

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219209Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	219209
Priority or standard	Priority
Submit date(s)	5/30/2024
Received date(s)	5/30/2024
PDUFA goal date	1/30/2025
Division/office	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Review completion date	1/30/2025
Established/proper name	Suzetrigine
(Proposed) proprietary name	Journavx
Pharmacologic class	Sodium channel blocker
Other product name(s)	VX-548
Applicant	Vertex Pharmaceuticals Inc
Dosage form/formulation	Tablet
Dosing regimen	100 mg, then 50 mg every 12 hours
Applicant-proposed indication/ population	Treatment of moderate to severe acute pain in adults
SNOMED CT code for proposed indication disease term(s)¹	22253000
Regulatory action	Approval
Approved dosage (if applicable)	(b) (4)
Approved indication/ population (if applicable)	Treatment of Moderate to Severe Acute Pain in Adults
SNOMED CT code for approved indication disease term(s)¹	22253000

¹ For internal tracking purposes only.

Abbreviations: DAAP, Division of Anesthesiology, Addiction Medicine, and Pain Medicine; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0-(X)h}$	area under the concentration-time curve from 0 to X hours (X=12 or 24)
AUC_{ss}	area under the concentration-time curve at steady state
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BOCF	baseline observation carried forward
CFR	Code of Federal Regulations
CI	confidence interval
CL_{iv}	intravenous clearance
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
CMC	chemistry, manufacturing, and controls
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CrCl	creatinine clearance
CSS	Controlled Substance Staff
$C_{trough,ss}$	trough plasma concentration at steady state
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
dEFD	definitive embryo-fetal development
DILI	drug-induced liver injury
DPMH	Division of Pediatric and Maternal Health
DPN	diabetic peripheral neuropathy
DRG	dorsal root ganglion
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EE	ethinyl estradiol
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
E_{max}	maximum effect
EOP2	end-of-phase 2
EPC	established pharmacologic class
E-R	exposure-response
FAS	full analysis set
FaSSIF	fasted-state simulated intestinal fluid
FDA	Food and Drug Administration

FDCA	Federal Food, Drug, and Cosmetic Act
fmCYP	fraction of hepatic clearance of the substrate mediated by an individual CYP enzyme
FMO	flavin-containing monooxygenase
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
HB/APAP	hydrocodone bitartrate/acetaminophen
HD	high dose
hERG	human ether-à-go-go-related gene
HI	hepatic impairment
HLM	human liver microsome
IC ₅₀	half-maximal inhibitory concentration
ICE	intercurrent event
ICH	International Council for Harmonisation
IND	investigational new drug
IPD	important protocol deviation
IR	information request
ITT	intent-to-treat
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometric detection
LD	loading dose
LN	levonorgestrel
LOCF	last observation carried forward
LOE	lack of efficacy
LS	least-squares
MATE	multidrug and toxin extrusion protein
MD	mid dose
MDCK-KO	Madin-Darby canine kidney – knockout
MI	multiple imputation
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no-observed-adverse-effect level
NPRS	numeric pain rating scale
NSAID	nonsteroidal anti-inflammatory drug
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OPQ	Office of Pharmaceutical Quality
P _{app}	apparent permeability coefficient
pAUC	partial area under the concentration-time curve
PBPK	physiologically based pharmacokinetics
PD	pharmacodynamic
PGA	Patient Global Assessment
PI	prescribing information
PK	pharmacokinetic

PMR	postmarketing requirement
popPK	population pharmacokinetic
PPND	pre- and postnatal development
PR	progesterone receptor
PT	preferred term
P-gp	P-glycoprotein
qd	once daily
QSAR	quantitative structure-activity relationship
QTc	QT corrected for heart rate
QTcF	corrected QT interval, Fridericia's calculation
SAE	serious adverse event
SAP	statistical analysis plan
(b) (4)	(b) (4)
SEE	substantial evidence of effectiveness
SOC	system organ class
SPID	sum of the pain intensity difference
SPID(X)	time-weighted SPID as recorded on the NPRS from 0 to X hours (X=12, 24, 36, or 48)
SpO2	oxygen saturation
SUZ	suzetrigine (also referred to as VX-548 and VRT-1737548)
s/p	status post
TBM	to-be-marketed
T _{max}	time to maximum concentration
TRA	total radioactivity
UGT	uridine 5'-diphospho-glucuronosyltransferase
VRS	verbal rating scale

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Under the 505(b)(1) regulatory pathway, Vertex Pharmaceuticals submitted new drug application (NDA) 219209, suzetrigine (SUZ) for the treatment of moderate to severe acute pain in adults. SUZ is a selective inhibitor of voltage-gated sodium channel subtype 1.8 (Na_v1.8). These channels are expressed in peripheral sensory neurons, including dorsal root ganglion (DRG) neurons, and are believed to play a role in pain signaling.

The regulatory history is notable for Breakthrough Therapy designation and a Priority Review determination. This NDA was not presented at the Anesthetic and Analgesic Drug Products Advisory Committee because the benefit-risk assessment did not identify unexpected significant safety or efficacy issues, and no controversial issues arose that would benefit from advisory committee discussion.

Substantial evidence of effectiveness for SUZ in adults with moderate-to-severe acute pain was established using data from two adequate and well-controlled trials. These studies show that SUZ administered as 100 mg for the first dose, then 50 mg every 12 hours has significant reduction in acute pain compared to placebo.

The safety database for SUZ is sufficient for the evaluation of risk. The available safety data show that SUZ has a favorable safety profile and is safe for its intended use. Serious adverse events were generally consistent with known postoperative complications of surgery and their incidence was low and balanced between treatment arms. The most common adverse reactions (greater incidence in SUZ-treated subjects compared to placebo) were pruritis, muscle spasms, increased creatine phosphokinase, and rash. SUZ is associated with potentially significant drug interactions and subjects with moderate hepatic impairment had greater SUZ and M6-SUZ (active metabolite) exposure than those with normal hepatic function. Negative effects to fertility and pregnancy were observed in nonclinical studies; however, the clinical relevance of these findings is unclear.

This NDA was reviewed by a multidisciplinary review team. Each discipline recommends approval for adults with moderate-to-severe acute pain. The signatory authority concurs that identified risks and uncertainties can be mitigated through labeling and further evaluated through postmarketing studies and routine pharmacovigilance. The review team is requiring postmarketing studies to evaluate the use of SUZ in pediatric patients and the risks to pregnancy and lactation in females.

The overall benefit-risk is favorable as described in the Benefit-Risk Framework below ([Table 2](#)). For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Integrated Assessment document and the Product Quality Review.

1.2. Conclusions on Substantial Evidence of Effectiveness

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

The Applicant conducted two randomized, double-blind, placebo- and active-controlled phase 3 studies (Studies 104 and 105) using two different acute pain models to assess the efficacy of SUZ. These studies provided sufficient evidence for the efficacy of SUZ for the treatment of moderate-to-severe acute pain in adults.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Acute pain is a common and well-recognized medical condition that is nearly ubiquitous. - Moderate-to-severe acute pain is a serious clinical condition that has a significant impact on quality of life and physical function. - Symptoms can last hours, days, or weeks. - There are numerous causes of acute pain. These include surgery or other invasive procedures and nonsurgical causes, such as trauma. - Inadequate pain management negatively impacts patients' health and can increase the risk of developing chronic pain.	Acute pain is a serious and common condition that is associated with many different medical and surgical conditions. Undertreated acute pain can result in significant medical and economic consequences. There is an unmet need for novel analgesics.
Current treatment options	- Multiple prescription and nonprescription medications are used for the treatment of acute pain. A multimodal approach involving the simultaneous use of different analgesics is a commonly used strategy for treating acute pain. - Pharmacologic options for the treatment of acute pain include acetaminophen, NSAIDs, muscle relaxants, local anesthetics, and opioids. - Opioids are often the treatment of choice for surgical and nonsurgical causes of moderate-to-severe acute pain. - There are several significant risks associated with the use of opioids, including respiratory depression, addiction, overdose, and death. - The use of opioids can be limited by other side effects, such as constipation, nausea, and vomiting.	There are multiple medications currently used for the treatment of acute pain. These can be used as individual therapies or in conjunction with other analgesics. Acetaminophen and NSAIDs are frequently used as first-line therapy for mild-to-moderate pain, but their effectiveness can be limited for more severe pain. Opioids are frequently used for moderate-to-severe acute pain but are associated with multiple significant risks and side effects.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Non-opioid analgesics can also be associated with significant risks, such as NSAIDs and their potential effects on the cardiovascular, gastrointestinal, and renal systems.	
Benefit	- The Applicant conducted two randomized, multicenter, double-blind, placebo- and active-controlled phase 3 studies to assess the efficacy of SUZ for the treatment of moderate-to-severe acute pain in adults. Both studies evaluated a 100 mg loading dose followed by 50 mg every 12 hours for a 48-hour treatment period. - The primary efficacy endpoint in both studies was the time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours (SPID48) compared to placebo. The SPID48 is a cumulative assessment of pain reduction from baseline. - The key secondary efficacy endpoints in both studies were SPID48 compared to HB/APAP and time to ≥ 2-point reduction in NPRS from baseline compared to placebo. - Study 104 evaluated the efficacy of SUZ in a bunionectomy pain model. In this study, SUZ demonstrated a statistically greater reduction in pain than did placebo as measured by the SPID48 with a least-squares (LS) mean difference of 29.3. - Study 105 evaluated the efficacy of SUZ in an abdominoplasty pain model. In this study, SUZ demonstrated a statistically greater reduction in pain than did placebo as measured by the SPID48 with a LS mean difference of 48.4. - SUZ did not demonstrate greater pain reduction than did HB/APAP as measured by the SPID48 in either Study 104 or 105.	Two placebo- and active-comparator (HB/APAP), adequate and well-controlled phase 3 clinical studies were conducted using two different acute pain models representing bony and soft tissue pain. Compared to placebo, there is sufficient evidence of efficacy of SUZ 100 mg followed by 50 mg every 12 hours. These studies did not demonstrate superior efficacy of SUZ compared to HB/APAP 5/325 mg every 6 hours. Considering that this is a lower dosage regimen for HB/APAP, the use of SUZ as a sole agent may be insufficient for the treatment of more severe acute pain.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- A total of 1883 unique subjects were exposed to at least 1 dose of SUZ (1266 with acute pain at the to-be-marketed dose regimen in the phase 2 and 3 studies, 169 in the acute pain studies who received a lower dose of SUZ, 393 in the phase 1 studies in healthy subjects, and 55 in the phase 1 studies in special populations). The safety of SUZ was evaluated in 874 subjects with acute postoperative pain in controlled phase 3 studies 104 and 105 and 256 subjects in uncontrolled phase 3 study 107. - There were no deaths in subjects treated with SUZ. - In the controlled acute pain studies, the incidence of SAEs and AEs leading to discontinuation of the study drug was low overall, and there were no substantial differences between the treatment arms. - In the controlled acute pain studies, the most common AEs (incidence >2%) were nausea, constipation, headache, dizziness, and pruritis. - There is no evidence of abuse potential with SUZ. - Small changes in laboratory assessments of renal function were noted, which were considered unlikely to be clinically significant. - There were negative effects on fertility and pregnancy observed in nonclinical studies. However, there are insufficient clinical data regarding the use of SUZ in pregnancy and in patients of reproductive potential.	SUZ represents a new pharamcologic class of non-opioid therapy for acute pain. The size of the safety database was adequate to characterize the safety profile of SUZ. The safety profile was favorable in subjects with moderate-to-severe acute pain and the known risks can be adequately described in product labeling. There was no evidence of abuse potential. Uncertainties surrounding the effects of SUZ on fertility, pregnancy, and lactation will be addressed through labeling and postmarketing studies.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen; LS, least-squares; NPRS, numeric pain rating scale; NSAID, nonsteroidal anti-inflammatory drug; SAE, serious adverse event; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

2.2. Conclusions Regarding Benefit-Risk

Moderate-to-severe acute pain is a serious and nearly ubiquitous condition that can result from a wide variety of surgical and nonsurgical causes. Inadequately managed acute pain is significantly detrimental to patients' quality of life and is a risk factor for the development of chronic pain. There are multiple pharmacologic classes available for the treatment of acute pain, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. However, significant limitations exist with currently available therapies, such as the abuse potential and side effect profile of opioids and the limited effectiveness of non-opioids for severe pain. Therefore, the treatment of acute pain continues to have unmet needs.

SUZ is a selective inhibitor of voltage-gated sodium channel subtype 1.8 (Na_v1.8). This is predominantly expressed in peripheral sensory neurons including DRG neurons. The Applicant purported that this selectivity would lead to the avoidance of side effects that are associated with less selective sodium channel modulators and central nervous system (CNS)-active agents.

The Applicant provided substantial evidence of efficacy of SUZ from two adequate and well-controlled studies using the bunionectomy and abdominoplasty acute pain models. The benefit of SUZ is based on the time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48), which demonstrated statistically significant pain relief compared to placebo in both studies. The first key secondary endpoint, a comparison of SUZ versus an opioid active control (hydrocodone bitartrate/acetaminophen [HB/APAP] 5/325 mg every 6 hours) on SPID48, was not met in either study. In the study of acute pain post-bunionectomy, subjects in the SUZ group had less pain reduction compared to those in the HB/APAP group.

The safety evaluation of SUZ was adequate, and the demonstrated safety profile is acceptable for the indicated dose and population. There were no concerning major safety findings and the controlled phase 3 acute pain studies demonstrated that subjects treated with SUZ had a lower incidence of some of the adverse events (AEs) commonly associated with opioids, such as nausea, vomiting, and dizziness, than did those treated with HB/APAP. Additionally, the incidence of any AE was lower in the SUZ group than those in either the HB/APAP or placebo groups. SUZ does not appear to have a potential for abuse. SUZ is associated with potentially significant drug interactions including some hormonal contraceptives; dosage modifications are recommended for moderate CYP3A inhibitors and SUZ is contraindicated for use with strong CYP3A inhibitors. Subjects with moderate hepatic impairment had greater SUZ and M6-SUZ (active metabolite) exposure than those with normal hepatic function, and the recommended dosage is lower in patients with moderate hepatic impairment than those with normal hepatic function. Uncertainties regarding safety include use of SUZ in pediatric patients, patients with severe hepatic impairment or renal impairment of eGFR < 15 mL/min, and the risks to fertility, pregnancy, and lactation. These uncertainties will be addressed in the labeling and assessed through postmarketing studies.

There is a clear unmet medical need for new therapies for the treatment of pain. SUZ is the first member of a novel pharmacologic class of analgesics and has demonstrated efficacy for the treatment of moderate-to-severe acute pain in two adequate and well-controlled clinical studies. Considering the totality of the data, the benefits of SUZ clearly outweigh the risks. However, it is important to note that the performance of SUZ in clinical studies compared to a HB/APAP

comparator administered at a relatively low dose may indicate limited efficacy as a sole agent for the treatment of more severe acute pain. Nonetheless, its use as part of multimodal analgesic therapy may reduce reliance on currently used analgesics and subsequently mitigate the associated risks, such as abuse potential with opioid use. In summary, SUZ and the new pharmacologic class it represents have the potential to be valuable additions to the current armamentarium of analgesics.

II. Interdisciplinary Assessment

3. Introduction

Vertex Pharmaceuticals Inc. has developed suzetrigine (SUZ; VX-548), an inhibitor of voltage-gated sodium channel 1.8 (Na_v1.8). There are nine Na_v isoforms expressed in humans, and SUZ is selective for Na_v1.8, which plays a role in pain signaling. SUZ is the first potential member of this pharmacologic class of non-opioid analgesics. The Applicant asserts that because Na_v1.8 is selectively expressed in peripheral pain-sensing neurons in humans, Na_v1.8 inhibitors are not expected to have the abuse liability associated with opioids or the adverse effect profile observed with central nervous system (CNS)-active agents.

The proposed indication for SUZ is for the treatment of moderate-to-severe acute pain in adults. SUZ is an orally bioavailable small molecule, and the Applicant has developed a 50-mg tablet as the to-be-marketed formulation. The proposed dosing regimen is 100 mg for the first dose (loading), followed by 50 mg every 12 hours (b) (4)

Pain is a nearly ubiquitous experience that impacts multiple facets of patients' lives, including physical functioning and mental health. There is a significant economic burden associated with the management of pain. Acute pain is usually time-limited and can be associated with a variety of surgical and nonsurgical conditions. Inadequately treated acute pain can increase the risk of developing chronic pain. Moderate-to-severe acute pain is considered a serious clinical condition for which there is an urgent need for safe and effective treatments.

There are multiple classes of FDA-approved medications for the management of acute pain in adults. These include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics. Muscle relaxants are indicated as an adjunct for the treatment of discomfort and muscle spasm associated with acute, painful musculoskeletal conditions. However, these medications are all associated with various adverse effects across multiple different organ systems. Opioids, in particular, have gained significant attention given their abuse liability and the growing public health concerns regarding addiction and overdose.

Two phase 3 clinical studies (Studies 104 and 105) were conducted to assess the safety and establish the efficacy of SUZ in moderate-to-severe acute pain. These studies were both randomized, double-blind, placebo- and active-controlled in design. Study 104 used bunionectomy and Study 105 used abdominoplasty as the postsurgical acute pain models. The phase 3 program also included Study 107, a single-arm, uncontrolled study that evaluated SUZ in various acute surgical and nonsurgical painful conditions for up to 14 days of treatment. In the two controlled phase 3 studies, the primary endpoint was the time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48) for SUZ compared to placebo.

SUZ was granted Breakthrough Therapy designation after review of data from its phase 2 clinical studies suggesting favorable efficacy compared to placebo, as well as a favorable clinical safety profile and a mechanistic rationale for less abuse potential compared to opioids. This NDA was granted Priority Review designation considering the potential for SUZ to be a significant improvement in the safety of the treatment of acute pain.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Differences in Efficacy Between Pain Models

3.1.1.2. Handling of Intercurrent Events

3.1.2. Key Safety Review Issues

3.1.2.1. Risks of Negative Effects on Renal Function

3.1.2.2. Duration of Use

3.1.2.3. Risk of Reproductive and Developmental Effects

3.2. Approach to the Clinical Review

The primary evidence for the efficacy and safety of SUZ for the proposed indication of the treatment of moderate-to-severe acute pain in adults was provided by two adequate and well-controlled studies conducted in the United States (Studies 104 and 105). These were both randomized, double-blind, placebo- and active-controlled phase 3 studies. The active comparator in both studies was hydrocodone bitartrate/acetaminophen, an opioid-containing combination medication. In addition, a single-arm phase 3 study (Study 107) provided supportive safety data. All of the phase 3 studies were conducted in accordance with good clinical practice (GCP) as described in Integrated Addendum to International Council for Harmonisation (ICH) guideline E6(R2) *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice* ([November 2016](#)).

Additional supportive safety information from the phase 2 acute pain studies (Studies 101 and 102) was reviewed. These were both randomized, double-blind, placebo-controlled, and active-controlled studies conducted in the United States using the same acute pain models (bunionectomy and abdominoplasty) as the controlled phase 3 studies. These studies evaluated different dose regimens of SUZ in addition to the to-be-marketed regimen. This included 60 mg for the first dose, then 30 mg q12h (Studies 101 and 102) and 20 mg for the first dose, then 10 mg q12h (Study 101).

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):
The treatment of moderate to severe acute pain in adults.
2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
 - a. Adequate and well-controlled clinical investigation(s):
 - i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
 - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations**OR**
 - b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}
OR
 - c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²
3. Complete response, if applicable
 - a. ☐ SEE was established
 - b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#))

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([May 1998](#))

³ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#))

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations¹ for SUZ

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
VX22-548-104	Subjects with moderate or severe pain after a bunionectomy	Phase 3 Control type: Placebo concurrent, active concurrent Randomization: Stratified randomization by site and baseline NPRS (<8 versus ≥8) Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Treatment: SUZ 100 mg loading dose followed by 50 mg q12h Active control: HB/APAP 5 mg/325 mg q6h Number treated: SUZ: 426 HB/APAP: 431 Placebo: 216 Duration: 48 hours	Primary: • SPID48 compared to placebo Key secondary: • SPID48 compared to HB/APAP • Time to ≥2-point reduction in NPRS from baseline compared to placebo	Planned: 1000 Actual: 1075 randomized	Centers: 21 Countries: 1 (US)
VX22-548-105	Subjects with moderate or severe pain after an abdominoplasty	Phase 3 Control type: Placebo concurrent, active concurrent Randomization: Stratified randomization by site and baseline NPRS (<8 versus ≥8) Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Treatment: SUZ 100 mg loading dose followed by 50 mg q12h Active Control: HB/APAP 5 mg/325 mg q6h Number treated: SUZ: 447 HB/APAP: 448 Placebo: 223 Duration: 48 hours	Primary: • SPID48 compared to placebo Key secondary: • SPID48 compared to HB/APAP • Time to ≥2-point reduction in NPRS from baseline compared to placebo	Planned: 1000 Actual: 1118 randomized	Centers: 12 Countries: 1 (US)

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
VX22-548-107	Subjects with moderate or severe pain after an ambulatory surgical procedure or nonsurgical conditions	Phase 3 Single-arm Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Treatment: SUZ 100 mg loading dose followed by 50 mg q12h Number treated: 256 Duration: Up to 14 days	Primary: - Safety and tolerability based on TEAEs, laboratory test results, vital signs, and ECGs Key secondary: - Proportion of subjects reporting good, very good, or excellent on a PGA	Planned: 250 Actual: 256	Centers: 13 Countries: 1 (US)
VX21-548-101	Subjects with moderate or severe pain after a bunionectomy	Phase 2 Control type: Placebo concurrent, active concurrent Randomization: Stratified randomization by site and baseline NPRS (<8 versus ≥8) Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Treatment: SUZ 100, 60, or 20 mg loading dose followed by 50, 30, or 10 mg q12h, respectively Active Control: HB/APAP 5 mg/325 mg q6h Number treated: SUZ: 155 HB/APAP: 60 Placebo: 59 Duration: 48 hours	Primary: - SPID48 compared to placebo Secondary: - SPID24 - NPRS responder rate at 48 hours - PK parameter estimates - Safety and tolerability	Planned: 243 Actual: 274 randomized	Centers: 9 Countries: 1 (US)

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
VX21-548-102	Subjects with moderate or severe pain after an abdominoplasty	Phase 2 Control type: Placebo concurrent, active concurrent Randomization: Stratified randomization by site and baseline NPRS (<8 versus ≥8) Blinding: Double-blind Biomarkers: No biomarkers	Treatment: SUZ 100 or 60 mg loading dose followed by 50 or 30 mg q12h, respectively Active control: HB/APAP 5 mg/325 mg q6h Number treated: SUZ: 150 HB/APAP: 76 Placebo: 77	Primary: • SPID48 at rest compared to placebo Secondary: • SPID24 at rest • NPRS responder rate at 48 hours • Safety and tolerability	Planned: 256 Actual: 303 randomized	Centers: 7 Countries: 1 (US)
Innovative design features: None			Duration: 48 hours			

Source: Reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

Abbreviations: ECG, electrocardiogram; HB/APAP, hydrocodone bitartrate/acetaminophen; NPRS, numeric pain rating scale; PGA, Patient Global Assessment; PK, pharmacokinetic; q6h, every 6 hours; q12h, every 12 hours; SPID24/48, sum of the pain intensity difference as recorded on the NPRS from 0 to 24/48 hours; SUZ, suzetrigine; TEAE, treatment-emergent adverse event; US, United States

4. Patient Experience Data

The Applicant submitted patient experience data to assess the efficacy of SUZ. The NPRS is a patient-reported pain intensity measure that was collected at scheduled time points throughout the controlled phase 3 studies. These measurements were used to produce the SPID48, which was the primary efficacy endpoint for these studies. The verbal rating scale (VRS) is another patient-reported pain intensity measure that was used as an inclusion criterion to ensure that all subjects had moderate or severe pain at baseline in the controlled and uncontrolled phase 3 studies. The Patient Global Assessment (PGA) of study drug is a patient-reported measure of overall pain control with the study drug that was also used in these studies. Safety monitoring in Study 107 included the Columbia-Suicide Severity Rating Scale, which is an assessment of suicidal thoughts and behaviors.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Sections 6 and 7
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

SUZ selectively inhibits voltage-gated sodium channel subtype 1.8 ($\text{Na}_v1.8$), which is expressed in peripheral sensory neurons, including dorsal root ganglion (DRG) neurons, among other known voltage-gated sodium channel subtypes (Na_v 1.1 through 1.9). The inhibitory activity of SUZ for Na_v 1.8 was evaluated in DRG neurons of human, monkey, rat, mouse, rabbit, and dog in vitro. The half-maximal inhibitory concentration (IC_{50}) values of SUZ against human and monkey $\text{Na}_v1.8$ were 0.68nM and 0.75nM, respectively. SUZ was at least 80-fold less potent in rodent $\text{Na}_v1.8$ (IC_{50} : 56nM) than in human $\text{Na}_v1.8$. Therefore, in vivo primary pharmacology studies were not conducted in rodents. A major human metabolite, M6-SUZ (also referred to as VRT-1875420, M6), was also demonstrated to be a potent human $\text{Na}_v1.8$ blocker with an IC_{50} of 2.5nM in in vitro assays using human DRG neurons.

5.2. Clinical Pharmacology / Pharmacokinetics

SUZ is a new molecular entity with a mechanism of action of blocking the voltage-gated sodium channel Na_v1.8 currents. This represents a new class of drugs, and there is currently no established pharmacologic class (EPC) for this class. The Applicant proposed (b) (4) as the preferred EPC; however, the review team did not consider this acceptable. The review team recommends “sodium channel blocker” as an appropriate EPC for this class. Refer to Section 23 for a discussion on the rationale for selecting “sodium channel blocker” as the appropriate EPC for SUZ.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information															
	Pharmacologic Activity															
Established pharmacologic class (EPC)	SUZ is a sodium channel blocker.															
Mechanism of action	SUZ is a selective blocker of the Na _v 1.8 voltage-gated sodium channel compared to other known voltage-gated sodium channels (i.e., Na _v 1.1 through 1.9). Na _v 1.8 is predominantly expressed in peripheral sensory neurons, including dorsal root ganglion (DRG) neurons, where its role is to transmit pain signals (action potentials). By selectively inhibiting Na _v 1.8 channels, SUZ inhibits transmission of pain signals to the spinal cord and brain. Based on an in vitro electrophysiology assay in human DRG neurons, M6-SUZ is a less potent blocker of Na _v 1.8 than SUZ by 3.7fold.															
Active moieties	SUZ and M6-SUZ are active moieties.															
QT prolongation	At 2 times the exposure of the maximum recommended dose, clinically significant QTc prolongation was not observed															
	General Information															
Bioanalysis	A validated LC-MS/MS method was used to measure plasma concentrations SUZ and M6-SUZ. For all studies, the cumulative accuracy (% bias) was < ±15% and precision (%CV) was <15% for QC samples and calibration curves used the LC-MS/MS bioanalytical assay. The results of incurred samples reanalysis were within acceptable limits.															
Healthy subjects versus patients	Clinically relevant differences in PK are not expected between healthy subjects versus patients.															
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<table><tr><th colspan="3">Table 6. Steady-State Pharmacokinetics</th></tr><tr><th></th><th colspan="2">Mean (%CV)</th></tr><tr><th>PK Parameter</th><th>Suzetrigine</th><th>M6-SUZ (Active Metabolite)</th></tr><tr><td>AUC (µg·h/mL)</td><td>11.5 (25.6%)</td><td>34.7 (25.6%)</td></tr><tr><td>C_{max} (µg/mL)</td><td>0.623 (27.7%)</td><td>1.52 (24.5%)</td></tr></table> Source: Adapted from Report U049 Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation	Table 6. Steady-State Pharmacokinetics				Mean (%CV)		PK Parameter	Suzetrigine	M6-SUZ (Active Metabolite)	AUC (µg·h/mL)	11.5 (25.6%)	34.7 (25.6%)	C _{max} (µg/mL)	0.623 (27.7%)	1.52 (24.5%)
Table 6. Steady-State Pharmacokinetics																
	Mean (%CV)															
PK Parameter	Suzetrigine	M6-SUZ (Active Metabolite)														
AUC (µg·h/mL)	11.5 (25.6%)	34.7 (25.6%)														
C _{max} (µg/mL)	0.623 (27.7%)	1.52 (24.5%)														

Characteristic	Drug Information
Range of effective dose(s) or exposure	The effective dosing regimen determined based on phase 2 dose ranging studies was 100 mg loading dose/50 mg q12h and was studied in pivotal phase 3 trials
Maximally tolerated dose or exposure	The maximum tolerated dose of SUZ has not been determined. In healthy adult subjects, the highest single dose evaluated was 395 mg (Study 005 Part A) and the highest multiple dose and duration was 178 mg qd x 14 days (Study 005 Part B) and 200 mg x 7 days (QT study- Study 009).
Dose proportionality	The single doses of SUZ were evaluated in the range of 7.5 mg to 395 mg. The AUC_{0-inf} of SUZ and M6-SUZ increased approximately dose proportionally up to and including 171 mg and increased less than dose proportionally at higher doses, while C_{max} of SUZ and M6-SUZ increased less than dose proportionally across all doses. The PK after multiple doses of SUZ was evaluated up to 178 mg qd for 14 days. After multiple doses, both AUC_{0-24h} and C_{max} of SUZ and M6-SUZ on Day 14 increased approximately dose proportionally through doses up to 65 mg and slightly less than dose proportionally at higher doses.
Accumulation	The accumulation ratio based on simulations of a dose of 50 mg q12h for SUZ and M6-SUZ were 3.37 and 4.49, respectively.
Time to achieve steady-state	The concentrations near steady state (90% of steady state) are reached by Day 3 for SUZ and Day 5 for M6-SUZ and the steady state is reached by Day 16 for SUZ and Day 21 for M6-SUZ.
Bridge between to-be-marketed and clinical trial/study formulations	The 50 mg to-be-marketed tablet formulation was evaluated in the phase 3 studies. The bridge between phase 2 formulation (10-mg tablets) and to-be-marketed formulation (50-mg tablets) was via an in vivo relative BA study (Study 011).
Absorption	
Bioavailability	Absolute bioavailability of SUZ has not been determined.
T _{max}	SUZ: 3 hours (range: 1.5 to 5 hours); M6-SUZ: 10 hours (range: 4 to 48 hours)
Food effect (fed/fasted) Geometric least square mean and 90% CI	Administration of SUZ 100 mg with a high-fat meal (800 to 1000 calories, 50% derived from fat), a moderate-fat meal (600 calories, 30% derived from fat) and a low-fat meal (up to 500 calories with no more than 25% derived from fat) results in decreased initial concentrations of SUZ and M6-SUZ in comparison to a fasted state. The median T_{max} of SUZ and M6-SUZ in the fasted state is 3 hours and 8 to 10 hours, respectively. When administered in the fed state (a high-fat meal or a moderate-fat meal), the median T_{max} of SUZ was delayed to 5 hours and the median T_{max} of M6-SUZ was delayed to 24 hours. The C_{max} and AUC of SUZ and M6-SUZ were not affected by any of the meal conditions including a high-fat meal consumed 1 hour after the administration of SUZ. Administration of the second dose of 50 mg with or without regard to meals is predicted to not affect the systemic exposures of SUZ and M6-SUZ. Based on the observed decreased initial concentrations and delayed T_{max} with both moderate- and high-fat meals in comparison to a fasted condition, the labeling recommendation for food effect is, "Avoid consuming food from 2 hours before until 1 hour after the <u>first dose of JOURNAVX</u> to avoid delay in onset of pain relief. Subsequent doses of JOURNAVX can be taken with or without food."

Characteristic	Drug Information
	<i>Distribution</i>
Volume of distribution	Apparent volume of distribution based on the terminal phase (V_z/F) of SUZ is 495 L.
Plasma protein binding	Plasma protein binding was 99% for SUZ and 96% for M6-SUZ. Both albumin and alpha-1 acid glycoprotein contribute to SUZ and M6-SUZ binding in human plasma. In vitro blood-to-plasma concentration ratio was approximately 0.6 for both SUZ and M6-SUZ in humans.
Drug as substrate of transporters	SUZ is not a substrate for transporters (P-gp, BCRP, OATP1B1 or OATP1B3). M6-SUZ is a substrate for P-gp, but not other transporters.
	<i>Elimination</i>
Mass balance results	Following [^{14}C]SUZ oral administration, ~94% of the administered dose was recovered, out of which ~50% is recovered in feces [primarily as metabolites, unchanged parent (9.1%) and unchanged M6-SUZ (<0.9%)] and ~44% in urine (as metabolites)
Clearance	The mean plasma apparent clearance is 13.9 L/h
Half-life	Effective half-lives of SUZ and M6-SUZ are 24 hours and 33 hours, respectively.
Metabolic pathway(s)	SUZ and M6-SUZ are primarily metabolized by CYP3A, with a minor contribution from CYP2C9, CYP2C19, and CYP2C8.
Primary excretion pathways (% dose)	SUZ was mainly cleared by oxidative metabolism. After a single oral dose of [^{14}C]SUZ, 44.0% and 49.9% of the dose is excreted in urine and feces, respectively.
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	Body weight (44-126kg) did not have a clinically relevant impact on the PK of SUZ and M6-SUZ.
Age	Age (18-75 years) does not have a clinically relevant impact on the PK of SUZ and M6-SUZ.
Renal impairment	The PK of SUZ and M6-SUZ were not altered in patients with renal impairment of eGFR 15 to <60 mL/min (estimated by CKD-EPI equation with adjustment for the body surface area). The effect of renal impairment (eGFR <15 mL/min) and kidney failure not receiving dialysis on SUZ and M6-SUZ pharmacokinetics is unknown.
Hepatic impairment	In patients with moderate hepatic impairment (Child-Pugh Class B), the $C_{\max}$ and AUC_{0-12} SUZ were increased by 31% and 50%, respectively, and hence reduced dosing regimen of SUZ is needed in patients with moderate hepatic impairment (Child-Pugh Class B). SUZ was not studied in subjects with severe hepatic impairment (Child-Pugh Class C) and should not be used in that population.

Characteristic	Drug Information
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	SUZ inhibits CYP2C8, CYP2C9, and CYP2C19, but is not expected to result in clinically significant drug interactions. SUZ does not inhibit CYP1A2, CYP2B6, CYP2D6, and CYP3A enzymes, and M6-SUZ does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes. SUZ is CYP3A inducer in vitro. SUZ decreased the AUC of midazolam (a sensitive CYP3A substrate) by 48% and C_{max} by 37% (Study 010). Since SUZ decreases the exposure of CYP3A substrates and may compromise the efficacy, the review team included labeling recommendations for certain CYP3A substrates (refer to section 8.2.2). Compared to CYP3A, SUZ has lesser potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19. SUZ does not induce CYP1A2. SUZ has no significant effect on the PK of levonorgestrel and ethinyl estradiol and therefore, SUZ can be used with oral contraceptives containing levonorgestrel, norethindrone and ethinyl estradiol.
Inhibition/induction of transporter systems	SUZ is an inhibitor of P-gp in vitro. However, a clinical DDI study (010) showed that SUZ did not affect the PK of digoxin (P-gp substrate). No dosage adjustment of SUZ is needed when administered with P-gp substrates. SUZ and M6-SUZ inhibit OATP1B1, OATP1B3, OAT3 but is not expected to result in clinically significant drug interactions. SUZ and M6-SUZ does not inhibit BCRP OAT1, OCT2, MATE1, and MATE2/K transporters.
	<i>Drug Interaction Liability (Drug as Substrate)</i>
Inhibitors and inducers of metabolism	SUZ and M6-SUZ are CYP3A substrates. Itraconazole, a strong CYP3A inhibitor increased the AUC of SUZ and M6-SUZ by 4.79-fold and 4.42-fold, respectively (Study 008). Therefore, concomitant use with strong CYP3A inhibitors is contraindicated. When SUZ is concomitantly used with moderate CYP3A inhibitors, a dosage reduction of SUZ is recommended. Rifampin, a strong CYP3A inducer, decreased AUC of SUZ and M6-SUZ by 93% and 85%, respectively, and decreased the C_{max} of SUZ by 80% and increased that of M6-SUZ by 30% (Study 013). Avoid concomitant use of SUZ with strong and moderate CYP3A inducers.
Inhibitors/inducers of transporter systems	SUZ and M6-SUZ are not substrates of BCRP, OATP1B1 or OATP1B3. SUZ is not a P-gp substrate, but M6-SUZ is a P-gp substrate.

Source: Compiled data from 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods and 2.7.2 Summary of Clinical Pharmacology Studies

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; BE, bioequivalence or bioequivalent; CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; CL/F, apparent clearance; C_{max} , maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; DDI, drug-drug interaction; DRG, dorsal root ganglion; EPC, established pharmacologic class; FDA, Food and Drug Administration; h, hour; hrs, hours; kcal, kilocalorie; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MATE, multidrug and toxin extrusion protein; MS, mass spectrometry; ms, milliseconds; MTD, maximum tolerated dose; M6-SUZ, M6- metabolite of suzetrigine (active metabolite); Na_v , voltage-gated sodium channel; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetic; QTc, QT corrected for heart rate; SD, standard deviation; SUZ- suzetrigine; T_{max} , time to maximum plasma concentration; TQT, thorough QT; Vz/F, apparent volume of distribution

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Dosing regimen selection for the acute pain indication of SUZ is based on two phase 2 randomized, double-blind, placebo- and active-controlled dose-ranging studies in bunionectomy (Study 101) and abdominoplasty (Study 102). Study 101 evaluated the efficacy of three dosing regimens: 1) 100-mg loading dose (LD)/50 mg q12h for 36 hours, 2) 60-mg LD/30 mg q12h for 36 hours, and 3) 20-mg LD/10 mg q12h for 36 hours, while Study 102 evaluated two dosing regimens: 1) 100-mg LD/50 mg q12h for 36 hours, and 2) 60-mg LD/30 mg q12h for 36 hours. Regimens were evaluated against an active comparator, hydrocodone/acetaminophen 5/325 mg q6h for 36 hours, and against placebo. In each trial, pain intensity was measured using a patient-reported 11-point NPRS, ranging from 0 to 10, where 0 corresponded to no pain and 10 corresponded to the worst pain imaginable. The efficacy of SUZ was evaluated by SPID48 compared to placebo and HB/APAP. The primary efficacy criteria of SPID48 for SUZ compared to placebo was met at the highest dosing regimen, 100 mg/50 mg dosed at q12h for 36 hours. The magnitude of effect in the SUZ group with the highest dosing regimen was greater than those of the lower-dose groups, and no SUZ dose group other than the highest dose showed a statistically significant difference from placebo. Therefore, the highest dosing regimen of 100-mg LD/50 mg q12h was utilized in the pivotal phase 3 trials in the same pain models of bunionectomy and abdominoplasty. In both phase 3 trials, treatment with SUZ demonstrated statistically significant superior reduction in pain compared to placebo.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Study VX22-548-104 (Study 104)

6.2.1.1. Design, Study 104

Study 104 was a randomized, double-blind, placebo-controlled, three-arm, parallel-group study evaluating the efficacy and safety of SUZ in treating acute pain after a bunionectomy. The primary efficacy endpoint was the time-weighted SPID48 compared to placebo. The key secondary efficacy endpoints included SPID48 compared to HB/APAP and time to ≥ 2 -point reduction in NPRS from baseline compared to placebo. Additional design information is available in Section [15.1](#).

As described in the draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* ([February 2022](#)), the randomized, double-blind, repeat-dose design of this superiority study with a treatment duration of 48 hours is acceptable to support a finding of efficacy for a non-opioid analgesic. The primary outcome measure of NPRS is a patient-reported measure of pain

intensity that is well defined and reliable. The primary endpoint of sum of the pain intensity difference (SPID) over the prespecified treatment period is an acceptable analysis for an analgesic intended for acute pain. The time to onset of SUZ as an acute analgesic was evaluated in an acceptable manner using the times to ≥ 2 -point and ≥ 1 -point reduction in NPRS from baseline compared to placebo, as discussed at the July 14, 2022, end-of-phase 2 meeting.

6.2.1.2. Eligibility Criteria, Study 104

Males and females 18 to 80 years of age, inclusive, scheduled to undergo a primary unilateral bunionectomy with distal first metatarsal osteotomy (i.e., Austin procedure) and internal fixation under regional anesthesia (Mayo and popliteal sciatic block) were eligible for this study. After surgery, subjects must have reported pain that was moderate or severe on the VRS and ≥ 4 on the NPRS within 9 hours after removal of the popliteal sciatic block on Day 1.

Subjects who had a prior history of bunionectomy or other foot surgery on the index foot, or bunionectomy on the opposite foot as part of this study, were excluded. Subjects who had chronic use of opioids or NSAIDs with dose escalation within 30 days before admission or were unwilling or unable to stop analgesics at least 5 half-lives or 2 days (whichever was longer) before admission were also excluded.

See Section [15.1](#) for other inclusion and exclusion criteria.

6.2.1.3. Statistical Analysis Plan, Study 104

Study 104 assumed a standardized effect size of 0.4 for SUZ compared to placebo and 0.25 for SUZ compared to HB/APAP; 338 evaluable subjects per group for SUZ and HB/APAP and 169 evaluable subjects for placebo would provide more than 90% power for the primary endpoint of SUZ versus placebo on SPID48 and 90% power for the first key secondary endpoint of SUZ versus HB/APAP on SPID48. These calculations were based on two-sample t-tests at a two-sided significance level of 0.05. To account for a 15% dropout rate, a total of approximately 1,000 subjects were planned to be enrolled in Study 104.

The treatment effects assumed in the sample size planning for Study 104 appeared to be conservative as compared to the treatment effects estimated from the previously completed phase 2 study for bunionectomy surgical model; the estimated standardized effect size was 0.85 for SUZ versus placebo on SPID48 and 0.69 for SUZ versus HB/APAP on SPID48.

Analysis Sets

The all subjects set included all subjects who had been randomized or had received at least one dose of the study drug. This analysis set was used for subject listings and the disposition summary table.

The intent-to-treat (ITT) set included all randomized subjects. Subjects in the ITT set were analyzed according to their randomized treatment group.

The full analysis set (FAS) included all randomized subjects who had received at least one dose of study drug. Subjects in the FAS were analyzed according to their randomized treatment group. The FAS was used for summaries of subject demographics and baseline characteristics, and all efficacy analyses.

The safety set included all subjects who received at least one dose of study drug. Subjects in the safety set were analyzed according to the treatment they received. The safety set was used for all safety analyses.

Multiplicity Adjustment

A hierarchical testing procedure was used to control the overall type I error rate at a two-sided alpha level of 0.05 accounting for all the tests planned for the primary and key secondary endpoints. The testing order was as follows:

1. Primary endpoint: SUZ versus placebo on SPID48
2. First key secondary endpoint: SUZ versus HB/APAP on SPID48
3. Second key secondary endpoint: SUZ versus placebo on time to a ≥ 2 -point reduction in NPRS from baseline

Analysis of Primary Endpoint: SUZ Versus Placebo on SPID48

The Applicant defined pain intensity difference as the difference of NPRS scores between the baseline and a given time point. SPID was calculated as $\sum (t_{i-1} - t_i) \times PID_{t_i}$, where t_i was the scheduled time since first dose (in hours) for time point i , and PID_{t_i} was the NPRS at time point i minus NPRS at baseline. The primary endpoint was SPID48.

The primary analysis of SPID48 was based on the analysis of covariance model, which included SPID48 as the dependent variable, treatment arm (SUZ, HB/APAP, or placebo) as a fixed effect, and site and baseline NPRS as covariates. The treatment effect was estimated by the least-squares (LS) mean difference between SUZ and placebo at a two-sided alpha level of 0.05. The LS mean and its 95% confidence interval (CI) were provided for both the group comparison and each treatment group.

The Applicant used the following imputation methods under four different conditions:

1. Rescue medication use: A fixed imputation window of 6 hours was prespecified for ibuprofen. The prerescue NPRS score was collected immediately before the administration of rescue medication. The previous NPRS score was used if the prerescue score was missing, provided that the previous NPRS score did not include any observed score from the previous rescue period. In case of multiple administrations of rescue medication that led to overlapping rescue periods, the prerescue NPRS score (b) (4) replaced all NPRS scores (b) (4) through the end of the last overlapping rescue period.
2. Intercurrent event (ICE) of treatment discontinuation: The single imputation method of baseline observation carried forward (BOCF) was used for the treatment discontinuation due to an adverse event (AE). The single imputation method of last observation carried forward (LOCF) was used for treatment discontinuation due to all other reasons than AE.
3. Subject who completed the treatment but with missing data from a certain time point to hour 48: A single imputation method of LOCF was used to impute missing data.
4. Intermittently missing NPRS scores: Linear interpolation was used to impute intermittent missing data.

Sensitivity Analysis of the Primary Endpoint

The Applicant planned and conducted two sensitivity analyses for the primary endpoint. In the first sensitivity analysis, the last NPRS score prior to discontinuation was used to impute the missing NPRS scores following treatment discontinuation due to an AE. In the second sensitivity analysis, the same primary analysis was performed using the ITT Set. Randomized subjects who did not receive any study drug were assigned a value of 0 for the primary endpoint of SPID48.

Analysis of the Key Secondary Endpoints

For the first key secondary endpoint of SUZ versus HB/APAP on SPID48, the Applicant used the same imputation methods as described for the primary endpoint.

The second key secondary endpoint, time to ≥ 2 -point reduction in NPRS from baseline compared to placebo, was defined as the time elapsed from the first dose of the study drug until the first time the subject had at least a 2-point reduction in the NPRS from baseline. A Kaplan-Meier method was used to estimate the median time and the survival curve for each treatment group, and a log-rank test was used to compare the survival curves between the treatment groups. The median time with 95% CI from the Kaplan-Meier analysis and the p-value for the group comparison from the log-rank test were reported.

Subgroup Analyses

Subgroup analyses were performed for sex, age, and race.

6.2.1.4. Results of Analyses, Study 104

Demographics and Clinical Characteristics

The demographic and baseline characteristics of the FAS for Study 104 are shown in [Table 7](#). Percentages were calculated using the number of participants in each treatment group as the denominator. The three treatment groups were generally balanced on demographics and baseline characteristics. Overall, the study population was predominantly female (85%), White (71%) or Black or African American (24%), and aged 18 to 65 (91%).

Table 7. Baseline Demographics and Clinical Characteristics, FAS, Study 104

Characteristic	Placebo N=216	HB/APAP N=431	SUZ N=426	Total Population N=1073
Sex, n (%)				
Male	29 (13.4)	72 (16.7)	60 (14.1)	161 (15)
Female	187 (86.6)	359 (83.3)	366 (85.9)	912 (85)
Age, years				
Mean (SD)	48.1(13.5)	48.3 (12.6)	47.7 (13.3)	48.0 (13.1)
Median	49.0	50.0	49.0	49.0
Min, max	18, 74	18, 73	18, 75	18, 75
Age group (years), n (%)				
≥ 18 to <65	193 (89.4)	397 (92.1)	383 (89.9)	973 (90.7)
≥ 65	23 (10.6)	34 (7.9)	43 (10.1)	100 (9.3)

Characteristic	Placebo N=216	HB/APAP N=431	SUZ N=426	Total Population N=1073
Race, n (%)				
American Indian or Alaska Native	0	7 (1.6)	4 (0.9)	11 (1.0)
Asian	8 (3.7)	7 (1.6)	9 (2.1)	24 (2.2)
Black or African American	48 (22.2)	96 (22.3)	116 (27.2)	260 (24.2)
Multiracial	0	3 (0.7)	6 (1.4)	9 (0.8)
Native Hawaiian or other Pacific Islander	0	1 (0.2)	1 (0.2)	2 (0.2)
White	160 (74.1)	314 (72.9)	285 (66.9)	759 (70.7)
Missing		1 (0.2)	2 (0.5)	3 (0.3)
Other	0	2 (0.5)	3 (0.7)	5 (0.5)
Ethnicity, n (%)				
Hispanic	84 (38.9)	149 (34.6)	131 (30.8)	364 (33.9)
Non-Hispanic	132 (61.1)	282 (65.4)	295 (69.2)	709 (66.1)
Weight, kg				
Mean (SD)	75.66 (15.35)	75.65 (15.89)	75.78 (15.87)	75.70 (15.76)
Median	74.35	74	73.2	73.8
Min, max	46.2, 125.2	41.0, 123.4	44.0, 126.0	41.0, 126.0
Height, cm				
Mean (SD)	163.32 (8.87)	163.85 (9.32)	163.96 (8.93)	163.79 (9.07)
Median	162.56	163.00	163.00	163.00
Min, max	144.0, 198.0	142.2, 192.0	137.2, 194.0	137.2, 198.0
BMI, kg/m ²				
Mean (SD)	28.29 (4.77)	28.07 (4.82)	28.10 (4.93)	28.13 (4.85)
Median	27.79	27.54	27.77	27.75
Min, max	18.7, 39.6	17.8, 40.2	18.3, 39.7	17.8, 40.2
NPRS				
Mean (SD)	6.8 (1.8)	6.8 (1.9)	6.7 (1.8)	6.8 (1.8)
Median	7	7	7	7
Min, max	4, 10	4, 10	4, 10	4, 10
NPRS category, n (%)				
<8	143 (66.2)	274 (63.6)	274 (64.3)	691 (64.4)
≥8	73 (33.8)	157 (36.4)	152 (35.7)	382 (35.6)
VRS, n (%)				
Moderate	147 (68.1)	279 (64.7)	291 (68.3)	717 (66.8)
Severe	69 (31.9)	152 (35.3)	135 (31.7)	356 (33.2)

Source: Tables 10-2, 10-3 on page 32-34 of Clinical Study Report of VX22-548-104

Baseline value was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: BMI, body mass index; FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; max, maximum; min, minimum; N, number of patients in treatment arm; n, number of patients with given characteristic; NPRS, numeric pain rating scale; SD, standard deviation; SUZ, suzetrigine; VRS, verbal rating scale

Subject Disposition

In Study 104, a total of 1,075 subjects were randomized. There were two subjects who were randomized but not dosed, resulting in a total of 1,073 subjects in the FAS. Among them, 938 (87.4%) completed treatment. The most common reason for discontinuation of treatment was lack of efficacy (11.2%). The SUZ group had fewer discontinuations due to lack of efficacy (12.0%) than did the placebo group (16.2%) but had more than the HB/APAP group did (7.9%). One subject in the HB/APAP group discontinued due to a pretreatment AE. [Table 8](#) shows subject disposition.

Table 8. Subject Disposition, Study 104

Parameter n (%)	Placebo N=216	HB/APAP N=431	SUZ N=428	Total N=1075
Subjects enrolled and randomized	216 (100)	431 (100)	428 (100)	1075 (100)
All subjects set	216 (100)	431 (100)	428 (100)	1075 (100)
Full analysis set	216 (100)	431 (100)	426 (99.5)	1073 (99.8)
Safety set	216 (100)	431 (100)	426 (99.5)	1073 (99.8)
Completed treatment	177 (81.9)	389 (90.3)	372 (87.3)	938 (87.4)
Discontinued treatment	39 (18.1)	42 (9.7)	54 (12.7)	135 (12.6)
Adverse event	0	1 (0.2)	0	1 (0.1)
Lack of efficacy	35 (16.2)	34 (7.9)	51 (12.0)	120 (11.2)
Subject refused further dosing (not due to AE)	0	3 (0.7)	1 (0.2)	4 (0.4)
Did not meet eligibility criteria	0	1 (0.2)	0	1 (0.1)
Other noncompliance	2 (0.9)	1 (0.2)	1 (0.2)	4 (0.4)
Applicant decision	0	0	1 (0.2)	1 (0.1)
Other	2 (0.9)	2 (0.5)	0	4 (0.4)
Completed study ^a	208 (96.3)	419 (97.2)	418 (98.1)	1045 (97.4)
Discontinued study	8 (3.7)	12 (2.8)	8 (1.9)	28 (2.6)
Lost to follow-up	3 (1.4)	3 (0.7)	3 (0.7)	9 (0.8)
Withdrawal by subject	4 (1.9)	8 (1.9)	5 (1.2)	17 (1.6)
Other noncompliance	1 (0.5)	1 (0.2)	0	2 (0.2)

Source: Tables 10-1, page 31-32, of Applicant's Clinical Study Report of VX22-548-104

Notes: The all subjects set was defined as all subjects who were randomized or received at least 1 dose of study drug. The FAS was defined as all randomized subjects who received at least 1 dose of study drug; subjects were analyzed according to their randomized treatment group. The Safety Set was defined as all subjects who received at least 1 dose of study drug; subjects were analyzed according to the treatment they received. Percentages were calculated relative to the number of subjects in the FAS.

