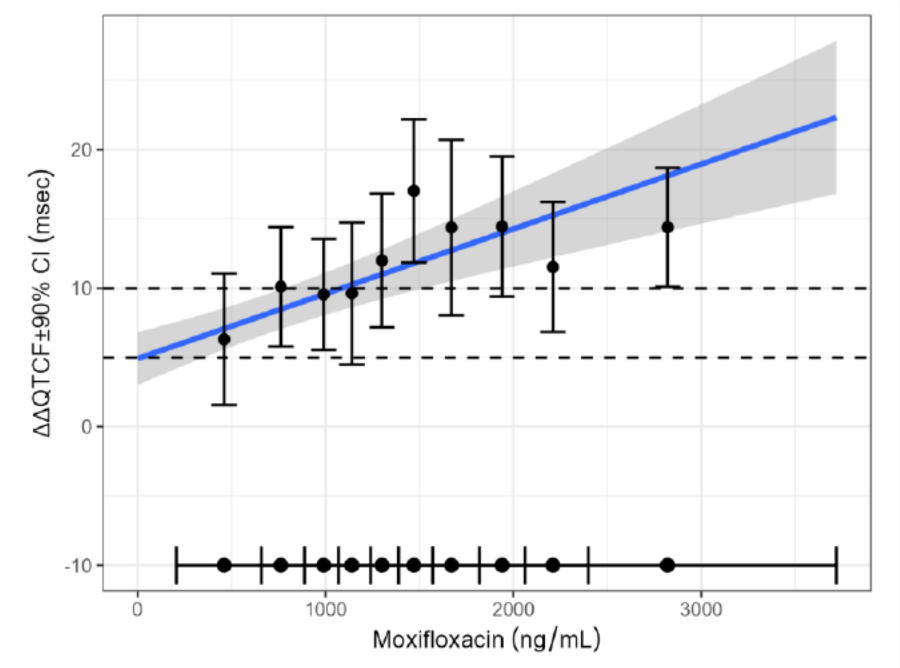


Table 6: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	2,141.1	14.9	(12.0 to 17.9)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DEVI KOZELI on behalf of FERDOUSE BEGUM
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Signing on behalf of Ferdouse as she is OOO

DALONG HUANG
07/31/2024 09:32:58 AM

RAKESH GOLLEN
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ELIFORD N KITABI
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MICHAEL Y LI
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YANYAN JI
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CHRISTINE E GARNETT
07/31/2024 10:53:32 AM