^a All subjects who completed the Safety Follow-up Visit

Abbreviations: AE, adverse event; FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; SUZ, suzetrigine

Protocol Deviations

An important protocol deviation (IPD) was defined as any protocol deviation that may have significantly affected the completeness, accuracy, and/or reliability of the study data or one that may have significantly affected a subject's rights, safety, or well-being.

A total of 54 (5.0%) subjects (17 subjects in SUZ, 22 subjects in HB/APAP, and 15 subjects in placebo) had one or more IPDs. Among all the IPDs, the most common protocol deviations were related to the study conduct/procedures (18 subjects, 1.7%). The next most common deviations were related to the randomization criteria (15 subjects, 1.4%), followed by deviations related to the eligibility criteria (14 subjects, 1.3%).

In general, the number of major protocol deviations that could potentially impact the efficacy analysis was small. The frequency of minor protocol deviations was similar across the three treatment groups. The minor protocol deviations that occurred were not anticipated to have a measurable effect on the efficacy analysis.

Rescue Medication Use

Rescue medication was ibuprofen 400 mg administered orally q6h as needed. [Table 9](#) below summarizes the rescue medication use from 0 to 48 hours by treatment group. The mean total usage was 1,009.3 mg in the placebo group and 862.9 mg in the SUZ group. [Table 10](#) below stratifies the rescue medication use by treatment group over time. The SUZ group had a similar proportion of subjects using rescue medication (69.5%) compared to the placebo group (69.4%) in the first 6 hours. The proportion of subjects using rescue medication in the SUZ and placebo

groups remained similar in each block of time through 48 hours. In contrast, the proportion of subjects using rescue medication in the HB/APAP group in the first 6 hours was considerably less (55.7%) than the SUZ and placebo groups.

Table 9. Summary of Rescue Medication Use From 0 to 48 Hours, FAS, Study 104

Characteristic	Placebo N=216	HB/APAP N=431	SUZ N=426
Number of subjects with use from 0 to 48 hours, n (%)	185 (85.6)	345 (80.0)	364 (85.4)
Total usage from 0 to 48 hours (mg)			
Mean (SD)	1,009.3 (741.0)	752.7 (665.1)	862.9 (655.8)
Median	800.0	400.0	800.0
Min, max	0, 3,200	0, 3,200	0, 3,200

Source: Table 11-10, page 46 of Applicant's Clinical Study Report of VX22-548-104

Note: Rescue medication was ibuprofen 400 mg administered orally q6h as needed.

Abbreviations: FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; max, maximum value; min, minimum value; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; q6h, every 6 hours; SUZ, suzetrigine

Table 10. Rescue Medication Use, Trial VX22-548-104

Characteristic	Placebo N=216 n (%)	HB/APAP N=431 n (%)	SUZ N=426 n (%)
Subjects using rescue medication from 0 to 6 hours	150 (69.4)	240 (55.7)	296 (69.5)
Subjects using rescue medication from 0 to 12 hours	173 (80.1)	304 (70.5)	346 (81.2)
Subjects using rescue medication from 0 to 24 hours	181 (83.8)	337 (78.2)	362 (85.0)
Subjects using rescue medication from 0 to 48 hours	185 (85.6)	345 (80.0)	364 (85.4)

Source: adcmres.xpt; Software: R; Table generated by the FDA CDS

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; N, number of subjects in the analysis set; SUZ, suzetrigine

Efficacy Results – Primary Endpoint

Study 104 demonstrated a statistically significant difference in SPID48 between SUZ and placebo groups. The results are presented in [Table 11](#). There was an estimated least squares (LS) mean difference in SPID48 of 29.3 (95% CI: 14.0, 44.6; p=0.0002) for SUZ compared to placebo. The two sensitivity analyses yielded similar results to the primary analysis.

Table 11. Primary Analysis of SPID48 Compared to Placebo, FAS, Study 104

Parameter	Placebo N=216	SUZ N=426
LS mean (SE)	70.6 (6.3)	99.9 (4.5)
LS mean difference (SE)	--	29.3 (7.8)
95% CI of LS mean difference	--	14.0, 44.6
p-value versus placebo	--	0.0002

Source: Table 11-2, page 38 of Applicant's Clinical Study Report of VX22-548-104

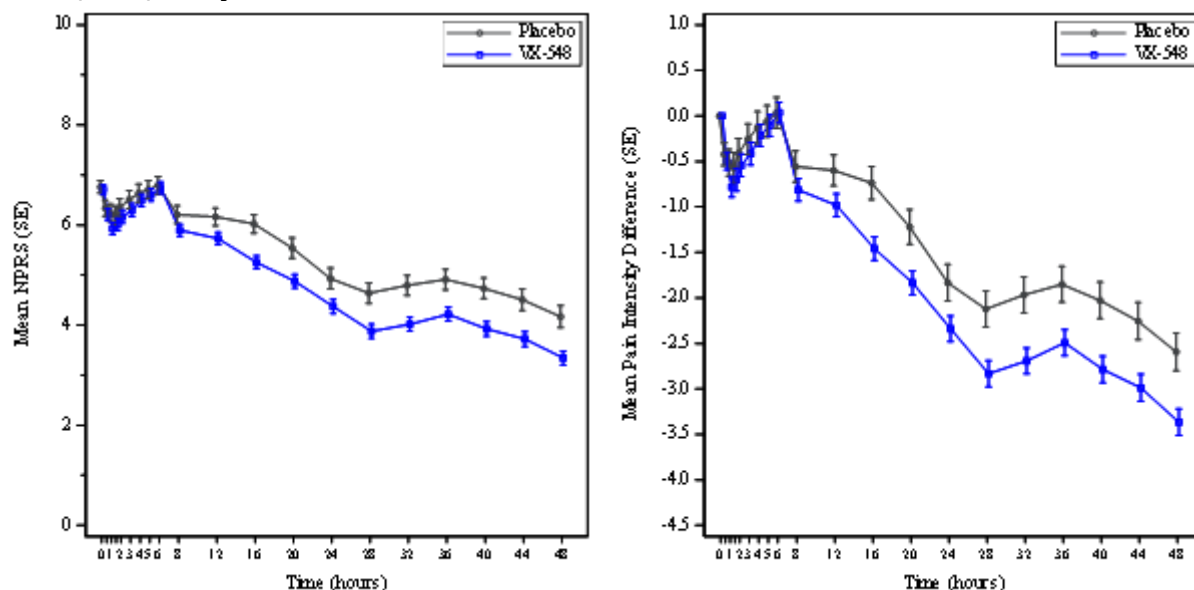
Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Subjects who received placebo, HB/APAP, or SUZ were included in the analysis; results for placebo and SUZ only are presented in this table.

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least-squares; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SE, standard error; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

[Figure 1](#) [left] displays the mean NPRS scores of the SUZ and placebo groups for Study 104. SUZ showed slightly lower mean NPRS scores from 2 to 8 hours and separated from the placebo group after Hour 8. [Figure 1](#) [right] displays mean pain intensity differences (defined as the

changes from baseline in NPRS score) of the SUZ and placebo groups for Study 104. The curves in both figures show a similar pattern.

Figure 1. Mean (SE) of NPRS (Left) and PID (Right) for the Primary Analysis at Scheduled Time Points, FAS, Study 104



Sources: Figure 11-1 on page 39 of Applicant's Clinical Study Report of VX22-548-104

Notes: NPRS scores and PID at baseline (defined as the most recent nonmissing measurement [scheduled or unscheduled] collected before the first dose of study drug) were plotted at 0 hours on the x-axis. At each scheduled time point, the PID was defined as the NPRS score at that time point - NPRS score at baseline.

Abbreviations: FAS, full analysis set; NPRS, numeric pain rating scale; PID, pain intensity difference; SE, standard error; SUZ, suzetrigine (VX-548)

The review team was able to verify the primary and sensitivity results of the primary endpoint using the datasets submitted by the Applicant.

Efficacy Results - Secondary Endpoints

The analysis results of the first key secondary endpoint of SUZ versus HB/APAP on SPID48 are shown in [Table 12](#). The Applicant conducted a two-sided test for comparing SUZ to HB/APAP on SPID48, which resulted in a p-value of 0.0016, indicating that there was a statistically significant difference between SUZ and HB/APAP in terms of SPID48. The LS mean difference calculated as SPID48 in SUZ minus SPID48 in HB/APAP, where the HB/APAP group was treated as the reference group, was estimated to be -20.2 (95% CI: -32.7, -7.7), further indicating that subjects in the SUZ group had less pain reduction than did those in the HB/APAP group. Above mentioned results indicate that the Applicant failed to demonstrate superiority of SUZ over HB/APAP on SPID48.

Table 12. First Key Secondary Analysis of SPID48 Compared to HB/APAP, FAS, Study 104

Statistic	HB/APAP N=431	SUZ N=426
LS mean (SE)	120.1 (4.5)	99.9 (4.5)
LS mean difference (SE)	--	-20.2 (6.4)
95% CI of LS mean difference	--	-32.7, -7.7
p-value ^a versus HB/APAP	--	0.0016 ^b

Source: Table 11-4, page 41 of Applicant's Clinical Study Report of VX22-548-104.

Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Subjects who received placebo, HB/APAP, or SUZ were included in the analysis; results for HB/APAP and SUZ only are presented in this table. Analysis was performed using the same imputation scheme as the primary analysis (Table 9-3).

^a The HB/APAP group was considered as reference group in the analysis. P-value was obtained from a two-sided test of SUZ compared to HB/APAP.

^b The p-value from a two-sided test for a difference between SUZ and HB/APAP was 0.0016. Based on the reviewer's calculation, a one-sided test for a superiority of SUZ over HB/APAP resulted in a p-value of 0.9992.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; LS, least-squares; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SE, standard error; SUZ, suzetrigine

The testing hierarchy stopped at this first key secondary endpoint, and any analysis of the second key secondary endpoint was considered exploratory. Results of the second key secondary endpoint of time to ≥ 2 -point reduction in NPRS from baseline compared to placebo are summarized in Section [16](#) considering its exploratory nature.

6.2.2. Study VX22-548-105 (Study 105)

6.2.2.1. Design, Study 105

Study 105 was a randomized, double-blind, placebo-controlled, three-arm, parallel-group study evaluating the efficacy and safety of SUZ in treating acute pain after an abdominoplasty. The primary efficacy endpoint was the SPID48 compared to placebo. The key secondary efficacy endpoints included SPID48 compared to HB/APAP and time to ≥ 2 -point reduction in NPRS from baseline compared to placebo. The overall study design was consistent with that of Study 104. The major differences were study procedures related to abdominoplasty, the anesthetic used for surgery, and procedure-specific subject selection criteria. As with Study 104, the design of this superiority study with a treatment duration of 48 hours was acceptable to support a finding of efficacy for a non-opioid analgesic. Additional design information is available in Section [14.7](#).

6.2.2.2. Eligibility Criteria, Study 105

Males and females 18 to 80 years of age, inclusive, scheduled to undergo a standard ("full") abdominoplasty procedure were eligible for this study. Additional inclusion criteria regarding the procedure consisted of the following: the procedure must have included a horizontally oriented incision approximately extending to each anterior superior iliac spine, umbilical dissection and relocation, and plication of the fascia of the rectus muscle above and/or below the umbilical stalk; may have included drain placement and skin closure at the discretion of the surgeon; and must NOT have included a vertically oriented supraumbilical incision or collateral procedures (e.g., liposuction). After surgery, subjects must have reported pain that was moderate or severe on the VRS and ≥ 4 on the NPRS within 4 hours after surgery completion on Day 1. In addition,

the abdominoplasty procedure duration must have been ≤ 3 hours. Lastly, all analgesic guidelines must have been followed during and after abdominoplasty including the use of intravenous general anesthesia along with infiltration of 1% lidocaine without epinephrine at the surgical site after completing the rectus plication.

Subjects who had a prior history of abdominoplasty were excluded. Subjects who had a history of intra-abdominal and/or pelvic surgery that resulted in any complications or, in the opinion of the investigator or medical monitor, would preclude participation in the study were also excluded. The eligibility criteria were otherwise generally consistent with those of Study 104.

See Section [15.2](#) for other inclusion and exclusion criteria.

6.2.2.3. Statistical Analysis Plan, Study 105

The sample size planning for Study 105 was identical to that for Study 104. The treatment effects assumed in the sample size planning for Study 105 were also conservative as compared to the treatment effects estimated from the previously completed phase 2 study in the abdominoplasty surgical model; the estimated standardized effect size was 0.88 for SUZ versus placebo on SPID48, and 0.78 for SUZ versus HB/APAP on SPID48.

Since the statistical approaches used in Study 105 were identical to those used in Study 104, refer to Section [6.2.1.3](#) for details of the statistical analysis plan (SAP).

6.2.2.4. Results of Analyses, Study 105

Demographics and Clinical Characteristics

The demographic and baseline characteristics of the FAS for Study 105 are shown in [Table 13](#). Percentages were calculated using the number of participants in each treatment group as the denominator. The three treatment groups were generally balanced on demographics and baseline characteristics. Overall, the study population was predominantly female (98%), White (70%) or Black or African American (27%), and aged 18 to 65 (>99%).

Table 13. Baseline Demographics and Clinical Characteristics, FAS, Study 105

Characteristic	Placebo N=223	HB/APAP N=448	SUZ N=447	Total Population N=1118
Sex, n (%)				
Male	3 (1.3)	7 (1.6)	10 (2.2)	20 (1.8)
Female	220 (98.7)	441 (98.4)	437 (97.8)	1098 (98.2)
Age, years				
Mean (SD)	41.5 (8.5)	42.1 (8.7)	41.5 (9.1)	41.8 (8.8)
Median	42.0	42.0	41.0	41.0
(min, max)	18, 62	21, 67	19, 69	18, 69
Age group (years), n (%)				
≥18 to <65	223 (100.0)	447 (99.8)	443 (99.1)	1113 (99.6)
≥65	0	1 (0.2)	4 (0.9)	5 (0.4)
Race, n (%)				
American Indian or Alaska Native	1 (0.4)	0	5 (1.1)	6 (0.5)
Asian	0	9 (2.0)	7 (1.6)	16 (1.4)
Black or African American	62 (27.8)	114 (25.4)	123 (27.5)	299 (26.7)
Multiracial	2 (0.9)	4 (0.9)	2 (0.4)	8 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.4)	5 (1.1)	3 (0.7)	9 (0.8)
White	155 (69.5)	316 (70.5)	307 (68.7)	778 (69.6)
Other	2 (0.9)	0	0	2 (0.2)
Ethnicity, n (%)				
Hispanic	73 (32.7)	157 (35.0)	150 (33.6)	380 (34.0)
Non-Hispanic	150 (67.3)	288 (64.3)	297 (66.4)	735 (65.7)
Missing	0	3 (0.7)	0	3 (0.3)
Weight, kg				
Mean (SD)	79.49 (12.55)	78.25 (13.79)	78.12 (13.32)	78.44 (13.36)
Median	78.47	77.95	76.0	77.0
Min, max	51.0, 110.8	42.0, 118.0	49.5, 122.0	42.0, 122.0
Height, cm				
Mean (SD)	163.87 (7.65)	162.99 (7.23)	163.32 (7.28)	163.30 (7.33)
Median	164.00	163.00	163.00	163.00
Min, max	137.2, 195.6	136.0, 186.0	144.8, 191.0	136.0, 195.6
BMI, (kg/m ²)				
Mean (SD)	29.58 (4.20)	29.38 (4.37)	29.21 (4.06)	29.35 (4.21)
Median	29.10	29.46	29.07	29.35
Min, max	20.5, 41.5	19.6, 41.1	19.4, 39.2	19.4, 41.5
NPRS				
Mean (SD)	7.5 (1.7)	7.4 (1.7)	7.3 (1.7)	7.4 (1.7)
Median	8	7	7	7
Min, max	4, 10	4, 10	4, 10	4, 10
NPRS category, n (%)				
<8	111 (49.8)	229 (51.1)	227 (50.8)	567 (50.7)
≥8	112 (50.2)	219 (48.9)	220 (49.2)	551 (49.3)
VRS, n (%)				
Moderate	127 (57.0)	262 (58.5)	266 (59.5)	655 (58.6)
Severe	96 (43.0)	186 (41.5)	181 (40.5)	463 (41.4)

Source: Tables 10-2, 10-3 on page 33-34 of Applicant's Clinical Study Report of VX22-548-105

Baseline value was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: BMI, body mass index; FAS, full analysis set; max, maximum; min, minimum; N, number of patients in treatment arm; n, number of patients with given characteristic; NPRS, numeric pain rating scale; SD, standard deviation; SUZ, suzetrigine; VRS, verbal rating scale

In Study 105, a total of 1,118 subjects were randomized. All randomized subjects received at least one dose of study drug, resulting in a total of 1,118 subjects in the FAS. The most common reason for discontinuation of treatment was lack of efficacy (13.3%). The SUZ group had fewer discontinuations due to lack of efficacy (9.4%) than did the placebo group (21.5%) and the HB/APAP group (13.2%). A total of 12 (1.1%) subjects discontinued the treatment due to AEs. There was one subject who was randomized to the placebo group yet received one dose of SUZ due to an error in dispensing study drug kits at a single site. This subject was counted in the placebo group for the FAS and in the SUZ group for the safety set. [Table 14](#) shows the subject disposition for Study 105.

Table 14. Subject Disposition, Study 105

Parameter n (%)	Placebo	HB/APAP	SUZ	Total
Subjects enrolled and randomized	223 (100)	448 (100)	447 (100)	1118 (100)
All subjects set	223 (100)	448 (100)	447 (100)	1118 (100)
Full analysis set ^a	223 (100)	448 (100)	447 (100)	1118 (100)
Safety set ^a	222 (99.6)	448 (100)	448 (100 ^a)	1118 (100)
Completed treatment	168 (75.3)	382 (85.3)	396 (88.6)	946 (84.6)
Discontinued treatment	55 (24.7)	66 (14.7)	51 (11.4)	172 (15.4)
Adverse event	1 (0.4)	5 (1.1)	6 (1.3)	12 (1.1)
Lack of efficacy	48 (21.5)	59 (13.2)	42 (9.4)	149 (13.3)
Subject refused further dosing (not due to AE)	1 (0.4)	0	0	1 (0.1)
Did not meet eligibility criteria	0	0	1 (0.2)	1 (0.1)
Other noncompliance	3 (1.3)	1 (0.2)	1 (0.2)	5 (0.4)
Applicant decision	1 (0.4)	0	1 (0.2)	2 (0.2)
Other	1 (0.4)	1 (0.2)	0	2 (0.2)
Completed study ^b	206 (92.4)	426 (95.1)	423 (94.6)	1055 (94.4)
Discontinued study	17 (7.6)	22 (4.9)	24 (5.4)	63 (5.6)
Lost to follow-up	10 (4.5)	17 (3.8)	19 (4.3)	46 (4.1)
Adverse event	1 (0.4)	2 (0.4)	0	3 (0.3)
Withdrawal by subject	3 (1.3)	2 (0.4)	2 (0.4)	7 (0.6)
Death	1 (0.4)	0	0	1 (0.1)
Applicant decision	1 (0.4)	0	0	1 (0.1)
Other	1 (0.4)	0	1 (0.2)	2 (0.2)
Other noncompliance	0	1 (0.2)	2 (0.4)	3 (0.3)

Source: Tables 10-1, page 31-32, of Applicant's Clinical Study Report of VX22-548-105

Notes: The all subjects set was defined as all subjects who were randomized or received at least 1 dose of study drug. The FAS was defined as all randomized subjects who received at least 1 dose of study drug; subjects were analyzed according to their randomized treatment group. The Safety Set was defined as all subjects who received at least 1 dose of study drug; subjects were analyzed according to the treatment they received. Percentages were calculated relative to the number of subjects in the FAS

^a Due to an error in dispensing study drug kits at 1 site, 1 subject was randomized to the placebo group yet received 1 dose of active SUZ. This subject was counted in the placebo group for the FAS and in the SUZ group for the Safety Set

^b All subjects who completed the Safety Follow-up Visit

Abbreviations: AE, adverse event; FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; SUZ, suzetrigine

Protocol Deviations

A total of 49 (4.4%) subjects (19 subjects in SUZ, 17 subjects in HB/APAP, and 13 subjects in placebo) had one or more IPDs. Among those IPDs, the most common protocol deviations were related to the eligibility criteria (26 subjects, 2.3%). The next most common deviations were related to the informed consent (10 subjects, 0.9%), followed by deviations related to the randomization criteria (9 subjects, 0.8%).

In general, the number of major protocol deviations that could potentially impact the efficacy analysis was small. The frequency of minor protocol deviations was similar across the three treatment groups. The minor protocol deviations that occurred were not anticipated to have a measurable effect on the efficacy analysis.

Rescue Medication Use

Rescue medication was ibuprofen 400 mg administered orally q6h as needed. [Table 15](#) below summarizes the rescue medication use from 0 to 48 hours by treatment group. The mean total usage was 1,164.1 mg in the placebo group and 979 mg in the SUZ group. [Table 16](#) stratifies the rescue medication use by treatment group over time. The SUZ group had a lower proportion of subjects using rescue medication (64.5%) compared to the placebo group (82.4%) in the first 6 hours. The proportion of subjects using rescue medication in the HB/APAP group in the first 6 hours was 72.1% which is more than the SUZ group (64.5%) but less than the placebo group (82.4%).

Table 15. Summary of Rescue Medication Use From 0 to 48 Hours, FAS, Study 105

Characteristic	Placebo N=223	HB/APAP N=448	SUZ N=447
Number of subjects with use from 0 to 48 hours, n (%)	196 (87.9)	370 (82.6)	362 (81.0)
Total usage from 0 to 48 hours (mg)			
Mean (SD)	1164.1 (872.5)	942.0 (773.7)	979.0 (817.0)
Median	1200.0	800.0	800.0
Min, max	0, 3200	0, 3600	0, 3200

Source: Table 11-10, page 46 of Applicant's Clinical Study Report of VX22-548-105

Note: Rescue medication was ibuprofen 400 mg administered orally q6h as needed.

Abbreviations: FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; max, maximum value; min, minimum value; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; q6h, every 6 hours; SD, standard deviation; SUZ, suzetrigine

Table 16. Rescue Medication Use, Study 105

Characteristic	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Subjects using rescue medication from 0 to 6 hours	289 (64.5)	323 (72.1)	183 (82.4)
Subjects using rescue medication from 0 to 12 hours	321 (71.7)	348 (77.7)	191 (86.0)
Subjects using rescue medication from 0 to 24 hours	352 (78.6)	360 (80.4)	194 (87.4)
Subjects using rescue medication from 0 to 48 hours	363 (81.0)	370 (82.6)	195 (87.8)

Source: adcmres.xpt; Software: R; Table generated by the FDA CDS

Efficacy Results – Primary Endpoint

Study 105 demonstrated a statistically significant difference in SPID48 between the SUZ and placebo groups. The results are presented in [Table 17](#). There was an estimated LS mean difference in SPID48 of 48.4 (95% CI: 33.6, 63.1; p <0.0001) for SUZ compared to placebo. The two sensitivity analyses yielded similar results to the primary analysis.

Table 17. Primary Analysis of SPID48 Compared to Placebo, FAS, Study 105

Statistic	Placebo N=223	SUZ N=447
LS mean (SE)	70.1 (6.1)	118.4 (4.3)
LS mean difference (SE)	--	48.4 (7.5)
95% CI of LS mean difference	--	33.6, 63.1
p-value versus placebo	--	<0.0001

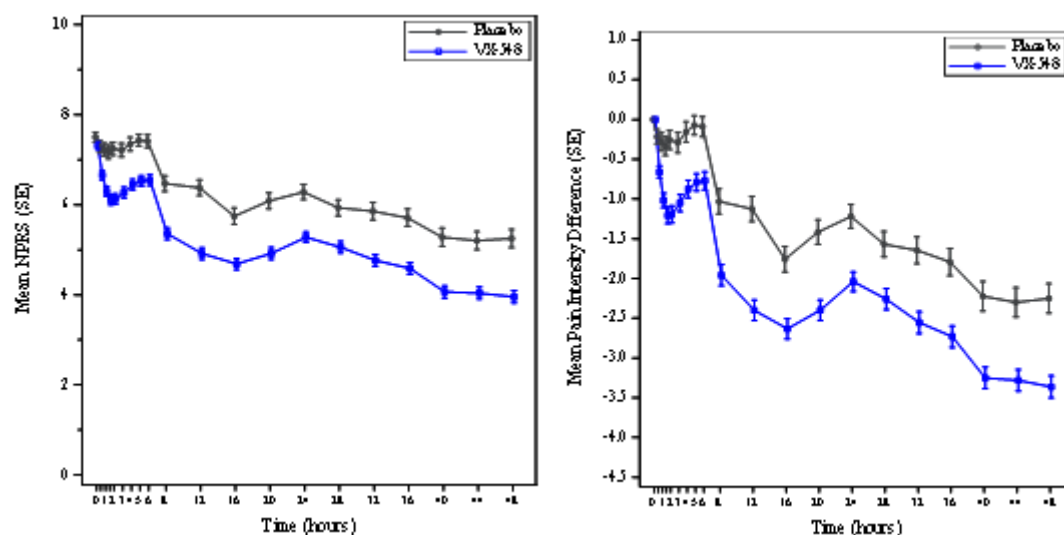
Source: Table 11-2, page 38 of Applicant's Clinical Study Report of VX22-548-105

Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Subjects who received placebo, HB/APAP, or SUZ were included in the analysis; results for placebo and SUZ only are presented in this table.

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least-squares; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SE, standard error; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

[Figure 2](#) [left] displays the mean NPRS scores of the SUZ and placebo groups for Study 105. SUZ showed significantly lower mean NPRS scores compared to placebo starting at a very early stage (first evaluated time point) in the study. [Figure 2](#) [right] displays the mean pain intensity differences of the SUZ and placebo groups for Study 105. The curves in both figures show a similar pattern.

Figure 2. Mean (SE) of NPRS (Left) and PID (Right) for the Primary Analysis at Scheduled Time Points, FAS, Study 105



Sources: Figure 11-1 on page 39 of Applicant's Clinical Study Report of VX22-548-105

Notes: NPRS scores and PID at baseline (defined as the most recent nonmissing measurement [scheduled or unscheduled] collected before the first dose of study drug) were plotted at 0 hours on the x-axis. At each scheduled time point, the PID was defined as the NPRS score at that time point - NPRS score at baseline.

Abbreviations: FAS, full analysis set; NPRS, numeric pain rating scale; PID, pain intensity difference; SE, standard error; SUZ, suzetrigine (VX-548)

Efficacy Results—Secondary Endpoints

The analysis results of the first key secondary endpoint of SUZ versus HB/APAP on SPID48 are shown in [Table 18](#). In Study 105, both a two-sided p-value of 0.2781 and an estimated LS mean difference (SPID48 in SUZ minus SPID48 in HB/APAP), where the HB/APAP group was treated as the reference group, of 6.6 (95% CI: -5.4, 18.7) indicate that the Applicant failed to demonstrate superiority of SUZ over HB/APAP on SPID48.

Table 18. First Key Secondary Analysis of SPID48 Compared to HB/APAP, FAS, Study 105

Statistic	Study 105	
	HB/APAP N=216	SUZ N=447
LS mean (SE)	111.8 (4.3)	118.4 (4.3)
LS mean difference (SE)	--	6.6 (6.1)
95% CI of LS mean difference	--	-5.4, 18.7
p-value ^a versus HB/APAP	--	0.2781 ^b

Source: Table 11-4, page 41 of Applicant's Clinical Study Report of VX22-548-104, Table 11-4, page 41 of Applicant's Clinical Study Report of VX22-548-105

Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Subjects who received placebo, HB/APAP, or SUZ were included in the analysis; results for HB/APAP and SUZ only are presented in this table. Analysis was performed using the same imputation scheme as the primary analysis (Table 9-3).

^a The HB/APAP group was considered as reference group in the analysis. P-value was obtained from a two-sided test of SUZ compared to HB/APAP.

^b The p-value from a two-sided test for a difference between SUZ and HB/APAP was 0.2781. Based on the reviewer's calculation, a one-sided test for a superiority of SUZ over HB/APAP resulted in a p-value of 0.1391.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; LS, least-squares; n, number of subjects; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SE, standard error; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

The testing hierarchy stopped at this first key secondary endpoint and any analysis of the second key secondary endpoint was considered exploratory. Results of the second key secondary endpoint of time to ≥ 2 -point reduction in NPRS from baseline compared to placebo are summarized in Section [16.2](#) considering its exploratory nature.

6.3. Key Efficacy Review Issues

6.3.1. Potential Differences in Efficacy Between Pain Models

Issue

Is there a major difference in the efficacy of SUZ between the bony and soft tissue pain models evaluated in the phase 3 acute pain studies?

Background

The results from two randomized, double-blind, placebo- and active-controlled phase 3 studies were used to demonstrate the efficacy of SUZ in treating moderate to severe acute pain. Two established acute pain models were utilized: bunionectomy for bony tissue pain (Study 104) and abdominoplasty for soft tissue pain (Study 105). Though each study was convincing on its own to establish effectiveness, differences in the time course of pain relief were observed suggesting that the effect of SUZ on acute pain could be pain model dependent. Specifically, in the abdominoplasty study the SUZ group demonstrated a greater mean pain intensity difference (PID) compared to placebo with sustained separation between the groups at all evaluated time points (i.e., 0 to 48 hours). For the bunionectomy study, the SUZ group also demonstrated a greater mean PID compared to placebo; however, the separation between pain curves was only sustained from 8 through 48 hours. To evaluate this difference in the time course of pain relief

and the potential cause(s), perioperative pain management, baseline characteristics, and rescue medication use were assessed between Study 104 and Study 105.

Perioperative Pain Management

In Study 104, the bunionectomy was performed under regional anesthesia (Mayo and popliteal sciatic block) with intravenous sedation. Postoperatively, a continuous popliteal sciatic block infusion (0.2% ropivacaine) was initiated and remained in place until approximately 3 a.m., but no later than 5 a.m., on post-operative Day 1. Subjects were eligible for the study if they met the VRS and NPRS criteria within 9 hours after removal of the popliteal sciatic infusion.

Ropivacaine boluses and/or infusion rate changes were permitted to be used as needed prior to removal of the popliteal block for subjects with an NPRS score of ≥ 4 ; however, boluses were not to be used at the time of block removal.

In Study 105, the abdominoplasty was performed under intravenous general anesthesia with fentanyl citrate and propofol, along with infiltration of 1% lidocaine at the surgical site, after completing the rectus plication. The rectus plication is typically performed toward the end of the abdominoplasty and involves suturing separated abdominal muscles together to restore abdominal strength. Subjects were eligible for the study if they met the VRS and NPRS criteria within 4 hours after surgery completion.

Baseline Characteristics

Baseline characteristics were compared between Study 104 and 105. Refer to the Tables of Baseline Demographics for Studies 104 and 105 in Section 6.2. While the baseline characteristics were similar between the SUZ and placebo groups within each study, there were differences in baseline characteristics between Study 104 and 105. Overall, the SUZ group in Study 104 (bunionectomy) as compared to Study 105 (abdominoplasty) enrolled a decreased percentage of women (85.9 vs. 97.8), subjects of increased age (median: 49 vs. 41 years), and lower BMI (median 27.77 vs. 29 kg/m²). As noted in the excerpted tables below, though the median NPRS scores were similar between Study 104 and 105, the mean NPRS was lower in Study 104 (6.7 vs. 7.3 in Study 105) and a lower percentage of subjects reported severe pain on the VRS in Study 104 (31.7 vs. 40.5 in Study 105).

Table 19. Baseline Demographics and Clinical Characteristics, FAS, Study 104

Characteristic	Placebo N=216	HB/APAP N=431	SUZ N=426	Total Population N=1073
NPRS				
Mean (SD)	6.8 (1.8)	6.8 (1.9)	6.7 (1.8)	6.8 (1.8)
Median	7	7	7	7
Min, max	4, 10	4, 10	4, 10	4, 10
NPRS category, n (%)				
<8	143 (66.2)	274 (63.6)	274 (64.3)	691 (64.4)
≥ 8	73 (33.8)	157 (36.4)	152 (35.7)	382 (35.6)

Characteristic	Placebo N=216	HB/APAP N=431	SUZ N=426	Total Population N=1073
VRS, n (%)				
Moderate	147 (68.1)	279 (64.7)	291 (68.3)	717 (66.8)
Severe	69 (31.9)	152 (35.3)	135 (31.7)	356 (33.2)

Source: Tables 10-2, 10-3 on page 32-34 of Clinical Study Report of VX22-548-104

Baseline value was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; max, maximum; min, minimum; N, number of patients in treatment arm; n, number of patients with given characteristic; NPRS, numeric pain rating scale; SD, standard deviation; SUZ, suzetrigine; VRS, verbal rating scale

Table 20. Baseline Demographics and Clinical Characteristics, FAS, Study 105

Characteristic	Placebo N=223	HB/APAP N=448	SUZ N=447	Total Population N=1118
NPRS				
Mean (SD)	7.5 (1.7)	7.4 (1.7)	7.3 (1.7)	7.4 (1.7)
Median	8	7	7	7
Min, max	4, 10	4, 10	4, 10	4, 10
NPRS category, n (%)				
<8	111 (49.8)	229 (51.1)	227 (50.8)	567 (50.7)
≥8	112 (50.2)	219 (48.9)	220 (49.2)	551 (49.3)
VRS, n (%)				
Moderate	127 (57.0)	262 (58.5)	266 (59.5)	655 (58.6)
Severe	96 (43.0)	186 (41.5)	181 (40.5)	463 (41.4)

Source: Tables 10-2, 10-3 on page 33-34 of Applicant's Clinical Study Report of VX22-548-105

Baseline value was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: FAS, full analysis set; max, maximum; min, minimum; N, number of patients in treatment arm; n, number of patients with given characteristic; NPRS, numeric pain rating scale; SD, standard deviation; SUZ, suzetrigine; VRS, verbal rating scale

Rescue Medication Use

Study 104 and 105 used ibuprofen 400 mg orally q6h as needed for rescue medication. [Table 21](#) and [Table 22](#) are reproduced below from sections [6.2.1.4](#) and [6.2.2.4](#), respectively, so that the rescue medication use can be compared between the SUZ and placebo groups in Studies 104 and 105. The percentage of subjects using rescue medication from 0 to 6 hours was of greatest interest in assessing the potential cause(s) of differences in the time course of pain relief (i.e., separation or non-separation of pain curves). [Table 21](#) shows that the percentage of subjects using rescue medication in Study 104 (bunionectomy) was nearly identical between the placebo and SUZ groups during the 0- to 6-hour time block (69.4% vs. 69.5%) as well as throughout the study. [Table 22](#) shows that the percentage of subjects using rescue medication in Study 105 (abdominoplasty) was higher in the placebo group compared to the SUZ group for the 0- to 6-hour time block (82.4% vs. 64.5%) as well as at 48 hours.

Table 21. Rescue Medication Use, Study 104

Characteristic	Placebo N=216 n (%)	HB/APAP N=431 n (%)	SUZ N=426 n (%)
Subjects using rescue medication from 0 to 6 hours	150 (69.4)	240 (55.7)	296 (69.5)
Subjects using rescue medication from 0 to 12 hours	173 (80.1)	304 (70.5)	346 (81.2)
Subjects using rescue medication from 0 to 24 hours	181 (83.8)	337 (78.2)	362 (85.0)
Subjects using rescue medication from 0 to 48 hours	185 (85.6)	345 (80.0)	364 (85.4)

Source: adcmres.xpt; Software: R; Table generated by the FDA CDS

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; N, number of subjects in the analysis set; SUZ, suzetrigine

Table 22. Rescue Medication Use, Study 105

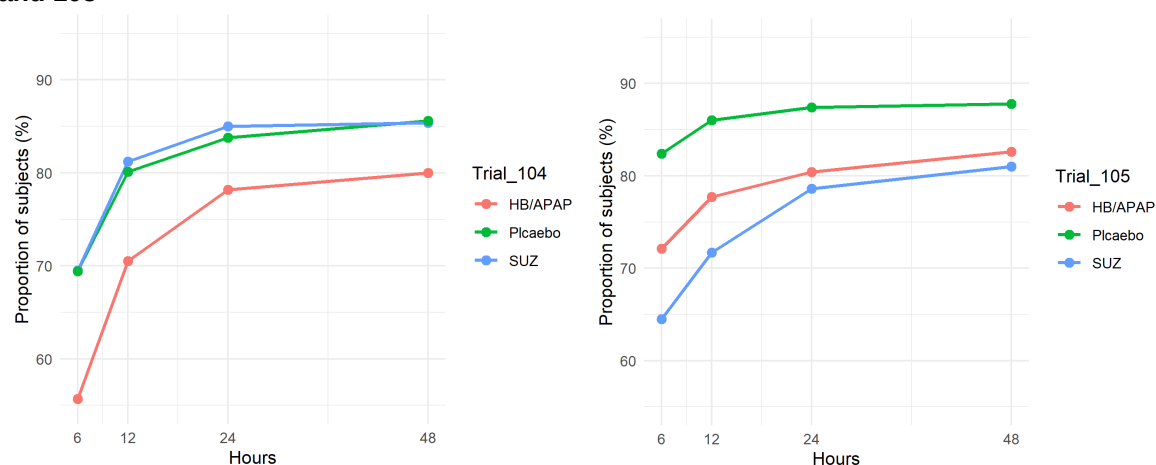
Characteristic	Placebo N=222 n (%)	HB/APAP N=448 n (%)	SUZ N=448 n (%)
Subjects using rescue medication from 0 to 6 hours	183 (82.4)	323 (72.1)	289 (64.5)
Subjects using rescue medication from 0 to 12 hours	191 (86.0)	348 (77.7)	321 (71.7)
Subjects using rescue medication from 0 to 24 hours	194 (87.4)	360 (80.4)	352 (78.6)
Subjects using rescue medication from 0 to 48 hours	195 (87.8)	370 (82.6)	363 (81.0)

Source: adcmres.xpt; Software: R; Table generated by the FDA CDS

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; N, number of subjects in the analysis set; SUZ, suzetrigine

Below are figures plotted at timepoints of 6, 12, 24, 48 hours to illustrate trends based on proportions of subjects using rescue medication.

Figure 3. Proportion of Subjects Using Rescue Medication at Specified Time Points, Studies 104 and 105



Source: CDS-generated figures

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen; SUZ, suzetrigine

Assessment

The study populations enrolled in Study 104 and Study 105 had some differences in baseline demographics and clinical characteristics, including a difference in mean NPRS between Study 104 and Study 105 (6.7 vs. 7.3). However, it is unlikely that these accounted for the differences in the time course of pain relief between the two studies (i.e., the lack of separation of the pain curves from 0 to 8 hours in Study 104 as compared to Study 105). Additionally, Studies 104 and

105 were identical with respect to study drug administration, endpoints assessed, and statistical analysis.

Moreover, the rescue medication use in Study 104 was evaluated to determine if significant differences in usage between the SUZ and placebo groups accounted for the lack of separation of the pain curves in that study. [Table 21](#) showed that the percentage of subjects using rescue medication use was nearly identical between the SUZ and placebo groups from 0 to 6 hours and remained similar for the duration of the treatment period (i.e., through 48 hours). Therefore, rescue medication use does not appear to account for the lack of separation of pain curves in Study 104.

Lastly, there were significant differences in perioperative pain management between Study 104 (bunionectomy) and Study 105 (abdominoplasty). As noted above, Study 104 was performed under regional anesthesia with ropivacaine, both as the nerve block and then as a postoperative nerve block infusion. Notably, ropivacaine is a non-selective sodium channel blocker which targets voltage-gated sodium channels, including Nav1.8. In contrast, Study 105 used intravenous general anesthesia, which does not act on sodium channels, during the procedure. However, lidocaine, a non-selective sodium channel blocker, was administered for localized anesthesia toward the end of the abdominoplasty procedure while performing the rectus plication. Therefore, the duration of action of ropivacaine and lidocaine, and the overlap of the duration of action of each drug with the first administration of SUZ was critical to understanding the differences in pain curves between these two surgical pain models.

A nerve block with ropivacaine, as in Study 104, typically provides analgesia for at least 4-8 hours, and catheter placement extends the duration of analgesia. By contrast, analgesia provided by local infiltration with lidocaine, as performed in Study 105, typically lasts last for 1-2 hours. Given this duration of action and the overlap with the qualifying time period for first administration of SUZ, it is plausible that for Study 104, ropivacaine accounted for lack of separation of the pain curves between SUZ and placebo. Patients became eligible for the first dose of SUZ as soon as the ropivacaine infusion was discontinued and within the subsequent 9 hours. Therefore, there is significant overlap between the potential duration of action of ropivacaine and the first dose of SUZ. In comparison, for Study 105, the local infiltration of lidocaine is administered in advance of closure of the surgical wound, and therefore, despite an approximately 2-hour duration of action, the window of overlap with the qualifying SUZ administration period is much shorter. Therefore, the differences in perioperative pain management between the two studies, including the mechanism of action and the duration of action of those drugs provides a plausible explanation that may account for the difference in time course and degree of pain relief in Study 104.

Conclusion

Study 104 and Study 105 are adequate and well-controlled studies, each convincing on its own to establish effectiveness. The difference in time course of pain relief between the two studies may reflect the differences in perioperative pain management between the bunionectomy and abdominoplasty pain models.

6.3.2. Handling of Intercurrent Events

Issue

The Agency identified the following potential issues regarding the handling of intercurrent events in both Studies 104 and 105:

Imputation methods for handling intercurrent events of treatment discontinuation:

The single imputation methods (i.e., LOCF and BOCF) were used for imputing data following treatment discontinuation. Since single imputation methods may fail to reflect the uncertainty in data, the Agency recommended adding multiple imputation (MI) to the proposed handling strategies.

Per Agency request as outlined above, the Applicant imputed data following treatment discontinuation using the MI approaches. When imputing data from a normal distribution in the MI process, the Applicant (b) (4) (b) (4) The Agency recommended using a truncated normal distribution with limits of 0 and 10 instead.

Regarding the Applicant's proposed (b) (4) for treatment discontinuation due to LOE [lack of efficacy], the Agency recommended using the above-mentioned MI of BOCF method because treatment discontinuation due to lack of efficacy is generally viewed as a treatment failure.

Imputation strategy for rescue medication:

In case of multiple administrations of rescue medication leading to overlapping rescue periods, (b) (4) the Agency recommended carrying forward each of the pre-rescue score until the end of that given rescue period, or the time of the next rescue use, whichever comes first.

Past Communications

In the investigational new drug application (IND) review stage, the first issue regarding the handling strategy for ICE of treatment discontinuation was communicated between the Agency and the Applicant.

In the end-of-phase 2 (EOP2) meeting package, the Applicant proposed to impute missing NPRS scores following treatment discontinuation using the last observed NPRS score prior to discontinuation.

The Agency advised in the August 12, 2022, EOP2 meeting communication that:

Vertex proposed LOCF for subjects that discontinued the study or completed the treatment but with missing data from certain time point to 48 hours, which is not appropriate. For example, discontinuation due to lack of efficacy may suggest the assessments after the discontinuation will get worse and may be different from the observed assessments. An appropriate imputation scheme would be to assume these subjects do not contribute any treatment benefit in the primary analysis, such as multiple imputations of the subject's baseline score.

The first versions of the SAPs for Studies 104 and 105 were submitted on April 14, 2023. In the SAPs, the Applicant proposed to impute for subjects who discontinued the treatment due to lack of efficacy (LOE) or an AE using the last NPRS score prior to discontinuation.

The Agency provided comments regarding the imputation method to be used for ICEs of treatment discontinuation in an advice letter dated September 5, 2023. The Applicant responded to the comments and provided the following justifications to support their proposal: “Imputation using the last score does not attribute favorable pain scores to subjects who discontinue treatment due to lack of efficacy in acute pain studies.”

The evidence to support this conclusion was their phase 2 study results where the pooled mean baseline NPRS scores was lower than the pooled mean last NPRS scores for Studies 101 and 102, which correspond to the two phase 3 Studies 104 and 105. The Applicant further stated, “However, imputation using the baseline score assumes subjects will have some improvement in pain if they hadn’t discontinued treatment due to lack of efficacy, which is not appropriate.”

The Agency provided the following follow-up comment in response to the Applicant’s justification:

The Division acknowledges your proposal to lock the database for the VX22-548-105 Study. We have provided our comments in September 5, 2023 advice letter in response to your April 14, 2023 submission. We further acknowledge your response submitted on September 29 and October 6, 2023. Acceptability and adequacy of the data analysis will be a review issue when the full NDA is submitted.

In the final versions of the SAPs submitted on January 5, 2024, the Applicant changed the handling strategy for ICEs of treatment discontinuation due to an AE to BOCF as the Agency recommended, while the handling strategy for ICE of treatment discontinuation due to LOE remained as LOCF.

Assessment

To address the issues outlined above, results from additional sensitivity analyses performed by the Agency and Applicant are summarized below.

Sensitivity Analysis 1

[Table 23](#) below compares the results from the primary analysis, in which a single imputation method of LOCF was used to impute data following treatment discontinuation due to lack of efficacy, and the results from three sensitivity analyses wherein:

1. A single imputation method of BOCF was used for ICE of treatment discontinuation due to LOE instead (hereafter referred to as Sensitivity Analysis 1-1)
2. An MI method of BOCF was used for ICE of treatment discontinuation due to LOE, in which the imputed scores outside the [0, 10] range were forced to be 0 and 10, respectively (hereafter referred to as Sensitivity Analysis 1-2)
3. An MI method of BOCF was used for ICE of treatment discontinuation due to LOE, in which the imputed scores were generated from a truncated normal distribution with limits of 0 and 10 (hereafter referred to as Sensitivity Analysis 1-3).

Sensitivity Analyses 1-2 and 1-3, in which an MI method of BOCF was used to impute data following treatment discontinuation due to LOE, yielded the least treatment differences as compared to the primary analysis in which a single imputation of LOCF was used.

Table 23. Analyses for Primary Endpoint, Based on the Applicant-Proposed Approach and the Agency-Recommended Approaches for Handling ICE of Treatment Discontinuation Due to LOE, FAS, Studies 104 and 105

Statistic	Study 104		Study 105	
	Placebo N=216	SUZ N=426	Placebo N=223	SUZ N=447
Primary analysis ^a				
LS mean (SE)	70.6 (6.3)	99.9 (4.5)	70.1 (6.1)	118.4 (4.3)
LS mean difference (SE)	--	29.3 (7.8)	--	48.4 (7.5)
95% CI of LS mean difference	--	14.0, 44.6	--	33.6, 63.1
p-value versus HB/APAP	--	0.0002	--	<0.0001
Sensitivity analysis 1-1 ^b				
LS mean (SE)	79.9 (5.8)	105.2 (4.1)	75.9 (5.7)	120.4 (4.0)
LS mean difference (SE)	--	25.3 (7.1)	--	44.5 (7.0)
95% CI of LS mean difference	--	11.4, 39.3	--	30.9, 58.2
p-value versus HB/APAP	--	0.0004	--	<0.0001
Sensitivity analysis 1-2 ^c				
LS mean (SE)	81.6 (5.7)	106.1 (4.1)	78.8 (5.6)	121.5 (3.9)
LS mean difference (SE)	--	24.5 (7.0)	--	42.7 (6.8)
95% CI of LS mean difference	--	10.7, 38.2	--	29.3, 56.1
p-value versus HB/APAP	--	0.0005	--	<0.0001
Sensitivity analysis 1-3 ^d				
LS mean (SE)	83.8 (5.6)	107.5 (4.0)	82.8 (5.4)	123.0 (3.8)
LS mean difference (SE)	--	23.7 (6.9)	--	40.2 (6.6)
95% CI of LS mean difference	--	10.2, 37.2	--	27.3, 53.1
p-value versus HB/APAP	--	0.0006	--	<0.0001

Sources: Table 5 and Table 6, page 5-7 of Applicant's response to FDA Information Request dated September 25, 2024

Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Imputation methods for each analysis are outlined below.

^a The following imputation methods were used for the primary analysis: (1) NPRS scores during the rescue period (within 6 hours after rescue medication) were replaced by the prerescue NPRS score; (2) Missing NPRS following treatment discontinuation due to AE was imputed with the baseline NPRS while the NPRS following treatment discontinuation due to other reasons was imputed with the last NPRS prior to discontinuation; (3) Missing NPRS for subjects who completed the treatment but with missing data from a certain time point to 48 hours was imputed with the last NPRS; and (4) Intermittently missing NPRS was imputed using linear interpolation.

^b The same imputation methods as for the primary analysis (footnote "a") were used except for in (2), missing NPRS following treatment discontinuation due to lack of efficacy or AE were imputed with the MI of truncated normal distribution based on baseline NPRS while the NPRS following treatment discontinuation due to other reasons were imputed with the last NPRS prior to discontinuation.

^c The following imputation methods were used: (1) NPRS during the rescue period (within 6 hours after rescue medication) were replaced by the prerescue NPRS; (2) Intermittently missing NPRS were imputed using linear interpolation; (3) Missing NPRS following treatment discontinuation due to lack of efficacy or AE were imputed using multiple imputations of the subject's baseline NPRS score while the NPRS following treatment discontinuation due to other reasons were imputed using multiple imputations of the subject's last NPRS score prior to discontinuation; (4) Missing NPRS for subjects who completed the treatment but with missing data from a certain time point to 48 hours were imputed using multiple imputations of the subject's last NPRS score.

^d The same imputation methods as for Sensitivity Analysis 1-2 (footnote "c") were used except for (3) and (4), MI was performed with a truncated normal distribution.

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; ICE, intercurrent event; LOE, lack of efficacy; LS, least-squares; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SE, standard error; SPID48: time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

Sensitivity Analysis 2

A large portion of the population (more than 50%) had two or more doses of rescue medication across all three treatment groups in both studies. However, the percentage of multiple administrations of the rescue medications that led to overlapping imputation periods was small (ranging from 0.6% to 0.8% among treatment groups in the two studies). [Table 24](#) below compares the results from the primary analysis where first pre-rescue scores were carried forward until the end of the last overlapping rescue period and the results from a sensitivity analysis (hereafter referred to as Sensitivity Analysis 2) where pre-rescue scores were carried forward until the end of the rescue period or the time of the next rescue use, whichever came first. This sensitivity analysis yielded similar results to the primary analysis.

Table 24. Analyses for Primary Endpoint, Based on the Applicant-Proposed Approach and the Agency-Recommended Approaches for Handling ICE of Treatment Discontinuation Due to LOE, FAS, Studies 104 and 105

Statistic	Study 104		Study 105	
	Placebo N=216	SUZ N=426	Placebo N=223	SUZ N=447
Primary analysis				
LS mean (SE)	70.6 (6.3)	99.9 (4.5)	70.1 (6.1)	118.4 (4.3)
LS mean difference (SE)	--	29.3 (7.8)	--	48.4 (7.5)
95% CI of LS mean difference	--	14.0, 44.6	--	33.6, 63.1
p-value versus HB/APAP	--	0.0002	--	<0.0001
Sensitivity analysis 2 ^a				
LS mean (SE)	70.5 (6.4)	99.9 (4.5)	70.3 (6.1)	118.7 (4.3)
LS mean difference (SE)	--	29.4 (7.8)	--	48.4 (7.5)
95% CI of LS mean difference	--	14.1, 44.7	--	33.6, 63.1
p-value versus HB/APAP	--	0.0002	--	<0.0001

Sources: Table 3 and Table 4, page 3-4 of Applicant's response to FDA Information Request dated September 25, 2024

Notes: Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. The following imputation methods were used for the primary analysis: (1) NPRS scores during the rescue period (within 6 hours after rescue medication) were replaced by the prerescue NPRS score; (2) Missing NPRS following treatment discontinuation due to AE was imputed with the baseline NPRS while the NPRS following treatment discontinuation due to other reasons was imputed with the last NPRS prior to discontinuation; (3) Missing NPRS for subjects who completed the treatment but with missing data from a certain time point to 48 hours was imputed with the last NPRS; and (4) Intermittently missing NPRS was imputed using linear interpolation.

^a Identical imputation methods were used for the Sensitivity Analysis, except if there were multiple administrations of rescue medication leading to overlapping rescue periods, in which case the prerescue NPRS was used to replace NPRS during each rescue period until the next prerescue NPRS.

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BOCF, baseline observation carried forward; CI, confidence interval; FAS, full analysis set; IR, information request; LOCF, last observation carried forward; LOE, lack of efficacy; LS, least-squares; N, number of subjects in the analysis set; NPRS, numeric pain rating scale; SPID48: time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

Conclusion

Despite the slight treatment differences between the SUZ and placebo groups obtained from the sensitivity analyses as compared to that obtained from the primary analysis, the conclusion that SUZ is superior to placebo in SPID48 remains unchanged.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Appropriate nonclinical studies were submitted to support the safety of SUZ (also referred to as VX-548 and VRT-1737548); a major human metabolite, VRT-1875420; and impurities in the drug substance and drug product. The following studies were submitted: primary and secondary pharmacology, safety pharmacology in the monkey in addition to in vitro human ether-à-go-go-related gene (hERG) assays; absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic (PK) studies; repeat-dose toxicology studies in the rat and monkey for durations of 28 days and 13 weeks; a full battery of reproductive toxicology studies in the rat and rabbit; and a full battery of genetic toxicology studies (Ames, in vitro chromosomal aberration, and in vivo rat micronucleus assays).

All levels of excipients in the 50-mg tablet drug product formulation are within the levels of previously approved FDA drug products by the proposed oral route at the maximum daily dose of 150 mg; therefore, there is no safety concern from the excipients.

General toxicity studies and reproductive toxicity studies performed in rats suggested SUZ may pose risks with respect to adverse effects on female reproductive tissues, fertility, pregnancy, and development. Nonclinical findings that may be relevant to human risks or are causes of safety concerns are highlighted below. However, overall, the nonclinical data support the safety of the drug product for the proposed acute indication; therefore, the new drug application (NDA) may be approved from a nonclinical perspective with the recommended labeling changes, which describe risks for reproductive and developmental effects based on animal studies.

7.1.1. General Toxicology Findings

The systemic safety of SUZ and a major human metabolite, M6-SUZ (also referred to as M6 and VRT-1875420), were evaluated in 28-day repeat-dose toxicity studies in rats and monkeys. In addition, the safety of SUZ and impurities/degradants in the drug substance and drug product was evaluated in 91-day repeat-dose toxicity studies in rats and monkeys.

In the 28-day rat study, organ weights of the liver and ovaries increased in the high-dose groups. However, there were no associated histopathological changes in the liver or ovaries. In the 28-day monkey study, increased incidences of soft/watery feces were observed in treated groups. The mean organ weight of the thyroid/parathyroid was increased in the females without statistical significance.

In the 91-day rat study, oral administration of SUZ to female rats for 91 days resulted in ovarian cyst formation, decreased number of corpora lutea, pituitary gland hyperplasia, and mammary hyperplasia/dilatation. In the 13-week monkey study, reduced weights of testes (-43 to -46%), epididymis (-14 to -38%), and prostate gland (-47 to -49%) were observed in SUZ treated males without histopathological correlates. While the testis weights appeared to be within the range of organ weights of untreated Cynomolgus monkey of similar ages based on published literature ([Haruyama et al. 2012](#); [Amato et al. 2022](#)), it is unclear whether there were testicular functional

effects. Of note, no significant changes in these organ weights in the 28-day monkey studies were noted. Therefore, there is minimal concern for the proposed indication.

Table 25. Safety Margins of SUZ Based on the NOAEL From General Toxicology Studies

Species/ Duration	Nonclinical			Clinical Safety Margins Based On	
	NOAEL (mg/kg)	AUC (µg·h/mL)	C _{max} (µg/mL)	AUC*	C _{max} *
28-day rat male	1000	152	13.5	13.2	21.8
28-day rat female	300	206	13.4	17.9	21.6
28-day monkey	100	19.4	2.73	1.7	4.4
91-day rat male	1000	191	12.7	16.6	20.5
91-day rat female	10	15.1	2.04	1.3	3.3
13-week monkey	150	24.1	2.75	2.1	4.4

Source: Study No. VRT-1737548-TX-011, Page 29, Text Table 11; Study No. VRT-1737548-TX-012, Page 26, Text Table 9; Study No. VX-548-TX-001, Page 35, Text Table 18; Study No. VX-548-TX-002, Page 21, Text Table 10

* Based on simulated human PK data listed in Summary of Clinical Pharmacology Studies, Table 20: AUC_{0-24h} 11.5 µg·h/mL, C_{max} 0.62 µg/mL (SUZ dosing regimen of 150 mg loading dose and 50 mg maintenance dose every 12h)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; h, hour(s); NOAEL, no-observed-adverse-effect level

Table 26. Safety Margins of M6-SUZ (Major Human Metabolite) Based on the NOAEL From General Toxicology Studies

Species/ Duration	Nonclinical			Clinical Safety Margins Based On	
	NOAEL (mg/kg)	AUC (µg·h/mL)	C _{max} (µg/mL)	AUC*	C _{max} *
28-day rat male	1000	35.2	3.63	1.0	2.4
28-day rat female	300	62.4	3.58	1.8	2.4
28-day monkey	100	64.4	6.96	1.9	4.6
91-day rat male	1000	61.5	3.61	1.8	2.4
91-day rat female	10	1.92	0.207	0.06	0.14
13-week monkey	150	68.4	6.33	2.0	4.2

Source: Study No. VRT-1737548-TX-011, Page 29, Text Table 11; Study No. VRT-1737548-TX-012, Page 26, Text Table 9; Study No. VX-548-TX-001, Page 36, Text Table 19; Study No. VX-548-TX-002, Page 21, Text Table 10

* Based on simulated human PK data listed in Summary of Clinical Pharmacology Studies, Table 20: AUC_{0-24h} 34.7 µg·h/mL, C_{max} 1.52 µg/mL of M6-SUZ (SUZ dosing regimen of 115 mg loading dose and 57.5 mg maintenance dose every 12h)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; h, hour(s); NOAEL, no-observed-adverse-effect level; SUZ, suzetrigine

7.1.2. Reproductive and Developmental Toxicology

Reproductive and developmental toxicities of SUZ were assessed in male and female fertility and early embryonic development studies in rats, embryo-fetal development (EFD) studies in rats/rabbits, and a pre- and postnatal development (PPND) study in rats.

SUZ doses up to 1000 mg/kg did not affect male reproductive performance when administered at least 28 days before mating and throughout mating. In a female fertility study in rats, increased preimplantation loss was observed at oral SUZ doses of 15 mg/kg when administered prior to mating and through gestation day (GD) 7. These effects on fertility in female rats appear to be reversible as pre-implantation loss was not observed when female rats were mated following discontinuation of SUZ for 4 weeks.

In the rabbit EFD study, higher postimplantation loss and lower fetal body weights were observed at 200 mg/kg/day when administered on GDs 7 to 20. In the rat EFD study, higher

postimplantation loss and lower fetal body weights were observed at 15 mg/kg/day and higher when administered on GDs 6 to 17.

In the rat PPND study, reduced mean gestation duration and increased postnatal pup mortality between birth and postnatal day 4 were observed at ≥ 10 mg/kg, and increased incidences of fully resorbed litters, fewer live newborn pups, and reductions in pup body weights were observed at 15 mg/kg when SUZ was orally administered to pregnant rats from GD 6 to lactation day 20. No effects on learning and memory or sexual maturation were observed at doses up to 15 mg/kg.

Table 27. Safety Margins of SUZ Based on NOAEL From Reproductive Toxicology Studies

Species/Duration	Nonclinical			Clinical Safety Margins Based On	
	NOAEL (mg/kg)	AUC ($\mu\text{g}\cdot\text{h/mL}$)	C_{max} ($\mu\text{g/mL}$)	AUC*	C_{max} *
Male rat fertility	1000	159	10.7	13.8	17.3
Female rat fertility	10	18.4**	1.53**	1.6	2.5
Rat EFD (GD 17)	10	18.4	1.53	1.6	2.5
Rabbit EFD (GD 20)	100	35.9	3.19	3.1	5.1
Rat PPND	5	6.54**	0.71**	0.57	0.9

Source: Study No. VX-548-TX-013, Page 24, Text Table 15; Study No. VX-548-TX-007, Page 19, Text Table 11; Study No. VX-548-TX-009, Page 20, Text Table 11; Study No. VX-548-TX-019, Page 31, Text Table 14

* Based on simulated human PK data listed in Summary of Clinical Pharmacology Studies, Table 20: AUC_{0-24h} 11.5 $\mu\text{g}\cdot\text{h/mL}$, C_{max} 0.62 $\mu\text{g/mL}$ (SUZ dosing regimen of 150 mg loading dose and 50 mg maintenance dose every 12h)

** TK from rat EFD study (GD 17)

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; EFD, embryo-fetal development; GD, gestation day; h, hour(s); NOAEL, no-observed-adverse-effect level; PPND, pre- and postnatal development

Table 28. Safety Margins of M6-SUZ (Major Human Metabolite) Based on NOAEL From Reproductive Toxicology Studies

Species/Duration	Nonclinical			Clinical Safety Margins Based On	
	NOAEL (mg/kg)	AUC ($\mu\text{g}\cdot\text{h/mL}$)	C_{max} ($\mu\text{g/mL}$)	AUC*	C_{max} *
Male rat fertility	1000	48.9	2.95	1.4	1.9
Female rat fertility	10	2.29**	0.183**	0.07	0.12
Rat EFD (GD 17)	10	2.29	0.183	0.07	0.12
Rabbit EFD (GD 20)	100	45.6	3.87	1.3	2.5
Rat PPND	5	0.467**	0.0371**	0.01	0.02

Source: Study No. VX-548-TX-013, Page 25, Text Table 16; Study No. VX-548-TX-007, Page 20, Text Table 12; Study No. VX-548-TX-009, Page 21, Text Table 12

* Based on simulated human PK data listed in Summary of Clinical Pharmacology Studies, Table 20: AUC_{0-24h} 34.7 $\mu\text{g}\cdot\text{h/mL}$, C_{max} 1.5 $\mu\text{g/mL}$ of M6-SUZ (SUZ dosing regimen of 115 mg loading dose and 57.5 mg maintenance dose every 12h)

** TK from rat EFD study (GD 17)

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; EFD, embryo-fetal development; GD, gestation day; h, hour(s); NOAEL, no-observed-adverse-effect level; PPND, pre- and postnatal development; SUZ, suzetrigine

Based on the reproductive toxicity findings, the Applicant conducted further investigative studies to understand the cause of concerns. The Applicant provided additional information (b) (4)

They noted (b) (4)

referenced published studies that demonstrated Na_v1.8 knockout mice are fertile (Akopian et al. 1999). In addition, the Applicant demonstrated SUZ is a potent rat progesterone receptor (PR) antagonist by conducting in vitro PR reporter assays (b) (4)

(b) (4) While it is reasonable to conclude that the reproductive toxicity findings observed in rats may not be due to the on-target effect inhibiting Na_v1.8, the submitted data/information are insufficient to dismiss other potential off-target effects in addition to rat PR antagonism effects of SUZ. Additionally, the Applicant (b) (4)

However, a direct comparison of IC₅₀ values from these two independent assays, which used engineered cell systems overexpressing human or rat PR, is very challenging because it is difficult to normalize these two systems and compare their values. In addition, there are some limitations to predicting in vivo inhibitory activity from the submitted in vitro data. Taken together, there are insufficient data to allow us to definitively conclude (b) (4)

7.1.3. Mutagenesis and Carcinogenesis

SUZ was evaluated for genotoxic potential in a full battery of genotoxicity studies, including an in vitro Ames, an in vitro micronucleus assay, and an in vivo micronucleus assay in rats. SUZ was not considered mutagenic nor clastogenic in these assays.

The major human metabolite, M6-SUZ, was also negative in an Ames assay and posed minimal concern for clastogenicity.

7.1.4. Other Toxicity

SUZ drug substance was nonirritant in an in vitro skin irritation test and was not a skin sensitizer in a local lymph node assay in the mouse. SUZ was not considered an eye irritant based on an eye hazard potential evaluation using the reconstructed human cornea-like epithelium model. SUZ was nonphotoreactive based on in vitro and in vivo studies.

7.1.5. Impurities

The proposed specifications for drug substance impurities and drug product degradants are acceptable. Additional impurities of concern were adequately justified for safety.

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

SUZ is a selective Na_v1.8 blocker that represents a new pharmacologic class of analgesic medications. Aside from the safety data for SUZ that were reviewed in this NDA, there are limited data available to inform safety concerns based on drug class.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

SUZ has not been approved in any country or region for marketing. Therefore, no postmarketing experience is available at the time of this review.

7.4. FDA Approach to the Safety Review

The primary sources of safety data are the two controlled phase 3 studies (Studies 104 and 105) and an open-label, uncontrolled phase 3 study (Study 107). Additional data are available from two phase 2 studies (Studies 101 and 102). Studies 101 and 104 were conducted in subjects after bunionectomy, while Studies 102 and 105 were conducted in subjects after abdominoplasty. Study 107 was an open-label evaluation of SUZ in subjects with acute pain resulting from a variety of surgical or nonsurgical conditions. In addition, 13 phase 1 studies evaluated SUZ in healthy subjects and special populations (subjects with hepatic and renal impairment).

The Applicant performed analyses for the individual studies and two pooled populations. These pooled populations consisted of the pooled phase 3 controlled studies (Studies 104 and 105) and the pooled phase 2 and 3 controlled studies (Studies 101, 102, 104, and 105). The Applicant states that the latter pool is a supportive data pool. Data from the phase 1 and open-label phase 3 studies were not pooled given significant differences in their study designs and/or populations.

The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to coding and categorizing adverse events. This review focused primarily on comparisons between the treatment arms in the phase 3 controlled studies. The major differences between these two studies were those relating to the acute pain model studied and procedure-specific subject selection criteria and anesthetic techniques. Pooling of the safety data from these studies is acceptable considering the otherwise similar study designs and selection criteria. The use of descriptive analyses of safety was predefined in the protocol for summarizing the safety outcomes. Separate analyses of the individual phase 3 controlled studies are described in Section [17.2](#) of this review.

7.5. Adequacy of the Clinical Safety Database

The safety database provided by the Applicant is acceptable for a comprehensive safety assessment of SUZ for the proposed indication, dosage regimen, and duration. In the 18 clinical studies mentioned in Section [7.4](#), a total of 1,883 unique subjects received at least one dose of SUZ. This included 1,266 subjects with acute pain who received the to-be-marketed dose regimen in the phase 2 and 3 studies, 169 subjects in the acute pain studies who received a lower dose of SUZ, 393 healthy subjects in the phase 1 studies, and 55 subjects in the phase 1 studies in special populations. In the controlled phase 3 studies, 874 subjects received at least one dose of SUZ at the to-be-marketed dose regimen. In the open-label, uncontrolled phase 3 study, 256 subjects received at least one dose of SUZ at the to-be-marketed dose regimen. A summary of the duration of exposure in the phase 3 studies is shown below in [Table 29](#) and [Table 30](#).

Table 29. Duration of Exposure, Safety Population, Pooled Studies 104 and 105

Parameter	SUZ N=874	HB/APAP N=879	Placebo N=438
Duration of treatment, days			
Mean (SD)	2.6 (0.7)	2.5 (0.7)	2.4 (0.8)
Median (Q1, Q3)	3 (2, 3)	3 (2, 3)	3 (2, 3)
Min, max	1, 3	1, 3	1, 3
Total exposure (person years)	6	6	3
Patients treated, by duration, n (%)			
<1 days	0	0	0
≥1 to <2 days	90 (10.3)	96 (10.9)	82 (18.7)
≥2 to <3 days	188 (21.5)	209 (23.8)	91 (20.8)
≥3 to <4 days	596 (68.2)	574 (65.3)	265 (60.5)
≥4 days	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is 48 hours.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 30. Duration of Exposure, Safety Population, Study 107

Parameter	SUZ N=256
Duration of treatment, days	
Mean (SD)	9.6 (4.7)
Median (Q1, Q3)	11 (5, 14)
Min, max	1, 18
Total exposure (person years)	7
Patients treated, by duration, n (%)	
<4 days	40 (15.6)
≥4 to <8 days	57 (22.3)
≥8 to <11 days	30 (11.7)
≥11 to <15 days	107 (41.8)
≥15 to <19 days	22 (8.6)
≥19 days	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 14 days.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Studies VX22-548-104 and VX22-548-105 (Studies 104 and 105)

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Studies 104 and 105

The safety evaluation for SUZ was adequate, and the demonstrated safety profile of this medication administered in subjects with moderate or severe acute pain is acceptable for the indicated doses. There were no deaths in subjects treated with SUZ. The incidence of serious

adverse events (SAEs) and AEs leading to discontinuation of the study drug was low overall, and there were no substantial differences between the treatment arms. The incidence of any AE was lower in the SUZ arm than in both the HB/APAP and placebo arms.

Table 31. Overview of Adverse Events, Safety Population, Pooled Studies 104 and 105

Event Category	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
SAE	11 (1.3)	7 (0.8)	5 (1.1)
SAEs with fatal outcome	0	0	1 (0.2)
Life-threatening SAEs	2 (0.2)	2 (0.2)	0
SAEs requiring hospitalization	7 (0.8)	6 (0.7)	4 (0.9)
SAEs resulting in substantial disruption of normal life functions	2 (0.2)	1 (0.1)	1 (0.2)
Other	6 (0.7)	2 (0.2)	3 (0.7)
AE leading to permanent discontinuation of study drug	5 (0.6)	5 (0.6)	1 (0.2)
AE leading to dose modification of study drug	0	1 (0.1)	0
AE leading to interruption of study drug	0	1 (0.1)	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Any AE	356 (40.7)	452 (51.4)	201 (45.9)
Severe and worse	11 (1.3)	15 (1.7)	7 (1.6)
Moderate	110 (12.6)	154 (17.5)	61 (13.9)
Mild	235 (26.9)	283 (32.2)	133 (30.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.2. Deaths, Pooled Analyses, Studies 104 and 105

There was one death in the placebo group of Study 105 due to an SAE of pulmonary embolism. There were no deaths in subjects treated with SUZ.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Studies 104 and 105

There was no substantial difference in overall incidence of SAEs experienced by subjects in the SUZ arm compared to the HB/APAP and placebo arms. The majority of SAEs were experienced by only one subject in any given treatment arm. There were no substantial differences between the treatment arms for any specific SAE. No SAEs were considered to be related or possibly related to the study drug by the study investigators. Most of these SAEs, such as those related to bleeding, respiratory disorders, and infections, are known risks associated with surgical procedures and would not be unexpected considering the surgical acute pain models used in these studies. Additional details regarding these SAEs can be found in Section [17.3](#).

Table 32. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Studies 104 and 105

System Organ Class Preferred Term	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
Any SAE	11 (1.3)	7 (0.8)	5 (1.1)
Blood and lymphatic system disorders (SOC)	1 (0.1)	0	1 (0.2)
Anaemia	1 (0.1)	0	0
Disseminated intravascular coagulation	0	0	1 (0.2)
Cardiac disorders (SOC)	0	0	1 (0.2)
Cardiogenic shock	0	0	1 (0.2)
Gastrointestinal disorders (SOC)	1 (0.1)	2 (0.2)	0
Small intestinal obstruction	1 (0.1)	0	0
Intra-abdominal haematoma	0	1 (0.1)	0
Volvulus	0	1 (0.1)	0
General disorders and administration site conditions (SOC)	1 (0.1)	0	0
Impaired healing	1 (0.1)	0	0
Immune system disorders (SOC)	0	0	1 (0.2)
Drug hypersensitivity	0	0	1 (0.2)
Infections and infestations (SOC)	2 (0.2)	1 (0.1)	0
Infected seroma	1 (0.1)	0	0
Medical device site infection	1 (0.1)	0	0
Pneumonia	0	1 (0.1)	0
Injury, poisoning and procedural complications (SOC)	2 (0.2)	3 (0.3)	3 (0.7)
Post procedural haematoma	2 (0.2)	1 (0.1)	2 (0.5)
Post procedural haemorrhage	0	0	1 (0.2)
Anaemia postoperative	0	2 (0.2)	0
Nervous system disorders (SOC)	1 (0.1)	0	0
Syncope	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	3 (0.3)	2 (0.2)	1 (0.2)
Hypoxia	1 (0.1)	0	0
Pulmonary embolism	2 (0.2)	2 (0.2)	1 (0.2)
Vascular disorders (SOC)	0	0	1 (0.2)
Hypotension	0	0	1 (0.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 48 hours.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Pooled Analyses, Studies 104 and 105

There were no substantial differences in the incidence of AEs leading to discontinuation in the SUZ arm compared to the HB/APAP and placebo arms. The majority of AEs leading to discontinuation were experienced by only one subject in any given treatment arm.

There were no substantial differences between the treatment arms in the incidence of any specific AE leading to discontinuation. Similar to the SAEs described in Section [7.6.1.3](#), many of the

AEs leading to discontinuation are known to be associated with surgical procedures and would not be unexpected considering the surgical acute pain models used in these studies.

Table 33. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Studies 104 and 105

System Organ Class Preferred Term	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
Any AE leading to discontinuation	5 (0.6)	5 (0.6)	1 (0.2)
Cardiac disorders (SOC)	0	0	1 (0.2)
Tachycardia	0	0	1 (0.2)
Gastrointestinal disorders (SOC)	0	1 (0.1)	0
Intra-abdominal haematoma	0	1 (0.1)	0
Nausea	0	1 (0.1)	0
General disorders and administration site conditions (SOC)	0	1 (0.1)	0
Pyrexia	0	1 (0.1)	0
Injury, poisoning and procedural complications (SOC)	2 (0.2)	0	0
Post procedural haematoma	2 (0.2)	0	0
Nervous system disorders (SOC)	1 (0.1)	1 (0.1)	0
Syncope	1 (0.1)	0	0
Migraine	0	1 (0.1)	0
Vascular disorders (SOC)	2 (0.2)	2 (0.2)	1 (0.2)
Hypotension	2 (0.2)	1 (0.1)	1 (0.2)
Orthostatic hypotension	0	1 (0.1)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Studies 104 and 105

[Table 34](#) presents the common AEs by preferred term (PT) and system organ class (SOC) in Studies 104 and 105 which occurred in at least 0.3% of subjects in any arm. The percentage of subjects with any AEs was lower in the SUZ treatment arm than in the HB/APAP and placebo arms. There were no PTs or SOCs for which the incidence was substantially higher in the SUZ treatment arm than in the HB/APAP or placebo arms.

No AEs occurred more frequently in the SUZ arm compared to the placebo arm by an incidence of 1.0% or greater. Notable imbalances in AEs between the treatment arms were generally favorable for the safety profile of SUZ. Notable findings included a lower percentage of subjects with the AEs of nausea, dizziness, and hypotension in the SUZ treatment arm than in the placebo arm, as well as a lower percentage of subjects with the AEs of vomiting, nausea, and headache in the SUZ treatment arm than in the HB/APAP arm.

Table 34. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.3% of Subjects in Any Arm, Safety Population, Pooled Studies 104 and 105

System Organ Class Preferred Term	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
Any AE	356 (40.7)	452 (51.4)	201 (45.9)
Blood and lymphatic system disorders (SOC)	5 (0.6)	5 (0.6)	2 (0.5)
Anaemia	2 (0.2)	3 (0.3)	0
Cardiac disorders (SOC)	5 (0.6)	9 (1.0)	7 (1.6)
Tachycardia	1 (0.1)	7 (0.8)	5 (1.1)
Ear and labyrinth disorders (SOC)	3 (0.3)	0	1 (0.2)
Eye disorders (SOC)	1 (0.1)	3 (0.3)	2 (0.5)
Gastrointestinal disorders (SOC)	196 (22.4)	287 (32.7)	123 (28.1)
Diarrhoea	5 (0.6)	3 (0.3)	3 (0.7)
Gastrooesophageal reflux disease	4 (0.5)	2 (0.2)	2 (0.5)
Constipation	62 (7.1)	61 (6.9)	33 (7.5)
Flatulence	10 (1.1)	12 (1.4)	5 (1.1)
Abdominal discomfort	0	3 (0.3)	0
Abdominal distension	0	3 (0.3)	2 (0.5)
Dyspepsia	9 (1.0)	15 (1.7)	4 (0.9)
Vomiting	17 (1.9)	37 (4.2)	9 (2.1)
Nausea	120 (13.7)	209 (23.8)	79 (18.0)
General disorders and administration site conditions (SOC)	17 (1.9)	19 (2.2)	9 (2.1)
Oedema peripheral	3 (0.3)	0	2 (0.5)
Pyrexia	3 (0.3)	6 (0.7)	3 (0.7)
Peripheral swelling	0	3 (0.3)	1 (0.2)
Infections and infestations (SOC)	19 (2.2)	18 (2.0)	8 (1.8)
Postoperative wound infection	6 (0.7)	4 (0.5)	3 (0.7)
Medical device site infection	3 (0.3)	1 (0.1)	0
Pharyngitis	3 (0.3)	1 (0.1)	0
COVID-19	0	3 (0.3)	1 (0.2)
Injury, poisoning and procedural complications (SOC)	21 (2.4)	30 (3.4)	18 (4.1)
Skin abrasion	3 (0.3)	1 (0.1)	2 (0.5)
Procedural nausea	1 (0.1)	0	2 (0.5)
Post procedural haematoma	2 (0.2)	2 (0.2)	2 (0.5)
Anaemia postoperative	2 (0.2)	8 (0.9)	4 (0.9)
Investigations (SOC)	30 (3.4)	34 (3.9)	17 (3.9)
Blood creatine phosphokinase increased	10 (1.1)	7 (0.8)	2 (0.5)
Hepatic enzyme increased	1 (0.1)	2 (0.2)	3 (0.7)
White blood cells urine positive	0	1 (0.1)	2 (0.5)
Gamma-glutamyltransferase increased	1 (0.1)	10 (1.1)	3 (0.7)
Aspartate aminotransferase increased	5 (0.6)	16 (1.8)	4 (0.9)
Alanine aminotransferase increased	6 (0.7)	18 (2.0)	5 (1.1)
Metabolism and nutrition disorders (SOC)	3 (0.3)	6 (0.7)	2 (0.5)
Musculoskeletal and connective tissue disorders (SOC)	24 (2.7)	16 (1.8)	8 (1.8)
Muscle spasms	11 (1.3)	6 (0.7)	2 (0.5)
Back pain	4 (0.5)	2 (0.2)	2 (0.5)
Pain in extremity	4 (0.5)	5 (0.6)	2 (0.5)

System Organ Class Preferred Term	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
Nervous system disorders (SOC)	85 (9.7)	135 (15.4)	60 (13.7)
Presyncope	4 (0.5)	1 (0.1)	1 (0.2)
Somnolence	1 (0.1)	1 (0.1)	2 (0.5)
Paraesthesia	5 (0.6)	6 (0.7)	1 (0.2)
Syncope	7 (0.8)	9 (1.0)	5 (1.1)
Migraine	0	3 (0.3)	0
Dizziness	33 (3.8)	47 (5.3)	28 (6.4)
Headache	40 (4.6)	77 (8.8)	31 (7.1)
Renal and urinary disorders (SOC)	2 (0.2)	10 (1.1)	6 (1.4)
Urinary retention	1 (0.1)	3 (0.3)	3 (0.7)
Haematuria	0	5 (0.6)	2 (0.5)
Reproductive system and breast disorders (SOC)	7 (0.8)	1 (0.1)	1 (0.2)
Respiratory, thoracic and mediastinal disorders (SOC)	23 (2.6)	24 (2.7)	14 (3.2)
Dyspnoea	4 (0.5)	2 (0.2)	1 (0.2)
Cough	5 (0.6)	4 (0.5)	4 (0.9)
Oropharyngeal pain	5 (0.6)	5 (0.6)	3 (0.7)
Hypoxia	6 (0.7)	8 (0.9)	1 (0.2)
Skin and subcutaneous tissue disorders (SOC)	51 (5.8)	62 (7.1)	23 (5.3)
Rash	10 (1.1)	6 (0.7)	2 (0.5)
Blister	5 (0.6)	2 (0.2)	1 (0.2)
Dermatitis contact	8 (0.9)	7 (0.8)	3 (0.7)
Hyperhidrosis	3 (0.3)	5 (0.6)	5 (1.1)
Ecchymosis	1 (0.1)	3 (0.3)	0
Erythema	0	7 (0.8)	1 (0.2)
Pruritus	18 (2.1)	30 (3.4)	7 (1.6)
Vascular disorders (SOC)	20 (2.3)	23 (2.6)	21 (4.8)
Hypertension	3 (0.3)	2 (0.2)	1 (0.2)
Orthostatic hypotension	2 (0.2)	1 (0.1)	3 (0.7)
Hypotension	11 (1.3)	16 (1.8)	16 (3.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.6. Laboratory Findings, Pooled Analyses, Studies 104 and 105

Analyses of laboratory data did not raise major safety concerns. Median changes from baseline to the end of treatment were similar between the treatment arms for the majority of the laboratory assessments conducted in these studies.

There were some laboratory parameters with notable imbalances between the SUZ treatment arm and the HB/APAP and placebo treatment arms. [Table 35](#) and [Table 36](#) demonstrate that a higher percentage of subjects in the SUZ treatment arm had creatine phosphokinase (CPK) and estimated glomerular filtration rate (eGFR) values exceeding certain threshold levels compared to the other treatment arms. [Table 37](#) demonstrates that the mean changes in creatine phosphokinase and creatinine from baseline were higher and the mean change in eGFR from

baseline was lower in the SUZ treatment arm at 48 hours. However, the magnitude of these changes is relatively small and unlikely to be clinically significant.

Table 35. Subjects With CPK Values Exceeding Specified Levels, Safety Population, Pooled Studies 104 and 105

Laboratory Parameter	SUZ N=874 n/N _w (%)	HB/APAP N=879 n/N _w (%)	Placebo N=438 n/N _w (%)
CPK, high (U/L)			
Level 1 (>3× ULN)	25/866 (2.9)	9/860 (1.0)	5/425 (1.2)
Level 2 (>5× ULN)	9/866 (1.0)	2/860 (0.2)	1/425 (0.2)
Level 3 (>10× ULN)	4/866 (0.5)	1/860 (0.1)	0/425 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 48 hours.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CPK, creatine phosphokinase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

Table 36. Subjects With eGFR Values Exceeding Specified Levels, Safety Population, Pooled Studies 104 and 105

Laboratory Parameter	SUZ N=874 n/N _w (%)	HB/APAP N=879 n/N _w (%)	Placebo N=438 n/N _w (%)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥25% decrease)	23/855 (2.7)	6/852 (0.7)	6/421 (1.4)
Level 2 (≥50% decrease)	1/855 (0.1)	2/852 (0.2)	2/421 (0.5)
Level 3 (≥75% decrease)	0/855 (0)	1/852 (0.1)	1/421 (0.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 48 hours.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: eGFR, estimated glomerular filtration rate; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 37. Selected Chemistry Assessments and Changes From Baseline at 48 Hours, Pooled Studies 104 and 105

Laboratory Parameter	SUZ N=874	HB/APAP N=879	Placebo N=438
Creatine kinase (U/L)			
N	856	852	422
Mean (SD)	36.9 (223.5)	14.5 (632.0)	15.3 (134.2)
Median	4.0	1.0	4.0
Creatinine (μmol/L)			
N	858	855	423
Mean (SD)	-0.1 (10.9)	-4.1 (15.9)	-3.5 (23.9)
Median	0.0	0.0	0.0
Glomerular filtration rate, estimated (mL/min/1.73 m ²)			
N	858	855	423
Mean (SD)	0.2 (12.1)	4.1 (11.0)	3.5 (13.4)
Median	0.0	0.0	0.0

Source: Modified from ISS, Table 2.3.4.1, Pages 9, 10, 13

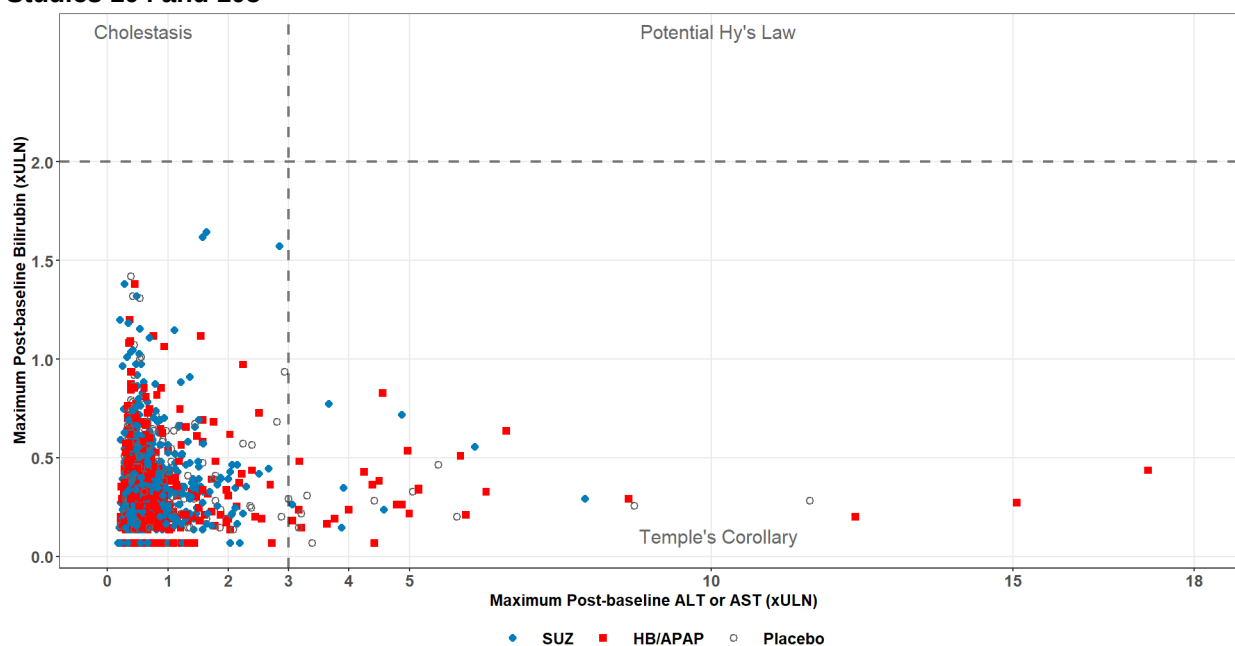
Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Studies 104 and 105

[Figure 4](#) shows a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no subjects in any treatment arm in the Cholestasis and Potential Hy's Law quadrants. There was a lower percentage of subjects in the SUZ treatment arm (1%) in the Temple's Corollary quadrant compared to the HB/APAP (3%) and placebo (2.6%) treatment arms. These findings do not suggest a significant relationship between SUZ and drug-induced liver injury.

Figure 4. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Studies 104 and 105



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and Temple's Corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

7.6.1.8. Vital Signs and ECG, Pooled Analyses, Studies 104 and 105

Review of the vital sign data and electrocardiogram (ECG) parameters did not reveal significant clinically meaningful safety concerns. As depicted in [Table 38](#) and [Table 39](#), during the treatment period, there were larger decreases from baseline in the mean systolic and diastolic blood pressures in the SUZ arm compared to the placebo arm. However, the magnitude of this difference was small and unlikely to be clinically significant.

Table 38. Systolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Studies 104 and 105

Time Point		Change From Baseline		
		SUZ N=874	HB/APAP N=879	Placebo N=438
2 hours	n	874	878	436
	Mean (SD)	-2.1 (15.6)	-3.0 (15.7)	0.5 (15.2)
	Median	-2.0	-3.0	1.0
4 hours	n	871	876	434
	Mean (SD)	-3.1 (15.9)	-3.6 (16.1)	-1.2 (14.9)
	Median	-3.0	-3.0	-1.0
24 hours	n	862	861	428
	Mean (SD)	-7.5 (16.2)	-5.8 (16.1)	-3.2 (15.7)
	Median	-7.0	-5.0	-2.5
48 hours	n	862	858	426
	Mean (SD)	-5.4 (16.8)	-3.5 (16.4)	-3.2 (16.2)
	Median	-5.0	-3.0	-3.0
Safety follow-up	n	842	846	412
	Mean (SD)	-2.3 (18.2)	-0.9 (17.3)	-0.8 (17.5)
	Median	-1.5	-1.0	0.0

Source: Modified from ISS, Table 2.3.5.1, Pages 1-2

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 39. Diastolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Studies 104 and 105

Time Point		Change From Baseline		
		SUZ N=874	HB/APAP N=879	Placebo N=438
2 hours	N	874	878	436
	Mean (SD)	-0.7 (10.8)	-1.4 (11.5)	0.0 (10.5)
	Median	-1.0	-2.0	0.0
4 hours	N	871	876	434
	Mean (SD)	-2.1 (10.8)	-2.2 (11.4)	-1.1 (9.9)
	Median	-2.0	-2.0	-2.0
24 hours	N	862	861	428
	Mean (SD)	-4.3 (11.2)	-3.4 (11.7)	-1.7 (11.6)
	Median	-4.0	-3.0	-2.0
48 hours	N	862	858	426
	Mean (SD)	-2.3 (11.8)	-1.2 (11.9)	-0.9 (12.0)
	Median	-3.0	-1.0	-1.0
Safety follow-up	N	842	846	412
	Mean (SD)	3.3 (12.1)	3.9 (12.2)	3.6 (12.8)
	Median	4.0	4.0	4.0

Source: Modified from ISS, Table 2.3.5.1, Pages 3-4

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; ISS, integrated summary of safety; N, number of patients in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.1.9. Subgroups, Pooled Analyses, Studies 104 and 105

[Table 40](#) depicts the number of subjects in each specific subgroup among the different treatment arms. The finding of a lower incidence of AEs in the SUZ arm compared to the HB/APAP and placebo arms was generally consistent across subgroups. However, there were notable imbalances in terms of the number of subjects between subgroups, which limited the conclusions that could be drawn from these data. There were significantly fewer males, subjects ≥ 65 years of age, and subjects of races other than Black, African American, or White exposed to SUZ.

Table 40. Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Studies 104 and 105

Characteristic	SUZ N=874 n/N _s (%)	HB/APAP N=879 n/N _s (%)	Placebo N=438 n/N _s (%)
Sex			
Female	334/804 (41.5)	432/800 (54.0)	189/406 (46.6)
Male	22/70 (31.4)	20/79 (25.3)	12/32 (37.5)
Age group, years			
≥ 18 to < 65	343/827 (41.5)	439/844 (52.0)	192/415 (46.3)
≥ 65	13/47 (27.7)	13/35 (37.1)	9/23 (39.1)
Age group ≥ 75 , years			
≥ 75	0/1 (0)	0/0 (NA)	0/0 (NA)
Race			
American Indian or Alaska Native	2/9 (22.2)	6/7 (85.7)	0/1 (0)
Asian	9/16 (56.2)	11/16 (68.8)	5/8 (62.5)
Black or African American	87/239 (36.4)	90/210 (42.9)	46/110 (41.8)
Multiple	6/8 (75.0)	4/7 (57.1)	1/2 (50.0)
Native Hawaiian or other Pacific Islander	1/4 (25.0)	3/6 (50.0)	1/1 (100)
Other	1/3 (33.3)	0/2 (0)	2/2 (100)
White	249/593 (42.0)	337/630 (53.5)	146/314 (46.5)
Missing	1/2 (50.0)	1/1 (100)	0/0 (NA)
Ethnicity			
Hispanic or Latino	107/281 (38.1)	174/306 (56.9)	68/157 (43.3)
Not Hispanic or Latino	249/593 (42.0)	276/570 (48.4)	133/281 (47.3)
Missing	0/0 (NA)	2/3 (66.7)	0/0 (NA)

Source: adae.xpt; Software: R

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.2. Safety Results, Study VX22-548-107 (Study 107)

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 107

There were no deaths. The incidence of SAEs and AEs leading to discontinuation of the study drug was low. The majority of AEs were mild in severity. The following analyses of the safety results in Study 107 are limited by the lack of a comparator given the single-arm design of this study.

Table 41. Overview of Adverse Events, Safety Population, Study 107

Event Category	SUZ N=256 n (%)
SAE	2 (0.8)
SAEs with fatal outcome	0
Life-threatening SAEs	0
SAEs requiring hospitalization	1 (0.4)
Other	1 (0.4)
AE leading to permanent discontinuation of study drug	5 (2.0)
AE leading to dose modification of study drug	0
AE leading to interruption of study drug	0
AE leading to reduction of study drug	0
AE leading to dose delay of study drug	0
Any AE	94 (36.7)
Severe and worse	2 (0.8)
Moderate	21 (8.2)
Mild	71 (27.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that worsened or started after the first dose of study drug through the end of the TE Period.

Duration is up to 14 days.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event;

SAE, serious adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; TE, treatment-emergent

7.6.2.2. Deaths, Study 107

There were no deaths.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study 107

There were two SAEs. No SAEs were considered to be related to the study drug by the study investigators. The SAE of cellulitis occurred in a subject who underwent a brachioplasty, and postoperative infection is a known risk associated with surgical procedures. The SAE of suicidal ideation occurred in a subject with situational social stressors that appeared unrelated to the study treatment. Additional details regarding these SAEs can be found in Section [17.3](#).

Table 42. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 107

System Organ Class Preferred Term	SUZ N=256 n (%)
Any SAE	2 (0.8)
Infections and infestations (SOC)	1 (0.4)
Cellulitis	1 (0.4)
Psychiatric disorders (SOC)	1 (0.4)
Suicidal ideation	1 (0.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that worsened or started after the first dose of study drug through the end of the TE Period.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is up to 14 days.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; TE, treatment-emergent

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, Study 107

There were five AEs leading to discontinuation. There was no discernable pattern in these AEs. There was no more than one instance of any individual AE (by preferred term) leading to discontinuation. Furthermore, each of these AEs was in a separate SOC.

Table 43. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study 107

System Organ Class Preferred Term	SUZ N=256 n (%)
Any AE leading to discontinuation	5 (2.0)
Cardiac disorders (SOC)	1 (0.4)
Arrhythmia	1 (0.4)
Gastrointestinal disorders (SOC)	1 (0.4)
Nausea	1 (0.4)
Injury, poisoning and procedural complications (SOC)	1 (0.4)
Accidental overdose	1 (0.4)
Nervous system disorders (SOC)	1 (0.4)
Somnolence	1 (0.4)
Skin and subcutaneous tissue disorders (SOC)	1 (0.4)
Rash	1 (0.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that worsened or started after the first dose of study drug through the end of the TE Period.

Duration is up to 14 days.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; TE, treatment-emergent

7.6.2.5. Treatment-Emergent Adverse Events, Study 107

The incidence of AEs was similar to that seen in the SUZ treatment arm of the pooled, controlled phase 3 studies. The most common AEs ($\geq 2\%$ incidence) were generally consistent with those seen in the pooled, controlled phase 3 studies. The one exception is the AE of fall, which was more common in Study 107 than in the pooled, controlled phase 3 studies. All subjects who experienced this AE had undergone a lower extremity surgery, and these AEs were all mild in severity. In these subjects, the study drug dose was not changed in response to the AE.

Table 44. Subjects With Adverse Events, Safety Population, Study 107

Preferred Term	SUZ N=256 n (%)
Any AE	94 (36.7)
Headache	18 (7.0)
Constipation	9 (3.5)
Nausea	8 (3.1)
Fall	6 (2.3)
Rash	5 (2.0)
Hypoaesthesia	4 (1.6)
Rhinitis allergic	4 (1.6)
Alanine aminotransferase increased	3 (1.2)
Diarrhoea	3 (1.2)
Dizziness	3 (1.2)
Limb injury	3 (1.2)
Nasopharyngitis	3 (1.2)
Paraesthesia	3 (1.2)
Postoperative wound infection	3 (1.2)
Pyrexia	3 (1.2)
Urinary tract infection	3 (1.2)
Vomiting	3 (1.2)
Activated partial thromboplastin time prolonged	2 (0.8)
Anxiety	2 (0.8)
Aspartate aminotransferase increased	2 (0.8)
Chills	2 (0.8)
Cough	2 (0.8)
Dry mouth	2 (0.8)
Fatigue	2 (0.8)
Gamma-glutamyltransferase increased	2 (0.8)
Haemorrhoids	2 (0.8)
Muscle spasms	2 (0.8)
Pain in extremity	2 (0.8)
Peripheral swelling	2 (0.8)
Pruritus	2 (0.8)
Vision blurred	2 (0.8)
Vulvovaginal mycotic infection	2 (0.8)
Abdominal discomfort	1 (0.4)
Accidental overdose	1 (0.4)
Acne	1 (0.4)
Arrhythmia	1 (0.4)
Arthralgia	1 (0.4)
Blood alkaline phosphatase increased	1 (0.4)
Blood bicarbonate increased	1 (0.4)
Blood creatine phosphokinase increased	1 (0.4)

Preferred Term	SUZ N=256 n (%)
Bronchitis	1 (0.4)
Burning sensation	1 (0.4)
Cellulitis	1 (0.4)
Cyst	1 (0.4)
Dermatitis contact	1 (0.4)
Dry eye	1 (0.4)
Dyspepsia	1 (0.4)
Epistaxis	1 (0.4)
Eye pruritus	1 (0.4)
Eye ulcer	1 (0.4)
Folliculitis	1 (0.4)
Gastroenteritis	1 (0.4)
Gastrooesophageal reflux disease	1 (0.4)
Generalised anxiety disorder	1 (0.4)
Haemoglobin decreased	1 (0.4)
Herpes zoster	1 (0.4)
Hyperhidrosis	1 (0.4)
Hypoaesthesia oral	1 (0.4)
Influenza	1 (0.4)
Insomnia	1 (0.4)
International normalised ratio increased	1 (0.4)
Joint swelling	1 (0.4)
Lipase increased	1 (0.4)
Localised infection	1 (0.4)
Medical device site rash	1 (0.4)
Migraine	1 (0.4)
Mouth ulceration	1 (0.4)
Musculoskeletal chest pain	1 (0.4)
Nerve injury	1 (0.4)
Neuralgia	1 (0.4)
Oropharyngeal pain	1 (0.4)
Peripheral coldness	1 (0.4)
Pollakiuria	1 (0.4)
Post procedural swelling	1 (0.4)
Productive cough	1 (0.4)
Seasonal allergy	1 (0.4)
Skin irritation	1 (0.4)
Somnolence	1 (0.4)
Suicidal ideation	1 (0.4)
Swelling	1 (0.4)
Tachycardia	1 (0.4)
Urticaria	1 (0.4)
Viral infection	1 (0.4)
Vulvovaginal candidiasis	1 (0.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that worsened or started after the first dose of study drug through the end of the TE Period.

Duration is up to 14 days.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; TE, treatment-emergent

7.6.2.6. Laboratory Findings, Study 107

Analysis of laboratory findings did not raise clinically meaningful safety concerns. The lack of a comparator in this single-arm study limits evaluation of the relationship between SUZ and the observed laboratory findings.

Changes in CPK, creatinine, and eGFR similar to those seen in the pooled, controlled phase 3 studies were observed. These are summarized in [Table 45](#). There was an increase in CPK at discharge compared to baseline, which resolved by end of treatment. There was an increase in creatinine and a decrease in eGFR at discharge compared to baseline. These changes from baseline were larger in magnitude at end of treatment, but resolved by safety follow-up. Overall, the magnitude of these changes was relatively small and unlikely to be clinically significant. Because the end of treatment in this study was Day 14, or earlier for subjects discontinuing study drug before Day 14, it is unknown whether these laboratory changes would have increased in magnitude to become clinically significant with longer duration of treatment.

Table 45. Selected Chemistry Assessments and Changes From Baseline at Discharge, End of Treatment, and Safety Follow-Up, Study 107

Laboratory Parameter	SUZ (N=256)		
	Discharge	End of Treatment	Safety Follow-Up
Creatine kinase (U/L)			
n	211	242	94
Mean (SD)	34.6 (167.1)	-4.0 (156.0)	-24.4 (75.2)
Median	2.0	-5.5	-9.5
Creatinine (μmol/L)			
n	212	245	97
Mean (SD)	1.2 (12.7)	3.9 (13.1)	-0.1 (14.3)
Median	0.0	0.0	0.0
Glomerular filtration rate, estimated (mL/min/1.73 m ²)			
n	212	245	97
Mean (SD)	-1.1 (12.5)	-3.8 (13.8)	0.0 (13.4)
Median	0.0	-1.0	0.0

Source: Modified from VX22-548-107 CSR, Table 14.3.4.1, Pages 19-22, 27-28

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Discharge assessments are completed for all surgical subjects and for any nonsurgical subjects who required inpatient admission.

The end of treatment is defined as either Day 14 or the End of Dosing Visit for subjects who complete or discontinue study drug treatment before Day 14.

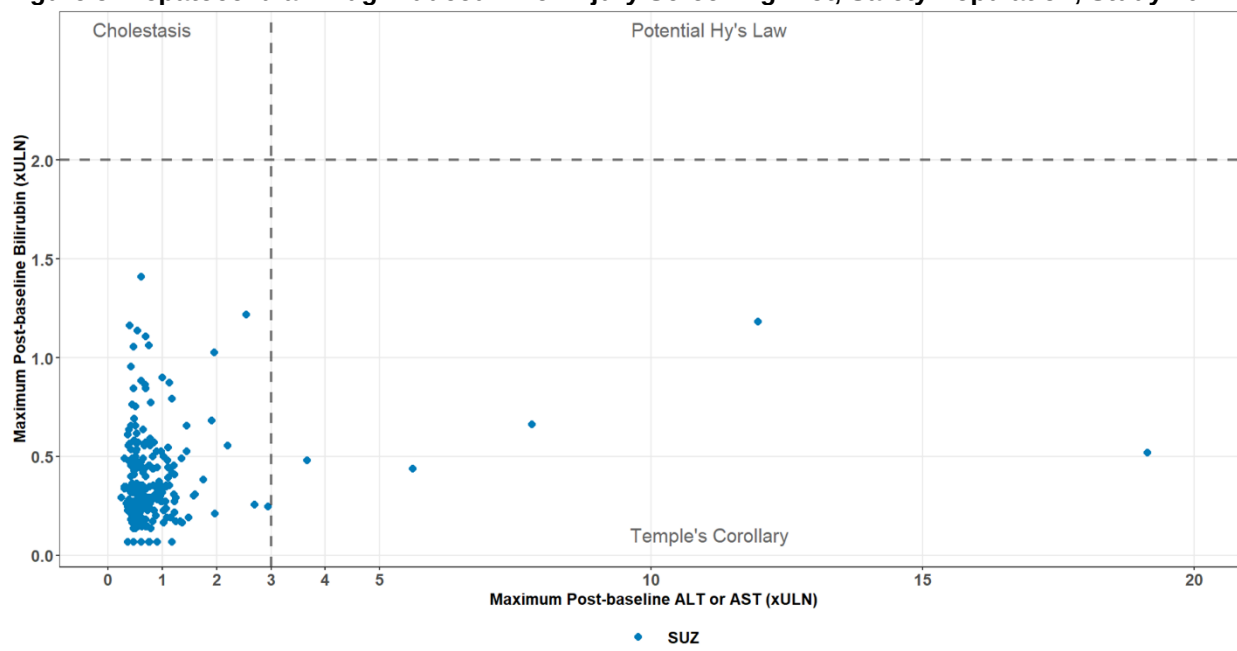
Lab assessments are required at Safety Follow-up only if a clinical finding during the Treatment Period requires follow-up.

Abbreviations: N, number of patients in treatment arm; SD, standard deviation; SUZ, suzetrigine

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study 107

[Figure 5](#) shows a screening assessment for potential cases of serious DILI. There were no subjects in the Cholestasis and Potential Hy's Law quadrants. There were five subjects (2%) in the Temple's Corollary quadrant. These results do not suggest a significant concern for drug-induced liver injury in this study.

Figure 5. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 107



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

7.6.2.8. Vital-Sign and ECG Analyses, Study 107

Review of the vital sign data and ECG parameters did not reveal significant clinically meaningful safety concerns. As depicted in [Table 46](#), there were mild decreases from baseline in both the mean systolic and diastolic blood pressures during the treatment period. The magnitude of this difference was generally small. Vital signs could have been affected by subjects' qualifying conditions for this study (i.e., being in the postoperative period), and the lack of a comparator arm limits the interpretability of these results.

Table 46. Blood Pressure (mm Hg) and Changes From Baseline by Visit, Study 107

		Change From Baseline	
		SUZ	
		N=256	
Time Point		Systolic BP	Diastolic BP
Discharge	N	215	215
	Mean (SD)	-7.5 (18.4)	-3.0 (12.9)
	Median	-6.0	-4.0
Day 7	N	165	165
	Mean (SD)	-1.3 (17.3)	-0.2 (11.9)
	Median	0.0	0.0
End of treatment	N	253	253
	Mean (SD)	-4.1 (16.7)	-0.1 (12.1)
	Median	-4.0	-1.0
Safety follow-up	N	238	238
	Mean (SD)	-3.0 (16.8)	0.8 (12.7)
	Median	-1.5	0.0

Source: Modified from Protocol VX22-548-107 CSR, Table 14.3.5.1, Pages 1-4

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Discharge assessments are completed for all surgical subjects and for any nonsurgical subjects who required inpatient admission.

The end of treatment is defined as either Day 14 or the End of Dosing Visit for subjects who complete or discontinue study drug treatment before Day 14.

Abbreviations: BP, blood pressure; N, number of patients in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

7.6.2.9. Columbia-Suicide Severity Rating Scale Analyses, Study 107

One subject (0.4%) experienced the suicidal ideation event of “wish to be dead” during the treatment-emergent period. This was considered an SAE. The subject felt that the suicidal ideation was situational and related to family/relationship issues and limited mobility due to her postsurgical condition. This SAE was considered by the investigator to be not related to the study drug. Additional details regarding this SAE are provided in Section [17.3](#).

7.6.3. Safety Results, Pooled Phase 2 and 3 Studies

The analyses of safety results from the pooled phase 2 and 3 studies in subjects exposed to a 100-mg loading dose of SUZ followed by 50 mg every 12 hours were generally supportive of the results from the pooled, controlled phase 3 studies. The incidence of SAEs and AEs leading to discontinuation of the study drug was low overall, and there were no substantial differences between the treatment arms. The incidence of AEs was lower in the SUZ arm than in both the HB/APAP and placebo arms. There were no deaths in the phase 2 studies. Adverse events by PT were generally consistent with those seen in the pooled, controlled phase 3 studies.

7.7. Key Safety Review Issues

7.7.1. Risk of Negative Effects on Renal Function

Issue

Changes in clinical laboratory assessments of renal function, including eGFR and creatinine, appear to be more common in the SUZ treatment arm than in the HB/APAP and placebo treatment arms.

Background

The Applicant is evaluating SUZ for the treatment of pain associated with diabetic peripheral neuropathy (DPN) in addition to the acute pain indication that is the subject of the current NDA review. They have conducted one phase 2 study in subjects with painful DPN (VX21-548-103), which evaluated the dose regimens of SUZ 69, 46, or 23 mg daily compared to pregabalin 100 mg three times daily for a 12-week treatment period.

In Study VX21-548-103, the most common AE in subjects who received SUZ was creatinine clearance (CrCl) decreased. As shown in [Table 47](#) and [Table 48](#), there appears to be a dose-response relationship, with the highest SUZ dose group having the highest incidence of this AE and the largest change from baseline in creatinine. Eleven subjects (8.0%) across the SUZ groups discontinued the study drug due to CrCl <60 mL/min compared to 4 (7.4%) subjects in the pregabalin group. Subjects who met this CrCl threshold were required to discontinue the study drug due to pregabalin labeling recommendations for decreased renal function. The Applicant asserts that the increased incidence of AEs of CrCl decreased and treatment discontinuations due to this AE in the SUZ 69 mg dose group compared to other groups was an artifact of study conduct related to baseline imbalances in CrCl.

Any risk of decreased renal function associated with SUZ should be characterized and described in the labeling to allow healthcare professionals to assess the benefit-risk profile. The review of this risk issue in the acute pain program focused on changes in clinical laboratory assessments of renal function, their clinical significance, and related AEs.

Table 47. AE of Creatinine Renal Clearance Decreased in Any Treatment Group at Week 12, Safety Set, Study VX21-548-103

PT, n (%)	Pregabalin 100 mg tid N=54	SUZ 23 mg qd N=28	SUZ 46 mg qd N=55	SUZ 69 mg qd N=55	SUZ Total N=138
Creatinine renal clearance decreased	1 (1.9)	0	1 (1.8)	6 (10.9)	7 (5.1)

Source: Modified from Type B End-of-Phase 2 Meeting Information Package, March 28, 2024, Table 13-31, page 96
Abbreviations: AE, adverse event; N, number of subjects in the Safety Set; n, number of subjects with event; PT, preferred term; qd, once daily; SUZ, suzetrigine; tid, 3 times per day

Table 48. Mean (SD) Baseline Values and Changes From Baseline in Creatinine at Week 12, Safety Set, Study VX21-548-103

Parameter Time Point	Pregabalin 100 mg tid N=54	SUZ 23 mg qd N=28	SUZ 46 mg qd N=55	SUZ 69 mg qd N=55
Creatinine (μmol/L)				
Baseline	68.8 (16.8)	73.6 (22.8)	79.9 (27.7)	81.0 (18.8)
Change from baseline at Week 12 ^a	3.5 (11.8)	1.9 (11.9)	1.3 (13.4)	4.6 (12.6)

Source: Modified from Type B End-of-Phase 2 Meeting Information Package, March 28, 2024, Table 13-32, page 99

Notes: Baseline value was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

^a At Week 12, the numbers of subjects with data (n) were 43, 28, 47, and 44 subjects for the pregabalin and SUZ 23-, 46-, and 69-mg qd groups, respectively.

Abbreviations: n, number of subjects with data; N, number of subjects in the analysis set; qd, once daily; SD, standard deviation; SUZ, suzetrigine; tid, 3 times per day

Assessment

Clinical laboratory assessments of renal function measured in the phase 3 studies included creatinine and eGFR. Creatinine clearance was not measured in these studies. Longer-term data regarding renal function were generally not available since serum chemistry was not routinely assessed at the safety follow-up visit in the phase 3 studies. In Study 107, this was assessed only if a clinical finding during the treatment period required follow-up.

As demonstrated in [Table 37](#), which depicts pooled data from Studies 104 and 105, the mean change from baseline at 48 hours was negative for creatinine and positive for eGFR in all three treatment arms. Considering that this pattern was observed in the placebo arm, this overall trend may be related to the peri- and intraoperative administration of intravenous fluids and a subsequent dilution effect. The magnitude of the decrease in creatinine and increase in eGFR was similar between the HB/APAP and placebo arms. However, the magnitude of these changes in the SUZ arm was smaller compared to the other arms.

Study 107 was a single-arm study; therefore, a comparison of changes in renal function parameters to another treatment was not possible. However, as demonstrated in [Table 45](#), there was a positive mean change in creatinine from baseline to discharge and end of treatment and a negative mean change in eGFR from baseline to discharge and end of treatment. There was essentially no mean change from baseline in these assessments at the safety follow-up visit.

The magnitude of the changes in the renal function laboratory values described above were overall small and were considered unlikely to be clinically significant based on the data available. In the SUZ arm of the phase 3 studies, there were no SAEs or AEs leading to study drug discontinuation that were directly related to renal function. In the phase 3 controlled studies, the incidence of AEs in the SOC of renal and urinary disorders was lower in the SUZ arm than in the other arms as demonstrated in [Table 49](#). There is no notable imbalance towards the SUZ arm for any of the other AEs listed in this table. In Study 107, the incidence of renal AEs was low.

Table 49. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Renal-Related Terms, Safety Population, Pooled Studies 104 and 105

System Organ Class Preferred Term	SUZ N=874 n (%)	HB/APAP N=879 n (%)	Placebo N=438 n (%)
Infections and infestations (SOC)	19 (2.2)	18 (2.0)	8 (1.8)
Urinary tract infection	2 (0.2)	0	1 (0.2)
Bacteriuria	0	1 (0.1)	1 (0.2)
Investigations (SOC)	30 (3.4)	34 (3.9)	17 (3.9)
Blood urine present	1 (0.1)	2 (0.2)	0
Glomerular filtration rate decreased	0	0	1 (0.2)
Glucose urine present	0	1 (0.1)	0
Red blood cells urine positive	0	1 (0.1)	1 (0.2)
Urinary squamous epithelial cells increased	0	0	1 (0.2)
White blood cells urine positive	0	1 (0.1)	2 (0.5)
Renal and urinary disorders (SOC)	2 (0.2)	10 (1.1)	6 (1.4)
Urinary incontinence	1 (0.1)	2 (0.2)	0
Urinary retention	1 (0.1)	3 (0.3)	3 (0.7)
Glycosuria	0	1 (0.1)	0
Haematuria	0	5 (0.6)	2 (0.5)
Proteinuria	0	0	1 (0.2)

Source: Adapted from ISS, Table 2.3.2.2.1

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Conclusion

There does not appear to be a clinically meaningful impact on renal function associated with SUZ in the acute pain setting. The population for the painful DPN indication may be at higher risk of changes in renal function associated with SUZ because of potential baseline renal impairment due to diabetes. It is also unknown whether the longer duration of treatment for chronic pain compared to acute pain is associated with increased risk of renal impairment in the painful DPN population. These concerns should be further evaluated in the Applicant's painful DPN studies with SUZ.

7.7.2. Duration of Use

Issue

The Applicant is proposing treatment with SUZ (b) (4).
However, there are limited data from the acute pain trials to inform duration of use.

Background

The proposed indication for SUZ is for the treatment of moderate-to-severe acute pain in adults. Acute pain is typically sudden in onset and time limited. The draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* (February 2022) defines acute pain as "lasting up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery." It is well known that a subset of subjects with acute pain will go on to develop chronic pain. (b) (4)

(b) (4)

Studies 104 and 105 were controlled phase 3 acute pain studies that evaluated SUZ for a treatment duration of 48 hours. Study 107 was a single-arm phase 3 acute pain study that evaluated SUZ for a treatment duration of up to 14 days or until pain resolved, whichever occurred first. No other studies have evaluated the acute pain dosage regimen of SUZ (100 mg first dose followed by 50 mg every 12 hours) for a longer treatment duration. (b) (4)

Assessment

Study 107 is the only source of clinical data to inform the safety of longer-term use of SUZ for acute pain. This was a single-arm study, which has significant limitations for the evaluation of safety or efficacy. Subjects in this study could complete study drug treatment due to reaching pain resolution, in addition to the usual reasons for study discontinuation, such as AEs. The median duration of treatment was 11 days as depicted in [Table 50](#), and 105 (41.0%) subjects completed treatment through Day 14. Only 22 subjects were exposed to SUZ for longer than 14 days. Therefore, there are limited clinical data to inform use of SUZ beyond 14 days.

Table 50. Duration of Exposure, Safety Population, Study 107

Parameter	SUZ N=256
Duration of treatment, days	
Mean (SD)	9.6 (4.7)
Median (Q1, Q3)	11 (5, 14)
Min, max	1, 18
Total exposure (person years)	7
Patients treated, by duration, n (%)	
<4 days	40 (15.6)
≥4 to <8 days	57 (22.3)
≥8 to <11 days	30 (11.7)
≥11 to <15 days	107 (41.8)
≥15 to <19 days	22 (8.6)
≥19 days	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is up to 14 days.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

The safety results from this study are discussed in [Section 7.6.2](#). In summary, there were no deaths, and the incidence of SAEs and AEs leading to discontinuation of the study drug was low. The most common AEs were generally consistent with those seen in the controlled phase 3 studies. An analysis of subjects who had at least one AE that occurred within different time windows after treatment started is depicted in [Table 51](#) and suggests that there was no consistent pattern between duration of treatment and incidence of AEs. There are no reliable efficacy data to inform duration of use given the design of Study 107 and the efficacy data collected (Patient Global Assessment of study drug).

Table 51. Overview of Adverse Events by AE Start Day, Safety Population, Study 107

Characteristic	SUZ
	N=256 n/N (%)
AE start day	
<4	52/94 (55.3)
≥4 to <8	26/94 (27.7)
≥8 to <11	12/94 (12.8)
≥11 to <15	10/94 (10.6)
≥15 to <19	6/94 (6.4)
≥19 days	20/94 (21.3)

Source: adae.xpt; Software: R

Duration is up to 14 days.

Abbreviations: AE, adverse event; N, number of subjects with at least 1 event; n, number of subjects with adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

The safety data in Study 107 are generally favorable.

(b) (4)

SUZ

has the potential to be widely used since the proposed indication of moderate-to-severe acute pain is broad and extremely common. SUZ represents a new pharmacologic class, which introduces uncertainty regarding risk and favors a conservative approach to risk management.

(b) (4)

Conclusion

The Applicant's proposal (b) (4) for duration of use is not acceptable. In the labeling, (b) (4)

language describing the duration of use studied will be used to inform prescribers about limitations in the available safety data.

7.7.3. Risk of Reproductive and Developmental Effects

Issues

Toxicities of SUZ were observed in rat reproductive and developmental studies such as increased pre-implantation loss, increased post-implantation loss, lower fetal body weights, and increased pup mortality.

Background

In a female fertility study in rats, increased pre-implantation loss was observed at oral SUZ doses of 15 mg/kg when administered prior to mating and through gestation day (GD) 7. These effects on fertility in female rats appear to be reversible as pre-implantation loss was not observed when female rats were mated following discontinuation of SUZ for 4 weeks.

In the rabbit EFD study, higher post-implantation loss and lower fetal body weights were observed at 200 mg/kg/day when administered on GDs 7 to 20. However, these effects occurred at a dose that also caused maternal toxicity so it is unclear if they are SUZ related. In the rat EFD study, higher post-implantation loss and lower fetal body weights were observed at 15 mg/kg/day

and higher when administered on GDs 6 to 17. These occurred in the absence of maternal toxicity.

In the rat PPND study, reduced mean gestation duration and increased postnatal pup mortality between birth and postnatal day 4 were observed at ≥ 10 mg/kg, and increased incidences of fully resorbed litters, fewer live newborn pups, and reductions in pup body weights were observed at 15 mg/kg when SUZ was orally administered to pregnant rats from GD 6 to lactation day 20. No effects on learning and memory or sexual maturation were observed at doses up to 15 mg/kg.

(b) (4)

The Applicant provided reproductive toxicity data with other Nav1.8 blockers, which did not show similar reproductive toxicity findings, to support that those reproductive toxicity findings observed in rats treated with SUZ are not due to Nav1.8 antagonism. In addition, the Applicant also provided IC₅₀ comparison of SUZ against human versus rat progesterone receptor (PR) by conducting two independent in vitro PR reporter assays (one against human PR and the other against rat PR).

(b) (4)

Table 52. PR Antagonism in the In Vitro Rat and Human PR Reporter Assays

Test Compound	Rat PR Reporter Assay	Human PR Reporter Assay	Human PR Assay With Coactivator
Progesterone*	100pM ^a	8nM ^a	2.07nM ^b
Positive control – PR antagonists	IC₅₀ for PR Antagonism (nM)		
Mifepristone	0.027	0.422	4.46
Ulipristal	0.022	0.428	
PF-02413873	4	95	
SUZ and metabolites			
SUZ	45	4240	29600
M6-SUZ	142	10920	
M3-SUZ	1448	24510	
M12-SUZ	4507	>30000	

Source: Study VX-548-TX-022, Page 14, and 16, Tables 2-3; Study No. VRT-1737548-TX-016, Page 7, and 24

* Preincubation with progesterone at *EC₈₀ and *EC₅₀

Abbreviations: EC₅₀, half-maximal effective concentration; EC₈₀, 80% maximal effective concentration; IC₅₀, half-maximal inhibitory concentration; PR, progesterone receptor; SUZ, Suzetrigine

Assessment

While it is reasonable to conclude that the reproductive toxicity findings observed in rats may not be due to the on-target effect inhibiting Nav1.8 and rat PR antagonism effects of SUZ may play a role in pre-/post-implantation loss observed in rats, the submitted data/information were insufficient to dismiss other potential off-target effects of SUZ in addition to rat PR antagonism effects. Additionally, the Applicant

(b) (4)

However, a direct comparison of IC₅₀ values from these two independent assays, which used engineered cell systems overexpressing human or rat PR, is very challenging because it is difficult to normalize these two independent systems and compare their values. Of note, even the positive controls produced IC₅₀ values in these assays were markedly different than indicated in the technical manual of the assay and in vivo values indicated in the public

domain; therefore, a direct comparison of IC₅₀ values from two independent in vitro assays was considered inappropriate. Lastly, there are some limitations to predicting in vivo inhibitory activity from the submitted in vitro data.

Conclusion

Taken together, there are insufficient data to allow us to definitively conclude

(b) (4)

Relevant

labeling languages were included in Section 8.3 and 13.1.

7.8. Abuse Potential

The Controlled Substance Staff (CSS) conducted a review of the abuse potential of SUZ. The abuse- and dependence-related TEAE data provided by the Applicant suggest that SUZ did not produce abuse- or dependence-related effects under the tested conditions. CSS does recommend that TEAEs be monitored for dependence if SUZ is investigated for chronic use. In summary, SUZ does not have a potential for abuse and should not be controlled under the Controlled Substances Act. CSS's review dated December 6, 2024, is excerpted below:

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 [Controlled Substances Act]. 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.

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

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

Study 007 compared the pharmacokinetics of orally administered SUZ in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment to age-, weight-, and sex-matched healthy subjects.

There was no clinically significant effect of mild hepatic impairment on the pharmacokinetics of SUZ and M6-SUZ; hence, no dosage adjustment is needed in these patients.

In subjects with moderate hepatic impairment, SUZ and M6-SUZ exposures (area under the concentration-time curve [AUC]) were 1.50-fold and 1.15-fold higher, respectively, than those in matched healthy subjects. Therefore, a reduced loading dose of 100 mg, followed by 50 mg q12h for the next three doses, followed by 50 mg once daily (qd) for all subsequent doses, not to exceed 14 days is recommended for subjects with moderate hepatic impairment. Modeling and simulation of the regular dosing regimen (100 mg loading dose, followed by 50 mg q12h) and the proposed reduced dosing regimen (100 mg loading dose, followed by 50 mg q12h for the next three doses, followed by 50 mg qd) indicated that exposure during the first 2 to 3 days was similar between the two dosing regimens. At steady state, subjects with hepatic impairment exhibited higher accumulation than did healthy subjects under the regular dosing regimen. In contrast, the reduced dosing regimen resulted in an approximately 20% reduction in PK metrics at steady state, including a 17% reduction in maximum plasma concentration at steady state ($C_{max,ss}$), a 22% reduction in trough plasma concentration at steady state ($C_{trough,ss}$), and a 23% reduction in daily AUC_{ss} (refer to pharmacometric analysis in Section [14.5](#) of this review). Hence, the review team agrees with the proposed reduced dosing in moderate hepatic impairment.

SUZ has not been studied in patients with severe hepatic impairment, and therefore should not be used in these patients.

Renal Impairment

The mass balance study showed that renal excretion of SUZ is minimal. In a dedicated renal impairment study, the pharmacokinetics of SUZ and M6-SUZ were not altered in subjects with renal impairment of eGFR 15 to <60 mL/min (estimated by the chronic kidney disease epidemiology collaboration equation with adjustment for body surface area). Therefore, the review team agrees that no dosage adjustment is needed in patients with renal impairment of eGFR >15 mL/min.

The effect of kidney failure not receiving dialysis (eGFR <15 mL/min) on SUZ and M6-SUZ pharmacokinetics is unknown.

Other Intrinsic Factors

Based on population PK analysis, no clinically significant differences in the pharmacokinetics of SUZ and M6-SUZ were observed based on age (18 to 75 years), sex, body weight (44 to 128 kg), or race.

8.2. Extrinsic Factors

8.2.1. Effect of Food

The proposed indication for SUZ is acute pain and therefore, the attainment of sufficient initial concentrations after dosing is an expectation for the onset of pain relief. In the phase 3 studies of SUZ (104, 105 and 107), the first dose (100 mg) was administered in fasting condition, and subsequent doses were administered without regard to food. In the phase 3 studies, with the first dose under a fasted state, the median time to onset of perceptible pain relief in abdominoplasty (Study 105) and bunionectomy (Study 104) was 34 minutes and 60 minutes, respectively. (b) (4)

The effect of food on the pharmacokinetics of SUZ and M6-SUZ was evaluated in two studies, 011 and 016, using the 50 mg to-be-marketed formulation at a dose of 100 mg. Study 011 evaluated the effect of a high-fat meal (800 to 1000 calories, 50% derived from fat) on the pharmacokinetics of SUZ and M6-SUZ. Study 016 evaluated the effects of various meal types (low-fat meal [up to 500 calories with no more than 25% derived from fat], moderate-fat meal [600 calories, 30% derived from fat], and high-fat meal) and the timing of meal administration (60 minutes predose, at 0 hours, and 60 minutes postdose) on SUZ and M6-SUZ pharmacokinetics.

Administration of SUZ after consuming high-fat meals and moderate-fat meals resulted in considerable reduction in SUZ concentrations in initial time points. This decrease in initial concentrations was well represented in individual level PK data where multiple subjects showed very low concentrations for the first 2 to 3 hours postdose in the fed state versus fasted state (Figure 18 and Figure 19). The high-fat meal and moderate-fat meal delayed the median time to maximum concentration (T_{max}) of SUZ from 3 hours in the fasted state to 5 hours in the fed state and that of M6-SUZ from 8 to 10 hours in the fasted state to 24 hours in the fed state. The C_{max} and AUC of SUZ and M6-SUZ were not affected by any of the meal conditions.

A high-fat meal consumed 1 hour after the administration of SUZ did not affect the systemic exposures of SUZ and M6-SUZ. Administration of the second dose of 50 mg with or without a meal is also predicted to not affect the systemic exposures of SUZ and M6-SUZ.

Based on the observed decreased initial concentrations and delayed T_{max} with both moderate- and high-fat meals in comparison to a fasted condition, (b) (4)

(b) (4) Based on overall data, the review team's recommendation for food effect is as follows: "Avoid consuming food from 2 hours before until 1 hour after the first dose of JOURNAVX to avoid delay in onset of pain relief. Subsequent doses of JOURNAVX can be taken with or without food." Taking the first dose with food may result in a delayed onset of pain relief.

Relative Bioavailability Comparison Between Phase 2 Formulation and To-Be Marketed Formulation

Study 011 evaluated the relative bioavailability between the to-be-marketed SUZ 50-mg tablet and the phase 2 formulation, SUZ 10-mg tablet, at a dose of 100 mg in the fasted state.

At the 100-mg dose, the SUZ 50-mg tablets (to-be-marketed formulation) showed bioequivalence to the 10-mg tablets (phase 2 formulation) in terms of $AUC_{0-\infty}$ while the C_{max} was approximately 15% lower with the lower 90% CI value marginally outside bioequivalence limits. M6-SUZ showed bioequivalence for both $AUC_{0-\infty}$ and C_{max} . The SUZ T_{max} was unchanged between the two formulations (3 hours) while the 50-mg tablets showed delayed T_{max} (10 hours) versus 10-mg tablets (5 hours) for M6-SUZ. Since the dosing regimen of SUZ is a 100-mg loading dose followed by 50 mg twice daily (b) (4) the minor differences in pharmacokinetics between the to-be-marketed formulation and the phase 2 formulation are considered not clinically relevant. In addition, the phase 3 studies (104 and 105) were conducted with the 50-mg to-be-marketed (TBM) tablet, which achieved statistical significance for efficacy in comparison to placebo for the treatment of acute pain.

8.2.2. Drug Interactions

Effect of Other Drugs on SUZ

Strong CYP3A Inhibitors

SUZ and M6-SUZ are cytochrome P450 (CYP) 3A substrates. The effect of itraconazole, a strong CYP3A inhibitor, on the PK of SUZ and M6-SUZ was evaluated in Study 008. The coadministration of SUZ with itraconazole increased the AUC of SUZ and M6-SUZ by 4.79-fold (90% CI: 4.28, 5.35) and 4.42-fold (90% CI: 3.64, 5.37), respectively. The upper bound of the 90% CI was greater than 5; therefore, SUZ and M6-SUZ can be considered sensitive substrates of CYP3A. The coadministration of SUZ with itraconazole resulted in an increase of SUZ C_{max} by 1.47-fold and a 31.7% decrease in the C_{max} of M6-SUZ. These results indicated that CYP3A is the main enzyme involved in metabolism for both SUZ and M6-SUZ.

The Applicant proposed that SUZ (b) (4) Since the increase in exposure of SUZ and M6-SUZ is close to 5-fold, where a 100-mg loading dose of SUZ can behave as a 500-mg single dose for which there is no safety coverage (the maximum single dose of SUZ evaluated was 395 mg), the review team proposed the "contraindication" of SUZ with strong CYP3A inhibitors in the label.

Moderate CYP3A Inhibitors

For the effects of moderate CYP3A inhibitors on the PK of SUZ and M6-SUZ, the Applicant predicted an exposure increase using physiologically based pharmacokinetic (PBPK) modeling.

The FDA's PBPK review team conducted its own analysis. Results of the FDA's PBPK model indicated that fluconazole (a moderate CYP3A inhibitor) is predicted to increase the geometric mean (90% CI) AUC of SUZ and M6-SUZ by 3.0-fold (2.9 to 3.1) and 2.6-fold (2.5 to 2.6), respectively; increase the $C_{\max}$ of SUZ by 1.20-fold (1.2 to 1.2); and decrease the $C_{\max}$ M6-SUZ by 26% (23 to 28).

Based on the increased exposure with moderate CYP3A inhibitors, the Applicant proposed a reduced SUZ dosing regimen of a 100-mg loading dose, followed by 50 mg q12h for the next three doses, followed by 50 mg qd for all subsequent doses for up to 14 days. The proposed adjusted dose regimen is expected to result in a 25% increase in $C_{\max,ss}$, 27% increases in both $C_{trough,ss}$ and daily AUC_{ss} . These changes in the PK metrics are unlikely to impact efficacy. Based on the population pharmacokinetic (popPK) analysis, the proposed reduced dosing regimen with moderate CYP3A inhibitors is considered acceptable. Refer to PBPK and popPK reviews for additional details (Section [14.5](#) of the review).

Weak CYP3A Inhibitors

For weak CYP3A inhibitors, PBPK simulation results predicted a SUZ PK exposure ratio of approximately 1.1 after a single SUZ dose in the presence of cimetidine. Therefore, no dosage adjustment is needed with weak CYP3A inhibitors.

Strong and Moderate CYP3A Inducers

The effect of a strong CYP3A inducer, rifampin, on the PK of SUZ and M6-SUZ was evaluated in Study 013 (Part B), while the effect of a moderate inducer was predicted using PBPK modeling.

Based on the observed results, rifampin decreased the geometric mean (90% CI) AUC of SUZ and M6-SUZ by 93% (91 to 94%) and 85% (83 to 86%), respectively, indicating that SUZ is a sensitive CYP3A substrate. Rifampin decreased the $C_{\max}$ (90% CI) of SUZ by 80% (75 to 83%) and increased the $C_{\max}$ of M6-SUZ by 30% (14 to 46%).

Based on PBPK modeling, efavirenz (a moderate CYP3A inducer) was predicted to decrease the geometric mean (90% CI) AUC of SUZ and M6-SUZ by 63% (61 to 65) and 60% (58 to 62), respectively. Efavirenz was predicted to decrease the $C_{\max}$ of SUZ by 29% (27 to 32) and increase the $C_{\max}$ of M6-SUZ by 32% (28 to 36). Therefore, the Applicant proposes that SUZ (b) (4) Since the exposure significantly decreased with strong and moderate CYP3A inducers, the review team's proposal is to "avoid concomitant use of SUZ with strong and moderate CYP3A inducers."

Weak CYP3A Inducers

For weak CYP3A inducers, the PBPK simulation results predicted a PK exposure ratio of approximately 0.8 to 1.0 following a single 100-mg dose. No dosage adjustment is needed with weak CYP3A inhibitors.

Proton Pump Inhibitors (Omeprazole)

Study 013 (Part A) evaluated the effect of omeprazole on the pharmacokinetics of SUZ and M6-SUZ in healthy subjects. Relative to SUZ administered alone, the coadministration of SUZ and omeprazole resulted in a 28% increase in AUC, a 4.5% decrease in $C_{\max}$, and no change in

$T_{\max}$ for SUZ. Mean SUZ and M6-SUZ concentrations with and without omeprazole were similar over the first 6 hours postdose, during which the maximum effect is expected. M6-SUZ $C_{\max}$ (7% increase) and AUC (17% increase) were not affected by omeprazole. Since omeprazole did not affect the oral absorption or decrease the systemic exposure of SUZ, no dosage adjustment is needed.

Effect of SUZ on Other Drugs

Certain CYP3A Substrates

SUZ is a CYP3A inducer. Study 010 evaluated the effect of SUZ on the pharmacokinetics of a sensitive CYP3A substrate, midazolam. SUZ decreased the mean (min-max) AUC of midazolam by 48% (43-53) and $C_{\max}$ by 37% (27-45). The Applicant has not proposed any labeling recommendations for CYP3A substrates. Since SUZ decreases the exposure and thereby compromises the efficacy of certain CYP3A substrates, the review team included following labeling recommendations for 1) CYP3A substrates for which minimal concentration changes may lead to loss of efficacy, and 2) sensitive CYP3A substrates:

- Avoid concomitant use of SUZ with CYP3A substrates where minimal concentration changes may lead to loss of efficacy unless otherwise recommended in the Prescribing Information for CYP3A substrates.
- When using SUZ with sensitive CYP3A substrates, consider increasing the dose of substrate drugs based on their Prescribing Information if needed or use alternative medications.

P-gp Substrates

SUZ is an inhibitor of P-glycoprotein (P-gp) based on in vitro studies. The effect of repeated doses of SUZ on the pharmacokinetics of digoxin (a P-gp substrate) was evaluated in Study 010. SUZ did not affect the pharmacokinetics of digoxin, indicating that SUZ is not an inducer or inhibitor of P-gp. No dosage adjustment is needed for P-gp substrates when administered with SUZ.

Hormonal Contraceptives

SUZ induces CYP3A4, which is one of the enzymes involved in the metabolism of oral hormonal contraceptives. Therefore, the Applicant evaluated the effect of repeated doses of SUZ on the pharmacokinetics of oral hormonal contraceptives levonorgestrel and ethinyl estradiol in Study 010. Levonorgestrel and ethinyl estradiol are synthetic progestin- and synthetic estrogen-containing contraceptives, respectively. SUZ did not show any significant effect on the systemic exposure of levonorgestrel and ethinyl estradiol as measured by AUC and $C_{\max}$. Therefore, SUZ can be used with oral contraceptives containing levonorgestrel and ethinyl estradiol.

In the label, in addition to levonorgestrel, the Applicant included another progestin, norethindrone, based on the sensitivity of progestins to CYP3A induction ([Wiesinger et al. 2020](#)). Based on this literature article, norethindrone has comparable or lower sensitivity than levonorgestrel to CYP3A induction caused by a strong CYP3A inducer (rifampin). Since there was no interaction between SUZ and levonorgestrel, no interaction is expected between SUZ and norethindrone. The Applicant's proposal to add norethindrone along with levonorgestrel in the

label is acceptable. The review team included the following labeling recommendations for 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.

8.3. Plans for Pediatric Drug Development

No studies in the pediatric population have been submitted in this NDA application. The Applicant is requesting a deferral for the initiation of pediatric clinical studies in subjects from birth to <17 years of age until SUZ is determined to have a positive benefit-risk profile in the adult population for the treatment of moderate-to-severe acute pain.

The Applicant plans to fulfill the Pediatric Research Equity Act requirement through four randomized, double-blind, placebo-controlled clinical studies in pediatric subjects with moderate-to-severe acute pain as proposed in the agreed initial pediatric study plan from May 3, 2024. Each study will include two parts evaluating the safety and pharmacokinetics (parts A and B) and efficacy (part B) of SUZ. Part A will be open-label and used to confirm or adjust the planned doses of SUZ before dosing additional subjects in the same age group in part B.

The studies will be conducted progressively from <17 years of age to birth per the following sequence:

1. Study C1: Subjects 12 to <17 years of age with moderate-to-severe acute pain (b) (4)
2. Study C2: Subjects 6 to <12 years of age with moderate-to-severe acute pain (b) (4)
3. Study C3: Subjects 1 to <6 years of age with moderate-to-severe acute pain.
4. Study C4: Subjects from birth to <1 year of age with moderate-to-severe acute pain.

Two pivotal good laboratory practice (GLP) nonclinical juvenile studies are planned to support pediatric clinical studies:

1. Study N2: Conduct a juvenile animal study in the rodent model to characterize the impact of SUZ on the developing brain to support clinical studies in pediatric subjects from birth to <3 years of age.
2. Study N4: Conduct a juvenile animal study in the rodent model to characterize the impact of SUZ on the developing brain to support clinical studies in pediatric subjects from 3 to <12 years of age.

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

Pregnant individuals experience acute pain due to both obstetric and nonobstetric causes. SUZ 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. The Division of Pediatrics and Maternal Health (DPMH) was consulted for this NDA. Key portions of their review are summarized below. DPMH provided labeling recommendations for subsections 8.1, 8.2, 8.3 and section 17 of labeling for compliance with the Pregnancy and Lactation Labeling Rule. Refer to DPMH's full review for additional details.

Pregnancy

There are insufficient data on SUZ use in pregnancy to allow an assessment of the drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The Applicant reported two subjects with positive pregnancy tests during the clinical development program (Study VX22-548-107) as follows:

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 SUZ 100 mg/50 mg q12h. 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 two positive urine pregnancy tests at their safety follow-up visit. On (b) (6), a serum human chorionic gonadotropin test was positive. The estimated date of conception was (b) (6) with a last menstrual period of (b) (6). Follow-up information reported that a (b) (6) g male infant was delivered (b) (6) via elective cesarean 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 SUZ 100 mg/50 mg q12h for the treatment of acute pain in the left upper extremity. The subject had a negative urine pregnancy test the same day. The subject took rescue medications, including ibuprofen and acetaminophen. On (b) (6) (Study Day 14), the subject received their last dose of SUZ. The same day, the subject had a positive pregnancy test. The subject was lost to follow-up.

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, chart review is necessary as part of the claims database complementary study for outcome validation to minimize misattribution of events as drug-related.

Lactation

Lactation data for SUZ are not currently available for humans. Since SUZ use during lactation is anticipated and the physicochemical properties of SUZ 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 SUZ is present in human breast milk, and if so, in what amounts. If a clinical milk-only lactation study demonstrates a clinically important amount of SUZ 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 preimplantation loss at oral SUZ 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, SUZ may impair female fertility.

A drug-drug interaction study was performed with an oral combined contraceptive containing ethinyl estradiol and levonorgestrel, and SUZ did not have a clinically relevant effect on the exposures of the tested hormones. Norethindrone was not evaluated in the dedicated drug-drug interaction (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 SUZ with hormonal contraceptives containing other progestins or to use an alternative hormonal or nonhormonal contraceptive during coadministration with SUZ and for 28 days after the final dose is warranted in labeling subsection 8.3.

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 219209 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. Therefore, OPQ recommends approval of this NDA from a quality perspective. The requested expiry of 24 months is granted with the storage conditions of controlled room temperature: 68°F to 77°F (20°C to 25°C), excursions permitted to 59°F to 86°F (15°C to 30°C).

9.1. Device or Combination Product Considerations

Not applicable.

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

Human Subjects Protections

The Applicant has provided attestation that all clinical studies were performed in compliance with GCP as described in ICH guideline E6 ([November 2016](#)).

Clinical Site Inspections

The section below is excerpted from the Office of Scientific Investigations' (OSI) clinical inspection summary dated November 27, 2024. Refer to their review for additional details.

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.

Financial Disclosure Review

The Applicant adequately disclosed financial interests/arrangements with clinical investigators per 21 CFR part 54. They provided a completed Form 3454 for Studies 104, 105, and 107. They certified that they had not entered into any financial arrangements with the listed clinical investigators as defined in 21 CFR 54.2(a), that no listed clinical investigator who was required to disclose any financial interests as defined in 21 CFR 54.2(b) disclosed any such interests, and that no listed investigator was the recipient of significant payments from the Applicant as defined in 21 CFR 54.2(f).

As noted in the minutes from the December 13, 2023, type B guidance meeting, "Study 107, while supportive of the positive results of Study 104 and 105, will not be relied upon to establish the efficacy of SUZ, and therefore, does not require a financial disclosure." As noted in the meeting discussion, "although Study 107 is not designed to evaluate a specific safety signal and may not meet the criteria for a covered clinical study (i.e., studies for which financial disclosure is required), Vertex may submit a financial disclosure for Study 107 for completeness of the NDA submission."

The investigator financial disclosures do not raise questions about the integrity of the data.

11. Advisory Committee Summary

SUZ was not taken to an FDA advisory committee because no unexpected significant safety or efficacy issues were identified, and no controversial issues arose that would benefit from advisory committee discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

On May 30, 2024, Vertex Pharmaceuticals Inc. (Vertex) submitted an original new molecular entity new drug application (NDA 219209) for suzetrigine (SUZ, also referred to as VX-548 and VRT-1737548) tablets, a selective voltage-gated sodium channel (Na_v1.8) inhibitor, for the treatment of moderate-to-severe acute pain in adults. NDA 219209 received a priority review determination and was filed under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) on July 30, 2024. The NDA was reviewed according to the provisions of “the Program,” with a priority designation, under the Prescription Drug User Fee Act VII.

Vertex Pharmaceuticals initiated the SUZ development program under investigational new drug application (IND) 146185, which was submitted on January 8, 2020. The Applicant conducted two randomized, double-blind, placebo- and active-controlled phase 3 studies, 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* (Study 104) and 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* (Study 105), which were the primary sources of efficacy data for SUZ. Studies 104 and 105 provided controlled safety data over a 48-hour treatment period, while VX22-548-107: *A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of Suzetrigine for Acute Pain* (Study 107) provided uncontrolled safety data over a treatment period of up to 14 days. Study 107 was a phase 3 open-label study that evaluated subjects with moderate-to-severe acute pain from a variety of surgical and nonsurgical conditions.

Notable regulatory milestones for this application include:

- Fast Track designation for SUZ for the treatment of moderate-to-severe acute pain was granted on March 5, 2020.
- Breakthrough Therapy designation for SUZ for the treatment of moderate-to-severe acute pain was granted on June 30, 2022.
- Rolling review was granted on March 18, 2024.

Milestone meetings related to the request for marketing approval:

- A type B, end-of-phase 2 (EOP2) meeting was held on July 14, 2022, to obtain the Division’s input on the proposed development plan and phase 3 clinical studies to support the registration of SUZ for the indication to treat moderate-to-severe acute pain. Vertex’s planned pivotal phase 3 program consisted of two adequate and well-controlled studies, one in bunionectomy and the other in abdominoplasty, and a single-arm safety and effectiveness study in a broad range of surgical and nonsurgical acute pain conditions.
- Type B, EOP2, chemistry, manufacturing, and controls (CMC) only, written responses were sent to Vertex on December 1, 2022, with preliminary feedback on Vertex’s proposed regulatory starting materials, impurity control strategy, and SUZ drug substance formal stability data proposal.

- Type B, Breakthrough Therapy, written responses were sent to Vertex on December 22, 2022, regarding Vertex's abuse liability assessment plan. The Controlled Substance Staff (CSS) agreed that no further nonclinical studies or human abuse potential studies were required at that time to assess the abuse potential of SUZ. CSS suggested that Vertex conduct an animal physical dependence and withdrawal study for assessment of dependence. The requested physical dependence and withdrawal study was conducted in rats, and the study design was agreed upon with CSS prior the study initiation. The results and report were provided at the time of NDA submission.
- A type D, guidance, CMC-only meeting was held on June 8, 2023, to discuss Vertex's intention to leverage FDA Manual of Policies and Procedures 5015.13 to expedite the time to NDA submission, assessment, and marketing approval for SUZ and to receive Agency feedback regarding the proposed SUZ drug substance and drug product stability data package.
- A type B, guidance meeting was held on December 13, 2023, to obtain alignment with the Division on several procedural topics related to the upcoming NDA submission and adequacy for filing for SUZ.

On May 30, 2024, Vertex submitted a proposed proprietary name request for JOURNAVX, which was found conditionally acceptable on August 15, 2024. The midcycle communication meeting occurred on October 2, 2024, with minutes issued on November 1, 2024. Labeling negotiations for the NDA were opened with Vertex on November 26, 2024. The late-cycle communication meeting occurred on December 5, 2024, with meeting minutes issued on January 2, 2025. Pediatric studies required by section 505B(a) of the FDCA were deferred for birth to less than 17 years, and four clinical postmarketing requirements (PMRs) and two nonclinical PMRs were issued. PMRs were also issued under section 505(o)(3) of the FDCA for a pregnancy exposure registry study, a complementary pregnancy study, and a clinical lactation study.

13. Pharmacology Toxicology

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

The nonclinical safety profile of SUZ (also referred to as VRT-1737548 and VX-548) supporting this NDA was originally reviewed under IND 146185. All nonclinical safety studies conducted in support of SUZ were also submitted to the present NDA and are reviewed in the following sections.

13.1.1. Primary Pharmacology

SUZ is a selective human voltage-gated sodium channel subtype 1.8 (Na_V1.8) blocker. The selectivity of SUZ relative to other known voltage-gated sodium channels (Na_V 1.1 through 1.9) was tested in vitro, and the half-maximal inhibitory concentration (IC₅₀) of SUZ on Na_V1.8 was 0.7nM, over 30,000× lower than the IC₅₀ of other Na_V channels. In addition, SUZ was tested for its inhibitory activity of Na_V1.8 in dorsal root ganglion (DRG) neurons of human, monkey, rat,

mouse, rabbit, and dog in vitro for species selectivity. SUZ was at least 70-fold less potent in rodent Na_v1.8 than in human or monkey Na_v1.8. Of note, a major human metabolite, M6-SUZ (also referred to as VRT-1875420 and M6), is also a potent human Na_v1.8 blocker with an IC₅₀ value of 0.5nM. See [Table 53](#) for additional details.

Table 53. Summary of the In Vitro Pharmacology Studies for SUZ

Study/Study No.	Findings
Mechanism of action	SUZ selectively inhibits a voltage-gated sodium channel subtype 1.8 (Na _v 1.8), which is expressed in DRG neurons, suppressing action potential firing in DRG neurons and reducing pain signaling.
Non-GLP In Vitro Characterization of VRT-1737548	SUZ inhibited Na _v 1.8 (TTX-resistant) currents in primary DRG neurons in single cell voltage-clamp using a manual patch-clamp electrophysiology (IC ₅₀ of 0.68±0.16nM).
Pharmacology and Selectivity/ Study No. P272	SUZ inhibited action potential firing in primary human DRG in current-clamp manual patch electrophysiology. Based on IC₅₀ levels, SUZ inhibition of Na_v1.8 current in DRG neurons was more potent in human and monkey than in rat, mouse, rabbit, and dog DRG neurons in vitro. See Table 54 and Figure 6 below.

Table 54. IC₅₀ of SUZ for Human, Monkey, Rat, Mouse, Rabbit, and Dog TTX-Resistant DRG Na_v Current

Species	Mean IC ₅₀ (nM)
Human	0.68
Monkey	0.75
Rat	56
Mouse	210
Rabbit	52
Dog	740

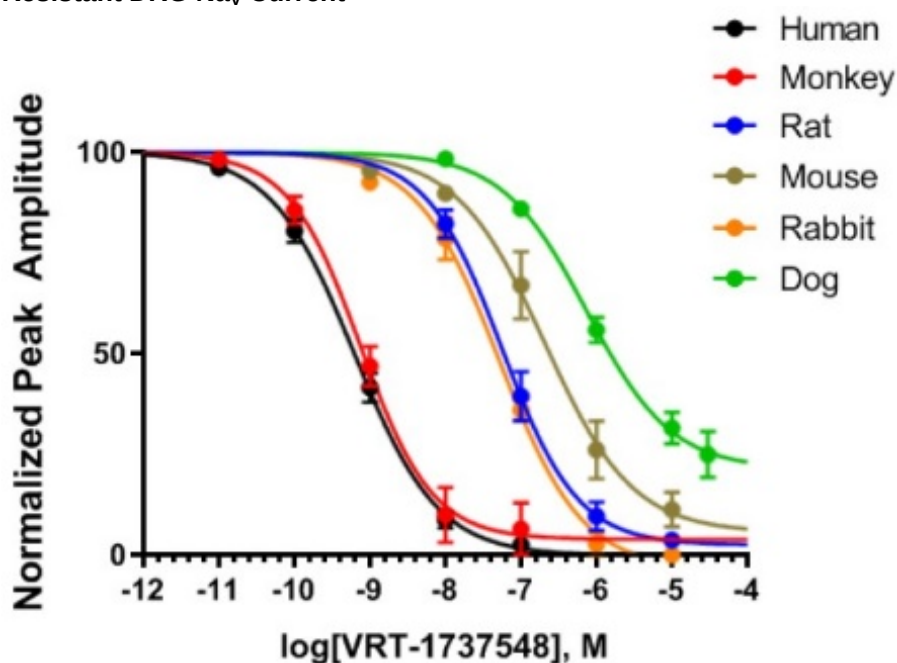
Source: Study P272, Page 17

Abbreviations: DRG, dorsal root ganglion; IC₅₀, half maximal inhibitory concentration; Na_v, voltage-gated sodium channel; TTX, tetrodotoxin

Continued

Table 53, continued

Study/Study No.	Findings
Non-GLP In Vitro Characterization of VRT-1737548 Pharmacology and Selectivity/ Study No. P272 (continued)	Figure 6. SUZ for Human, Monkey, Rat, Mouse, Rabbit, and Dog TTX-Resistant DRG Na_v Current



Source: Study P272, Page 18, Figure 9-3
Abbreviations: DRG, dorsal root ganglion; Na_v, voltage-gated sodium channel; TTX, tetrodotoxin

SUZ selectively inhibit Na_v1.8 among other subtype voltage-gated sodium channels in vitro.

Table 55. SUZ Selectivity Against Na_v Channels

Nav Channel	Primary Physiological Roles	Vertex		Charles River		Fold Selectivity
		IC ₅₀ (μM) Mean ± SE (N)	Max % Inhibition	IC ₅₀ (μM) Mean	Max % Inhibition	
Nav1.1	Neuronal excitability	--	--	>30	43	>42,000
Nav1.2	Neuronal excitability	28 ± 1.6 (5)	50	29	51	40,000
Nav1.3	Neuronal excitability	--	--	>30	43	>42,000
Nav1.4	Skeletal muscle	--	--	24	55	34,000
Nav1.5	Cardiac function	>32 ± 0 (4)	38	>30	45	>42,000
Nav1.6	Neuronal excitability	--	--	27	54	38,000
Nav1.7	Nociception	32 ± 0.4 (6)	38	>30	41	>42,000
Nav1.8	Nociception	0.0007 ± 0.0002 (3)	100	<0.01	97	--

Source: Study P272, Page 21, Table 9-2
Abbreviations: IC₅₀, half maximal inhibitory concentration; Na_v, voltage-gated sodium channel; SE, standard error

Continued

Table 53, continued

Study/Study No.	Findings
Non-GLP In Vitro Characterization of VRT-1737548 and VRT-1875420 Activity on Voltage-Gated Sodium Channel Na _v 1.9/ Study No. S048	SUZ and M6-SUZ were not potent blockers of Na _v 1.9 in vitro.

Table 56. IC₅₀ of SUZ and M6-SUZ Against Na_v 1.8 and Na_v1.9 Channels

		VRT-1737548		VRT-1875420	
		IC ₅₀ (μM) Mean ± SE (Max % inhibition; N)	Fold Selectivity	IC ₅₀ (μM) Mean ± SE (Max % inhibition; N)	Fold Selectivity
Nav1.8	Nociception	0.0007 ± 0.0002 (100; 3)	-	0.0005 ± 0.0001 (99; 3)	-
Nav1.9	Nociception	22 ± 3.8 (74; 3)	31,000	38 ± 6.7 (59; 3)	76,000

Source: Study S048, Page 10, Table 9-1

Abbreviations: IC₅₀, half maximal inhibitory concentration; Na_v, voltage-gated sodium channel; SE, standard error; VRT-1737548, suzetrigine; VRT-1875420, M6-SUZ

Non-GLP In Vitro Characterization of VRT-1875420, VRT-1875424, and VRT-1875671 Voltage-Gated Sodium Channel Subtype Selectivity/ Study No. P277

Metabolites (M6-SUZ, a major human metabolite; M3-SUZ; and M12-SUZ) are also potent Na_v1.8 blockers in vitro.

Table 57. SUZ Metabolites Selectivity Against Na_v Channels

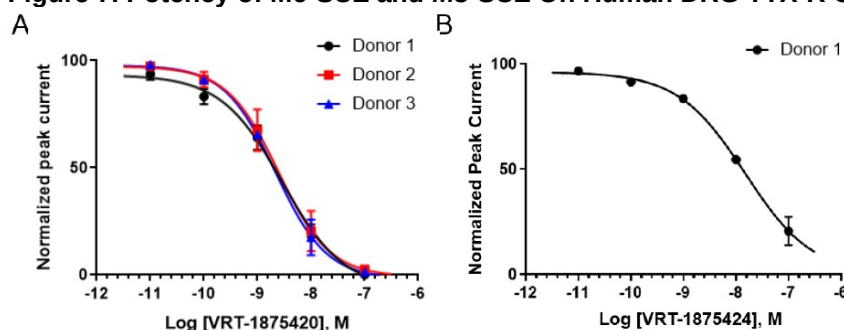
		VRT-1875420		VRT-1875424		VRT-1875671	
		IC ₅₀ (μM) Mean ± SE (Max % inhibition; N)	Fold Selectivity	IC ₅₀ (μM) Mean ± SE (Max % inhibition; N)	Fold Selectivity	IC ₅₀ (μM) Mean ± SE (Max % inhibition; N)	Fold Selectivity
Nav1.2	Neuronal excitability	>32 ± 0 (34; 10)	>64,000	27 ± 2.1 (59; 7)	1,900	>32 ± 0 (15; 4)	>350
Nav1.5	Cardiac function	>32 ± 0 (27; 8)	>64,000	>32 ± 0 (29; 6)	>2,300	>32 ± 0 (12; 3)	>350
Nav1.7	Nociception	>32 ± 0 (38; 6)	>64,000	20 ± 2.0 (66; 5)	1,400	>32 ± 0 (24; 3)	>350
Nav1.8	Nociception	0.0005 ± 0.0001 (99; 3)	-	0.014 ± 0.002 (99; 3)	-	0.091 ± 0.02 (94; 3)	-

Source: P277, Page 13, Table 9-1

Abbreviations: IC₅₀, half maximal inhibitory concentration; Na_v, voltage-gated sodium channel; SE, standard error; SUZ, suzetrigine; VRT-1875420, M6-SUZ; VRT-1875424, M3-SUZ; VRT-1875671, M12-SUZ

M6-SUZ and M3-SUZ also showed inhibition of TTX-resistant currents in primary human DRG neurons in vitro (IC₅₀ of 2.5±0.20nM for M6-SUZ, 14nM for M3-SUZ). See [Figure 7](#) below.

Figure 7. Potency of M6-SUZ and M3-SUZ On Human DRG TTX-R Current



Source: Study P277, Page 14, Figure 9-1

Abbreviations: DRG, dorsal root ganglion; TTX-R, tetrodotoxin-resistant

Source: Study No. P272, Study No. S048, and Study No. P277

Abbreviations: DRG, dorsal root ganglion; GLP, good laboratory practice; IC₅₀, half maximal inhibitory concentration; Na_v, voltage-gated sodium channel; TTX, tetrodotoxin; VRT-1737548, suzetrigine (VX-548)

13.1.2. Secondary Pharmacology

Secondary pharmacology studies of SUZ and M6-SUZ (a major human metabolite) were conducted to screen activity/binding against other ion channels, receptors, enzyme, and transporters (176 targets). The in vitro secondary pharmacology screens demonstrated SUZ binds to several targets, including the human glucocorticoid receptor, human OX1 receptor, human progesterone receptor (PR)-B (80%), and human norepinephrine transporter, with the highest binding affinity to the human progesterone receptor (IC_{50} : 0.39 μ M) out of the targets evaluated.

Table 58. Summary of Secondary Pharmacology Studies

Study/Study No.	Findings
In Vitro Pharmacology Study of VRT-1875420 and VX-548 (VRT-1737548)/ Study No. 100063774	SUZ (VX-548) inhibited GABA-gated chloride channel antagonist (picrotoxin) binding (IC_{50} : 13 μ M). VRT-1875420 inhibited glucocorticoid receptor agonist (dexamethasone) binding (IC_{50} 4.9 μ M) and OX1 receptor agonist (orexin-A) binding (IC_{50} : 2 μ M).
Effects of VRT-1682058 and VRT-1767548 on Ion Channels Expressed in Mammalian Cells/ Study No. VRT-1737548-TX-004	SUZ inhibited hCav1.2 ion channel current (IC_{50} 5.5 μ M).
Data Report for Pharmacology Services/ Study No. VRT-1737548-TX-015	SUZ inhibited human glucocorticoid receptor binding (85%), human PR-B receptor binding (80%), guinea pig adenosine transporter binding (53%), and human norepinephrine transporter binding (50%) at 10 μ M.
Data Report for Pharmacology Services/ Study No. VRT-1737548-TX-016	SUZ inhibited human glucocorticoid receptor binding (IC_{50} : 2.39 μ M), human PR-B receptor binding (IC_{50} : 0.39 μ M), guinea pig adenosine transporter binding (IC_{50} 8.8 μ M), human dopamine transporter binding (IC_{50} : 4.72 μ M), and human norepinephrine transporter binding (IC_{50} : 5.76 μ M). SUZ was not a potent antagonist (IC_{50} : 29.6 μ M) in a TR-FRET coactivator assay.
Data Report for Pharmacology Services/ Study No. TW04-0012354	VRT-1875420 inhibited progesterone binding on PR-B (IC_{50} : 3.91 μ M)
In Vitro Pharmacology: Gq Cellular Functional Assays Study of VRT-1875420/ Study No. 100064117_VRT-1875420	VRT-1875420 inhibited OX1 receptor agonist (orexin-A) effect (IC_{50} : 2.7 μ M).
Data Report for Pharmacology Services/ Study No. VRT-1875420-TX-001	VRT-1875420 inhibited Orexin OX1 receptor binding (59%), human progesterone PR-B receptor binding (62%) at 10 μ M.
In Vitro Pharmacology Study of VRT-1875420 and VX-548 (VRT-1737548)/ Study No. VRT-1875420-TX-002	SUZ inhibited glucocorticoid receptor agonist (dexamethasone) binding (93.2%) and GABA-gated chloride channel antagonist (picrotoxin) binding (52.5%) at 10 μ M. VRT-1875420 inhibited human OX1 receptor agonist (orexin-A) binding (66.5%) and glucocorticoid receptor agonist (dexamethasone) binding (63%) at 10 μ M.

Study/Study No.	Findings
In Vitro Assessment of Rat and Human Progesterone Receptor Antagonism by VRT-1737548, and Its Metabolites VRT-1875420, VRT-1875424, VRT-1875671/ Study No. VX-548-TX-022	The Applicant compared IC₅₀ values of SUZ against human versus rat progesterone receptor (PR) by conducting two independent in vitro PR reporter assays (one against human PR and the other against rat PR) and concluded SUZ is 94-fold less potent in inhibiting human PR (IC₅₀: 4240nM) compared to the rat PR (IC₅₀: 45nM), concluding there are approximately 94-fold differences. A direct comparison of IC₅₀ values from these assays is challenging because it is not clear how comparable these two different engineered system overexpressing human or rat PRs are based on differences in EC₅₀ used in these assays. See Table 59 below. Of note, it appears that the human PR reporter assays conducted by the Applicant reported an IC₅₀ value of 0.422nM for one of the positive controls, mifepristone, a known progesterone receptor inhibitor. This is greater than 10-fold higher than the IC₅₀ value of mifepristone to human PR reported in the public domain and in the assay technical manual.

Table 59. PR Antagonism in the In Vitro Rat and Human PR Reporter Assays

Test Compound	Rat PR Reporter Assay	Human PR Reporter Assay	Human PR Assay With Coactivator
Progesterone*	100pM ^a	8nM ^a	2.07nM ^b
Positive control – PR antagonists			
	IC₅₀ for PR Antagonism (nM)		
Mifepristone	0.027	0.422	4.46
Ulipristal	0.022	0.428	
PF-02413873	4	95	
SUZ and metabolites			
SUZ	45	4240	29600
M6-SUZ	142	10920	
M3-SUZ	1448	24510	
M12-SUZ	4507	>30000	

Source: Study VX-548-TX-022, Page 14, and 16, Tables 2-3; Study No. VRT-1737548-TX-016, Page 7, and 24

* Preincubation with progesterone at ^aEC₈₀ and ^bEC₅₀

Abbreviations: EC₅₀, half-maximal effective concentration; EC₈₀, 80% maximal effective concentration; IC₅₀, half-maximal inhibitory concentration; PR, progesterone receptor; SUZ, suzetrigine

Source: Study No. 100063774, Study No. VRT-1737548-TX-004, Study No. VRT-1737548-TX-015, Study No. VRT-1737548-TX-016, Study No. TW04-0012354, Study No. 100064117_VRT-1875420, Study No. VRT-1875420-TX-001, Study No. VRT-1875420-TX-002, and Study No. VX-548-TX-022

Abbreviations: GABA, gamma-aminobutyric acid; IC₅₀, half maximal inhibitory concentration; OX, orexin receptor; PR, progesterone receptor; SUZ, suzetrigine; TR-FRET, time-resolved fluorescence energy transfer; VRT-1737548, suzetrigine (VX-548)

13.1.3. Safety Pharmacology

SUZ and M6-SUZ were evaluated in good laboratory practice (GLP) in vitro human ether-à-go-go-related gene (hERG) assays, and they had no effect on hERG channel activity (IC₅₀ greater than 10μM). SUZ was tested for effects on the central nervous system (CNS), cardiovascular system, and respiratory system in a GLP single-dose safety pharmacology study and a GLP 28-day repeat-dose toxicity study in monkeys. SUZ and M6-SUZ had no effects on CNS, cardiovascular, and

respiratory parameters at doses up to 100 mg/kg. Of note, M6-SUZ, which is a major human metabolite, is also a major metabolite in monkeys. Based on toxicokinetic data of this metabolite in the 28-day repeat-dose toxicity study in monkeys, there are approximately $\geq 2\times$ safety margin for the maximum recommended human dose (MRHD) of suzetrigine (i.e., 100 mg loading dose and 50 mg maintenance dose every 12 hours).

Table 60. Summary of Pivotal Safety Pharmacology Studies

Study	Design	Findings
In vitro hERG (GLP) Study No. VRT-1737548-TX-014 Study No. VRT-1875420-TX-003	SUZ (up to 30 μ M) and M6-SUZ (up to 10 μ M) were tested in hERG-transfected HEK-293 cells.	IC ₅₀ : 22.9 μ M for SUZ IC ₅₀ >10 μ M for M6-SUZ
CV (Monkey) GLP Study no. VRT-1737548-TX-013	Cardiovascular evaluations (systolic, diastolic, and mean arterial blood pressure, pulse pressure, heart rate, and the electrocardiogram (ECG)) were evaluated after a single dose of 0, 20, 50, and 100 mg/kg in male monkeys only (N=4/group).	No effect on cardiovascular evaluations up to 100 mg/kg
GLP Study no. VRT-1737548-TX-012	ECG was evaluated at 4h postdose on Day 5 and Day 26 after repeated treatment of 20, 50, and 100 mg/kg/day in male and female monkeys (N=4/sex/group).	No effect on ECG up to 100 mg/kg
Respiratory (Monkey/GLP) Study no. VRT-1737548-TX-013	Respiratory function (respiratory rate, tidal volume, and minute volume) was evaluated after a single dose of 0, 20, 50 and 100 mg/kg in male monkeys only (N=4/group).	No effect on respiratory function up to 100 mg/kg
CNS (Monkey/GLP) Study no. VRT-1737548-TX-012	Functional observation battery (FOB) evaluations (i.e., activity level, posture, lacrimation, salivation, tremors, convulsions, fasciculations, stereotype behavior, facial muscle movement, palpebral closure, pupil response, response to stimuli, body temperature, Chaddock and Babinski reflexes, proprioception, paresis, ataxia, dysmetria, and slope assessment) were evaluated at 4h and 24h postdose on after 2 consecutive treatment days repeated treatment of 20, 50, and 100 mg/kg/day in male and female monkeys (N=4/sex/group).	No effect in FOB up to 100 mg/kg

Source: Study No. VRT-1737548-TX-014, Study No. VRT-1875420-TX-003, Study no. VRT-1737548-TX-013, and Study no. VRT-1737548-TX-012

Abbreviations: CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; FOB, functional observational battery; GLP, good laboratory practice; HEK, human embryonic kidney; IC₅₀, half maximal inhibitory concentration; SUZ, suzetrigine (VX-548, VRT-1737548)

13.1.4. ADME / PK

The in vitro and in vivo studies designed to assess absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetics are described below. Based on similarities in potency against Na_v1.8 and metabolic profile between monkeys and humans, monkeys were considered an appropriate species for use in the pivotal nonclinical safety studies. Additionally, the Applicant selected the rat as the rodent species based on the metabolism profile and achievable free drug maximum plasma concentration (C_{max}), which was up to 9-fold higher than the rat IC₅₀ for Na_v1.8 inhibition in vitro. While there appeared to be significant potency differences (approximately 80-folds) for SUZ inhibition of rat versus human Na_v1.8 in vitro, the Applicant

investigated the potency of SUZ for Nav1.8 in several species (i.e., mice, rat, dog, monkey, and rabbit) to demonstrate due diligence. Based on the Applicant's justifications noted above, the review team agreed that rat was an acceptable species for toxicity testing.

13.1.4.1. Absorption and PK

In vivo pharmacokinetic (PK) studies were conducted in monkeys, mice, dogs, and rats via oral or intravenous (IV) administration. See [Table 61](#) below.

Table 61. Summary of Absorption/PK Studies for SUZ

Study Title/Study No.	Study Design/Findings
Pharmacokinetics, Absorption, Metabolism, and Excretion of [¹⁴ C]VX-548 Following Oral and Intravenous Administration to Monkeys/ Study No. SDPK37598	Male cynomolgus monkeys were treated with [¹⁴ C]SUZ up to 15 mg/kg via oral gavage or 2.5 mg/kg via a single IV injection (N=3/group). Half-life was 38.0h in blood, and 30.2h in plasma after a single oral dose of 15 mg/kg and oral bioavailability was 69.5% in blood and 72.2% in plasma. After 2.5 mg/kg single intravenous dosing in monkeys (N=3), the mean volume of distribution levels in blood and plasma were 2000 and 1350 g/kg, respectively, and 75.2% of the dose was recovered in bile.
Pharmacokinetics of VRT-1737548 in Male Cynomolgus Monkeys following Oral Administration of Single Doses (b) (4) at 30, 100, and 300 mg/kg and (b) (4) at 30 mg/kg/ Study No. S099	In cynomolgus monkeys (N=3/group), a single oral administration of 30 mg/kg SUZ (b) (4) achieved 3.9-fold higher AUC _{0-inf} level compared to SUZ (b) (4)
Pharmacokinetics of VRT-1737548 Following a Single Intravenous Bolus Administration to Male CD-1 Mice/ Study No. P194	After a single intravenous dose of 1 mg/kg in male CD-1 mice (N=4), the half-life of SUZ was 3.75h.
Pharmacokinetics of VRT-1737548 Following a Single Intravenous or Oral Administration to Male Beagle Dogs/ Study No. P197	Oral bioavailability (b) (4) was >100% with SUZ in dogs. The effective half-life of SUZ in the male dogs was 22.8 hours after single intravenous bolus injection (1 mg/kg, N=3).
Pharmacokinetics of VRT-1737548 Following a Single Intravenous or Oral Administration to Sprague-Dawley Rats/ Study No. P199	Half-life of SUZ (b) (4) in the male rats (N=2) was 0.861h after single intravenous infusion of 1 mg/kg. Oral bioavailability was 68.1% in male rats after single oral administration (3 mg/kg, solution formulation, N=3). Exposure of SUZ (AUC _{0-inf} and C _{max}) was similar at 30 mg/kg and 2.44-fold higher at 300 mg/kg when dosed (b) (4) than when dosed (b) (4) in female rats (N=3/group) via the oral route.

Study Title/Study No.	Study Design/Findings
Pharmacokinetics of VRT-1737548 Following a Single Intravenous or Oral Administration to Male Cynomolgus Monkeys/ P228	Following a single oral administration of SUZ (b) (4) at 3 mg/kg (b) (4) in male monkeys (N=3), the bioavailability was approximately 22.6%. Following a single intravenous dose of 1 mg/kg of SUZ in male monkeys (N=2), plasma SUZ AUC_{0-inf} was 2.64 µg·h/mL and plasma clearance of SUZ was 6.34 mL/min/kg. The steady-state volume of distribution was 2.18 L/kg and the half-life of SUZ in the monkey was 3.99 hours.

Source: Study No. SDPK37598, Study No. S099, Study No. P194, Study No. P197, Study No. P199, and Study No. 228
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetic; (b) (4) SUZ, suzetrigine (VX-548; VRT-1737548)

Table 62. Oral Bioavailability of SUZ in Animals

Species	Findings
Monkey	69.5% in blood at [¹⁴ C]SUZ (15 mg/kg)
Study No.	72.2% in plasma at [¹⁴ C]SUZ (15 mg/kg)
SDPK37598	22.6% at 3 mg/kg (b) (4) formulation)
Study No. P228	
Dog	>100% at 1 mg/kg (solution formulation)
Study No. P197	>100% at 1 mg/kg (b) (4) formulation)
Rat	68.1% at 3 mg/kg (solution formulation)
Study No. P199	9.14% at 3 mg/kg (b) (4) formulation)

Source: Study No. SDPK37598, Study No. P228, Study No. P197, and Study No. P199
Abbreviation: (b) (4) SUZ, suzetrigine

Table 63. PK Parameters of SUZ and M6-SUZ in Rats After Single-Dose Oral SUZ

Species	Sex	Dose (mg/kg/day)	API/Major Metabolite	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	AUC _{0-48h} (µg·h/mL)	AUC _{0-inf} (µg·h/mL)	T _{max} (h)
Rat	F	1000	SUZ	19.1	336	659	733	36
(Sprague-Dawley)			M6-SUZ	4.46	38.5	119	142	36
		2000	SUZ	23.7	388	840	1030	36
			M6-SUZ	6.16	43.4	166	233	36

Source: Study No. U198, Page 9, Table 3

Abbreviations: API, active pharmaceutical ingredient; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; PK, pharmacokinetic; SUZ, suzetrigine; T_{max}, time to maximum concentration

Table 64. PK Parameters of SUZ and Major Metabolites (M6-SUZ, M3-SUZ, and M12-SUZ) in Rats and Monkeys After Repeat-Dose Oral SUZ

Study	Day	Sex	Dose (mg/kg/day)	API/ Metabolites	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	T _{max} (h)
28-Day Repeat Dose Toxicity Study in Rats (Sprague-Dawley)	28	M	200	SUZ	2.99	30.3	1
				M6-SUZ	0.360	3.53	4
				M3-SUZ	20.5	332	8
				M12-SUZ	2.37	24.2	4
			600	SUZ	6.25	95.9	4
				M6-SUZ	1.39	20.2	4
				M3-SUZ	30.1	482	8
				M12-SUZ	8.82	133	12
Study No. VRT-1737548-TX-011			1000	SUZ	13.5	152	4
				M6-SUZ	3.63	35.2	4
				M3-SUZ	38.7	633	12
				M12-SUZ	13.8	206	4

Study	Day	Sex	Dose (mg/kg/day)	API/ Metabolites	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	T _{max} (h)
91-Day Oral Repeat-Dose Toxicity Study in Rats Study No. VX-548-TX-001	91	F	10	SUZ	1.64	19.9	1
				M6-SUZ	0.167	2.65	2
				M3-SUZ	2.87	57.2	4
				M12-SUZ	0.362	5.69	4
			30	SUZ	4.92	77.5	4
				M6-SUZ	0.955	15.2	4
				M3-SUZ	7.42	139	8
				M12-SUZ	1.90	37.5	4
			300	SUZ	13.4	206	4
				M6-SUZ	3.58	62.4	8
				M3-SUZ	19.0	377	4
				M12-SUZ	8.63	162	8
	91	M	200	SUZ	3.47	42.3	4
				M6-SUZ	0.507	5.51	8
				M3-SUZ	31.3	420	4
				M12-SUZ	3.53	42.3	8
			600	SUZ	13.5	160	4
				M6-SUZ	2.76	40.5	4
				M3-SUZ	31.4	572	8
				M12-SUZ	14.3	225	12
			1000	SUZ	12.7	191	4
				M6-SUZ	3.61	61.5	12
				M3-SUZ	34.3	620	12
				M12-SUZ	22.1	347	12
28-day repeat dose toxicity study in Cynomolgus monkeys Study No. VRT-1737548-TX-012	28	F	10	SUZ	2.04	15.1	2
				M6-SUZ	0.207	1.92	2
				M3-SUZ	4.01	70.4	4
				M12-SUZ	0.305	4.55	12
			100	SUZ	12.2	175	4
				M6-SUZ	2.67	45.6	8
				M3-SUZ	18.2	350	12
				M12-SUZ	5.50	105	12
			1000	SUZ	42.7	619	4
				M6-SUZ	12.1	196	4
				M3-SUZ	43.4	863	0
				M12-SUZ	25.5	454	12
	28	M/F	20	SUZ	0.682	5.44	4
				M6-SUZ	1.80	16.1	4
				M3-SUZ	0.0968	1.70	12
				M12-SUZ	0.427	4.38	4
			50	SUZ	1.57	11.7	4
				M6-SUZ	4.95	43.6	4
				M3-SUZ	0.196	3.13	2
				M12-SUZ	0.925	8.85	4
			100	SUZ	2.73	19.4	4
				M6-SUZ	6.96	64.4	4
				M3-SUZ	0.197	2.93	4
				M12-SUZ	0.903	9.01	4

Study	Day	Sex	Dose (mg/kg/day)	API/ Metabolites	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	T _{max} (h)
13-week repeat dose toxicity study in Cynomolgus monkeys	91	M/F	20	SUZ	0.705	6.15	2
				M6-SUZ	1.49	16.7	2
				M3-SUZ	0.134	1.80	NA
				M12-SUZ	0.303	3.92	2
			50	SUZ	1.32	10.8	2
				M6-SUZ	2.93	30.4	2
				M3-SUZ	0.184	2.64	2
				M12-SUZ	0.471	5.46	2
Study No. VX-548-TX-002			150	SUZ	2.75	24.1	2
				M6-SUZ	6.33	68.4	2
				M3-SUZ	0.305	4.06	2
				M12-SUZ	0.843	9.19	2

Source: VRT-1737548-TX-011, Page 29-30, Text Table 11, Study No. VX-548-TX-001, Pages 35-38, Text Tables 18-21, Study No. VRT-1737548-TX-012, Page 26-27, Text Table 9; Study No. VX-548-TX-002, Pages 20-21, Text Table 10
Abbreviations: API, active pharmaceutical ingredient; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; M, male; SUZ, suzetrigine (VX-548; VRT-1737548); TK, pharmacokinetics; T_{max}, time to maximum concentration

Table 65. TK Parameters of SUZ and Major Metabolites (M6-SUZ, M3-SUZ, and M12-SUZ) in Rats and Rabbits Reproductive and Developmental Studies of SUZ

Species	Duration	Sex	Dose (mg/kg/day)	API/ Metabolites	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	T _{max} (h)
Rat (Sprague-Dawley)	56 days (FEED study)	M	200	SUZ	3.93	41.1	2
				M6-SUZ	0.543	6.36	8
				M3-SUZ	23.7	356	4
				M12-SUZ	3.07	35.3	8
			600	SUZ	8.34	112	8
				M6-SUZ	2.20	30.1	8
				M3-SUZ	31.3	507	8
				M12-SUZ	11.4	159	8
			1000	SUZ	10.7	159	4
				M6-SUZ	2.95	48.9	4
				M3-SUZ	25.7	449	8
				M12-SUZ	13.5	225	8
Rat (Sprague-Dawley)	GD 6 (EFD)	F	5	SUZ	0.359	3.28	1
				M6-SUZ	0.0184	0.168	2.67
				M3-SUZ	1.44	22.6	4
				M12-SUZ	0.0478	0.579	4
			10	SUZ	0.811	9.32	2.54
				M6-SUZ	0.0490	0.681	2.54
				M3-SUZ	2.00	36.6	4
				M12-SUZ	0.112	1.77	8
			15	SUZ	1.22	12.5	2.48
				M6-SUZ	0.0648	0.761	2.48
				M3-SUZ	3.62	57.4	8
				M12-SUZ	0.124	1.78	2.48
	GD 17 (EFD)	F	5	SUZ	0.713	6.54	2
				M6-SUZ	0.0371	0.467	2
				M3-SUZ	1.40	23.3	8
				M12-SUZ	0.0765	1.06	8
			10	SUZ	1.53	18.4	2
				M6-SUZ	0.183	2.29	2
				M3-SUZ	1.82	36.8	8
				M12-SUZ	0.224	3.65	8

Species	Duration	Sex	Dose (mg/kg/day)	API/ Metabolites	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	T _{max} (h)
Rabbit (New Zealand White)	GD 7 (EFD)	F	15	SUZ	1.89	25.7	4
				M6-SUZ	0.198	2.71	4
				M3-SUZ	3.29	65.6	8
				M12-SUZ	0.279	4.67	4
			50	SUZ	1.86	20.1	4
				M6-SUZ	1.26	14.9	N/A
				M3-SUZ	0.982	16.6	4
				M12-SUZ	0.876	11.7	N/A
			100	SUZ	3.79	46.5	4
				M6-SUZ	2.23	32.9	8
				M3-SUZ	1.82	32.5	4
				M12-SUZ	1.05	16.6	8
			200	SUZ	4.93	77.5	8
				M6-SUZ	3.61	53.9	12
				M3-SUZ	2.13	39.3	N/A
				M12-SUZ	1.47	26.6	N/A
	GD 20 (EFD)	F	50	SUZ	1.74	18.4	N/A
				M6-SUZ	1.76	19.6	4
				M3-SUZ	1.77	30.9	N/A
				M12-SUZ	1.67	20.9	N/A
			100	SUZ	3.19	35.9	4
				M6-SUZ	3.87	45.6	N/A
				M3-SUZ	3.39	60.9	4
				M12-SUZ	2.57	36.2	N/A
			200	SUZ	4.88	67.6	8
				M6-SUZ	6.21	86.1	8
				M3-SUZ	3.43	67.3	N/A
				M12-SUZ	2.61	44.4	8
Rat (Sprague-Dawley)	PND 14 (PPND)	M/F	5	SUZ	0.0124	0.286	24
				M6-SUZ			
				M3-SUZ	0.0973	2.29	24
				M12-SUZ	0.00326	0.0682	4
			10	SUZ	0.0357	0.632	24
				M6-SUZ			
				M3-SUZ	0.182	4.35	1.11
				M12-SUZ	0.00952	0.188	24
			15	SUZ	0.0497	0.873	4
				M6-SUZ			
				M3-SUZ	0.415	8.31	4
				M12-SUZ	0.0143	0.300	4

Source: Study No. VX-548-TX-013, Pages 24-25, Text Tables 15-18; Study No. VX-548-TX-007, Pages 19-21, Text Tables 11-14; Study No. VX-548-TX-009, Pages 20-23, Text Tables 11-14; Study No. VX-548-TX-019, Pages 31-32, Text Tables 14-16

M6-SUZ samples were all below the lower limit of quantitation (5 ng/mL)

Abbreviations: API, active pharmaceutical ingredient; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; F, female; FEED, fertility and early embryonic development; GD, gestation day; M, male; PND, postnatal day; PPND, pre- and postnatal development; SUZ, suzetrigine (VX-548); TK, toxicokinetic; T_{max}, time to maximum concentration

13.1.4.2. Distribution

Plasma protein binding of SUZ, M6-SUZ, and M3-SUZ, which was evaluated in vitro, was high and similar across species (i.e., >98% in rat and monkey and $\geq$ 99% in dog and human for SUZ; >91% in rat, monkey, and human and 99% in dog for M6-SUZ; >97% in rat, monkey, dog, and human for M3-SUZ).

Volume of distribution at steady state of SUZ was 1.01, 3.54, and 2.18 L/kg after an intravenous dose of 1 mg/kg in male beagle dogs, Sprague-Dawley rats, and cynomolgus monkeys, respectively.

Distribution to CNS was observed in rats (brain and spinal cord) after oral administration and in monkeys (cerebrospinal fluid, brain, spinal cord, and DRG) after IV or oral administration. See [Table 66](#) through [Table 70](#) below.

Radioactivity concentrations in melanin-containing tissues in rats (i.e., the uveal tract, pigmented skin, and meninges) peaked between 1 and 4 hours postdose then declined to undetectable levels by 72 hours postdose. Therefore, binding to melanin-containing tissues does not appear to be irreversible.

Table 66. Distribution of SUZ to CNS After Single Oral Dose of 30 mg/kg SUZ in Male Sprague-Dawley Rats

Analyte	Mean Free Tissue Concentration to Free Plasma Ratio at 4 Hours	
	Brain	Spinal Cord
SUZ	0.565	0.761

Source: Study P198, Page 9, Table 2

Abbreviation: CNS, central nervous system; SUZ, suzetrigine

Table 67. Tissue Distribution of SUZ and M6-SUZ Following Single Oral Administration of 3 mg/kg SUZ to Male Cynomolgus Monkeys

Parameter	Plasma	Brain	Spinal Cord	CSF	DRG
Total concentration at 4 hours					
SUZ	612 ng/mL	2010 ng/g	1430 ng/g	6.11 ng/mL	1590 ng/g
M6-SUZ	186 ng/mL	209 ng/g	200 ng/g	5.29 ng/mL	266 ng/g
Free fraction (Fu)					
SUZ	0.0141	0.00548	0.00435	0.967	0.00397
M6-SUZ	0.0550	0.0144	0.00542	0.840	0.0110

Source: Study P296, Page 2, Tables 1-2

Abbreviations: CSF, cerebrospinal fluid; DRG, dorsal root ganglion; Fu, fraction unbound; SUZ, suzetrigine

Table 68. Distribution of SUZ and Metabolites Into Cerebrospinal Fluid Following Single Oral Administration of 10 mg/kg SUZ to Male Cynomolgus Monkeys

Analyte	Matrix	AUC _{last} ng·h/mL	C _{max} ng/mL	T _{max} h	Mean CSF/ Free Plasma
SUZ	Plasma	26000	1940	6	1.18
	CSF	239	36.9	5	
	Mean CSF/free plasma				
M6-SUZ	Plasma	12100	888	6.5	0.39
	CSF	131	24.6	8	
	Mean CSF/free plasma				

Analyte	Matrix	AUC _{last} ng·h/mL	C _{max} ng/mL	T _{max} h	Mean CSF/ Free Plasma
M3-SUZ	CSF	3.36	0.552	6	
M12-SUZ	CSF	81.2	15.9	5	

Source: Study P196, Pages 8-9, Tables 2-3

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; CSF, cerebrospinal fluid; SUZ, suzetrigine

Table 69. Distribution of M6-SUZ Into Cerebrospinal Fluid Following a Single IV Administration of 1 mg/kg M6-SUZ to Male Cynomolgus Monkeys

Analyte	Matrix	AUC _{0-t} ng·h/mL	AUC _{0-inf} ng·h/mL	C _{max} ng/mL
M6-SUZ	Plasma (total)	4190	4220	1570
	Plasma (free)	348	350	130
	CSF	152	164	27.6
	Mean CSF/ free plasma ratio	0.439	0.473	0.247

Source: Study P195, Page 8, Table 2

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; CSF, cerebrospinal fluid; IV, intravenous

Table 70. Tissue Distribution of SUZ and M6-SUZ Following Single Oral Administration of 3 mg/kg SUZ to Male Cynomolgus Monkeys

Analyte	Mean Free Tissue Concentration to Free Plasma Ratio at 4 Hours			
	Brain	Spinal Cord	CSF	DRG
SUZ	1.28	0.721	0.692	0.738
M6-SUZ	0.291	0.105	0.430	0.281

Source: Study P296, Page 2, Table 3

Abbreviations: CSF, cerebrospinal fluid; DRG, dorsal root ganglion; SUZ, suzetrigine

Table 71. Summary of the In Vitro and In Vivo Distribution Studies

Table 72. Summary of the In Vivo and In Vitro Distribution Studies					
Study/Study No.	Findings				
In Vitro Binding of VRT-1737548 and Its Major Metabolite to Hepatocytes/ P170	Unbound fraction of SUZ in rat hepatocytes was 0.136. Unbound fraction of M6-SUZ in rat hepatocytes was 0.4.				
In Vitro Binding of VRT-1737548 and Its Major Metabolites to Plasma Proteins/ Study No. P171	Table 72. Unbound Fraction of SUZ, M6-SUZ, and M3-SUZ in Plasma				
	Test Substance (Concentration)	Human	Monkey	Dog	Rat
	SUZ (10µM)	0.01	0.018	0.003	0.018
	M6-SUZ (10µM)	0.04	0.083	0.01	0.075
	M3-SUZ (10µM)	0.019	0.025	0.021	0.017

Source: Study P171, Pages 8-9, Tables 8-1, 8-2, and 8-3

Abbreviations: SUZ, suzetrigine

Continued

Table 71, continued

Study/Study No.	Findings					
Distribution of VRT-1737548 and Metabolites Into Cerebrospinal Fluid Following Single Oral Administration of VRT-1737548 to Male Cynomolgus Monkeys/ Study No. P196	Table 73. Distribution of SUZ and Metabolites Into CNS in Male Cynomolgus Monkeys Following a Single Oral Administration at 10 mg/kg					
Analyte	Time hours	Total Plasma Conc. ng/mL(SD)	Free Plasma Conc. ng/mL(SD)	CSF Conc. ng/mL (SD)	CSF/Free Plasma ratio	Mean CSF/Free Plasma (SD)
VRT-1737548	1	959 (303)	17.7 (5.57)	20.3 (4.66)	1.15	1.18 (0.0463)
	4	1660 (319)	30.5 (5.87)	37.4 (9.25)	1.23	
	8	1580 (277)	29.0 (5.09)	33.6 (8.07)	1.16	
VRT-1875420	1	189 (41.8)	15.6 (3.47)	5.97 (1.49)	0.38	0.39 (0.0287)
	4	576 (110)	47.8 (9.10)	19.9 (5.38)	0.42	
	8	824 (358)	68.4 (29.7)	24.6 (6.00)	0.36	
VRT-1875424	1	ND	ND	0.316 (0.101)	ND	ND
	4	ND	ND	0.500 (0.123)	ND	
	8	ND	ND	0.488 (0.152)	ND	
VRT-1875671	1	ND	ND	4.13 (4.00)	ND	ND
	4	ND	ND	15.6 (5.44)	ND	
	8	ND	ND	9.11 (3.89)	ND	

Source: Study P196, Page 9, Table 3

Abbreviations: CNS, central nervous system; conc., concentration; CSF, cerebrospinal fluid; ND, not detected; SD, standard deviation; SUZ, suzetrigine

In Vitro Binding of VRT-1737548 and Its Metabolite VRT-1875420 to Proteins in Monkey Plasma, CSF, Brain, Spinal Cord and DRG/ Study No. P298	Table 74. Average Fraction of Unbound (Mean±SD) of SUZ and M6-SUZ in Monkey Plasma, CSF, Brain, Spinal Cord, and DRG					
		Plasma	CSF	Brain	Spinal Cord	DRG
	VRT-1737548	0.0141 ±	0.967 ±	0.00548 ±	0.00435 ±	0.00397 ±
		0.0016	0.015	0.00083	0.00067	0.00058
VRT-1875420	0.0550 ±	0.840 ±	0.0144 ±	0.00542 ±	0.0110 ±	
	0.0067	0.100	0.0015	0.00029	0.0014	

Source: Study P298, Page 7, Table 1

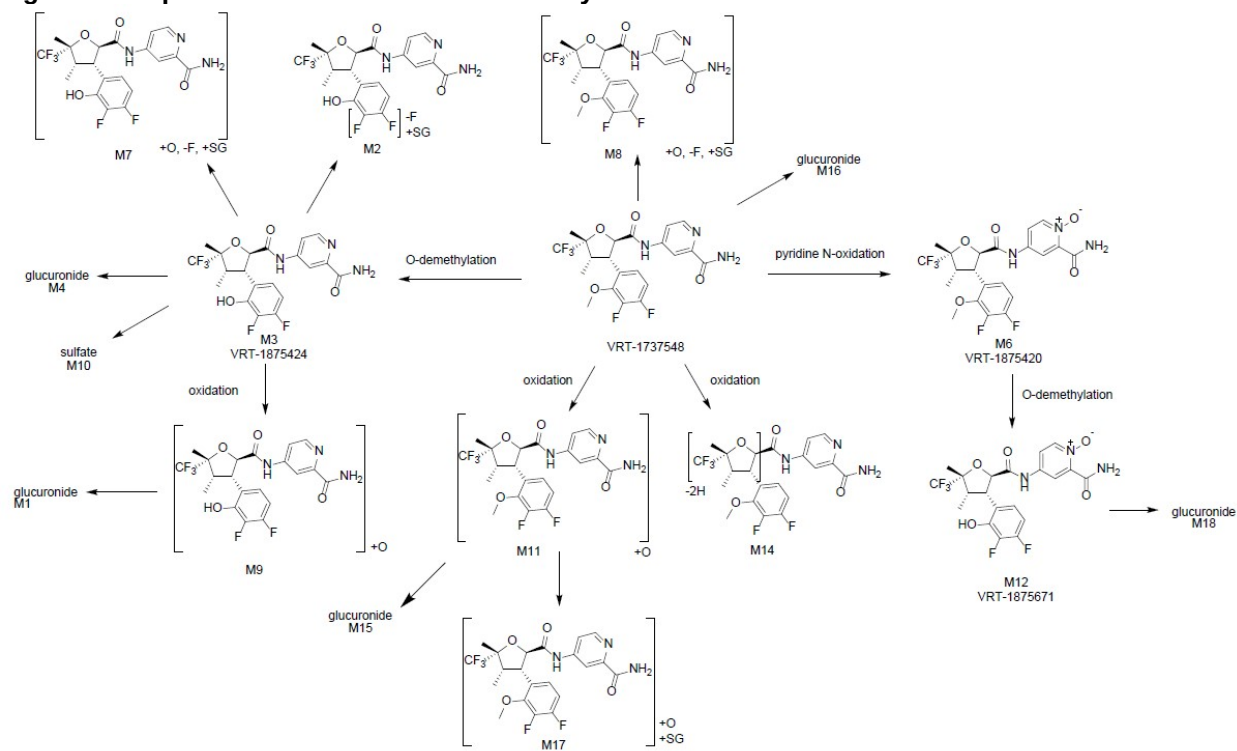
Abbreviations: CSF, cerebrospinal fluid; DRG, dorsal root ganglion; SD, standard deviation; SUZ, suzetrigine (VRT-1737548); VRT-1875420, M6-SUZ

Source: Study No. P170, Study No. P171, Study No. P196, and Study No. P298

Abbreviations: CSF, cerebrospinal fluid; DRG, dorsal root ganglion; SUZ, suzetrigine (VRT-1737548)

13.1.4.3. Metabolism

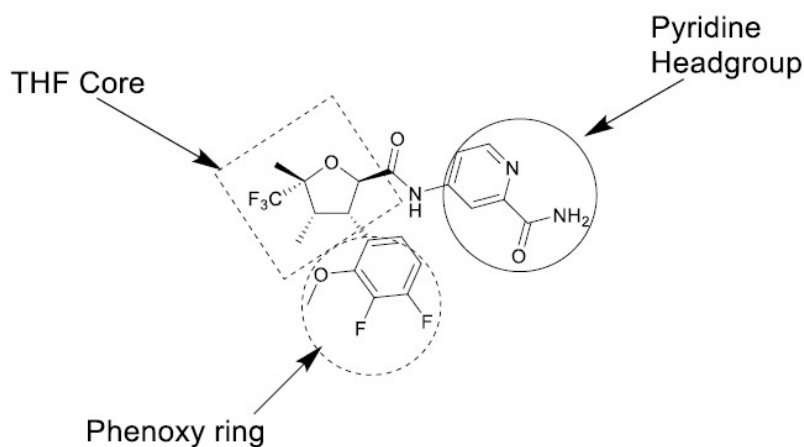
Figure 8. Proposed Biotransformation Pathway of SUZ



Source: Study P158, Page 16, Figure 4
Abbreviations: SUZ, suzetrigine

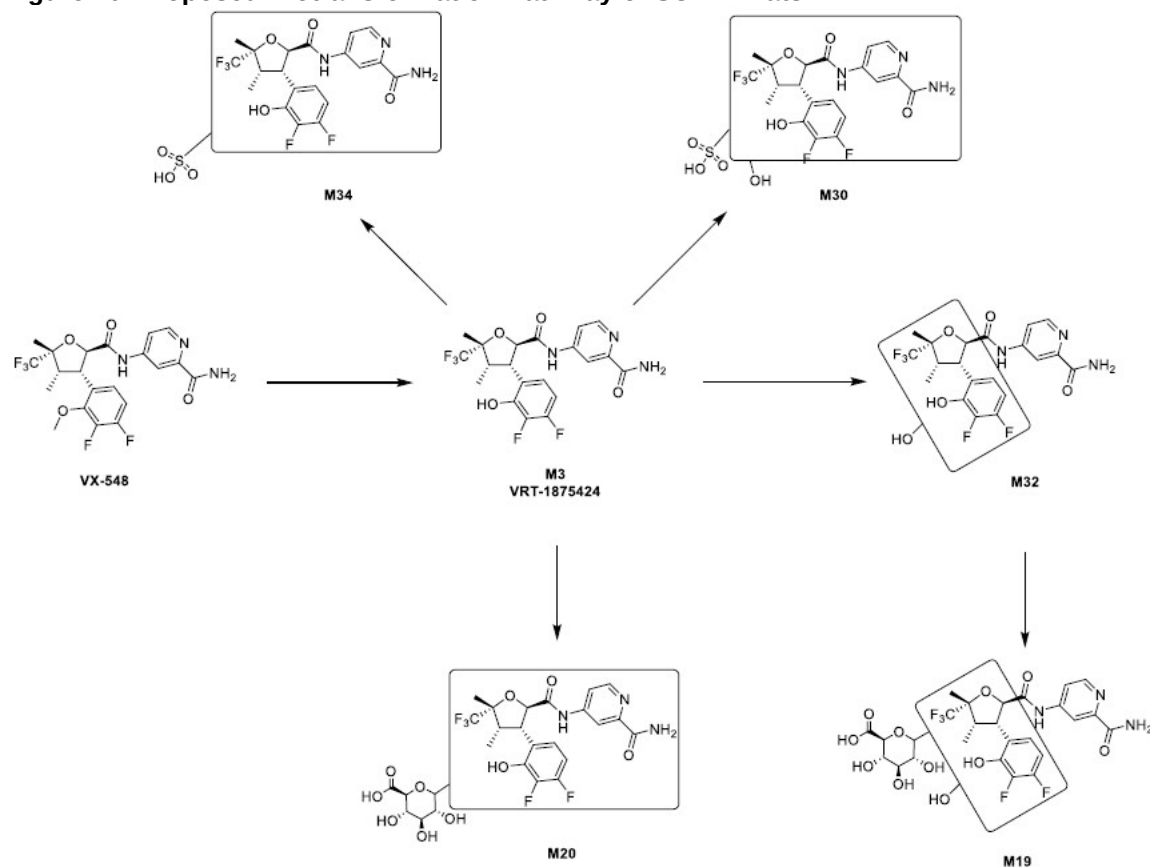
SUZ was mainly cleared by metabolism in rats, and unchanged SUZ was not detected in bile and was minimal in urine (<0.1%) and feces (0.2%) after IV administration. In rats, M3-SUZ was the major metabolite in plasma (95.9%). M19-SUZ and M20-SUZ were major metabolites in rat bile.

Figure 9. Structural and Description of Moieties of SUZ



Source: Study Q262, Page 9, Figure 1
Abbreviation: SUZ, suzetrigine; THF, tetrahydrofuran

Figure 10. Proposed Biotransformation Pathway of SUZ in Rats

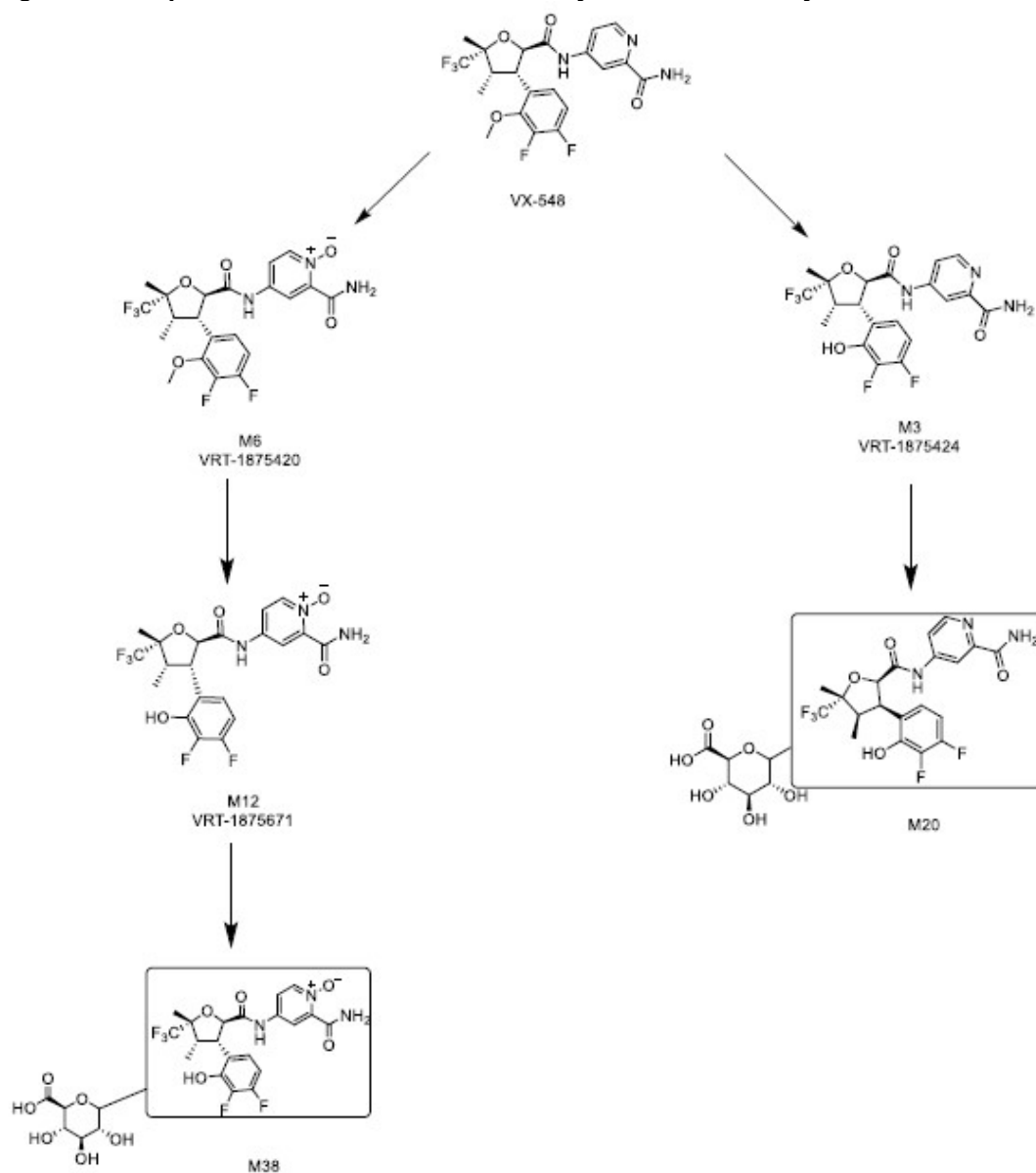


Note: Only metabolites > 3% of administered dose or >2 % of circulating total radioactivity are shown in the scheme.

Source: Study Q262, Page 40, Figure 2
Abbreviations: SUZ, suzetrigine (VX-548)

In monkeys, M6-SUZ and M12-SUZ were major metabolites in the plasma. M20-SUZ and M38-SUZ were major metabolites in monkey bile. Unchanged SUZ was not detected in bile and was minimal in feces (<2% of the radioactive dose) and urine (1% of the radioactive dose) following both oral and IV dosing in monkeys.

Figure 11. Proposed Biotransformation Pathway of SUZ in Monkeys



Note: Only metabolites > 5% of administered dose or circulating total radioactivity are shown in the scheme.

***M12 is formed from M6 only⁴**

Source: Study S001, Page 33, Figure 2
Abbreviations: SUZ, suzetrigine (VX-548)

Cytochrome P450 (CYP) 3A4, CYP3A5, and CYP2C19 were major SUZ biotransformation enzymes in vitro. M6-SUZ was metabolized to M12-SUZ by CYP3A4 and CYP2C9 in vitro. Non-CYP contribution was 20 to 30% in vitro.

Table 75. SUZ Metabolites in Plasma After Oral Administration of 10 mg/kg (200 µCi/kg) [¹⁴C]SUZ in Male Long-Evans Rats

Species/Route	Matrix	Metabolite	Percent of Radioactivity in Each Run
Rat/oral	Pooled plasma (0-24h) (Long Evans rat)	M3-SUZ	95.9%
		M19-SUZ	2.9%
		SUZ	1.2%

Source: Study No. Q262, Page 16, Table 8-1

Abbreviations: SUZ, suzetrigine

Table 76. SUZ Metabolites in Bile After Oral (10 mg/kg [200 µCi/kg] [¹⁴C]SUZ) or Intravenous Administration (3 mg/kg [200 µCi/kg] [¹⁴C]SUZ) in Male Sprague-Dawley Rats

Species/Route	Matrix	Metabolite	Percent of Radioactive Dose
Rat/oral	Pooled bile	M19-SUZ	25.9%
		M20-SUZ	40.4%
Rat/intravenous	Pooled bile	M19-SUZ	35.5%
		M20-SUZ	32.0%

Source: Study No. Q262, Pages 16-17, Tables 8-2 and 8-3

Abbreviations: SUZ, suzetrigine

Table 77. SUZ Metabolites in Plasma After Oral Administration of 15 mg/kg (100 µCi/kg) [¹⁴C]SUZ in Male Monkeys

Species/Route	Matrix	Metabolite	Percent of Radioactivity (% Total Peak Area)
Monkey/oral	Pooled plasma	SUZ	36.1%
		M6-SUZ	27.6%
		M12-SUZ	14.0%
		M3-SUZ	8.52%
		M38-SUZ	7.78%
		M20-SUZ	6.02%

Source: Study No. S001, Page 15, Table 8-1

Abbreviations: SUZ, suzetrigine

Table 78. SUZ Metabolites in Urine and Feces After Oral Administration of 15 mg/kg (100 µCi/kg) [¹⁴C]SUZ in Monkeys

Species/Route	Matrix	Metabolite	Percent of Radioactive Dose
Monkey/oral	Pooled feces	SUZ	1.02%
		M3-SUZ	52.5%
	Pooled urine	SUZ	0.560%
		M38-SUZ	7.01%
		M20-SUZ	5.38%
		M3-SUZ	0.761%
		M12-SUZ	0.457%

Source: Study No. S001, Page 16, Tables 8-2 and 8-3

Abbreviations: SUZ, suzetrigine

Table 79. SUZ Metabolites in Plasma After Intravenous Administration of 2.5 mg/kg (100 µCi/kg) [¹⁴C]SUZ in Bile-Duct-Cannulated Monkeys

Species/Route	Matrix	Metabolite	Percent of Radioactivity (% Total Peak Area)
Bile-duct-cannulated monkey/ intravenous	Pooled plasma	SUZ	40.7%
		M6-SUZ	26.8%
		M12-SUZ	15.9%
		M38-SUZ	11.2%
		M20-SUZ	3.18%
		M3-SUZ	2.15%

Source: Study No. S001, Page 17, Table 8-4
Abbreviations: SUZ, suzetrigine

Table 80. SUZ Metabolites in Bile, Feces, and Urine After Intravenous Administration of 2.5 mg/kg (100 µCi/kg) [¹⁴C]SUZ in Bile-Duct-Cannulated Monkeys

Species/Route	Matrix	Metabolite	Percent of Radioactive Dose
Bile-duct-cannulated monkey/ intravenous	Pooled bile	M38-SUZ	45.7%
		M20-SUZ	27.7%
		M12-SUZ	0.274%
	Pooled feces	SUZ	0.207%
		M3-SUZ	0.822%
		M12-SUZ	0.182%
	Pooled urine	M38-SUZ	7.49%
		M20-SUZ	1.05%
		M12-SUZ	0.194%

Source: Study No. S001, Pages 18-19, Tables 8-5, 8-6, and 8-7
Abbreviations: SUZ, suzetrigine

Table 81. Summary of the In Vitro and In Vivo Metabolism Studies for SUZ

Study/Study No.	Findings
Characterization of VRT-1737548 Metabolites in Vitro and In Vivo Across Species/ Study No. P158	Table 82. Summary of SUZ Metabolites Formed Across Species Hepatocytes Incubations In Vitro

Name	Mass Shift/ Modification	RRT	Mouse	Rat	Dog	Monkey	Human
M1	652 / -CH ₂ +O+Glu	0.78	+++	+++	-	-	-
M2	374 / -CH ₂ -F+GSH	0.81	++	+	-	-	-
M3 VRT-1875424	460 / -CH ₂	0.94	+++	+++	trace	trace	+
M4	636 / -CH ₂ +Glu	0.84	++	++	+++	+++	+
M6 VRT-1875420	490 / +O	0.97	++	-	+	+++	++
M7	382 / -CH ₂ -F+O+GSH	0.77	trace	-	-	-	-
M8	389 / -F+O+GSH	0.79	+	trace	-	-	-
M9	476 / -CH ₂ +O	0.88	trace	-	-	-	-
M10	540 / -CH ₂ +SO ₃ H	0.90	-	+	-	-	-
M11	490 / +O	0.90	trace	trace	-	-	-
M12 VRT-1875671	476 / -CH ₂ +O	0.91	++	trace	-	+	-

Note: trace <2%, + 2-5%, ++ 5-20%, +++ >20%, - Not observed. Percentage MS peak area by sum of area of all identified peaks in chromatogram. As no standards were available at the time of analysis, data is semi-quantitative only.

Source: Study P158, Page 11, Table 1

Abbreviations: MS, mass spectrometry; RRT, relative retention time; SUZ, suzetrigine

Continued

Table 81, continued

Study/Study No. Findings

Characterization of VRT-1737548 Metabolites in Vitro and In Vivo Across Species/ Study No. P158 (continued)

Table 83. SUZ Circulation Metabolites Formed Across Species In Vivo

Metabolite	Mass Shift / Modification	Human Hepatocytes	Male rat Plasma	Female rat Plasma	Dog plasma	Monkey plasma
M1	178 / -CH ₂ +O+Glu	-	+	-	-	-
M3 VRT-1875424	-14 / -CH ₂	+	++	++	-	trace
M4	162 / -CH ₂ +Glu	+	+	trace	-	+
M6 VRT-1875420	16 / +O	++	-	trace	+	++
M12 VRT-1875671	2 / -CH ₂ +O	-	-	+	-	+
M17	321 / +O+GSH	-	-	-	-	trace
M18	178 / -CH ₂ +O+Glu	-	-	-	-	+

Note: trace <2% AUC, + 2-10% AUC, ++ >10% AUC, - Not observed. Percentage MS peak area by sum of area of all identified peaks in chromatogram. As no standards were available at the time of analysis, data is semi-quantitative only.

Source: Study P158, Page 14, Table 2

Abbreviations: AUC, area under the concentration-time curve; MS, mass spectrometry; SUZ, suzetrigine

Intrinsic Clearance of VRT-1737548 and Major Metabolites in Hepatocytes From Various Species/ Study No. P173

Table 84. Mean Metabolic Intrinsic Clearance Values (μL/min/million cells) of SUZ, M6-SUZ, and M3-SUZ in Hepatocytes From Various Species

Test Substance (Concentration)	Human	Monkey	Dog	Rat
SUZ (1μM)	2.8	14.9	4.9	216.7
M6-SUZ (1μM)	1.5	7.2	1.4	109.9
M3-SUZ (1μM)	18.8	213.5	212.7	19.9

Source: Study P173, Pages 10-12, Tables 8-1, 8-2, and 8-3

Abbreviations: SUZ, suzetrigine

In Vitro Metabolism of VRT-1737548 Metabolites/ Study No. S164

Table 85. Summary of M6-SUZ Metabolites Formed Across Species Hepatocyte Incubations In Vitro

Name	Mass Shift/ Modification	r.t.	Rat	Dog	Monkey	Human
M1-420	+178 / -CH ₂ +O+Glu	5.80	+	-	-	-
M2-420	+162 / -CH ₂ +Glu	6.29	+	+	+	-
VRT-1875671	-14 / -CH ₂	7.08	+	+	+	+

Note: + observed, - Not observed.

Source: Study S164, Page 10, Table 1

Abbreviation: VRT-1875671, M12-SUZ; r.t., retention time

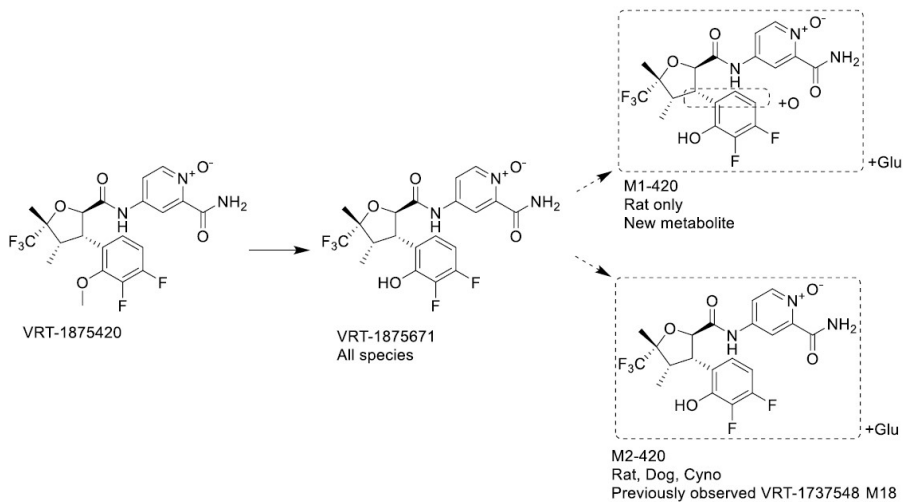
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Table 81, continued

Study/Study No. Findings

In Vitro
Metabolism of
VRT-1737548
Metabolites/
Study No. S164
(continued)

Figure 12. Biotransformation Pathway of M6-SUZ



Source: S164, Page 11, Figure 6-1
Abbreviation: Cyno, Cynomolgus monkey

Table 86. Summary of M3-SUZ Metabolites Formed Across Species Hepatocyte Incubations In Vitro

Name	Mass Shift/ Modification	r.t.	Rat	Dog	Monkey	Human
M1-424	+192 / +O +Glu	6.07	+	-	-	-
M2-424	+176 / +Glu	6.52	+	+	+	+

Source: S164, Page 11, Table 2
Abbreviation: r.t., retention time

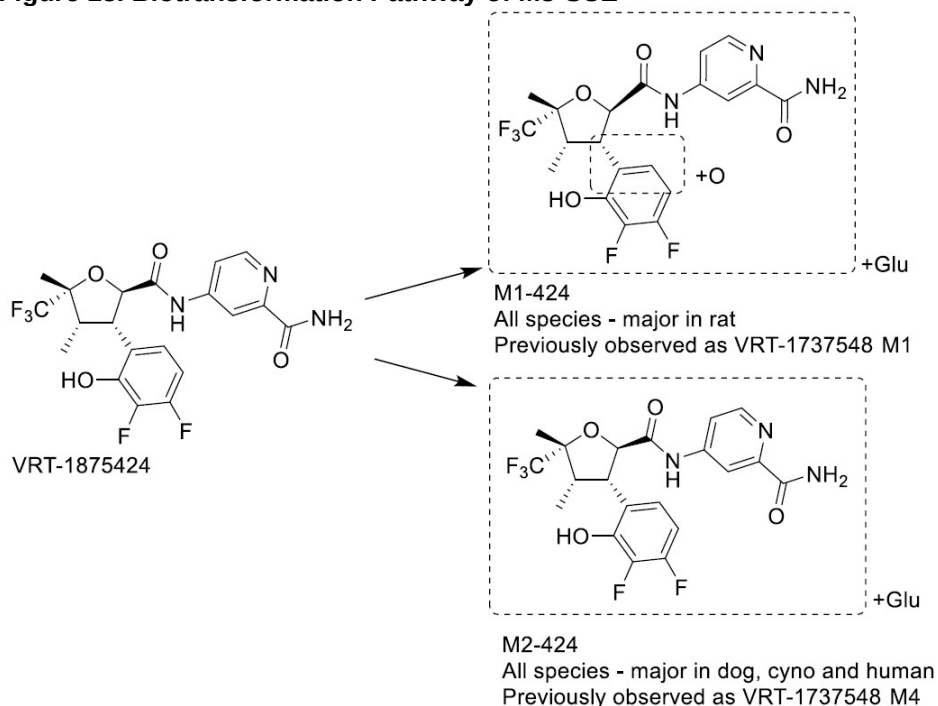
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Table 81, continued

Study/Study No. Findings

In Vitro
Metabolism of
VRT-1737548
Metabolites/
Study No. S164
(continued)

Figure 13. Biotransformation Pathway of M3-SUZ



Source: Study S164, Page 12, Figure 6-2

Table 87. Summary of M12-SUZ Metabolites Formed Across Species Hepatocyte Incubations In Vitro

Name	Mass Shift/ Modification	r.t.	Rat	Dog	Monkey	Human
M1-671	+192 / +O +Glu	5.80	+	-	+	+
M2-671	+176 / +Glu	6.28	+	+	+	+

Source: Study S164, Page 12, Table 3
Abbreviation: r.t., retention time

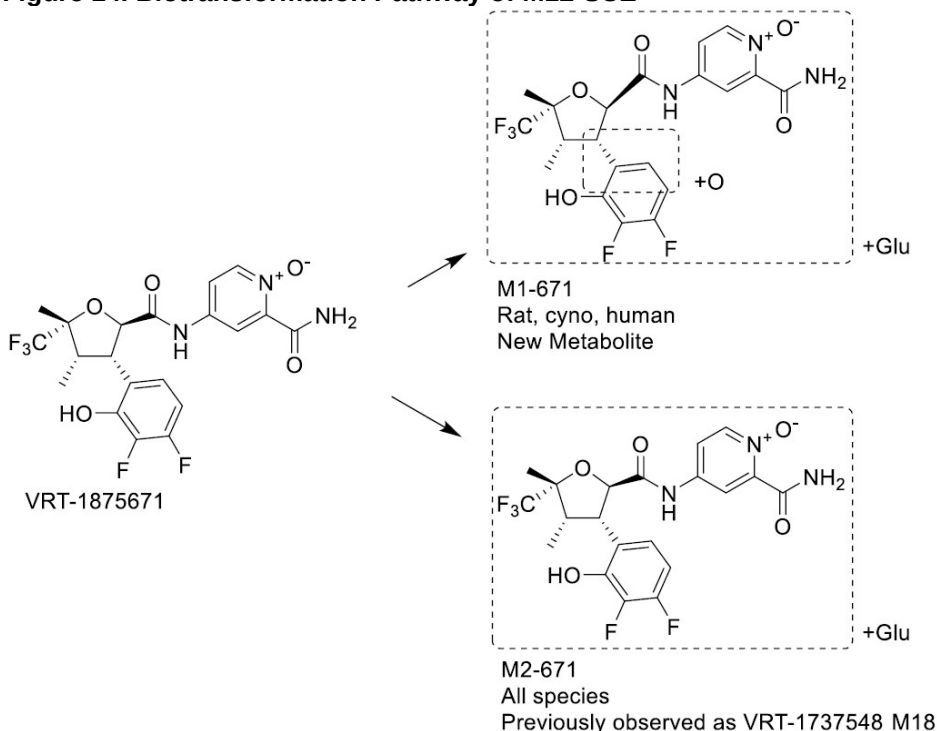
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Table 81, continued

Study/Study No. Findings

In Vitro
Metabolism of
VRT-1737548
Metabolites/
Study No. S164
(continued)

Figure 14. Biotransformation Pathway of M12-SUZ



Source: Study S164, Page 13, Figure 6-3
Abbreviation: cyno, cynomolgus monkey

Source: Study No. P158, Study No. P173, and Study No. S164
Abbreviations: SUZ, suzetrigine

13.1.4.4. Excretion

Biliary Excretion

In rats, 72 to 75% of the administered dose was excreted into bile after oral and IV administration. In monkeys, 75% of the administered dose was excreted into bile after the IV administration.

Placental Transfer/Lacteal Excretion

In GD 13 Sprague-Dawley rat fetuses, the highest radioactivity concentrations were observed in the lungs and spinal cord at 8 hours postdose.

In GD 18 Sprague-Dawley rat fetuses, the highest radioactivity concentrations were observed in the heart, spinal cord, and adrenal gland.

In lactating Sprague-Dawley rats (lactation day 10), exposure of total radioactivity in milk was approximately 3-fold higher than in blood and plasma after a single oral administration (10 mg/kg), with peak concentration at 2 hours postdose.

Table 88. Summary of Biliary Excretion and Placental Transfer/Lacteal Excretion of SUZ in Rats

Study/Study No.
Mass Balance, and
Biliary Excretion
Following a Single Oral
or Intravenous Dose of
[¹⁴C]VRT-1737548 in
Male Sprague-Dawley
Rats and Tissue
Distribution Using
Quantitative Whole
Body Autoradiography
(QWBA) Following a
Single Oral Dose of
[¹⁴C]VRT-1737548 in
Male Long-Evans and
Sprague-Dawley Rats/
Study No. RPTC20089

Findings

Table 89. Total Recovery of [¹⁴C]SUZ-Derived Radioactivity Following a Single Oral Dose of 10 mg [¹⁴C]SUZ/kg to Male Sprague-Dawley Rats

Sex	Animal Identification	Percent Administered Dose (0-96 h)				
		Bile	Urine	Feces	Cage Rinse/Wash	Total
Male	G2-01-M	64.33	3.86	28.70	0.24	97.13
	G2-02-M	86.05	1.19	9.48	0.19	96.91
	G2-03-M	66.94	1.39	25.55	1.34	95.22
	Mean	72.44	2.15	21.24	0.59	96.42
	SD	11.86	1.49	10.31	0.65	1.05

Source: Study RPTC20089, Page 38, Table 4

Abbreviation: SD, standard deviation; SUZ, suzetrigine

Table 90. Total Recovery of [¹⁴C]SUZ-Derived Radioactivity Following a Single Intravenous Dose of 3 mg [¹⁴C]SUZ/kg to Male Sprague-Dawley Rats

Sex	Animal Identification	Percent Administered Dose (0-96 h)				
		Bile	Urine	Feces	Cage Rinse/Wash	Total
Male	G3-01-M	64.60	0.90	8.63	0.19	74.32
	G3-02-M	81.54	1.34	7.18	0.15	90.21
	G3-03-M	79.76	1.02	6.34	0.25	87.37
	Mean	75.30	1.09	7.38	0.20	83.97
	SD	9.31	0.23	1.16	0.05	8.47

Source: Study RPTC20089, Page 41, Table 7

Abbreviation: SD, standard deviation; SUZ, suzetrigine

Declining radioactivity concentrations in melanin containing tissues (the uveal tract, pigmented skin, and meninges) after peaking at 1 to 4h suggest no irreversible binding to melanin-containing tissues.

Continued

Table 88, continued

Study/Study No.

Mass Balance, and Biliary Excretion Following a Single Oral or Intravenous Dose of [¹⁴C]VRT-1737548 in Male Sprague-Dawley Rats and Tissue Distribution Using Quantitative Whole Body Autoradiography (QWBA) Following a Single Oral Dose of [¹⁴C]VRT-1737548 in Male Long-Evans and Sprague-Dawley Rats/ Study No. RPTC20089

Findings

Table 91. Concentration of [¹⁴C]SUZ-Derived Radioactivity (µg equiv/g) in Plasma and Tissues of Male Long-Evans Rats Following an Oral Dose of [¹⁴C]SUZ at 10 mg/kg

Tissue Group	Tissue Name	[¹⁴ C]VRT-1737548-Derived Radioactivity (µg equiv/g)									
		Hours Post Dose									
		1	2	4	8	24	72	96	168	672	
Vascular	Plasma (LSC)	3.86	3.95	3.61	1.49	0.0320	BQL	BQL	BQL	BQL	
	Blood (LSC)	2.56	2.59	2.32	0.898	0.0220	BQL	BQL	BQL	BQL	
	Aorta	2.74	5.73	3.07	0.612	BQL	BQL	BQL	BQL	BQL	
	Blood (cardiac)	2.97	2.55	2.01	0.836	BQL	BQL	BQL	BQL	BQL	
Central Nervous System	Brain (whole)	0.856	0.707	0.359	0.0970	BQL	BQL	BQL	BQL	BQL	
	Meninges	1.16	0.629	0.226	0.297	BQL	BQL	BQL	BQL	BQL	
	Spinal cord	1.08	0.917	0.689	0.142	BQL	BQL	BQL	BQL	BQL	
	Eye	0.251	0.578	0.667	0.278	0.0443	BQL	BQL	BQL	BQL	
Ocular	Lens	BQL	0.0279	0.0536	BQL	BQL	BQL	BQL	BQL	BQL	
	Uveal tract	0.967	2.69	3.55	1.14	0.317	BQL	BQL	BQL	BQL	
	Non-pigmented skin	2.36	2.95	2.08	0.671	0.0598	BQL	BQL	BQL	BQL	
Dermal	Pigmented skin	2.12	3.03	2.47	0.543	0.0300	BQL	BQL	BQL	BQL	
	Adrenal cortex	10.0	12.2	7.57	2.71	0.120	0.0343	0.0440	BQL	BQL	
Endocrine	Adrenal gland	9.67	11.7	7.18	2.68	0.130	0.0334	0.0435	BQL	BQL	
	Adrenal medulla	9.48	11.5	6.26	2.68	0.156	BQL	0.0521	BQL	BQL	
	Pituitary gland	5.39	4.92	2.58	0.915	BQL	BQL	BQL	BQL	BQL	
	Thyroid gland	7.23	5.88	4.45	1.33	0.209	0.114	0.0499	0.0427	BQL	
	Brown fat	5.42	6.05	3.20	1.45	0.170	0.0671	BQL	BQL	BQL	
Fatty	White fat (inguinal)	1.29	2.63	2.48	0.857	BQL	BQL	BQL	BQL	BQL	
	Cecum mucosa	4.58	4.91	9.32	29.3	0.373	0.0605	0.0497	BQL	BQL	
Gastro Intestinal (GI) Tract	Esophagus wall	1.22	5.94	1.46	0.622	BQL	BQL	BQL	BQL	BQL	
	Large intestine wall	3.05	4.15	5.28	205	0.537	0.0339	0.0465	0.0333	BQL	
	Oral mucosa	2.08	2.39	1.43	0.484	BQL	BQL	BQL	BQL	BQL	
	Small intestine wall	50.9	52.3	161	6.30	0.119	BQL	BQL	BQL	BQL	
	Stomach wall (glandular)	28.5	8.54	6.95	1.78	0.212	0.0512	0.0641	0.0362	BQL	
	Stomach wall (non-glandular)	31.4	19.1	12.6	7.84	0.296	0.0765	BQL	BQL	BQL	
	Cecum contents	15.0	32.9	91.5	181	5.30	0.131	0.110	0.0341	BQL	
	Large intestine contents	0.157	3.94	31.4	287	7.03	0.105	0.0974	0.0346	BQL	
GI Tract Contents	Small intestine contents	125	158	279	151	2.26	0.0352	0.0701	BQL	BQL	
	Stomach contents	124	70.6	145	44.8	3.69	BQL	BQL	BQL	BQL	
	Urinary bladder contents	111	1.27	3.06	2.76	0.217	BQL	BQL	BQL	BQL	

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)
BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Tissue Group	Tissue Name	[¹⁴ C]VRT-1737548-Derived Radioactivity (µg equiv/g)									
		Hours Post Dose									
		1	2	4	8	24	72	96	168	672	
Lymphatic	Bone marrow (femur)	2.92	3.45	2.62	0.813	BQL	BQL	BQL	BQL	BQL	
	Lymph node (cervical)	3.29	2.69	1.76	0.479	BQL	BQL	BQL	BQL	BQL	
	Spleen	4.80	4.23	3.13	0.970	0.0328	BQL	BQL	BQL	BQL	
	Thymus	2.65	2.56	1.85	0.510	BQL	BQL	BQL	BQL	BQL	
Metabolic/Excretory	Bile (in duct)	107	95.4	171	27.0	1.62	BQL	BQL	BQL	BQL	
	Kidney	7.10	9.94	7.96	3.46	0.972	0.272	0.350	0.178	BQL	
	Kidney cortex	7.95	12.2	9.93	4.10	0.810	0.362	0.440	0.213	BQL	
	Kidney medulla	5.43	8.85	5.39	2.67	1.31	0.175	0.235	0.138	BQL	
	Liver	37.2	42.4	33.0	15.7	1.71	0.639	0.576	0.174	BQL	
	Urinary bladder wall	59.5	15.5	4.09	2.48	0.259	BQL	BQL	BQL	BQL	
Muscular	Heart	7.17	5.61	3.84	1.22	0.0863	0.0517	0.0654	BQL	BQL	
	Muscle (femoral)	2.77	3.67	2.97	0.892	0.0719	0.0460	0.0300	0.0299	BQL	
Reproductive	Epididymis	1.65	2.79	2.83	1.13	0.0365	BQL	BQL	BQL	BQL	
	Prostate	1.89	2.22	2.16	1.91	0.0725	BQL	BQL	BQL	BQL	
	Seminal vesicle	2.32	2.34	3.36	1.08	0.129	0.0480	BQL	BQL	BQL	
	Testis	0.951	1.17	1.23	0.345	BQL	BQL	BQL	BQL	BQL	
Respiratory	Lung	4.99	4.30	3.42	1.18	BQL	BQL	BQL	BQL	BQL	
	Nasal turbinates	1.59	1.10	0.811	0.237	BQL	BQL	BQL	BQL	BQL	
	Trachea	2.83	2.84	1.35	0.662	0.197	0.0356	BQL	BQL	BQL	
Secretory	Ex-orbital lachrymal gland	6.98	7.23	4.39	1.05	0.0371	BQL	BQL	BQL	BQL	
	Harderian gland	7.48	9.12	8.86	2.25	0.145	BQL	BQL	BQL	BQL	
	Intra-orbital lachrymal gland	6.20	7.46	5.05	1.13	0.0634	0.0324	BQL	BQL	BQL	
	Pancreas	9.05	8.85	6.44	1.85	0.0548	BQL	BQL	BQL	BQL	
	Salivary gland	6.29	5.43	4.12	1.14	0.0353	BQL	BQL	BQL	BQL	
Skeletal	Bone (femur)	0.676	0.925	1.53	0.314	0.0420	0.0407	BQL	BQL	0.112	
	Bone (humerus)	0.823	1.13	0.971	0.564	0.0315	0.0458	BQL	BQL	BQL	
	Bone (leg)	3.70	2.09	2.46	0.349	0.0492	0.213	0.0302	BQL	BQL	
	Bone (radius)	1.79	NS	NS	0.417	NS	NS	NS	BQL	NS	
	Bone (rib)	0.418	1.82	0.494	0.480	0.0369	BQL	0.164	BQL	BQL	
	Bone (skull)	1.81	0.883	0.648	0.296	BQL	BQL	BQL	0.0421	BQL	
	Bone (ulna)	0.387	NS	NS	0.0580	NS	NS	NS	0.0546	NS	
	Bone (vertebrae)	0.334	0.344	2.79	0.221	0.0604	BQL	BQL	BQL	BQL	

NS = No Sample

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)

BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Source: Study RPTC20089, Page 44-45, Table 10

Abbreviations: BQL, below quantitation limit; GI, gastrointestinal; LLOQ, lower limit of quantitation; LSC, liquid scintillation counting; QWBA, quantitative whole body autoradiography; SUZ, suzetrigine (VRT-1737548)

No significant change in the pigmented skin compared to nonpigmented skin in the Long-Evans rats.

Continued

Table 88, continued

Study/Study No.

Mass Balance, and Biliary Excretion Following a Single Oral or Intravenous Dose of [¹⁴C]VRT-1737548 in Male Sprague-Dawley Rats and Tissue Distribution Using Quantitative Whole Body Autoradiography (QWBA) Following a Single Oral Dose of [¹⁴C]VRT-1737548 in Male Long-Evans and Sprague-Dawley Rats/ Study No. RPTC20089

Findings

Table 92. PK Parameters of [¹⁴C]SUZ-Derived Radioactivity in Plasma and Tissues of Male Long-Evans Rats Following an Oral Dose of [¹⁴C]SUZ at 10 mg/kg

Tissue Group	Tissue Name	C _{max} (µg equiv/g)	t _{max} (h)	t _{1/2} (h)	AUC ₀₋₄ (µg equiv·h/g)	AUC _{0-∞} (µg equiv·h/g)	Tissue: Plasma*	r ²
Vascular	Plasma (LSC)	3.95	2.0	2.9	35.7	35.8	1.00	0.9998
	Blood (LSC)	2.59	2.0	3.0	22.5	22.6	0.63	1.0000
	Aorta	5.73	2.0	NC	21.8	NC	0.61	NC
	Blood (cardiac)	2.97	1.0	3.6	14.5	18.9	0.41	0.9829
Central Nervous System	Brain (whole)	0.856	1.0	2.1	3.19	3.48	0.09	0.9999
	Meninges†	1.1552	1.0	7.1	3.37	6.43	0.09	0.3131
	Spinal cord	1.0806	1.0	2.1	4.81	5.25	0.13	0.9640
Ocular	Eye	0.667	4.0	NC	6.25	NC	0.18	NC
	Lens	0.0536	4.0	NC	0.0954	NC	0.00	NC
	Uveal tract	3.55	4.0	NC	29.6	NC	0.83	NC
Dermal	Non-pigmented skin	2.95	2.0	4.1	20.2	20.6	0.57	0.9839
	Pigmented skin	3.03	2.0	3.3	19.7	19.9	0.55	0.9764
Endocrine	Adrenal cortex†	12.2	2.0	44.4	83.8	86.6	2.35	0.7518
	Adrenal gland†	11.7	2.0	40.5	81.4	83.9	2.28	0.7544
	Adrenal medulla†	11.5	2.0	19.4	78.0	79.4	2.18	0.6790
	Pituitary gland	5.39	1.0	2.5	22.3	25.6	0.63	0.9969
	Thyroid gland	7.23	1.0	61.7	57.4	61.2	1.61	0.8275
Fatty	Brown fat†	6.05	2.0	16.7	45.6	47.2	1.28	0.7657
	White fat (inguinal)	2.63	2.0	NC	14.4	NC	0.40	NC
Gastrointestinal (GI) Tract	Cecum mucosa	29.3	8.0	23.6	348	350	9.75	0.9410
	Esophagus wall	5.94	2.0	NC	15.7	NC	0.44	NC
	Large intestine wall†	205	8.0	578.5	2101	2129	58.85	0.1017
	Oral mucosa	2.39	2.0	NC	10.9	NC	0.31	NC
	Small intestine wall	161	4.0	NC	676	NC	18.93	NC
	Stomach wall (glandular)†	28.5	1.0	150.1	92.9	101	2.60	0.6392
	Stomach wall (non-glandular)†	31.4	1.0	11.2	187	189	5.25	0.7559

NC = Not calculated due to insufficient data.

* =Tissue:plasma ratio based on AUC₀₋₄

†: t_{1/2} and AUC_{0-∞} are approximated values since the correlation coefficient (r²) is < 0.8

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)

BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Tissue Group	Tissue Name	C _{max} (µg equiv/g)	t _{max} (h)	t _{1/2} (h)	AUC ₀₋₄ (µg equiv·h/g)	AUC _{0-∞} (µg equiv·h/g)	Tissue: Plasma*	r ²
Lymphatic	Bone marrow (femur)	3.45	2.0	NC	17.6	NC	0.49	NC
	Lymph node (cervical)	3.29	1.0	2.4	13.5	15.2	0.38	0.9911
	Spleen	4.80	1.0	3.1	30.5	30.6	0.85	0.9964
	Thymus	2.65	1.0	2.5	13.1	14.9	0.37	0.9800
Metabolic/Excretory	Bile (in duct)	171	4.0	NC	1046	NC	29.30	NC
	Kidney†	9.94	2.0	124.5	145	177	4.05	0.6634
	Kidney cortex†	12.2	2.0	105.2	165	197	4.62	0.7668
	Kidney medulla†	8.85	2.0	194.2	126	165	3.53	0.4502
	Liver	42.4	2.0	48.7	469	481	13.12	0.9712
	Urinary bladder wall	59.5	1.0	5.0	122	124	3.41	0.9997
Muscular	Heart†	7.17	1.0	143.6	44.8	58.3	1.25	0.4760
	Muscle (femoral)†	3.67	2.0	114.3	32.6	37.5	0.91	0.7579
Reproductive	Epididymis	2.83	4.0	NC	25.9	NC	0.73	NC
	Prostate	2.22	2.0	3.9	31.4	31.8	0.88	0.9748
	Seminal vesicle†	3.36	4.0	16.4	32.0	33.1	0.90	0.7789
	Testis	1.23	4.0	NC	7.09	NC	0.20	NC
Respiratory	Lung	4.99	1.0	3.1	24.1	29.4	0.67	0.9729
	Nasal turbinates	1.59	1.0	2.6	6.15	7.05	0.17	0.9796
	Trachea	2.84	2.0	16.0	24.9	25.7	0.70	0.9668
Secretory	Ex-orbital lachrymal gland	7.23	2.0	3.0	41.8	42.0	1.17	0.9888
	Harderian gland	9.12	2.0	3.5	71.4	72.1	2.00	0.9795
	Intra-orbital lachrymal gland†	7.46	2.0	15.1	46.7	47.4	1.31	0.6572
	Pancreas	9.05	1.0	3.0	60.6	60.8	1.70	0.9958
	Salivary glands	6.29	1.0	3.0	38.4	38.6	1.08	0.9945
Skeletal	Bone (femur)	1.53	4.0	NC	40.8	NC	1.14	NC
	Bone (skull)	1.81	1.0	47.7	9.56	12.5	0.27	0.9336

NC = Not calculated due to insufficient data.

* =Tissue:plasma ratio based on AUC₀₋₄

†: t_{1/2} and AUC_{0-∞} are approximated values since the correlation coefficient (r²) is < 0.8

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)

BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Source: Study RPTC20089, Page 46-47, Table 11

Abbreviations: AUC, area under the concentration-time curve; BQL, below quantitation limit; C_{max}, maximum plasma concentration; GI, gastrointestinal; LLOQ, lower limit of quantitation; LSC, liquid scintillation counting; PK, pharmacokinetic; SUZ, suzetrigine; t_{1/2}, apparent half-life; t_{max}, time to maximum plasma concentration; QWBA, quantitative whole body autoradiography

Continued

Table 88, continued

Study/Study No.

Mass Balance, and Biliary Excretion Following a Single Oral or Intravenous Dose of [¹⁴C]VRT-1737548 in Male Sprague-Dawley Rats and Tissue Distribution Using Quantitative Whole Body Autoradiography (QWBA) Following a Single Oral Dose of [¹⁴C]VRT-1737548 in Male Long-Evans and Sprague-Dawley Rats/ Study No. RPTC20089

Findings

Table 93. Concentration of [¹⁴C]SUZ-Derived Radioactivity (µg equiv/g) in Plasma and Tissues of Male Sprague-Dawley Rats Following an Oral Dose of [¹⁴C]SUZ at 10 mg/kg

Tissue Group	Tissue Name	[¹⁴ C]VRT-1737548-Derived Radioactivity (µg equiv/g)			
		Hours Post Dose			
		1	4	24	168
Vascular	Plasma (LSC)	2.35	3.00	0.287	BQL
	Blood (LSC)	1.62	2.15	0.177	BQL
	Aorta	1.96	1.60	0.137	BQL
	Blood (cardiac)	1.66	2.09	0.150	BQL
Central Nervous System	Brain (whole)	0.863	0.722	BQL	BQL
	Meninges	0.601	0.830	0.0449	BQL
	Spinal cord	1.12	0.885	BQL	BQL
Ocular	Eye	0.282	0.432	0.0366	BQL
	Lens	0.0468	0.0740	0.0665	BQL
	Uveal tract	0.947	1.19	0.133	BQL
Dermal	Non-pigmented skin	1.90	2.42	0.0770	BQL
Endocrine	Adrenal cortex	21.3	7.90	0.304	BQL
	Adrenal gland	23.9	8.09	0.281	BQL
	Adrenal medulla	25.5	8.86	0.215	BQL
	Pituitary gland	3.32	4.77	0.152	BQL
	Thyroid gland	4.17	4.93	0.0814	0.0344
Fatty	Brown fat	4.71	5.20	0.205	BQL
	White fat (inguinal)	1.95	2.39	0.0547	BQL
Gastro Intestinal (GI) Tract	Cecum mucosa	10.6	17.7	2.81	BQL
	Esophagus wall	0.893	2.70	0.201	BQL
	Large intestine wall	2.19	4.07	5.00	BQL
	Oral mucosa	1.08	2.12	0.0736	BQL
	Small intestine wall	4.45	24.5	0.946	BQL
	Stomach wall (glandular)	60.6	5.02	0.208	0.0303
	Stomach wall (non-glandular)	37.5	6.25	0.372	0.0543
GI Tract Contents	Cecum contents	0.753	34.2	16.8	BQL
	Large intestine contents	0.0352	6.79	42.6	0.0462
	Small intestine contents	3.30	320	16.9	BQL
	Stomach contents	131	118	3.47	0.0385
	Urinary bladder contents	0.186	0.585	0.518	BQL
Lymphatic	Bone marrow (femur)	2.91	2.77	0.120	BQL
	Lymph node (cervical)	2.52	2.97	BQL	BQL
	Spleen	7.40	4.19	0.108	BQL
	Thymus	1.25	2.03	0.0438	BQL
Metabolic/Excretory	Bile (in duct)	28.6	75.3	12.1	BQL
	Kidney	6.94	7.03	0.455	0.0297
	Kidney cortex	8.13	8.99	0.487	0.0401
	Kidney medulla	5.15	5.10	0.419	BQL
	Liver	21.4	25.9	1.36	0.0453
	Urinary bladder wall	2.86	3.01	0.653	BQL

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)

BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Continued

Table 88, continued

Study/Study No.

Mass Balance, and Biliary Excretion Following a Single Oral or Intravenous Dose of [¹⁴C]VRT-1737548 in Male Sprague-Dawley Rats and Tissue Distribution Using Quantitative Whole Body Autoradiography (QWBA) Following a Single Oral Dose of [¹⁴C]VRT-1737548 in Male Long-Evans and Sprague-Dawley Rats/ Study No. RPTC20089 (continued)

Findings

Table 93, continued

Tissue Group	Tissue Name	[¹⁴ C]VRT-1737548-Derived Radioactivity (µg equiv/g)			
		Hours Post Dose			
		1	4	24	168
Muscular	Heart	4.24	4.21	0.146	BQL
	Muscle (femoral)	2.36	2.85	0.101	BQL
Reproductive	Epididymis	0.863	3.17	0.123	BQL
	Prostate	2.16	2.38	0.100	BQL
	Seminal vesicle	1.12	3.25	0.123	BQL
	Testis	0.615	1.50	0.0586	BQL
Respiratory	Lung	3.21	4.41	0.164	BQL
	Nasal turbinates	1.02	1.58	0.0890	BQL
	Trachea	1.87	2.39	0.0814	BQL
Secretory	Ex-orbital lachrymal gland	4.79	6.18	0.178	BQL
	Harderian gland	4.82	9.63	0.432	BQL
	Intra-orbital lachrymal gland	4.21	6.00	0.168	BQL
	Pancreas	8.51	6.40	0.256	BQL
	Salivary gland	3.79	4.54	0.116	BQL
Skeletal	Bone (femur)	0.891	1.17	0.325	0.0289
	Bone (humerus)	1.37	2.38	0.0974	BQL
	Bone (leg)	1.30	2.19	0.180	BQL
	Bone (radius)	1.01	NS	NS	BQL
	Bone (rib)	0.779	1.18	0.0465	BQL
	Bone (skull)	0.933	1.09	0.0616	0.140
	Bone (ulna)	0.623	NS	NS	0.0465
	Bone (vertebrae)	1.38	1.82	0.118	0.0475

NS = No Sample

BQL = <LLOQ for LSC = <0.00742 µg equiv/g (plasma) or <0.0121 µg equiv/g (blood)

BQL = <LLOQ for QWBA = <0.0271 µg equiv/g

Source: Study RPTC20089, Page 48-49, Table 12

Abbreviations: BQL, below quantitation limit; GI, gastrointestinal; LLOQ, lower limit of quantitation; LSC, liquid scintillation counting; QWBA, quantitative whole body autoradiography; SUZ, suzetrigine

Continued

Table 88, continued

Study/Study No.	Findings
Placental Transfer and Lacteal Excretion of [¹⁴ C]VX-548 Following Administration of a Single Oral Dose to Pregnant and Lactating Rats/ Study No. 8519000	In gestation day (GD) 13 fetal tissues, the highest radioactivity concentration was observed in the lung and spinal cord at 8 hours postdose. Radioactivity in the fetal blood was quantifiable through 72 hours. In GD 18 fetal tissues, the highest radioactivity concentration was observed in the heart, spinal cord, and adrenal gland. Radioactivity in the fetal blood was quantifiable through 72 hours. In lactating rats at postnatal day (PND) 10, T_{max} was at 8 hours postdose in lactating rat but at 2 hours postdose in the milk. Exposure in the milk (AUC) was approximately 3-fold higher than in blood and plasma. Radioactivity was quantifiable in the milk from 1 to 72 hours postdose. See Table 94 below for the PK parameters for radioactivity in blood, plasma, and milk in lactating rats (PND 10).

Table 94. Pharmacokinetic Parameters for Radioactivity in Blood, Plasma, and Milk After an Oral Administration of [¹⁴C]SUZ to Female Sprague-Dawley Rats (10 mg/kg)

Sample	C _{max} (ng eq/g)	T _{max} (h)	AUC _{0-t} (h·ng eq/g)	AUC ₀₋₂₄ (h·ng eq/g)	AUC ₀₋₇₂ (h·ng eq/g)	AUC _{0-∞} (h·ng eq/g)	t _{1/2} (h)
Blood	1890	8.00	40200	32400	40200	40800	11.3
Plasma	2610	8.00	56400	45000	56400	57300	11.5
Milk	10700	2.00	145000	131000	145000	147000	8.92

eq
h Equivalents ¹⁴C-VX-548.
Hours.

Source: Study 8519000, Page 31, Table 8

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; SUZ, suzetrigine; t_{1/2}, apparent half-life; T_{max}, time to maximum concentration

Source: Study No. RPTC20089, and Study No. 8519000

Abbreviations: AUC, area under the concentration-time curve; GD, gestation day; PND, postnatal day; PK, pharmacokinetic; QWBA, quantitative whole body autoradiography; SUZ, suzetrigine (VX-548; VRT-1737548)

13.1.5. General Toxicology

Systemic safety of SUZ and M6-SUZ were evaluated in 28-day repeat-dose toxicity studies in rats and monkeys. In addition, the safety of SUZ and impurities/degradants in the drug substance/drug product were evaluated in 91-day repeat-dose toxicity studies in rats and monkeys.

In the 28-day rat study, weights of the liver and ovaries increased in the high-dose groups. However, there were no associated histopathological changes in the liver or ovaries. In the 28-day monkey study, increased incidences of soft/watery feces were observed in treated groups. The mean organ weight of the thyroid/parathyroid was increased in females without statistical significance. The no-observed-adverse-effect level (NOAEL) was determined to be 1,000 mg/kg/day (male) and 300 mg/kg/day (female) for rats and 100 mg/kg/day for both sexes in monkeys.

In a 91-day rat study, males were dosed at 0, 200, 600, and 1,000 mg/kg/day and females at 0, 10, 100, and 1,000 mg/kg/day via oral gavage. Ploughing, salivation, and wet fur at the mouth were observed in test article-treated animals at ≥ 100 mg/kg/day. Minimal-to-moderate ovarian follicular cysts were observed in female rats treated with the test article at ≥ 100 mg/kg/day. Higher incidences of minimal-to-mild decreased number of corpora lutea, minimal-to-mild distalis hyperplasia in the pituitary gland, moderate-to-marked dilatation in the mammary gland were observed in females treated at 100 mg/kg compared to the concurrent and historical controls. Minimal-to-mild cortical hypertrophy in the adrenal gland was observed in females treated at 1,000 mg/kg/day, which could be a result of stress responses. The NOAELs for males and females were 1,000 mg/kg/day and 10 mg/kg/day, respectively.

In a 13-week monkey study, animals were treated with SUZ at 0, 20, 50, and 150 mg/kg via oral gavage. Of note, no recovery group was included in this study. Test article-treated animals showed increased soft/liquid feces and decreased thymus weight, which is associated with decreased thymic cellularity, which could be related to stress responses. In addition, reduced weights of testis, epididymis, and prostate gland were observed in SUZ treated males; however, there were no adverse microscopic findings while all animals including the control group showed immaturity in the testis. There were no test article-related changes in body weights, ophthalmoscopy/electrocardiogram (ECG)/ hematology/clinical chemistry/urinalysis parameters, and thyroid biomarkers. The NOAEL for both sexes was determined to be 150 mg/kg.

Table 95. Summary of Repeat-Dose Toxicology Studies

Study/Study No.	Study Design/Findings
VRT-1737548: A 28-day Oral (Gavage) Toxicity and Toxicokinetics Study in Sprague-Dawley Rats/ Study No. VRT-1737548-TX-011	Animals were dosed at 0, 200, 600 and 1000 mg/kg for males and 0, 10, 30, and 300 mg/kg for females once daily for 28 days (N=10/group) via oral gavage. <u>Results:</u> - No effect on body weight, food consumption, ophthalmic, hematology parameters were observed. - Up to 2-fold increases in triglyceride and cholesterol were observed in male and female groups (see Table 96 below).

Table 96. Levels of Triglyceride and Cholesterol in Rats Treated With SUZ for 28 Days

Dose (mg/kg)	Male				Female			
	0	200	600	1000	0	10	30	300
Triglyceride (mg/dL)	47.4	68.5*	79.6**	80.1**	28.5	30.4	31.4	38.8**
Cholesterol (mg/dL)	63.5	69.2	96.8**	104.9**	73.6	72.5	77.6	140.9**

Source: Study VRT-1737548-TX-011, Pages 298 and 302
Abbreviations: SUZ, suzetrigine

- Increased urine volume and quantitative urine protein were observed in the 1000 mg/kg male group, but there were no effects on quantitative urine protein concentration and specific gravity.
- Increased liver weights (40 to 46%) were observed in males at ≥ 600 mg/kg and females from the 300 mg/kg group.
- Increased adrenal gland and ovary weights (~27% and ~36%, respectively) were observed in females that received 300 mg/kg.
- Decreased uterine weights (17 to 35%) were observed in all treated female groups.
- NOAEL was 1000 mg/kg in male and 300 mg/kg in female.

Continued

Table 95, continued

Study/Study No.	Study Design/Findings
VRT-1737548: A 28-Day Oral (Gavage) Toxicity and Toxicokinetics Study in Cynomolgus Monkeys With a Functional Observational Battery Assessment/ Study No. VRT-1737548-TX-012	Animals were dosed at 20, 50, and 100 mg/kg once daily for 28 days (N=4/sex/group) via oral gavage. <u>Results:</u> - Increased soft/watery feces was observed in all SUZ-treated groups. - No adverse effects were observed on FOB parameters, body weight, ophthalmic, ECG parameters, hematology/coagulation parameters, clinical chemistry parameters, urinalysis parameters. - Increased liver weights (13 to 17%) were observed in 50 and 100 mg/kg female groups. - Increased thyroid/parathyroid weights (37 to 48%) were observed in all treated female groups. - NOAEL was 100 mg/kg.
A 91-Day Oral (Gavage) Toxicity and Toxicokinetics Study in CD® [CrI:CD®(SD)] Rats/ 863-865 VX-548-TX-001	Animals were dosed at 0, 200, 600, and 1000 mg/kg for males, and 0, 10, 100, and 1000 mg/kg for females once daily for 91 days (N=10/sex/group) via oral gavage. <u>Results:</u> - Ploughing, salivation/wet fur at the mouth, struggle to dose, and expelled materials from mouth were observed in animals treated at ≥100 mg/kg/day. - No toxicologically significant adverse effects were observed on survival, body weights, ophthalmoscopy, hematology, clinical chemistry, or urinalysis parameters. - Ovarian follicular cysts and decreased number of corpora lutea were observed in females dosed at ≥100 mg/kg/day. - MD female – hyperplasia in the pituitary gland, glandular hyperplasia/dilation in the mammary gland - Centrilobular/panlobular hepatocellular hypertrophy in the liver was observed in mid-/high-dose groups. - Periportal vacuolation in the liver, hypertrophy in the thyroid gland, and cortical hypertrophy in the adrenal gland were observed in high-dose males and females. - The NOAEL was 1000 mg/kg for the male and 10 mg/kg for the female based on ovarian cyst formation, decreased number of corpora lutea, pituitary gland hyperplasia, and mammary hyperplasia/dilatation.

Continued

Table 95, continued

Study/Study No.	Study Design/Findings
VX-548: A 13-Week Oral (Gavage) Toxicity and Toxicokinetics Study in Cynomolgus Monkeys/863-866 VX-548-TX-002	Animals were dose at 0, 20, 50, and 150 mg/kg once daily for 13 weeks (N=4/sex/group) via oral gavage. <u>Results:</u> - No adverse effects were observed on survival, body weights, ophthalmoscopy, ECG, hematology, clinical chemistry, urinalysis, thyroid biomarker, or gross pathology. - Increased incidences of soft/liquid feces were observed in all SUZ-treated groups. - Decreased thymus weight (up to 37%) and minimal to mild decreased cortical cellularity in the thymus were observed in all SUZ-treated groups, which were considered as stress response. - Dose-dependent decreases were observed in male reproductive tissue organ weights across drug treated groups. Epididymis weights were decreased from -14 to -38% compared to control. Testis weights were decreased from -43 to -46% compared to control. Prostate weights were decreased from -47 to -49% compared to control. However, there were no microscopic correlates. In addition, the mean organ weights observed in the SUZ-treated groups were within the ranges of those in untreated cynomolgus monkeys of similar age. Also of note, changes in these organ weights in the 28-day and 9-month monkey studies were generally of lower magnitude, did not follow a dose-dependent trend for incidence, and the standard deviations were often very large and, in some cases, were larger than the mean values. In addition, the 28-day and 9-month monkey studies did not report histological correlates in these tissues. Therefore, the organ weight changes do not appear to be toxicologically significant and do not appear to have relevance for the proposed acute indication. Of note, Na_v1.8 is highly expressed in testes based on information the Applicant provided. Because of the low number of monkeys in the study, the lack of recovery groups, and known variability in male reproductive organ weights in this species, the nonhuman primate data do not provide an ideal model to evaluate the potential risk of SUZ to male reproductive tissues in these longer duration studies. Should further evaluation be deemed necessary to support long-term clinical use, studies in human could be considered. - The NOAEL was 150 mg/kg.

Source: Study No. VRT-1737548-TX-011, Study No. VRT-1737548-TX-012, Study No. VX-548-TX-001, and Study No. VX-548-TX-002

Abbreviations: ECG, electrocardiogram; FOB, functional observational battery; MD, mid dose; NOAEL, no-observed-adverse-effect level; SUZ, suzetrigine (VX-548; VRT-1737548)

13.1.6. Genetic Toxicology

SUZ was evaluated for genotoxicity potential in a full battery of genotoxicity studies, including an in vitro Ames assay, an in vitro micronucleus assay, and in vivo micronucleus assay in rats. SUZ was not considered mutagenic or clastogenic in these assays.

M6-SUZ (a major metabolite in human and monkeys) was also evaluated for genotoxicity potential. An Ames study that tested M6-SUZ demonstrated the metabolite was not mutagenic. An in vitro chromosomal aberration test was not conducted with M6-SUZ. However, the chromosomal aberration potential of M6-SUZ was assessed through the in vivo micronucleus assay that tested the parent SUZ, which was negative for genotoxicity. Although M6-SUZ is a

minor metabolite in rats, the systemic exposure levels of M6-SUZ achieved in rats after SUZ oral administration in this study exceeded the steady-state levels in humans at the maximum recommended daily dose. Together with the negative Ames result of M6-SUZ, negative genetic toxicology battery of SUZ, and in silico quantitative structure-activity relationship (QSAR) data with M6-SUZ, the weight of evidence supported minimal concern for clastogenicity.

Table 97. Summary of In Vitro and In Vivo Genetic Toxicology Studies for SUZ

Study/Study No.	Findings
VRT-1737548: Bacterial Reverse Mutation Assay/ Study no. VRT-1737548-TX-008	- Ames assay with <i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537) and <i>Escherichia coli</i> WP2 <i>uvrA</i> - Tested up to 5,000 µg/plate in the presence and absence of metabolic activation (rat liver S9) using a plate incorporation method - SUZ was not mutagenic under conditions of the assay.
VRT-1737548: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells/ Study no. VRT-1737548-TX-009	- Human lymphoblastoid TK6 cell - SUZ was negative for the induction of micronuclei in the nonactivated and rat liver S9-activated test systems in this study.
VRT-1737548: In Vivo Mammalian Erythrocyte Micronucleus Assay in Rats/ Study no. VRT-1737548-TX-010	0, 500, 1000, and 2000 mg/kg for female only - Femoral bone marrow collection at 24 and 48 hours following single oral gavage administration - SUZ did not affect incidence of micronucleated polychromatic erythrocytes or ratio of polychromatic erythrocytes - SUZ was negative under the study condition

Source: Study no. VRT-1737548-TX-008, Study no. VRT-1737548-TX-009, and Study no. VRT-1737548-TX-010
Abbreviations: SUZ, suzetrigine (VRT-1737548)

Table 98. Summary of Genotoxicity Potentials for M6-SUZ

Study/Study No.	Findings
VRT-1875420 Bacterial Reverse Mutation (Ames) Assay/ Study No. VRT-1875420-TX-004	- Ames assay with <i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537) and <i>Escherichia coli</i> WP2 <i>uvrA</i> - Up to 5,000 µg/plate - Presence and absence of metabolic activation (rat liver S9) - M6-SUZ was not mutagenic in the tested species

Source: Study No. VRT-1875420-TX-004

13.1.7. Reproductive and Developmental Toxicology

Reproductive and developmental toxicities of SUZ were assessed in fertility (male and female) and early embryonic development studies in rats, embryo-fetal development studies in rats/rabbits, and a pre- and postnatal development study in rats. SUZ did not affect male reproductive performance. However, SUZ produced pre- and postimplantation loss, lower fetal body weight, and lower postnatal survival in rats and postimplantation loss and lower fetal body weights in rabbits. Additional investigational studies demonstrated that SUZ affects the estrus cycle in rats and inhibits the rat PR, suggesting that inhibition of the PR may contribute to the SUZ effects on reproduction. Refer to Sections [7.1](#) and [13.1.8](#) for a summary of these studies and discussion about the adequacy of those data to support the Applicant's position.

13.1.7.1. Fertility and Early Embryonic Development

In a male fertility study, male rats were treated with 0, 200, 600, or 1,000 mg/kg of SUZ from at least 28 days before mating and throughout mating with untreated female rats, and there were no adverse effects on male reproductive performance or sperm parameters. Thus, the NOAEL for male reproductive toxicity was 1,000 mg/kg.

In a female fertility study, female rats were treated with 0, 5, 10, or 15 mg/kg of SUZ from a minimum of 14 days prior to mating, throughout mating with untreated male rats, and continuing until gestational day (GD) 7. There were higher mean preimplantation losses in the 15 mg/kg group. Thus, the NOAEL for female fertility toxicity was 10 mg/kg based on increased preimplantation loss.

Table 99. Summary of Fertility and Early Embryonic Development Studies

Study/Study No.	Findings
An Oral (Gavage) Study of the Effects of VX-548 on Fertility and Early Embryonic Development to Implantation in Crl:CD(SD) Sprague-Dawley Rats/ Study No. VX-548-TX-013	Male rats (N=22/sex/group) were treated orally with SUZ at 200, 600, and 1,000 mg/kg/day for a minimum of 28 days prior to mating and through mating with untreated females. Female rats (N=22/sex/group) were treated orally with SUZ at 5, 10, and 15 mg/kg/day for a minimum of 14 days prior to mating, throughout mating with untreated males, and through Gestation Day 7. <u>Results:</u> • No effect on survival, body weights, or food consumption in treated males, untreated females, or treated females • No effect on reproductive performance of treated males or treated females • No effect on sperm motility, sperm concentration, and sperm morphology • No male-mediated effects on implantation sites, or intrauterine survival in untreated females • No effect in estrous cycling in treated females • Mean preimplantation loss (17.8% per litter) in the 15 mg/kg treated females was higher compared to the control (4.8% per litter) and exceeded the (b) (4) historical control range (12.7% per litter) • NOAEL for male reproductive toxicity is 1,000 mg/kg • NOAEL for female reproductive toxicity was 10 mg/kg based on increased preimplantation loss
VX-548: A 4-Week Investigational Oral (Gavage) Study to Evaluate the Reversibility of the Effects of Estrous Cyclicity Following 4-and 6-Week Recovery Periods in Female Sprague-Dawley Rats/ Study No. VX-548-TX-023	Female rats received 0, 15, or 100 mg/kg SUZ for 4 weeks via oral gavage and then had a no-dosing period of 4 or 6 weeks prior to mating with untreated males (N=12/sex/group). Females were necropsied on GD 13. <u>Results:</u> • No SUZ related effect on reproductive performance: No effects on female mating index, female fertility index, female pregnancy index, precoital interval, estrous cycle length, or number of cycles • No SUZ related effect on ovarian/uterine examination: No effects on number of corpora lutea, number of implantations, preimplantation loss, number of live embryos, number of dead embryos, postimplantation loss, or number of early resorptions

Source: Study No. VX-548-TX-013, and Study No. VX-548-TX-023

Abbreviations: GD, gestation day; NOAEL, no-observed-adverse-effect level; SUZ, suzetrigine (VX-548)

13.1.7.2. Embryonic and Fetal Development

In dose range-finding studies for rat embryo-fetal development (EFD), all pregnant female rats that received ≥ 25 mg/kg (GDs 6 through 17) had 100% postimplantation loss, which was a basis for the dose selection for the definitive EFD (dEFD) study in rats. In a rat dEFD study, pregnant rats were dosed at 0, 5, 10, and 15 mg/kg of SUZ during GDs 6 through 17. The high-dose group (15 mg/kg) showed higher postimplantation loss and a lower number of live fetuses. However, there was no SUZ-related effect on malformations or variations in the fetuses. The maternal NOAEL was 15 mg/kg and the developmental NOAEL was 10 mg/kg based on increased postimplantation loss and a lower number of live fetuses.

In a rabbit dEFD study, pregnant rabbits received 0, 50, 100, and 200 mg/kg of SUZ during GDs 7 through 20. The high-dose group (200 mg/kg) showed body weight loss and lower food consumption during dosing period, lower mean gravid uterine weight, lower adjusted body weight gain, higher postimplantation loss, and lower fetal body weights. There was no SUZ-related effect on malformations or variations in fetuses. The maternal NOAEL was 100 mg/kg/day based on evidence of maternal toxicity, including body weight loss and lower food consumption during treatment period and lower adjusted body weight gain. The developmental NOAEL was 100 mg/kg/day based on postimplantation loss and lower fetal body weights.

Table 100. Summary of EFD Studies

Study/Study No.	Findings
An Oral (Gavage) Study of the Effects of VX-548 on Embryo/Fetal Development in Rats/ Study No. VX-548-TX-007	Pregnant rats (N=22/group) received SUZ orally once daily at 5, 10, and 15 mg/kg/day during GDs 6 to 17. Separate TK animals were included in this study. <u>Results:</u> - The mean gravid uterine weight of the HD was 27.2% lower than that of the control but not statistically significant. - Body weight gain was lower in the HD than in the control during the treatment period of GDs 6 to 18. - The mean postimplantation loss (26.1% per litter) in the HD was higher than that in the control group (5.1% per litter) and exceeded the (b) (4) historical control range (up to 12.6% per litter), although not statistically significant. - Four females in the HD had entirely resorbed litters (100% postimplantation loss). - The mean number of live fetuses (9.7 fetuses/dam) was lower than that in the control group (13.5 fetuses/dam) and below the (b) (4) historical control range (11.4 fetuses/dam). - No SUZ-related effect on malformations or variations. - The maternal NOAEL was 15 mg/kg/day. - The developmental NOAEL was 10 mg/kg/day based on increased postimplantation loss and lower number of live fetuses.

Study/Study No.	Findings
VX-548: An Oral (Gavage) Embryo/Fetal Development Study in New Zealand White Rabbits/ Study No. VX-548-TX-009	Pregnant rabbits (N=22/group) received SUZ orally once daily from GDs 7 to GD 20 at 50, 100, and 200 mg/kg/day. Separate TK animals were included in the study. <u>Results:</u> • The HD group lost body weight and ended the period at 9% below the body weight of the control group during treatment period (GD 7 to GD21). • The HD group showed lower mean gravid uterine weight (~16%) and adjusted body weight gain (~77%) than did the control group. • The HD group showed significantly lower food consumption (57%) during the entire dosing period (GDs 7 to 21) and significantly higher food consumption (26%) following the cessation of treatment (GDs 21 to 29) than did the control group. • The mean postimplantation loss (11.9% per litter) in the HD was significantly higher than that in the control group (4.0% per litter) and exceeded the (b) (4) historical control range (up to 9.8% per litter). • The mean male and female fetal body weights were lower than those of the control group. • No SUZ-related effect on malformations or variations. • The maternal NOAEL was 100 mg/kg/day based on body weight loss during treatment period, lower food consumption during treatment period, and lower adjusted body weight gain. • The developmental NOAEL was 100 mg/kg/day based on postimplantation loss and lower body weights.

Source: Study No. VX-548-TX-007 and Study No. VX-548-TX-009

Abbreviations: GD, gestation day; HD, high dose; NOAEL, no-observed-adverse-effect level; SUZ, suzetrigine (VX-548); TK, toxicokinetic

13.1.7.3. Prenatal and Postnatal Development

In a pre- and postnatal development (PPND) study, pregnant rats received 0, 5, 10, and 15 mg/kg of SUZ once daily via oral gavage from GD 6 to lactation day 20. Two out of 22 F0 females dosed at 10 mg/kg/day (9% dam) and 12 out of 30 F0 females dosed at 15 mg/kg (40% dam) showed fully resorbed litters. F0 females dosed at 15 mg/kg also showed lower body weights (-36%) during the gestation period (GD 6 to GD 20), lower food consumption during gestation/lactation period, fewer live newborn pups, and a shorter mean gestation length. F1 pups from dams dosed at 10 mg/kg and 15 mg/kg showed a lower viability index from birth to postnatal day 4 (84% and 34% per litter, respectively, versus 98% per litter in the control), lower birth weights (13 to 33%), and lower mean body weights (8 to 20%) on postnatal day 21. F1 pups from dams dosed at 15 mg/kg also showed late pinna detachment (4.6 days) compared to the control (3.2 days). There was no effect on eye opening, pupillary reflex, balanopreputial separation, vaginal opening, auditory startle response, motor activity, and Biel Maze swimming trials in F1 pups. There was no effect on reproductive parameters (precoital interval, mating index, fertility index, or pregnancy index) in the F1 generation. The maternal NOAEL was 10 mg/kg based on lower food consumption during the gestation and lactation periods. The developmental NOAEL was 5 mg/kg based on lower body weight gains during preweaning at 15 mg/kg, total resorptions of litters, shorter gestation length, decreased postnatal survival, and lower pup body weight at 10 mg/kg and 15 mg/kg.

Table 101. Summary of a Rat PPND Study

Study/Study No.	Findings
VX-548: An Oral Gavage Pre- and Postnatal Development Study, Including Maternal Function, in Crl:CD(SD) Sprague-Dawley Rats/ Study No. VX-548-TX-019	Pregnant rats (F0 generation, N=22/group for 0, 5, and 10 mg/kg, N=30 for 15 mg/kg group) were given SUZ at 0, 5, 10, and 15 mg/kg/day once daily via gavage from GD 6 to LD 20. TK animals were included in the study. <u>Results:</u> - F0 generation and F1 generation (preweaning) findings: 2 out of 22 MD F0 females (9%) and 12 out of 30 (40%) HD F0 females showed fully resorbed litters. 1 MD F0 female and 7 HD F0 females had no surviving pups from LD 0 to LD 3. - HD F0 females had lower gestational body weight due to 3 nongravid dams and 12 dams with fully resorbed litters. - HD F0 females showed significantly lower body weight on LDs 4 and 7. However, LD 21 body weight was comparable in all groups. - HD F0 females showed lower food consumption during overall gestation period (GD 6 to GD 20). - HD F0 females showed lower food consumption during the lactation period (LD 1 to LD 21). - HD F0 females had significantly fewer live newborn pups (7.5 per litter) than did the control group (11.7 per litter). - MD and HD F0 females had shorter mean gestation lengths (20.8 and 20.3 days, respectively) than did the control group (21.2 days). - MD and HD F1 pups had significantly lower viability index (84.14% and 34.4% per litter, respectively) than did the control pups (97.7% per litter). - MD and HD F1 pups had significantly lower mean male and female pup birth (PND 1) weights than did the control group. - HD F1 pups had lower pup body weight gain throughout the preweaning period (PND 1 to PND 21). - HD F1 pups had lower body weight on PND 21 than did the control group. - HD F1 pups had significantly later pinna detachment (4.6 days) than did the control group (3.2 days). - There was no effect on eye opening, pupillary reflex, balanopreputial separation, vaginal opening, auditory startle response, motor activity, and Biel Maze swimming trials. - F1 generation (postweaning) findings: - No mortality and no test article-related adverse clinical observations - MD and HD F1 pups had a lower mean body weight on PND 22 but a comparable mean body weight on PND 84. - F1 generation (fertility/mating) findings: - No effect on reproductive parameters – precoital interval, mating index, fertility index, or pregnancy index The maternal NOAEL was 10 mg/kg based on lower food consumption during the gestation and lactation period. The developmental NOAEL was 5 mg/kg based on lower body weight gains during preweaning at 15 mg/kg, total resorptions of litters, shorter gestation length, decreased postnatal survival, and lower pup body weight at 10 mg/kg.

Source: Study No. VX-548-TX-019

Abbreviations: GD, gestation day; HD, high dose; LD, lactation day; MD, mid dose; NOAEL, no-observed-adverse-effect level; PND, postnatal day; PPND, pre- and postnatal development; SUZ, suzetrigine (VX-548); TK, toxicokinetic

13.1.8. Special Studies

13.1.8.1. Investigative Studies

To evaluate the reversibility and effects on estrous cycle in female rats, female rats were dosed at 0, 15, or 100 mg/kg of SUZ for 4 weeks and had a no-dosing period of 4 or 6 weeks prior to mating with untreated males. There was no SUZ-related effect on reproductive performance (female mating index, female fertility index, female pregnancy index, precoital interval, estrous cycle length, or number of cycles), ovarian/uterine examination (number of corpora lutea, number of implantations, preimplantation loss, number of live embryos, number of dead embryos, postimplantation loss, or number of early resorptions), or macroscopic pathology.

In a 6-week investigational study, female rats received 0, 10, 100, or 300 mg/kg of SUZ for 6 weeks via oral gavage. While there were no test article-related effects on mortality, clinical signs, body weight, or food consumption, animals dosed at mid dose (MD) and high dose (HD) showed a significantly longer estrus state (93 to 120% increase in number of days) with an increase in the number of females in a state of prolonged/persistent estrus (≥ 7 days) and a significantly shorter diestrus state (40 to 54% decrease in number of days). In addition, the mean estradiol concentrations in estrous state in the MD and HD groups were higher than that in the control group (46 to 58% increase). Microscopically, increased incidences of ovarian cysts, increased atretic follicles in the ovary, decreased corpora lutea, persistent estrus in the vagina, and increased secretion in the mammary gland were observed in the MD and HD groups compared to the control group. Minimal severity of hyperplasia in the mammary gland was observed in one MD female and adrenal cortical hypertrophy was observed in two HD females.

In an 8-week investigational study, canulated female rats received 0 or 100 mg/kg of SUZ via oral gavage. Based on estrous cycle analysis, the SUZ-treated group had started a prolonged estrus state (7 or more consecutive days in estrus) generally within the first 2 to 3 weeks following initiation of dose administration. Hormone analyses showed that the SUZ-treated group showed higher mean estradiol, prolactin, and luteinizing hormone concentrations on both D2 (2nd day of diestrus) and D3 (3rd day of diestrus). Increased incidences of ovarian cysts, decreased number of corpora lutea, increased atretic follicles in the ovary, persistent estrus in the vagina, glandular dilatation, and atypical hyperplasia in the mammary gland were also observed.

Table 102. Summary of Investigative Studies Evaluating SUZ Effects on Estrous Cycle in Female Rats

Study/Study No.	Findings
VX-548: A 6-Week Investigative Oral (Gavage) Study of the Effects of VX-548 in Female Rats/ Study No. VX-548-TX-015	Female rats (N=20/group) received 0, 10, 100 or 300 mg/kg of SUZ once daily for 6 weeks via oral gavage. <u>Results:</u> • MD and HD groups had significantly longer estrus state with an increase in the number of females in a state of prolonged/persistent estrus and significantly shorter diestrus state. • Higher mean estradiol concentrations were observed in estrus state in MD and HD groups. • Ovarian cysts (MD and HD), enlarged adrenal gland (HD), and enlarged pituitary gland (MD) were observed. • Increased incidences of ovarian cysts, decreased corpora lutea, and atretic follicles in the ovary were observed at the MD and HD. • Persistent estrus in the vagina was observed at the MD and HD. • Increased secretion in the mammary gland was observed at the MD and HD. • Hyperplasia in the mammary gland was observed at the MD. • Adrenal cortical hypertrophy was observed at the HD. • The NOAEL was 10 mg/kg.
VX-548: A 8-Week Investigative Oral (Gavage) Study of the Effects of VX-548 in Cannulated Female Rats/ Study No. VX-548-TX-016	Cannulated female rats (N=25/group) received 0 or 100 mg/kg of SUZ for 8 weeks via oral gavage. • Started a state of prolonged estrus generally within the first 2 to 3 weeks following initiation of dose administration. • Higher mean estradiol concentrations were reported on both D2 (2nd day of diestrus) and D3 (3rd day of diestrus). • Higher serum prolactin levels were reported on D2 and D3. • Higher mean luteinizing hormone levels were reported on D2 and D3. • Ovarian cysts, pale cysts in the mammary gland, and enlarged pituitary glands were observed. • Increased incidence of ovarian cysts, decreased number of corpora lutea, and increased atretic follicles in the ovary were observed, • Persistent estrous in the vagina was observed. • Glandular dilatation and atypical hyperplasia in the mammary gland were observed. • The LOAEL was 100 mg/kg.

Source: Study No. VX-548-TX-015 and Study No. VX-548-TX-016

Abbreviations: D, day of diestrus; HD, high dose; MD, mid dose; LOAEL, lowest observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; SUZ, suzetrigine (VX-548)

13.1.8.2. Local Toxicities

SUZ drug substance was a nonirritant in an in vitro eye hazard assessment, and an in vitro skin irritation assay. SUZ (b) (4) was not a skin sensitizer in a local lymph node assay in the mouse.

Table 103. Summary of Local Toxicity Studies

Study/Study No.	Findings
VX-548: In Vitro Skin Irritation Test using a Human Skin Model/ Study No. VX-548-TX-026	Fifteen-minute application of solid form SUZ drug substance did not affect skin tissue viability in a three-dimensional human epidermis model [EPISKIN Small Model™ (EPISKIN-SM™, 0.38 cm²)]. SUZ is a nonirritant to the skin.

Table 104. Mean Absorption and Mean Tissue Viability in In Vitro Skin Irritation Test With SUZ

Parameter	Negative Control	SUZ	Positive Control
Mean absorption	1.140	1.096	0.129
Viability (%)	100	96	11

Source: Study No. VX-548-TX-026, Page 18, Tables 1-2

Negative control: 25 µL of PBS

Positive control: 25 µL of 5% SDS

Abbreviations: PBS, phosphate-buffered saline; SDS, sodium dodecyl sulfate; SUZ, suzetrigine (VX-548)

Evaluation of the Eye Hazard Potential With VX-548 Using the Reconstructed Human Cornea-Like Epithelium (RHCE) Model (OECD 492B)/ Study No. VX-548-TX-028	Application of neat SUZ drug substance on a three-dimensional RHCE model (SkinEthic™ HCE) composed of transformed human corneal keratinocytes did not affect tissue viability. SUZ is a nonirritant.
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Table 105. Mean Absorption and Mean Tissue Viability in In Vitro RHCE Test With SUZ

Parameter	Negative Control	SUZ	Positive Control
30-min application			
Mean absorption	1.746	1.601	1.480
Viability (%)	100	92	85
120-min application			
Mean absorption	1.848	1.622	1.268
Viability (%)	100	96	70

Source: Study No. VX-548-TX-028, Page 18, Tables 1-2

Negative control: 80 µL Ca²⁺, Mg²⁺-free D PBS

Positive control: 80 µL Lactic acid (1% w/v)

Abbreviations: PBS, phosphate-buffered saline; RHCE, reconstructed human cornea-like epithelium; SUZ, suzetrigine (VX-548)

Continued

Table 103, continued

Study/Study No.	Findings
A GLP Skin Sensitization Test (Local Lymph Node Assay) of VX-548 (b) (4) in the Mouse/Study No. VX-548-TX-027	In a local lymph node assay in CBA/CaOlaHsd mice (5 mice/group, 8-week-old mice), SUZ (b) (4) with (b) (4) % drug load was tested up to 10% in dimethylformamide (highest achievable concentration). SUZ increased stimulation index in a dose dependent manner up to 2.6, which was still lower than the threshold for a positive result (stimulation index of 3). SUZ has no sensitization potential in the local lymph node assay.

Table 106. DPN and Stimulation Index in LLNA Study With SUZ

Group	DPN	Stimulation Index
Negative control	108.0	1.0
2.5 % SUZ	91.1	0.8
5% SUZ	195.6	1.8
10% SUZ	279.7	2.6
Positive control (25% alpha-hexylcinnamaldehyde solution)	1735.7	16.1

Source: Study No. VX-548-TX-027, Page 36, Table 10

Abbreviations: DPN, radioactive disintegrations per node; LLNA, local lymph node assay; SUZ, suzetrigine (VX-548)

Source: Study No. VX-548-TX-026, Study No. VX-548-TX-028, and Study No. VX-548-TX-027

Abbreviations: GLP, good laboratory practice; HCE, human cornea-like epithelium; OECD, Organisation for Economic Co-operation and Development; (b) (4) SUZ, suzetrigine (VX-548)

13.1.8.3. Phototoxicity Assessment

The Applicant conducted a chemical photoreactivity assay per International Council for Harmonisation (ICH) guideline *S10 Photosafety Evaluation of Pharmaceuticals* (November 2013). The molecular extinction coefficient of SUZ was 1339 Lmol⁻¹cm⁻¹ at the maximum absorbance observed of 290 nm. However, SUZ was nonphotoreactive (no generation of singlet oxygen/superoxide anion) with UVA/B and visible light. In addition, radioactivity concentrations in melanin-containing tissues (the uveal tract, pigmented skin, and meninges) declined to undetectable levels by 72 hours after peaking between 1 and 4 hours postdose in rats, suggesting no irreversible binding to melanin-containing tissues. Therefore, SUZ has low potential for phototoxicity and no further assessment is necessary.

Table 107. Summary of Phototoxicity Studies

Study/Study No.	Findings
In Vitro Chemical Photoreactivity Potential of VRT-1737548 Study No. VX-548-TX-024	Photoreactivity potential of SUZ (Lot #2, 200 µM) was evaluated by measuring superoxide anion formation via reduction of nitroblue tetrazolium and singlet oxygen formation via p-nitrosodimethyl aniline bleaching after exposure to UVA/B and visible light for 40 min.
Photosafety Assessment of VX-548 Study No. VX-548-TX-025	SUZ was nonphotoreactive based on ROS generation potential after exposure to UVA/B and visible light. The molar extinction coefficient of SUZ (0.01 mg/mL in methanol) was 1339 L mol ⁻¹ cm ⁻¹ at the maximum absorbance observed of 290 nm.

Source: Study No. VX-548-TX-024 and Study No. VX-548-TX-025

Abbreviations: ROS, reactive oxygen species; SUZ, suzetrigine (VX-548; VRT-1737548); UV, ultraviolet

13.1.8.4. Impurities

The proposed specifications for drug substance impurities and drug product specifications are acceptable. In addition, additional impurities of concern were adequately justified for safety.

Safety qualification of five organic impurities (b) (4) in the drug substance, which exceeded the appropriate qualification threshold (0.15%) as recommended in ICH guideline *Q3A(R2) Impurities in New Drug Substances* (October 2006), and two degradation products (b) (4) in drug product, which exceeded the appropriate qualification threshold (0.2% or 3 mg, whichever is lower) as recommended in Q3B, were evaluated in a 13-week toxicity study in monkeys. All the impurities were negative for mutagenic potential based on QSAR assessment, and the levels of these impurities were less than 1 mg (see Table 108). Of note, no additional genotoxicity studies are needed as recommended in ICH harmonised guideline *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (April 2023) when the total daily intake is lower than 1 mg/day of each impurities/degradants in the drug product.

Table 108. Toxicology Qualification Summary of Specified Impurities

Impurity	Specification Limit (%w/w)	Maximum Qualified Level From the 13-week Monkey Study		Actual Daily Exposure at the Specification Limit (mg/day)**
		(mg/day)*	(%w/w)	
Drug Substance				
(b) (4)	NMT	(b) (4)		(b) (4)
	NMT			
	NMT			
	NMT			
	NMT			
Drug Product				
(b) (4)	NMT	(b) (4)		(b) (4)
	NMT			

Source: VX-548-TX-002

* Value is calculated based on the impurity levels in the test article lot E4109-23, considering the NOAEL dose of 150 mg/kg/day. A human equivalent dose (HED) conversion factor of 12 and human body surface area of 1.6 m² were applied.

** The actual daily exposure corresponds to intake of a maximum dose of 150 mg of Suzetrigine containing the impurity at the specification limit.

Abbreviations: HED, human equivalent dose; NMT, not more than; NOAEL, no-observed-adverse-effect level

In addition, two potential impurities (b) (4) were evaluated for mutagenic potential in Ames assays with a total of five *Salmonella* strains (TA98, TA100, TA1535, and TA1537 and the *E. coli* strain WP2 *uvrA*). Both (b) (4) induced point mutations in the genome of *Salmonella typhimurium*. At the proposed specification of byproduct (b) (4) which is then converted to (b) (4) the levels (b) (4) were detectable at (b) (4) ppm, which gives an estimated daily exposure of (b) (4) µg/day at the SUZ maximum daily dose of 150 mg, and it is less than the acceptable daily intake for a chronic use product as recommended in the ICH M7 guidance (April 2023). Therefore, controlling (b) (4) levels (b) (4) is acceptable and ensures acceptable levels (b) (4) in the drug substance. Refer to the CMC review for additional details on impurities (b) (4) of SUZ.

An in silico analysis report (Study Report Number: VX-548-TX-031) (b) (4) of SUZ for mutagenic potential using acceptable QSAR models was submitted. The submitted data were confirmed by FDA computational toxicology experts and overall, no additional safety concerns were identified.

Table 109. Summary of In Vitro Genotoxicity Studies With Potential Impurities From the Drug Substance Synthesis Process

Study/Study No.	Findings
(b) (4) Bacterial Reverse Mutation Assay/ Study No. (b) (4) (b) (4)-TX-001	Dose-dependent increases in the mean number of revertant colonies were observed in TA98 strain in the absence and presence of metabolic activation. Thus, (b) (4) induces point mutations in the genome of <i>Salmonella typhimurium</i> .

Table 110. Mean Revertant Counts of TA98 Strain When Treated With (b) (4)

Treatment	Dose (µg/plate)	Mean Revertants Per Plate	Fold Increase
Absence of Metabolic Activation			
DMSO	-	13.0	-
(b) (4)	100	20.0	1.5
	250	29.0	2.2
	500	35.3	2.7
	1000	71.7	5.5
	2500	29.7	2.3
	5000	-	-
2-Nitrofluorene	2.5	359.7	27.7
Presence of Metabolic Activation			
DMSO	-	14.0	-
(b) (4)	100	15.7	1.1
	250	23.3	1.7
	500	34.0	2.4
	1000	58.7	4.2
	2500	125.0	8.9
	5000	-	-
2-Aminoanthracene	2.5	1162.7	238.8

Source: Study (b) (4)-TX-001, Pages 21 – 22
Abbreviation: DMSO, dimethyl sulfoxide

Continued

Table 109, continued

Study/Study No.	Findings
(b) (4) Bacterial Reverse Mutation Assay/ Study No. (b) (4) (b) (4) -TX-001	The mean number of revertant colonies increased at 250 µg/plate and at ≥1,000 µg/plate in the TA98 stain in the absence of metabolic activation. A marginal increase in the mean number of revertant colonies was observed in the TA98 strain in the presence of metabolic activation. Thus, (b) (4) induces point mutations in the genome of <i>Salmonella typhimurium</i> .

Table 111. Mean Revertant Counts of TA98 Strain When Treated With (b) (4)

Treatment	Dose (µg/plate)	Mean Revertants Per Plate	Fold Increase
Absence of Metabolic Activation			
DMSO	-	13.3	-
(b) (4)	100	29.3	2.2
	250	63.0	4.7
	500	39.0	2.9
	1000	54.0	4.1
	2500	50.3	3.8
	5000	46.7	3.5
2-Nitrofluorene	2.5	271.7	20.4
Presence of Metabolic Activation			
DMSO	-	15.0	-
(b) (4)	100	27.7	1.8
	250	29.3	2.0
	500	32.7	2.2
	1000	32.7	2.2
	2500	28.0	1.9
	5000	27.0	1.8
2-Aminoanthracene	2.5	1031.7	68.8

Source: Study (b) (4) -TX-001, Pages 17 and 19
Abbreviation: DMSO, dimethyl sulfoxide

Source: (b) (4) -TX-001, and (b) (4) -TX-001

13.2. Individual Reviews of Studies Submitted With the New Drug Application

All studies were reviewed under IND 146185.

14. Clinical Pharmacology

14.1. In Vitro Studies

Key ADME properties of SUZ were characterized in the in vitro studies listed in [Table 112](#) and key results are summarized below.

Table 112. List of In Vitro Studies

Study Number	Study Title
Absorption and Disposition	
FDD-36383	Bi-Directional Permeability of VRT-1737548 Across Caco-2 Cell Monolayer
P171	In Vitro Binding of VRT-1737548 and Its Major Metabolites to Plasma Proteins
T095	In Vitro Binding of VRT-1737548 and VRT-1875420 to Human Serum Albumin and Alpha-1-Acid Glycoprotein
T409	In Vitro Binding of VRT-1737548 and VRT-1875420 to Human Serum Albumin and Alpha-1-Acid Glycoprotein
P172	In Vitro Blood: Plasma Partitioning of VRT-1737548 and Its Major Metabolites in Human
Metabolism	
P158	Characterization of VRT-1737548 Metabolites In Vitro and In Vivo Across Species
S164	In vitro Metabolism of VRT-1737548 Metabolites
P211	Recombinant CYP Metabolic Stability of VRT-1737548
P252	Recombinant CYP Metabolic Stability of VRT-1875420
P154	In vitro Stability of VRT-1737548 in Human Recombinant Flavin-Containing Monooxygenase Enzymes
R161	In Vitro Assessment of Fraction of VRT-1737548 Metabolized by Cytochrome P450 (CYP) Enzymes in Recombinant CYPs and Human Liver Microsomes (HLM) With CYP-Selective Inhibitor
R184	In Vitro Assessment of Fraction of VRT-1875420 Metabolized by Cytochrome P450 (CYP) Enzymes in Recombinant CYPs and Human Liver Microsomes (HLM) With CYP-Selective Inhibitor
R276	In Vitro Assessment of Fraction Metabolized (fm) of VX-548 Using Reaction Phenotyping Method With Cryopreserved Human Hepatocytes
U173	Determination of Free Fraction of VRT-1737548 and VRT-1875420 in Human Liver Microsomes
Inhibition/Induction of CYP450	
P164	In Vitro Inhibition of Human Cytochrome P450 Enzymes by VRT-1737548, VRT-1875420, and VRT-1875424
S010	In Vitro Time Dependent Inhibition of Human Cytochrome P450 Enzymes by VRT-1737548 and VRT-1875420
P169	Evaluation of VRT-1737548 and VRT-1875420 as an Inducers of CYP3A4/5, CYP2B6, and CYP1A2 Using Primary Cryopreserved Human Hepatocytes
S006	Evaluation of VRT-1737548 and VRT-1875420 as an Inducers of CYP2C8, CYP2C9, and CYP2C19 Using Primary Cryopreserved Human Hepatocytes
Inhibition of UGT	
P161	Inhibition of UGT1A1-Mediated Bilirubin Glucuronidation in Human Liver Microsomes by VRT-1737548, VRT-1875420, and VRT-1875424

Continued

Table 112, continued

Study Number	Study Title
Drug-Drug Interaction of Transporters	
R243	In Vitro Assessment of VRT-1737548, VRT-1875420, and VRT-1875424 for Passive Permeability and as Substrates of Human Multidrug Resistance 1 Transporter
U016	In Vitro Assessment of VRT-1737548 and VRT-1875420 as Substrates of Human Breast Cancer Resistance Protein
R100	In Vitro Assessment of VRT-1737548 and its Metabolite VRT-1875420 as Substrates of Human OATP1B1 and OATP1B3
P214	In Vitro Assessment of VRT-1737548 as an Inhibitor of P-glycoprotein
R072	In Vitro Assessment of VRT-1875420 as an Inhibitor of P-glycoprotein
R081	In Vitro Assessment of VRT-1737548 and VRT-1875420 as Inhibitors of Breast Cancer Resistance Protein
P220	In Vitro Assessment of VRT-1737548 and Its Metabolites, VRT-1875420 and VRT-1875424, as Inhibitors of OATP1B1
P221	In Vitro Assessment of VRT-1737548 and Its Metabolites, VRT-1875420 and VRT-1875424, as Inhibitors of OATP1B3
S011	In Vitro Assessment of VRT-1737548 and VRT-1875420 as Inhibitors of OAT1 and OAT3
S013	In Vitro Assessment of VRT-1737548 and VRT-1875420 as Inhibitors of OCT1 and OCT2
S014	In Vitro Assessment of VRT-1737548 and VRT-1875420 as Inhibitors of MATE1 and MATE2K
S309	Evaluation of VX-548 Drug-Drug Interaction Potential as CYP/Transporter Inhibitor or as CYP Inducer

Source: Reviewer's compilation of studies

Note: VRT-1737548 or VX-548 is SUZ, VRT-1875420 is M6-SUZ, and VRT-1875424 is M3-SUZ.

Abbreviations: CYP, cytochrome P450; HLM, human liver microsome; fm, fraction metabolized; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; SUZ, suzetrigine; UGT, uridine 5'-diphospho-glucuronosyltransferase

Absorption

The permeability of SUZ was evaluated using Caco-2-cells, and SUZ showed high permeability and low efflux. The apparent permeability coefficient (P_{app}) values were 12.3×10^{-6} cm/sec for $P_{app}(a-b)$ and 11.5×10^{-6} cm/sec for $P_{app}(b-a)$, and the efflux (b-a)/(a-b) ratio was 0.94 (Study FDD-36383).

Distribution

The protein binding of SUZ and its major metabolite M6-SUZ in human plasma are approximately 99% and 96%, respectively (Study P171). Both human serum albumin and α 1-acid glycoprotein contribute to SUZ and M6-SUZ binding in human plasma (Study T095). The plasma protein binding of SUZ and M6-SUZ are concentration-independent, and there was no interaction with regards to protein binding between SUZ and M6-SUZ; the presence of M6-SUZ did not impact the protein binding of SUZ, and vice versa (Study T409).

The blood-to-plasma partitioning ratio was 0.64 for SUZ and 0.62 for M6-SUZ (Study P172), which was consistent with the blood-to-plasma area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) ratio of 0.562 in the ^{14}C -radiolabeled human ADME study (Study 006), indicating SUZ and M6-SUZ did not preferentially distribute into red blood cells.

Metabolism

Metabolic profiling of SUZ was performed in vitro using hepatocytes from human as well as mouse, rat, dog, and monkey. The metabolites of SUZ identified in human hepatocyte incubation were pyridine N-oxide (M6-SUZ) and O-demethylated (M3-SUZ) derivatives, as well as M3 glucuronidase (M4-SUZ). Trace amounts of an O-demethylated, N-oxide derivative (M12-SUZ) was also detected. All metabolites identified in human hepatocytes were also identified in other species (Study P158). The further metabolic profiling of M6-SUZ and M3-SUZ using human hepatocytes identified that M6-SUZ could be further metabolized to M12-SUZ (Study S164).

Based on in vitro studies in recombinant CYP enzymes and human liver microsomes (HLMs) with CYP-selective chemical inhibitors (Reports P211, P154, R161, R276, and R184), the N-oxidation of SUZ to M6-SUZ is primarily mediated by CYP3A, with some contribution from CYP2C19. The O-demethylation of SUZ to M3-SUZ is primarily mediated by CYP3A, with minor contributions from CYP2C9 and CYP2C8. The metabolism of M6-SUZ is also mainly mediated by CYP3A4, with some contribution from CYP2C9. Flavin-containing monooxygenases (FMO1 and FMO3) are unlikely to be involved in SUZ oxidation (Report P154).

Drug-Drug Interactions

Inhibition of CYP450

The CYP inhibition potential of SUZ and its major metabolite M6-SUZ were evaluated in vitro. The IC_{50} values for reversible inhibition of a panel of CYP enzymes in HLMs, uncorrected or corrected for nonspecific binding of SUZ and M6-SUZ, are shown in [Table 113](#) (Studies P164, U173). SUZ and M6-SUZ are not time-dependent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 (Studies P164 and S010). At the efficacious dose, the estimated unbound steady-state plasma C_{max} of 0.0132 μ M for SUZ and 0.124 μ M for M6-SUZ were significantly lower than the IC_{50} values, regardless of correction for nonspecific binding in HLMs, indicating low clinical drug-drug interaction (DDI) potential of SUZ and M6-SUZ via inhibition of CYP enzymes.

As SUZ is an orally administered drug product, with a 100-mg loading dose, the estimated gut concentration of SUZ is 845 μ M (100 mg dosed with 250 mL liquid) and the calculated $R_{1, gut}$ value exceeds the cutoff value of 11, indicating potential inhibition of CYP enzymes by SUZ in the gut. However, further evaluation using a static mechanistic model predicted the AUC ratio of midazolam with and without SUZ was less than 1.25, indicating a low risk of DDI via CYP3A4 inhibition in the gut (Study S309).

Table 113. Inhibition of CYP Isozymes in Human Liver Microsomes by SUZ and M6-SUZ

		IC ₅₀ (μM)						
		CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Without F_u Correction	VX-548	>75	>75	12.8	22.8	5.2	58.0	35.6 ^a , >75 ^b
	M6-548	>75	62.7	31.8	>75	40.8	66.2	27.9 ^a , >75 ^b
With F_u Correction	VX-548	>30.3	>30.3	5.17	9.21	2.10	23.4	14.4 ^a , >30.3 ^b
	M6-548	>53.6	44.8	22.7	>53.6	29.1	47.3	19.9 ^a , >53.6 ^b

^a Testosterone as probe substrate

^b Midazolam as probe substrate

Note: Free IC₅₀, namely, IC₅₀ with F_u correction = F_u × IC₅₀ without F_u correction

Source: Adapted from Report S309 (original data from Study Report P164, F_u value from Study report U173)

Abbreviations: CYP, cytochrome P450; F_u, fraction unbound (same as free fraction); IC₅₀, half maximal inhibitory concentration; SUZ, suzetrigine

Inhibition of UGT

SUZ, M6-SUZ, and M3-SUZ showed low inhibition potential for uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 (Study P161) ([Table 114](#)).

Table 114. Inhibition Potential for UGT1A1

Parameter	Atazanavir (Positive Control)	Saquinavir (Positive Control)	SUZ	M6-SUZ	M3-SUZ
IC ₅₀ (μM)	1.23	3.20	28.2	70.4	28.2

Source: Summarized from Study Report P161

Abbreviations: IC₅₀, half maximal inhibitory concentration; UGT, uridine 5'-diphospho-glucuronosyltransferase; SUZ, suzetrigine

Induction of CYP450

SUZ and M6-SUZ induced CYP3A4 mRNA expression and functional activity in all three hepatocyte lots in a dose-dependent fashion. CYP2B6 mRNA expression and functional activity in all three hepatocyte lots were also induced by SUZ and M6-SUZ, but to a smaller extent than that of CYP3A4. Induction of CYP2C8, CYP2C9, and CYP2C19 mRNA expression was observed in at least one lot of hepatocytes. No induction of CYP1A2 by SUZ and M6-SUZ was observed (Studies P169, S006). Based on the in vitro data, SUZ was predicted to have the potential to be a weak to moderate CYP3A4 inducer at the efficacious dose, and the induction potential of M6-SUZ may increase the CYP3A4 induction risk. Therefore, further study of DDI risk caused by CYP3A4 induction was conducted (refer to Study 010). As the CYP2C enzymes are induced via activation of the pregnane X receptor, the same as CYP3A4, but are less sensitive, the CYP2C induction potential of SUZ is expected to be low ([Table 115](#)).

Table 115. Induction of CYP Isozymes in Human Hepatocyte Incubations by SUZ and M6-SUZ

		VX-548			M6-548		
		Hepatocyte LOT					
		NHI	JNT	8226	NHI	THM	8226
CYP3A4	E _{max} (fold)	15.3	32.9	17.9	8.57	8.98	8.36
	EC ₅₀ (μM)	0.830	1.08	0.558	1.91	1.46	1.15
CYP2B6	E _{max} (fold)	3.70	6.67	4.38	2.89	5.89	3.22
	EC ₅₀ (μM)	1.12	1.49	1.10	3.09	3.57	4.75
		NHI	THM	8226	NHI	THM	8226
CYP2C8	E _{max} (fold)	5.1	3.5	2.4	3.3	RND	3.5
	EC ₅₀ (μM)	1.5	2.2	0.9	1.6	RND	2.0
CYP2C9	E _{max} (fold)	2.3	2.2	<2.0	<2.0	2.8	<2.0
	EC ₅₀ (μM)	0.7	1.7	RND	RND	2.8	RND
CYP2C19	E _{max} (fold)	3.8	-	-	3.6	-	-
	EC ₅₀ (μM)	0.7	-	-	3.6	-	-

Source: Adapted from Report S309 (original data from Study Reports P169, S006)

Abbreviations: CYP, cytochrome P450; EC₅₀, half-maximal effective concentration; E_{max}, maximum effect; SUZ, suzetrigine

Substrate of Transporters

Based on the in vitro studies, SUZ is not a substrate for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3. M6-SUZ is a P-gp substrate, but not a substrate for BCRP, OATP1B1, or OATP1B3 (Studies R243, U016, and R100)

Inhibition of Transporters

The inhibition of major transporters involved in drug disposition by SUZ and M6-SUZ was studied in vitro (Studies P214, R072, R081, P220, P221, S011, S013, S014). The IC₅₀ values are shown in [Table 116](#). The calculated R values ([Table 117](#)), using the estimated unbound steady-state plasma C_{max} values of 0.0132μM for SUZ and 0.124μM for M6-SUZ, were less than the cutoff value of 1.1, except OAT3, which had an R value of 1.1 for M6-SUZ. These results indicated low systemic DDI potential via inhibition of the transporters. However, due to high concentration of SUZ in the gut (estimated gut concentration of 845μM), the analysis identified a potential for P-gp inhibition by SUZ in the gut (R value of 95.4). A dedicated clinical study to further evaluate the impact of SUZ on P-gp substrate was conducted (refer to Study 010).

Table 116. Inhibition of Transporters by SUZ and M6-SUZ

		IC ₅₀ Values (μM)							
		P-gp	BCRP	OATP-1B1	OATP-1B3	OAT1	OAT3	OCT2	MATE 1 K
VX-548		8.86	73.2	1.7	3.0	13.1	2.46	>39.6	16.3
M6-548		>100	>194	5.5	8.5	6.81	1.24	>36.8	>28.3

Source: Adapted from Report S309 (original data from Study Reports P214, R072, R081, P220, P221, S011, S013, and S014)
Abbreviations: BCRP, breast cancer resistance protein; MATE, multidrug and toxin extrusion; OATP, organic anion-transporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; SUZ, suzetrigine

Table 117. Inhibition Risk Assessment of Transporters

	R values									
	P-gp (gut)	P-gp (systemic)	BCRP	OATP- 1B1	OATP- 1B3	OAT1	OAT3	OCT2	MATE 1	MATE 2K
VX-548	*	1.001	1.0002	1.03- 1.05	1.02- 1.03	1.001	1.005	<1.0003	1.001	1.0005
M6-548	-	<1.001	<1.001	1.02	1.015	1.02	1.10	<1.003	<1.004	<1.004

*P-gp: $I_{gut} = 100 \text{ mg}/250 \text{ mL} = 845 \text{ } \mu\text{M}$. $I_{gut}/IC_{50} = 845/8.86 = 95.4 > 10$

For hepatic uptake transporters: $R\text{-value} = 1 + (f_u \times I_{in,max} / IC_{50})$, $I_{in,max} = C_{max} + (K_a \times \text{Dose} \times F_a \times F_g / Q_h)$

For VX-548: MW 473.4, $K_a=0.0373 \text{ min}^{-1}$, $f_u=0.01$, $F_a=F_g=1$, $Q_h = 97\text{L/hr}/70\text{kg}$, Dose=100 mg with $C_{max}=542 \text{ ng/mL}$ (Note: This is C_{max} upon a single loading dose of VX-548 at 100 mg, Report U049), or Dose=50 mg with $C_{max,ss}=623 \text{ ng/mL}$ (Report U049).

For M6-548, MW 489.4, $I_{in,max} = C_{max,ss} = 1520 \text{ ng/mL}$, $f_u=0.04$ (Report U049)

Source: Adapted from Report S309

Abbreviations: BCRP, breast cancer resistance protein; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state; F_a , fraction absorbed; F_g , intestinal availability; f_u , fraction unbound; IC_{50} , half maximal inhibitory concentration; I_{gut} , intestinal luminal concentration estimated as dose/250 mL; $I_{in,max}$, estimated maximum plasma inhibitor concentration at the inlet to the liver; K_a , absorption rate constant; MATE, multidrug and toxin extrusion; MW, molecular weight; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; Q_h , hepatic blood flow rate; VX-548, suzetrigine

14.2. In Vivo Studies

The clinical development program of SUZ consisted of 13 phase 1 clinical studies, two phase 2 dose-ranging studies, two pivotal phase 3 efficacy studies, and one phase 3 safety study. The list of clinical studies with PK assessments is shown in [Table 118](#) below.

Table 118. List of Clinical Studies With PK Assessments

Study Number	Study Description
Studies in Healthy Subjects	
Study 001	First-in-human: Randomized, double-blind, placebo- controlled, single ascending dose study evaluating safety, tolerability, PK, and food effect of SUZ
Study 002	Part A: Randomized, double-blind, placebo-controlled, multiple ascending dose study (dosing qd for 14 days) evaluating safety, PK, PD, and midazolam DDI of SUZ Part B: Randomized, open-label, relative BA and food effect study (single doses)
Study 004	Open-label, DDI study with oral contraceptives (LN and EE), evaluating effect of SUZ on the PK of LN/EE
Study 005	Randomized, double-blind, placebo-controlled, single (Part A) and multiple (Part B) ascending dose study evaluating the safety and PK of SUZ (Part B dosing qd or q12h for 14 days)
Study 006	Open-label, mass balance ADME study of [^{14}C]SUZ
Study 008	Open-label, DDI study with itraconazole, evaluating the effect of itraconazole on the PK of SUZ
Study 009	Randomized, double-blind, placebo- and active-controlled, thorough QT/QTc study
Study 010	Open-label, DDI study evaluating effect of SUZ on the PK of midazolam and digoxin
Study 011	Open-label, confirmatory relative BA and food effect study
Study 013	Open-label, DDI study evaluating impact of omeprazole (Part A) and rifampin (Part B) on the PK of SUZ
Study 016	Randomized, open-label, crossover study evaluating food effects on the PK of SUZ

Study	
Number	Study Description
Studies in Subjects with Acute Pain	
<i>Phase 2</i>	
Study 101	Randomized, double-blind, placebo-controlled, dose-ranging study evaluating efficacy, safety, tolerability, and PK of SUZ in subjects with acute pain after a bunionectomy
Study 102	Randomized double-blind, placebo-controlled, multidose study evaluating efficacy, safety, tolerability, and PK of SUZ in subjects with acute pain after an abdominoplasty
<i>Phase 3</i>	
Study 104	Randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, tolerability, and PK of VX-548 for acute pain after a bunionectomy
Study 105	Randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, tolerability, and PK of VX-548 for acute pain after an abdominoplasty
Studies in Special Populations	
<i>Phase 1</i>	
Study 007	Open-label PK and safety study of SUZ in subjects with mild or moderate hepatic impairment and in matched healthy subjects
Study 014	Open-label PK and safety study of VX-548 in subjects with severe or moderate renal impairment and in matched healthy subjects

Source: Adapted from Summary of Clinical Pharmacology (2.7.2) Table 3.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; BA, bioavailability; DDI, drug-drug interaction; EE, ethinyl estradiol; LN, levonorgestrel; PD, pharmacodynamics; PK, pharmacokinetics; q12h, every 12 hours; qd, once daily; QTc, corrected QT; SUZ, suzetrigine

Note: For the PK values in this review, the C_{max} and AUC values presented were arithmetic mean and coefficient of variation (%CV), while the statistical assessments of the C_{max} and AUC are based on the geometric least-squares means and its 90% confidence interval (CI).

Study 001 and Study 005 Part A (Single Ascending Dose)

Single Ascending Doses

Single ascending doses of SUZ ranging from 7.5 mg to 395 mg (solution formulation for doses less than 50 mg or suspension formulation for doses 50 mg and greater) under fasted conditions were evaluated in two studies, Study 001 (7.5 to 65 mg) and Study 005 Part A (90 to 395 mg). Serial blood samples for the PK analysis were collected up to 216 hours postdose.

After single dose administration:

- The highest mean SUZ exposures were 31.1 $\mu\text{g}\cdot\text{h/mL}$ ($\text{AUC}_{0-\infty}$) and 1.11 $\mu\text{g/mL}$ (C_{max}), after the 395-mg dose ([Table 120](#)). The mean terminal half-life of SUZ ranged from 35.8 to 59.8 hours across the single-dose cohorts.
- The highest mean M6-SUZ exposures achieved were 103 $\mu\text{g}\cdot\text{h/mL}$ ($\text{AUC}_{0-\infty}$) and 1.05 $\mu\text{g/mL}$ (C_{max}), after the 395-mg dose ([Table 120](#)). The mean terminal half-life of M6-SUZ ranged from 44.1 to 76.7 hours across the single-dose cohorts.
- M6-SUZ exposures ($\text{AUC}_{0-\infty}$) were approximately 3-fold higher than SUZ. This metabolite ratio for $\text{AUC}_{0-\infty}$ (M6-SUZ/SUZ) was consistent across all doses studied.

Dose proportionality was assessed statistically using a power model across single oral doses. After single doses of SUZ up to 395 mg, $\text{AUC}_{0-\infty}$ of SUZ and M6-SUZ increased approximately dose-proportionally up to and including 171 mg and increased less than dose-proportionally at higher doses. Exposures were therefore approximately dose-proportional through the highest

single dose (first dose) in the dosing regimen (100 mg). C_{max} of SUZ and M6-SUZ increased less than dose-proportionally across the range of doses tested.

Table 119. Plasma PK Parameters of SUZ and M6-SUZ – SAD (7.5 to 65 mg), Study 001

Dose	Analyte	N	Median [Range]	Mean (%CV)	
			T_{max} (h)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg·h/mL)
7.5 mg	SUZ	8	1.00 [0.50, 1.50]	0.0656 (36.9)	0.991 (21.8)
	M6-SUZ		3.25 [0.50, 8.00]	0.0302 (20.6)	2.86 (22.3)
22.5 mg	SUZ	8	1.03 [1.00, 2.00]	0.187 (19.0)	3.29 (36.3)
	M6-SUZ		2.50 [1.50, 5.00]	0.105 (13.4)	9.92 (32.1)
45 mg	SUZ	8	1.26 [1.00, 2.50]	0.291 (8.10)	6.70 (33.7)
	M6-SUZ		5.04 [4.00, 24.0]	0.215 (20.8)	20.9 (31.7)
65 mg	SUZ	8	2.00 [1.00, 4.00]	0.402 (41.0)	8.60 (51.1)
	M6-SUZ		5.50 [3.00, 24.0]	0.255 (21.2)	25.0 (43.1)

Source: Adapted from Clinical Study Report VX19-548-001, Table 11-1

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; N, sample size; SAD, single ascending dose; T_{max} , time to maximum concentration; SUZ, suzetrigine; PK, pharmacokinetic

Table 120. Plasma PK Parameters of SUZ and M6-SUZ – SAD (90 to 395 mg), Study 005 Part A

Dose	Analyte	N	Median [Range]	Mean (%CV)	
			T_{max} (h)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg·h/mL)
90 mg	SUZ	8	2.75 [1.00, 5.00]	0.468 (24.7)	12.4 (69.8)
	M6-SUZ		5.00 [3.00, 96.0]	0.315 (17.6)	31.1 (48.7) ^{a, b}
115 mg	SUZ	8	2.50 [1.00, 6.00]	0.624 (14.8)	19.7 (27.1)
	M6-SUZ		7.00 [3.00, 48.0]	0.367 (29.6)	50.7 (28.7) ^b
171 mg	SUZ	8	2.50 [1.00, 4.00]	0.812 (26.1)	21.0 (31.1)
	M6-SUZ		24.0 [8.00, 24.1]	0.567 (20.9)	58.2 (28.0) ^c
256 mg	SUZ	8	4.00 [2.00, 6.07]	0.944 (34.9)	24.1 (33.3)
	M6-SUZ		24.0 [4.00, 24.0]	0.798 (27.2)	76.2 (37.6) ^c
395 mg	SUZ	8	3.50 [2.00, 5.00]	1.11 (20.4)	31.1 (22.4)
	M6-SUZ		24.0 [8.00, 48.0]	1.05 (34.2)	103 (22.0)

Source: Adapted from Clinical Study Report VX21-548-005, Table 11.1

^a N = 7

^b $AUC_{0-\infty}$ % Extrapolation was >20% for 2 out of 8 subjects

^c $AUC_{0-\infty}$ % Extrapolation was >20% for 1 out of 8 subjects

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; N, sample size; PK, pharmacokinetic; SAD, single ascending dose; SUZ, suzetrigine; T_{max} , time to maximum concentration

Study 002 Part A and Study 005 Part B (Multiple Ascending Dose)

Multiple Ascending Doses

Multiple ascending doses of SUZ (solution/suspension formulation) ranging from 5 mg to 178 mg once daily (qd) for 14 days under fasted conditions were evaluated in two studies, Study 002 part A (5 to 65 mg qd) and Study 005 part B (90 mg and 178 mg qd). A solution formulation was used for doses less than 50 mg, and a suspension formulation was used for doses 50 mg and larger. One cohort in Study 005 evaluated a loading dose of 115 mg followed by 57.5 mg q12h. Serial blood samples for the PK analysis were collected on Day 1 (rich samples, 0 to 24 hours), Day 10 (rich samples, 0 to 24h), Day 14 (rich samples, 0 to 96 hours) and on Days 3, 4, 5, 6, 7, 8, 9, 11 (Study 002 only), 12, and 13 (predose, for trough levels).

The mean SUZ accumulation ratio was consistent through 65 mg qd (mean range: 1.65 to 1.98). The mean accumulation ratio decreased at higher doses (mean range: 1.34 to 1.41).

After multiple dose administration ([Table 121](#) and [Table 122](#)):

- The highest mean SUZ exposures achieved were 12.6 µg·h/mL (AUC_{0-24h} on Day 14) and 1.11 µg/mL (C_{max} on Day 2), at the 178-mg dose.
- The highest mean M6-SUZ exposures achieved were 39.3 µg·h/mL (AUC_{0-24h} on Day 14) and 2.05 µg/mL (C_{max} on Day 14), at the 178-mg dose.
- Across all dose levels, M6-SUZ exposures were approximately 3-fold higher than SUZ exposures on Day 14, consistent with observations from the single-dose studies. The mean M6-SUZ AUC accumulation ratio was 2.94 to 3.75, with no trends by dose.

Dose proportionality of SUZ and M6-SUZ C_{max} and AUC_{0-24h} on Day 14 after multiple doses were assessed using a power model across multiple oral doses from 5 to 178 mg. The C_{max} for cohort B2 (115 mg/57.5 mg q12h) was excluded as the dosing interval was different for this cohort, making the dose-normalized C_{max} not comparable. After repeated doses of SUZ up to 178 mg qd, both AUC_{0-24h} and C_{max} of SUZ and M6-SUZ on Day 14 increased approximately dose-proportionally through doses up to 65 mg, and slightly less than dose-proportionally at higher doses. The less-than-dose-proportional increase in exposure was likely due to autoinduction at higher doses.

Table 121. Plasma PK Parameters on Day 14 – MAD, Study 002 Part A

Dose	Analyte	N	Median [Range]	Mean (%CV)		AR
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	
5 mg qd; 14 days	SUZ	6	1.00 [1.00, 1.50]	0.0493 (27.6)	0.492 (49.4)	1.83 (33.7)
	M6-SUZ		1.75 [1.47, 3.00]	0.0831 (19.8)	1.54 (30.3)	3.00 (38.6)
15 mg qd; 14 days	SUZ	7	1.50 [1.00, 2.50]	0.163 (42.3)	1.63 (37.7)	1.98 (25.8)
	M6-SUZ		3.02 [1.00, 12.00]	0.249 (30.6)	4.84 (33.8)	3.52 (32.1)
45 mg qd; 14 days	SUZ	8	1.25 [0.50, 2.50]	0.397 (22.7)	4.32 (32.9)	1.65 (15.7)
	M6-SUZ		4.00 [2.00, 5.00]	0.785 (17.1)	14.2 (25.0)	2.94 (23.9)
65 mg qd; 14 days	SUZ	8	1.75 [0.50, 3.00]	0.614 (20.8)	6.97 (24.1)	1.82 (22.7)
	M6-SUZ		3.00 [2.00, 4.00]	1.16 (15.8)	22.3 (19.9)	3.75 (20.2)

Source: Adapted from Clinical Study Report VX20-548-002, Tables 11-1 and 11.2

Abbreviations: AR, accumulation ratio (calculated based on AUC_{0-24h}, Day 14/Day 1); AUC_{0-24h}, area under the plasma concentration-time curve from time 0 to 24h; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; N, sample size; qd, once daily; MAD, multiple ascending dose; PK, pharmacokinetic; SUZ, suzetrigine; T_{max}, time to maximum concentration

Table 122. Plasma PK Parameters on Day 14 – MAD, Study 005 Part B

Dose	Analyte	N	Median [Range]	Mean (%CV)		AR
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	
90 mg qd; 14 days	SUZ	7	2.50 [1.00, 4.00]	0.612 (31.8)	7.09 (27.8)	1.34 (18.2)
	M6-SUZ		5.00 [2.00, 8.00]	1.27 (16.4)	25.1 (20.8)	2.76 (19.5)
115 mg/ 57.5 mg q12h; 14 days	SUZ	8	1.75 [0.50, 3.00]	0.612 (16.2)	9.62 ^b (18.5)	NR ^c
	M6-SUZ		1.50 [1.00, 3.00]	1.46 (12.9)	30.2 ^b (15.4)	NR ^c

Dose	Analyte	N	Median [Range] T _{max} (h)	Mean (%CV)		AR
				C _{max} (µg/mL)	AUC _{0-24h} (µg·h/mL)	
178 mg qd; 14 days	SUZ	8	2.50 [1.00, 3.00]	1.07 ^d (21.4)	12.6 (26.9)	1.41 (27.6)
	M6-SUZ	4.50	[1.50, 6.00]	2.05 (23.5)	39.3 (27.3)	3.63 (47.3)

Source: Adapted from Clinical Study Report VX21-548-005, Tables 11-6

^b AUC_{0-24h} calculated as 2 × AUC_{0-12h} on Day 14

^c AR was not calculated due to lack of AUC_{0-24h} on Day 1. Day 1 AUC_{0-24h} was not able to be calculated due to q12h dosing with a loading dose and an insufficient number of samples between 12 and 24 hours postdose.

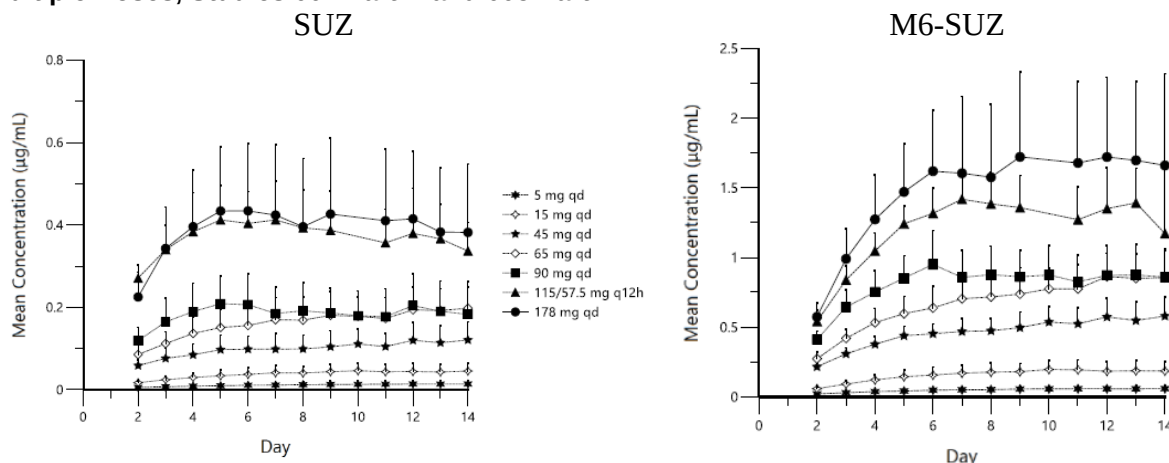
^d Highest observed mean C_{max} across days was 1.11 µg/mL, which occurred on Study Day 2.

Abbreviations: AR, accumulation ratio (calculated based on AUC_{0-24h}, Day 14/Day 1); AUC_{0-24h}, area under the plasma concentration-time curve from time 0 to 24h; C_{max}, maximum observed plasma concentration, CV, coefficient of variation; MAD, multiple ascending dose; N, sample size; NR, not reported; PK, pharmacokinetic; q12h, every 12 hours; qd, once daily; SUZ, suzetrigine; T_{max}, time to maximum concentration

Trough Levels

[Figure 15](#) shows the mean (+standard deviation) plasma trough-concentration-time profiles of SUZ and M6-SUZ across 14 days of SUZ dosing in Studies 002 part A and 005 part B. At doses up to 65 mg qd, SUZ and M6-SUZ trough concentrations increased for approximately 10 days, while at higher doses, the trough concentrations of SUZ and M6-SUZ increased for approximately 5 days. The appearance of an early plateau (instead of further increases in SUZ and M6-SUZ concentrations), may be due to an autoinduction mechanism on SUZ and M6-SUZ clearance. Trough concentrations were higher for the 115 mg/57.5 mg q12h cohort because this cohort was dosed q12h (57.5 mg q12h) while the other cohorts were dosed once daily ([Table 123](#)).

Figure 15. SUZ and M6-SUZ Mean (+SD) Plasma Trough-Concentration-Time Profiles Following Multiple Doses, Studies 002 Part A and 005 Part B



Source: Summary of Clinical Pharmacology Studies, 2.7.2

Abbreviations: SUZ, suzetrigine; SD, standard deviation; qd, once daily; q12h, every 12 hours

Table 123. Mean Plasma Daily Trough Concentration of SUZ (µg/mL) Across 14 Days of SUZ Dosing, Studies 002 Part A and 005 Part B)

Dosing, Studies 002 Part A and 003 Part B

Day	SUZ Trough Concentration (µg/mL)						115 mg/ 57.5 mg q12h
	SUZ qd 14 Days						
	5 mg	15 mg	45 mg	65 mg	90 mg	178 mg	
2	0.0055	0.0169	0.0585	0.085	0.119	0.225	0.271
3	0.0071	0.024	0.076	0.112	0.164	0.343	0.34
4	0.0086	0.0295	0.0846	0.136	0.189	0.395	0.383
5	0.0095	0.0338	0.0971	0.151	0.209	0.433	0.412
6	0.0108	0.0371	0.0982	0.156	0.206	0.434	0.403
7	0.0112	0.041	0.0984	0.170	0.185	0.424	0.412
8	0.0121	0.0405	0.0988	0.169	0.191	0.395	0.393
9	0.0126	0.0437	0.104	0.180	0.186	0.426	0.387
10	0.0130	0.0461	0.111	0.178	0.179	NA	NA
11	0.0132	0.0435	0.105	0.173	NA	0.41	0.356
12	0.0138	0.044	0.12	0.194	0.204	0.415	0.379
13	0.0135	0.0428	0.114	0.192	0.19	0.382	0.366
14	0.0137	0.0453	0.121	0.198	0.183	0.382	0.336

Source: Reviewer analysis from Studies 002 Part A and 005 Part B
Abbreviations: NA, not available; qd, once daily; SUZ, suzetrigine

Study 004

Study 004 was a phase 1, open-label, fixed-sequence, DDI study to evaluate the effects of repeated doses of SUZ on the PK of oral contraceptives, levonorgestrel (LN) and ethinyl estradiol (EE) in healthy female subjects. Each subject received SUZ tablets (70 mg qd) for 16 days (Dosing Period 2, Day 4 through Day 19). Each subject received two single doses of LN (150 µg)/EE (30 µg) (Dosing Period 1, Day 1 and Dosing Period 2, Day 17). Serial blood samples for the PK analysis of LN and EE were collected up to 72 hours postdose. The PK parameters of LN and EE with and without SUZ are shown in [Table 124](#). Concomitant administration of SUZ with an oral contraceptive (containing EE and LN) did not affect the systemic exposure of LN and EE as measured by AUC and C_{max} as the 90% CI of all parameters measured were within 80% to 125% limits. ([Table 124](#)).

Table 124. Effect of SUZ on LN/EE PK Parameters, Study 004

Analyte (Day)	Interacting Drug	N	Median [Range]	Mean (%CV)		GLSM Ratio ^a (90% CI)	
			T _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (ng·h/mL)	C _{max}	AUC _{0-∞}
LN (Day 1)	None	19	1.50 [1.00, 4.00]	2.78 (37.5)	38.8 (48.6)	--	--
LN (Day 17)	SUZ	19	1.50 [1.00, 4.22]	2.56 (36.9)	35.6 (45.7)	0.918 (0.834, 1.01)	0.912 (0.825, 1.01)
EE (Day 1)	None	19	2.00 [1.00, 3.00]	0.0474 (30.8)	0.599 (40.1)	--	--
EE (Day 17)	SUZ	19	2.00 [1.00, 4.00]	0.0443 (43.0)	0.614 (39.0)	0.907 (0.836, 0.984)	1.05 (0.965, 1.13)

Source: Adapted from Clinical Study Report VX21-548-004, Tables 11-1 and 11.2

^a LN/EE administered with SUZ compared to without SUZ

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; EE, ethinyl estradiol; LN, levonorgestrel; GLSM, geometric least-squares mean; N, sample size; T_{max}, time to maximum concentration; PK, pharmacokinetic; SUZ, suzetrigine

Study 006 (Mass Balance Study)

Study 006 was a phase 1, open-label, mass balance study to evaluate the absorption, distribution, metabolism, and excretion of [¹⁴C]SUZ in healthy male subjects (N=8). Each subject received a single oral dose of 80 mg/200 µCi [¹⁴C]SUZ capsules. Serial blood samples for the PK analysis of SUZ, M6-SUZ, M3-SUZ, and M12-SUZ were collected up to 264 hours postdose.

The results show that of the administered dose of [¹⁴C]SUZ (80 mg/200 µCi), 94% of the radioactivity was recovered, out of which 44.0% and 49.9% were recovered in urine and feces, respectively, primarily as metabolites. The details are provided below.

- Of the 49.9% of the dose excreted in feces, unchanged SUZ was 9.1%, unchanged M6-SUZ was <0.9%, and the remainder was other metabolites.
- Of the 44% of the dose excreted in urine, the majority was metabolites. Unchanged SUZ and unchanged M6-SUZ in urine were below the limit of quantitation.
- In plasma, the median time to maximum concentration (T_{max}) of unchanged SUZ was 2 hours. The mean half-life of SUZ was 48.1 hours. Total radioactivity (TRA) in plasma had a median T_{max} of 2.75 hours and mean half-life of 57.8 hours ([Table 125](#)).
- The mean plasma apparent clearance and apparent volume of distribution of unchanged SUZ were 9.08 L/h and 584 L, respectively.
- In plasma, unchanged SUZ $AUC_{0-\infty}$ was 19.9% of TRA $AUC_{0-\infty}$, indicating that the majority of circulating exposure was driven by metabolites. M6-SUZ $AUC_{0-\infty}$ was 63.6% of TRA $AUC_{0-\infty}$. There were no other major circulating metabolites of SUZ.
- Mean TRA $AUC_{0-\infty}$ blood to plasma ratio was 0.562, indicating no preferential distribution of SUZ into blood components.

Based on this study, it is noted that SUZ was primarily eliminated by oxidative metabolism in humans, as the mean unchanged SUZ recovered in urine and feces accounted for less than 10% of the administered radioactive dose.

Table 125. PK Parameters for SUZ, M6-SUZ, and Total Radioactivity

Analyte and Matrix	Median (Range)		Mean (CV%)			
	T_{max} (h)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
SUZ in plasma	2.00 (1.50, 2.48)	0.394 (20.0)	9.35 (24.6)	48.1 (39.2)	9.08 (28.0)	584 (26.5)
M6-SUZ in plasma	8.00 (3.00, 24.0)	0.304 (21.8)	30.2 (30.5)	54.4 (38.1)	2.83 (24.7)	209 (29.3)
TRA in plasma	2.75 (2.02, 3.00)	0.778 (14.9)	46.9 (20.7)	57.8 (23.6)	1.76 (18.7)	143 (18.6)
TRA in blood	2.26 (1.50, 3.00)	0.434 (15.2)	26.3 (21.0)	64.3 (47.5)	3.14 (18.7)	283 (47.5)

Source: Adapted from Clinical Study Report VX21-548-006, Tables 11-1

Note: TRA concentration units are µg Eq/mL.

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; CL/F, apparent clearance; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; N, total sample size; PK, pharmacokinetic; SUZ, suzetrigine; $t_{1/2}$, half-life; TRA, total radioactivity; Vz/F, apparent volume of distribution

Study 008 (DDI - SUZ With Itraconazole)

SUZ and M6-SUZ are CYP3A substrates. Study 008 was a phase 1, open-label, fixed-sequence, crossover, single-cohort, DDI study to evaluate the effect of itraconazole, a strong CYP3A inhibitor, on the PK of SUZ and M6-SUZ in healthy subjects. The study design of Study 008 is shown in [Table 126](#). Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 216 hours postdose.

Table 126. Study Design, Study 008

Dosing Period 1 Days 1 to 10 ^a	Treatment Period (Day 1 to Day 23)				Safety Follow-Up Visit
	Dosing Period 2 Days 11 to 13 ^b	Day 14 ^c	Days 15 to 22 ^b	Day 23	
Single dose of 20 mg SUZ on Day 1	200 mg itraconazole qd	200 mg itraconazole + 20 mg SUZ	200 mg itraconazole qd	Discharge	12 to 15 days after last dose of SUZ

Source: Adapted from Clinical Study Report VX21-548-008, Figure 9-1

^a Subjects received 20 mg SUZ approximately 2 hours after a moderate-fat meal.

^b Subjects received 200 mg itraconazole in the fed state.

^c Subjects received 200 mg itraconazole in the fed state followed by 20 mg SUZ approximately 2 hours later.

Abbreviations: qd, once daily; SUZ, suzetrigine

Coadministration of SUZ with itraconazole increased the $AUC_{0-\infty}$ of SUZ and M6-SUZ by 4.79-fold (90% CI: 4.28, 5.35) and 4.42-fold (90% CI: 3.64, 5.37), respectively. The upper bound of the 90% CI is greater than 5; therefore, SUZ and M6-SUZ can be considered as sensitive substrates of CYP3A. The coadministration of SUZ with itraconazole resulted in an increase of SUZ C_{max} by 1.47-fold and a 31.7% decrease in the C_{max} of M6-SUZ ([Table 127](#)). These results indicate that CYP3A is the main enzyme involved in metabolism for both SUZ and M6-SUZ. Based on the significant increase in SUZ and M6-SUZ exposure, concomitant use of SUZ with strong CYP3A inhibitors is contraindicated.

Table 127. Effect of Itraconazole on SUZ and M6-SUZ PK Parameters, Study 008

Analyte (Day of PK)	Interacting Drug	N	Median [Range]	Mean (%CV)		GLSM Ratio ^a (90% CI)	
			T_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max}	$AUC_{0-\infty}$
SUZ (Day 1)	None	14	2.00 [1.02, 4.00]	0.140 (20.9)	2.59 (27.6)	--	--
SUZ (Day 14)	ITZ	14	2.00 [1.00, 3.00]	0.204 (18.2)	12.9 (42.5)	1.47 (1.32, 1.64)	4.79 (4.28, 5.35)
M6-SUZ (Day 1)	None	14	3.51 [2.00, 48.0]	0.094 (26.0)	7.91 (20.7)	--	--
M6-SUZ (Day 14)	ITZ	14	72.0 [48.0, 216.0]	0.066 (37.6)	32.3 (30.3) ^b	0.68 (0.61, 0.76)	4.42 (3.64, 5.37)

Source: Adapted from Clinical Study Report VX21-548-008, Tables 11-1 and 11.2

^a SUZ administered with itraconazole compared to without itraconazole.

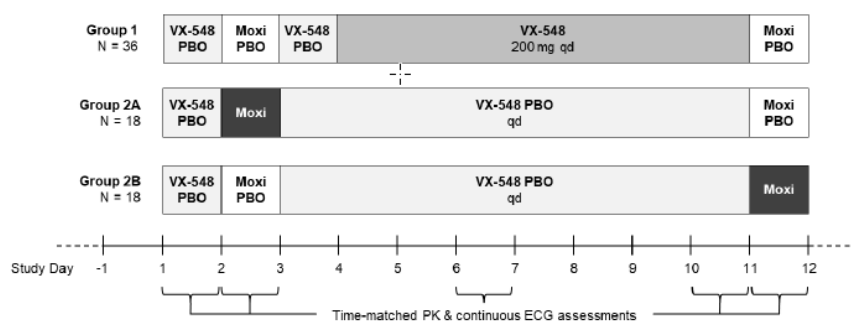
^b $AUC_{0-\infty}$ were able to be calculated for 7 of 14 subjects

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-\infty}$, AUC from the time of dosing extrapolated to infinity; CI, confidence interval; C_{max} , maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; ITZ, Itraconazole; N, total sample size; PK, pharmacokinetic; SUZ, suzetrigine; T_{max} , time to maximum concentration

Study 009 (QT/QTc)

Study 009 was a phase 1, randomized, double-blind, placebo- and active-controlled, thorough QT/QTc (QT corrected for heart rate) study of SUZ in healthy subjects. The subjects were randomized 2:1:1 to one of three groups (Groups 1, 2A, or 2B) as shown in [Figure 16](#). Subjects received a total of 11 days of double-blinded study drug treatment, starting with a single dose of SUZ-matching placebo on Day 1. Group 1 received supratherapeutic doses of SUZ (200 mg qd for 7 days) on Days 4 through 10. Groups 2A and 2B followed a nested crossover design for moxifloxacin and placebo, receiving a single 400 mg dose of moxifloxacin on either Day 2 (Group 2A) or Day 11 (Group 2B). All groups received SUZ-matching placebo on Day 3 to minimize the effects of moxifloxacin carryover in Group 2A. To maintain the blind, groups that did not receive active SUZ on Days 4 through 10 received SUZ-matching placebo, and groups that did not receive active moxifloxacin on Days 2 or 11 received moxifloxacin-matching placebo.

Figure 16. Study Design, Study 009
Study Design for Treatment Period



Source: Adapted from Clinical Study Report VX21-548-009, Figure 2-1

Notes: To maintain the blind, matching placebo was administered, as applicable, so that all subjects received the same number of tablets or capsules. On Day 1, continuous ECGs were extracted to establish baseline values for cardiodynamic analyses; PK blood samples were not collected. On other days indicated by brackets, time-matched PK and continuous ECG assessments were both performed.

Abbreviations: ECG, electrocardiogram; Moxi, moxifloxacin; N, total sample size; PBO, placebo; PK, pharmacokinetic; qd, once daily

The SUZ median T_{max} was 3 to 4 hours, with mean exposures ranging (C_{max} to C_{min} [minimum plasma concentration]) from 1.27 to 0.407 $\mu\text{g/mL}$ on Day 6, and from 1.19 to 0.439 $\mu\text{g/mL}$ on Day 10 after 200-mg qd doses of SUZ on Days 4 through 10. The M6-SUZ median T_{max} was 4 hours, with mean exposures ranging (C_{max} to C_{min}) from 1.71 to 1.15 $\mu\text{g/mL}$ on Day 6, and from 2.19 to 1.58 $\mu\text{g/mL}$ on Day 10 after 200-mg qd doses of SUZ on Days 4 through 10 ([Table 128](#)).

Based on concentration-QTc analysis, an effect on placebo-corrected ΔQTcF (corrected QT interval, Fridericia's calculation) exceeding 10 msec can be excluded within the full observed range of SUZ and M6-SUZ concentrations up to $\sim 2.16 \mu\text{g/mL}$ and $3.0 \mu\text{g/mL}$, respectively. Refer to the QT review for concentration-QTc analysis.

Table 128. Summary PK Parameters of SUZ and M6-SUZ on Days 6 and 10 After 200-mg qd Doses of SUZ on Days 4 Through 10

Analyte (Day of PK)	N	Median (Range)		Mean (%CV)		MR AUC _{0-24h}
		T _{max} (h)	C _{max} (µg/mL)	C _{min} (µg/mL)	AUC _{0-24h} (µg·h/mL)	
SUZ (Day 6) = Day 1	35	3.00 (2.00, 6.00)	1.27 (27.4)	0.407 (36.6)	15.4 (27.2)	NA
SUZ (Day 10) = Day 7	35	4.00 (1.00, 6.00)	1.19 (22.3)	0.439 (39.1)	15.5 (28.8)	NA
M6-SUZ (Day 6) = Day 1	35	4.00 (2.00, 23.8)	1.71 (19.3)	1.15 (23.0)	34.5 (19.9)	2.31 (17.2)
M6-SUZ (Day 10) = Day 7	35	4.00 (2.00, 8.07)	2.19 (20.2)	1.58 (29.2)	43.4 (24.5)	2.85 (12.2)
Moxifloxacin	36	2.00 (1.00, 4.00)	2.25 (31.7)		25.1 (24.8)	

Source: Adapted from Clinical Study Report VX21-548-009, Tables 11-1 and 11-2

Abbreviations: AUC_{0-24h}, area under the plasma concentration-time curve from time 0 to 24h; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV, coefficient of variation; h, hour; MR, metabolite ratio; N: total sample size; NA, not applicable; PK, pharmacokinetic; qd, once daily; SUZ, suzetrigine; T_{max}, time to maximum concentration

Study 010 (DDI - SUZ With Midazolam and Digoxin)

Study 010 was a phase 1, open-label, 2-period, fixed-sequence, crossover, DDI study to evaluate the effects of SUZ at a dose of 50 mg q12h on the PK of midazolam (CYP3A substrate) and digoxin (P-gp substrate) in healthy subjects. The treatment period (Days 1 to 24) included 2 dosing periods ([Table 129](#)). In both dosing periods, doses were administered following a 2-hour fast. Serial blood samples for the PK analysis were collected up to 24 hours postdose for midazolam and 96 hours postdose for digoxin.

Table 129. Study Design, Study 010

Treatment Period (Days 1 Through 24)					Safety Follow-Up Visit
Dosing Period 1	Dosing Period 2				
Days 1 to 5	Days 6-18	Day 19	Days 20-23	Day 24	
Day 1 (morning): Single dose of 2 mg midazolam (fasted) ^a ; 0.5 mg digoxin 1 hour later Days 2 to 5: No dosing	50 mg SUZ q12h (fasted) ^a	Morning: 50 mg SUZ and 2 mg midazolam (fasted) ^a ; 0.5 mg digoxin. 1 hour later Evening: 50 mg SUZ (fasted) ^{a,b}	50 mg SUZ q12h (fasted) ^a	Discharge	12 to 15 days after last dose of any study drug

Source: Adapted from Clinical Study Report VX21-548-010, Figure 2-1

^a After a 2-hour fast. No additional food or water was allowed for at least 2 hours after dosing of midazolam and/or SUZ.

^b Evening dose was given approximately 12 hours after the morning dose.

Abbreviations: SUZ, suzetrigine; q12h, every 12 hours

In this study there was a difference in sample number between number of subjects enrolled and subjects excluded. In the response to an information request sent to the Applicant in this regard, the Applicant stated that:

During study conduct, the number of subjects to be enrolled was increased to approximately 35 subjects due to important protocol deviations relating to PK sampling that led midazolam and/or digoxin PK data from 17 subjects to be unevaluable with PK sampling taken outside of acceptable window. Because midazolam and digoxin were administered 1 hour apart to subjects in the study, most subjects had exclusions for both.

Since noncompartmental analysis (NCA) uses the actual time points, this reviewer conducted additional analysis including all evaluable subjects and sponsor-excluded subjects. The reviewer's analysis showed no difference in the outcome in the fold changes compared to the Applicant's analysis. Therefore, the Applicant's analysis is acceptable ([Table 130](#)).

Coadministration of midazolam (a sensitive CYP3A substrate) with SUZ after 12 daily doses of SUZ at 50 mg q12h results in ~48.2% and 36.7% decrease in midazolam AUC_{0-∞} and C_{max}, respectively, indicating that SUZ is a weak-to-moderate inducer of CYP3A ([Table 130](#)). Based on the results of this evaluation, for sensitive CYP3A substrates, the review team included the following language in the label:

Avoid concomitant use of JOURNAVX with CYP3A substrates where minimal concentration changes may lead to loss of efficacy unless otherwise recommended in the Prescribing Information for CYP3A substrates. When using JOURNAVX with sensitive CYP3A substrates, consider increasing the dose of substrate drugs based on their Prescribing Information if needed or use alternative medications.

Digoxin exposures were comparable when it was administered alone and in the presence of SUZ at 12 daily doses of SUZ at 50 mg q12h, indicating that SUZ is not an inducer or inhibitor of P-gp.

Table 130. PK of Midazolam and Digoxin in the Absence and Presence of SUZ

Analyte (Day of PK)	Interacting Drug	N	Median [Range]	Mean (%CV)		GLSM Ratio ^a (90% CI)	
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
MDZ (Day 1)	None	21	0.52 [0.48, 0.98]	0.0104 (49.2)	0.0263 (44.0)	--	--
MDZ (Day 19)	SUZ	21	0.52 [0.50, 0.93]	0.00641 (39.4)	0.0133 (34.0)	0.633 (0.551, 0.727)	0.518 (0.475, 0.566)
Digoxin (Day 1)	None	25	1.97 [1.00, 2.03]	0.00193 (30.7)	0.0386 (23.5)	--	--
Digoxin (Day 19)	SUZ	26	2.00 [0.983, 2.05]	0.00226 (52.7)	0.0399 (21.3)	1.13 (1.01, 1.26)	1.03 (0.941, 1.12)

Source: Adapted from Clinical Study Report VX21-548-010, Tables 11-1 and 11-3

^a Midazolam or digoxin administered with SUZ compared to without SUZ

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; MDZ, midazolam, N, total sample size; PK, pharmacokinetics; T_{max}, time to maximum concentration

Study 013 (DDI - SUZ With Omeprazole and Rifampin)

Study 013 was a phase 1, two-part, open-label, fixed-sequence DDI study to evaluate the effects of omeprazole (part A) and rifampin (part B) on the PK of SUZ (100 mg) in healthy subjects. All study drugs were administered under fasted conditions. Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 216 hours postdose.

Omeprazole (40 mg qd for 4 days) did not affect the oral absorption or decrease the systemic exposure of SUZ. Relative to SUZ (100 mg) administered alone, coadministration of SUZ and omeprazole resulted in a 28% increase in AUC_{0-∞}, a 4.5% decrease in C_{max}, and no change in T_{max} for SUZ. Mean SUZ and M6-SUZ concentrations with and without omeprazole were similar over the first 6 hours postdose. M6-SUZ PK was not affected by omeprazole and the exposure change was less than 20% ([Table 131](#)).

Table 131. PK of SUZ and M6-SUZ in the Absence and Presence of Omeprazole, Study 013

Analyte	Interacting Drug	N	Median [Range]	Mean (%CV)		GLSM Ratio ^d (90% CI)	
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ	None	13	3.00 [1.50, 3.00]	0.566 (27.7)	13.1 (34.8)	--	--
SUZ	Omeprazole	12 ^a	3.00 [1.50, 8.00]	0.530 (21.6)	16.0 (31.4)	0.96 (0.83, 1.11)	1.28 (1.18, 1.39)
M6-SUZ	None	13	8.00 [3.00, 72.0]	0.322 (31.6)	35.7 ^b (38.0)	--	--
M6-SUZ	Omeprazole	6 ^c	15.0 [3.00, 24.0]	0.390 (11.2)	33.6 (20.7)	1.07 (0.92, 1.24)	117 (1.08, 1.25)

Source: Adapted from Clinical Study Report VX21-548-013, Tables 11-1 and 11-2

^a 1 subject was excluded due to carryover, with predose concentrations greater than 5% of the individual subsequent C_{max}.

^b 1 subject was excluded from the analysis because of >30% extrapolation in AUC_{0-∞}.

^c 7 subjects were excluded due to carryover, defined as subjects with predose concentrations greater than 5% of the individual subsequent C_{max}.

^d Omeprazole administered with SUZ compared to without SUZ

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; N, total sample size; PK, pharmacokinetics; SUZ, suzetrigine; T_{max}, time to maximum concentration

Relative to SUZ (100 mg) administered alone, when administered with rifampin (CYP3A inducer, 600 mg qd), the SUZ AUC_{0-∞} was decreased by 92.7% and C_{max} by 79.5%. The M6-SUZ AUC_{0-∞} decreased by 84.7% (Table 132). Rifampin decreased SUZ and M6-SUZ exposure (AUC_{0-∞}) by more than 80%, indicating that SUZ is a sensitive CYP3A substrate. Based on the observed decrease in exposure of SUZ, avoiding concomitant use of SUZ with strong and moderate CYP3A inducers is recommended. For the impact of moderate and weak CYP3A inducers on SUZ, refer to Section 14.7 Q4.

Table 132. PK of SUZ and M6-SUZ in the Absence and Presence of Rifampin

Analyte (Day of PK)	Interacting Drug	N	Median [Range]	Mean (%CV)		GLSM Ratio ^a (90% CI)	
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ (Day 1)	None	14	3.00 [1.00, 6.02]	0.559 (33.4)	11.4 (50.6)	--	--
SUZ (Day 19)	Rifampin	13 ^b	3.00 [1.50, 6.00]	0.118 (39.4)	0.763 (33.3)	0.205 (0.166, 0.252)	0.0727 (0.0602, 0.0879)
M6-SUZ (Day 1)	None	14	7.01 [3.00, 36.0]	0.344 (21.4)	29.2 ^c (28.8)	--	--
M6-SUZ (Day 19)	Rifampin	13 ^b	3.00 [2.00, 6.00]	0.447 (20.3)	4.40 (19.0)	1.29 (1.14, 1.46)	0.153 (0.136, 0.173)

Source: Adapted from Clinical Study Report VX21-548-013, Tables 11-3 and 11-4

^a SUZ administered with rifampin compared to without rifampin

^b 1 subject was withdrawn in Treatment Period 2

^c 1 subject was excluded because of >30% extrapolation in AUC_{0-∞}.

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; PK, pharmacokinetics; SUZ, suzetrigine; T_{max}, time to maximum concentration

Study 007 (Hepatic Impairment)

Study 007 was a phase 1, open-label, parallel-group study evaluating the PK, safety, and tolerability of SUZ in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (HI), compared to healthy subjects matched by sex, age, and weight. The

PK of SUZ and M6-SUZ was not studied in severe hepatic impairment subjects. In all treatments, subjects were administered SUZ q12h in the fasted state on Days 1 through 14. Subjects with mild HI and matched healthy subjects received 50 mg SUZ. Subjects with moderate HI and matched healthy subjects received 20 mg SUZ. Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 408 hours postdose.

Subjects with mild hepatic impairment had decreased SUZ AUC_{0-12h} (8.6%) and C_{max} (10.5%) and decreased M6-SUZ AUC_{0-12h} (17.3%) and C_{max} (17.3%) compared to matched healthy subjects (Table 133).

Subjects with moderate hepatic impairment had 1.50-fold increased SUZ AUC_{0-12h} and 1.31-fold increased SUZ C_{max}, while M6-SUZ AUC_{0-12h} and C_{max} both increased 1.15-fold compared to matched healthy subjects. SUZ and M6-SUZ had higher accumulation ratios and longer half-lives in subjects with moderate hepatic impairment compared to matched healthy subjects and subjects with mild hepatic impairment (Table 133).

The mean fraction unbound in plasma was consistent across all time points and was similar between subjects with HI and healthy subjects for SUZ (mean range: 0.896% to 1.07%) and M6-SUZ (mean range: 3.64% to 4.16%).

Table 133. PK Parameters for SUZ and M6-SUZ on Day 14 in Hepatic Impairment, Study 007

Group	N	Analyte	Median [Range]	C _{max} (μg/mL)	Mean (%CV)	t _{1/2} (h)	GLSM Ratio ^a (90% CI)	
			T _{max} (h)		AUC _{0-12h} (μg·h/mL)		C _{max}	AUC
Mild HI	10	SUZ	2.00	0.78 (31.5)	6.52 (38.2)	86.1 (39.5)	0.895	0.914
			[1.87, 4.00]				(0.592, 1.35)	(0.566, 1.48)
		M6-SUZ	2.50	1.50 (25.8)	15.8 (29.3)	85.5 (36.9)	0.827	0.827
			[1.87, 4.00]				(0.567, 1.21)	(0.545, 1.26)
Matched HS to mild	8	SUZ	3.00	0.79 (30.1)	6.32 (33.6)	58.9 (32.6)	--	--
			[2.00, 4.00]					
		M6-SUZ	3.00	1.72 (29.3)	18.0 (30.9)	61.7 ^b (24.4)	--	--
			[3.00, 4.00]					
Moderate HI	8	SUZ	2.50	0.41 (24.8)	3.81(30.6)	114 (29.6)	1.31	1.50
			(1.93,3.00)				(1.04, 1.65)	(1.08, 2.07)
		M6-SUZ	2.50	0.62 (22.7)	6.62 (21.8)	117 (34.6)	1.15	1.15
			[1.00, 3.00]				(0.84, 1.59)	(0.83, 1.58)
Matched HS to moderate	8	SUZ	2.00	0.33(36.2)	2.72 (46.9)	64.5 ^c (24.9)	--	--
			[1.00, 3.00]					
		M6-SUZ	3.50	0.58 (43.2)	6.25 (44.3)	64.1 ^c (26.1)	--	--
			[1.00, 6.00]					

Source: Adapted from Clinical Study Report VX21-548-013, Tables 11-3 and 11-4

^a Hepatic Impairment compared to matched HS

^b N = 7; 1 subject had AUC_{0-∞} extrapolation after last dose >20%, therefore t_{1/2} were excluded from summary statistics

^c N = 6; 2 subjects had AUC_{0-∞} extrapolation after last dose >20%, therefore t_{1/2} were excluded from summary statistics

Abbreviations: AUC₀₋₁₂, area under the plasma concentration-time curve from time 0 to 12h; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; HI, hepatic impairment; HS, healthy subjects; N, total sample size; t_{1/2}, apparent half-life; T_{max}, time to maximum concentration; h, hour; SUZ, suzetrigine; PK, pharmacokinetics

Study 014 (Renal Impairment)

Study 014 was a phase 1, open-label study to evaluate the PK and safety of single doses of SUZ in subjects with severe (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min, estimated by the chronic kidney disease epidemiology collaboration equation with adjustment for body surface area) or moderate renal impairment (eGFR 30 to 59 mL/min) and in matched healthy subjects. The severe- and moderate-impairment subjects were matched by sex, age, and body mass index (BMI) to healthy subjects. Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 312 hours postdose. Subjects with moderate and severe renal impairment showed clinically insignificant changes in the PK of SUZ and M6-SUZ. The details are shown below.

Moderate renal impairment versus healthy subjects:

- Subjects with moderate renal impairment had SUZ $AUC_{0-\infty}$ increased by 21% and C_{max} decreased by 19%, and M6-SUZ $AUC_{0-\infty}$ increased by 3% and C_{max} decreased by 24% compared to matched healthy subjects. The mean fraction unbound in plasma was consistent across all time points and was similar between subjects with moderate renal impairment and matched healthy subjects for SUZ (<1%) and M6-SUZ (3.7%) ([Table 134](#)).

Severe renal impairment versus healthy subjects:

- Subjects with severe renal impairment had SUZ $AUC_{0-\infty}$ increased by 17% and C_{max} increased by 12%, and M6-SUZ $AUC_{0-\infty}$ increased by 13% and C_{max} increased by 2% compared to matched healthy subjects. The mean fraction unbound in plasma was consistent across all time points and was similar between subjects with severe renal impairment and matched healthy subjects for SUZ (<1%) and M6-SUZ (~3.4%) ([Table 135](#)).

Table 134. SUZ and M6-SUZ Plasma PK Parameters After Single Oral Doses of 100 mg SUZ in Subjects With Moderate RI and Matched HS

Mean (%CV)	SUZ		M6-SUZ	
	Moderate RI	Matched HS	Moderate RI	Matched HS
N	9	9	9	9
T_{max}^a (h)	3.00 (1.50, 6.00)	3.00 (1.50, 4.00)	36.00 (2.03, 96.0)	4.00 (2.00, 6.08)
C_{max} (µg/mL)	0.618 (35.0)	0.759 (33.3)	0.285 (33.0)	0.368 (24.1)
$AUC_{0-\infty}$ (µg·h/mL)	24.7 (37.6)	20.1 (35.5)	54.7 (37.0) ^b	53.7 (37.8)
f_u	0.00881 (17.5)	0.00998 (20.2)	0.0365 (16.6)	0.0375 (16.8)

Source: Adapted from Clinical Study Report VX22-548-014, Tables 11-1 and 11.2

Note: Plasma protein binding samples were collected at 4 time points over 24 hours postdose. There was no concentration-dependent effect; therefore, the f_u presented is a mean of all 4 time points in all subjects.

^a Median (min, max).

^b N = 7: Two subjects were excluded, AUC % extrapolated >30%.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; CV, coefficient of variation; f_u , fraction unbound; HS, healthy subjects; max, maximum; min, minimum; N, total sample size; PK, pharmacokinetic; RI, renal impairment; SUZ, suzetrigine; T_{max} , time to C_{max}

Table 135. SUZ and M6-SUZ Plasma PK Parameters After Single Oral Doses of 100 mg SUZ in Subjects With Severe RI and Matched HS

Mean (%CV)	SUZ		M6-SUZ	
	Severe RI	Matched HS	Severe RI	Matched HS
N	9	9	9	9
T _{max} ^a (h)	2.00 (0.98, 3.0)	2.00 (1.50, 6.0)	24.00 (3.00, 95.6)	8.00 (1.50, 24.0)
C _{max} (µg/mL)	0.721 (36.6)	0.659 (49.2)	0.319 (32.5)	0.301 (20.4)
AUC _{0-∞} (µg·h/mL)	21.9 (49.4) ^b	18.0 (38.1)	51.9 (43.2) ^b	45.7 (28.7)
f _u	0.00816 (13.2)	0.00974 (12.6)	0.0335 (13.0)	0.0358 (11.0)

Source: Adapted from Clinical Study Report VX22-548-014, Tables 11-5 and 11.6

Note: Plasma protein binding samples were collected at 4 time points over 24 hours postdose. There was no concentration-dependent effect; therefore, the f_u presented is a mean of all 4 time points in all subjects.

^a Median (min, max)

^b N = 8: One subject was excluded, AUC % extrapolated >30%.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; f_u, fraction unbound; HS, healthy subjects; max, maximum; min, minimum; N, total sample size; PK, pharmacokinetic; RI, renal impairment; SUZ, suzetrigine; T_{max}, time to C_{max}

Food Effect Studies

The Applicant conducted two food effect studies, Studies 011 and 016. Study 011 evaluated the effect of a high-fat meal on the PK of SUZ and M6-SUZ. Study 016 evaluated various meal types (low-fat, moderate-fat, and high-fat) and timings of meal administration (60 minutes predose, at 0h, and 60 minutes postdose) on SUZ and M6-SUZ PK.

Study 011 (Relative Bioavailability and 1st Food Effect Study)

Study 011 was a phase 1, open-label, randomized, crossover study to evaluate 1) the relative bioavailability of the to-be-marketed (TBM) SUZ 50-mg tablet compared to phase 2 formulation, SUZ 10-mg tablet, at a dose of 100 mg, in the fasted state; and 2) food effect on SUZ 50-mg tablet at a dose of 100 mg in healthy adult subjects. Serial blood samples for the PK analysis were collected up to 216 hours postdose.

Relative bioavailability: at the 100-mg dose, the SUZ 50-mg tablets (TBM) showed bioequivalence to 10-mg tablets (phase 2 formulation) in terms of AUC_{0-∞} for SUZ, while the C_{max} was ~15% lower with lower 90% CI value marginally outside bioequivalence limits. M6-SUZ showed bioequivalence to both AUC_{0-∞} and C_{max}. The SUZ T_{max} was unchanged between the two formulations (3 hours), while 50-mg tablets showed delayed M6-SUZ T_{max} (10 hours) versus 10-mg tablets (5 hours). Since the dosing regimen of JOURNAVX is a 100-mg loading dose followed by a 50 mg twice daily (b) (4) the minor differences in PK between the TBM formulation and phase 2 formulation are not considered clinically relevant (Table 136). In addition, the phase 3 studies (104 and 105) were conducted with the TBM 50-mg tablet, which achieved statistical significance for the primary efficacy endpoint in comparison to placebo for the treatment of acute pain.

Table 136. Relative Bioavailability Assessment of To-Be-Marketed SUZ 50-mg Tablet Compared to Phase 2 Formulation SUZ 10-mg Tablet at a Dose of 100 mg in the Fasted State

Analyte	SUZ Formulation, Dose (mg)	N	Median [Range]	Mean (%CV)	GLSM Ratio (90% CI) 50-mg Tablet/ 10-mg Tablet		
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ	10-mg tablet, 100 mg	23 ^a	3.00 [1.50, 5.00]	0.614 (29.1)	16.3 (36.6)		
	50-mg tablet, 100 mg	24	3.00 [1.50, 5.03]	0.519 (23.9)	16.5 (37.0)	0.853 (0.785, 0.927)	0.995 (0.943, 1.05)
M6-SUZ	10-mg tablet, 100 mg	16 ^b	5.50 [1.50, 72.0]	0.380 (31.4)	42.5 (41.6)	--	--
	50-mg tablet, 100 mg	16 ^b	10.01 [4.00, 48.0]	0.347 (20.5)	38.9 (35.3)	0.931 (0.807, 1.07)	1.00 (0.929, 1.08)

Source: Adapted from Clinical Study Report VX21-548-011, Tables 11-1 and 11-2

^a One subject excluded from SUZ 10 mg analysis due to carryover

^b Eight subjects excluded from M6-SUZ analyses (SUZ 10 mg and SUZ 50 mg) due to carryover.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-∞}, AUC from the time of dosing extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; SUZ, suzetrigine; T_{max}, time to maximum concentration

Administration of SUZ with a high-fat meal at the time of dose (30 minutes for meal consumption) did not affect the C_{max} and AUC in comparison to fasted conditions for both SUZ and its metabolite; however, it resulted in a longer T_{max} (from 3 hours to 5 hours for SUZ and from 10 hours to 24 hours for M6-SUZ) compared to fasted conditions (Table 137). Although C_{max} and AUC after a high-fat meal were not affected, in an acute-pain setting, systemic exposures at early time points following the first dose are important to ensure rapid onset of pain relief. Hence the impact of food on the PK of SUZ and its metabolite was further analyzed by the reviewer as a part of this review.

Table 137. PK of SUZ and M6-SUZ After Administration of SUZ 100 mg (50 mg Tablet×2) Under Fasted and High-Fat Meal Given 30 Minutes Predose Conditions, Study 011

Analyte	Food Status	N	Median [Range]	Mean (%CV)	GLSM Ratio (90% CI) Fed/ Fasted		
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ	Fasted	24	3.00 [1.50, 5.03]	0.519 (23.9)	16.5 (37.0)	--	--
	Fed	24	5.00 [2.00, 8.00]	0.542 (27.3)	17.8 (31.4)	1.04 (0.94, 1.15)	1.11 (1.04, 1.18)
M6-SUZ	Fasted	16 ^b	10.0 [4.00, 48.0]	0.347 (20.5)	38.9 (35.3)	--	--
	Fed	13 ^a	24.0 [8.00, 48.0]	0.353 (17.4)	38.1 (26.4)	1.02 (0.92, 1.14)	1.08 (0.98, 1.19)

Source: Adapted from Clinical Study Report VX21-548-011, Tables 11-3 and 11-4

^a 11 subjects excluded for SUZ 50 mg Fed due to carryover

^b 8 subjects excluded for SUZ 50 mg Fasted due to carryover

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from the time of dosing extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; SUZ, suzetrigine; T_{max}, time to maximum concentration; PK, pharmacokinetics

Study 016 (2nd Food Effect Study)

Study 016 was a phase 1, randomized, open-label, crossover study evaluating the effect of food on the PK of SUZ in healthy adults. It evaluated various meal types (low-fat, moderate-fat, and

high-fat) and timings of meal administration (90 minutes predose, 30 minutes predose, and 60 minutes postdose) on SUZ and M6-SUZ PK.

The Study was evaluated in the following three parts.

- Part A: a low-fat and a moderate-fat meal at 0h⁴ (30 min predose) versus fasted condition
- Part B: a high-fat meal at 60 minutes predose⁴ (90 min predose, including 30 minutes for meal consumption) and 60 min postdose versus fasted condition
- Part C: a low-fat and moderate-fat meal at 60 minutes predose⁴ (90 min predose, including 30 minutes for meal consumption) versus fasted condition

The definitions of low-fat, moderate-fat, and high-fat breakfast are as follows:

- Low-fat breakfast: ~11 to 14 g of fat and 400 to 500 total calories with ~25% of calories from fat
- Moderate-fat breakfast: ~20 g of fat and 600 total calories with ~30% of calories from fat
- High-fat breakfast: ~55 to 65 g of fat and 800 to 1000 total calories with ~50% of calories

Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 336 hours postdose. The various meal types (low-fat, moderate-fat, and high-fat) and timings of meal administration (60 minutes predose, at 0h, and 60 minutes postdose) did not affect the C_{max} or AUC. However, the median T_{max} was delayed, for SUZ or M6-SUZ ([Table 138](#), [Table 139](#), and [Table 140](#)). Since SUZ is being developed for an acute pain indication, the attainment of sufficient concentrations in the earlier time points is expected for the onset of pain relief. Refer to the reviewer's analysis of food effect based on Studies 011 and 016 below.

Part A

Table 138. PK of SUZ and M6-SUZ After Administration of SUZ 100 mg Under Fasted, Low-Fat, and Moderate-Fat Meal at 0h (30 Minutes Predose – Takes 30 min for Meal Consumption)

Analyte	Food Status	N	Median (Range)	Mean (%CV)	GLSM Ratio (90% CI) Fed/ Fasted		
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ	Fasted	24	3.00 [1.00,5.00]	0.626 (24.4)	18.2 (38.4)		
	Low-fat meal at 0h	24	3.00 [2.00, 6.00]	0.694 (27.1)	18.2 (36.9)	1.10 (1.01, 1.21)	1.01 (0.96, 1.07)
	Moderate-fat meal at 0h	24	5.00 [2.00, 6.00]	0.541 (25.3)	19.2 (34.3)	0.87 (0.79, 0.95)	1.06 (1.01, 1.13)

⁴ Meal consumption took approximately 30 minutes. Meals taken 30 minutes predose are considered “at 0h.” Meals taken 90 minutes predose are considered “60 minutes predose.”

Analyte	Food Status	N	Median (Range)	Mean (%CV)	GLSM Ratio (90% CI) Fed/ Fasted	
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max} AUC
M6-SUZ ^a	Fasted	18	8.00 [4.00, 24.2]	0.433 (27.2)	46.0 (37.7)	
	Low-fat meal at 0h	19 ^b	8.00 [5.00, 48.0]	0.436 (24.1)	49.4 (39.9)	1.02 (0.94, 1.10)
	Moderate-fat meal at 0h	17 ^c	24.0 [6.00, 48.0]	0.410 (29.1)	46.6 (36.4)	0.93 (0.86, 1.00)
						1.03 (0.97, 1.10)

Source: Adapted from Clinical Study Report VX21-548-016, Tables 11-1 and 11-2

^a N= 18 in M6-SUZ Fasted group; 6 subjects excluded from analysis due to carryover.

^b Five subjects excluded from M6-SUZ low-fat meal analysis due to carryover.

^c Seven subjects excluded from M6-SUZ moderate-fat meal analysis due to carryover.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from the time of dosing extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; PK, pharmacokinetics; SUZ, suzetrigine; T_{max}, time to maximum concentration

Part B

Table 139. PK of SUZ and M6-SUZ After Administration of SUZ 100 mg Under Fasted and High-Fat Meal at 60 min Predose (90 Minutes Predose – Takes 30 Minutes for Meal Consumption) and 60 min Postdose

Analyte	Food Status	N	Median [Range]	Mean (%CV)	GLSM Ratio (90% CI) Fed/ Fasted	
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max} AUC
SUZ	Fasted	24	4.00 [1.98, 6.00]	0.514 (32.8)	13.7 (52.0)	
	High-fat meal 60 min predose	24	4.00 [1.00, 8.00]	0.584 (29.4)	14.4 (43.8)	1.15 (1.01, 1.31)
	High-fat meal 60 min postdose	23	2.00 [1.00, 6.00]	0.611 (36.2)	13.6 (40.8)	1.19 (1.04, 1.36)
						1.06 (0.99, 1.13)
M6-SUZ ^a	Fasted	21	6.00 [4.00, 24.00]	0.408 (18.2)	35.7 (30.6)	
	High-fat meal 60 min predose	22 ^b	24.0 [3.00, 48.00]	0.403 (26.8)	38.1 (36.8)	0.99 (0.93, 1.06)
	High-fat meal 60 min postdose	20 ^c	8.03 [2.00, 24.0]	0.390 (23.6)	35.5 (30.5)	0.94 (0.88, 1.01)
						1.01 (0.95, 1.08)

Source: Adapted from Clinical Study Report VX21-548-016, Tables 11-3 and 11-4

Note: Meals were given 90 minutes predose or 60 minutes postdose and completed within 30 minutes.

^a N = 21 in M6-SUZ Fasted group; 3 subjects excluded from M6-SUZ Fasted analysis due to carryover.

^b Two subjects excluded from M6-SUZ predose high-fat meal analysis due to carryover.

^c Three subjects excluded from M6-SUZ postdose high-fat meal analysis due to carryover.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from the time of dosing extrapolated to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; PK, pharmacokinetics; SUZ, suzetrigine; T_{max}, time of maximum concentration

Part C

Table 140. PK of SUZ and M6-SUZ After Administration of SUZ 100 mg Under Fasted and Low-Fat and Moderate-Fat Meals Given at 60 Minutes Predose (90 min Predose – Takes 30 Minutes for Meal Consumption)

Analyte	Food Status	N	Median (Range)	Mean (%CV)	GLSM Ratio (90% CI) Fed/ Fasted		
			T _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	C _{max}	AUC
SUZ	Fasted	24	3.00 (1.00, 6.05)	0.618 (26.1)	16.7 (43.4)		
	Low-fat meal 60 min predose	24	4.00 (2.00, 5.00)	0.636 (22.7)	16.3 (45.9)	1.04 (0.93, 1.16)	0.97 (0.92, 1.03)
	Moderate-fat meal 60 min predose	24	3.00 (2.00, 6.00)	0.669 (27.0)	18.2 (44.9)	1.08 (0.97, 1.21)	1.09 (1.03, 1.15)
M6-SUZ ^a	Fasted	21	5.00 (4.00, 24.0)	0.445 (22.7)	37.9 (30.3)		
	Low-fat meal 60 min predose	19 ^b	6.00 (5.00, 48.0)	0.443 (20.8)	40.4 (29.6)	1.03 (0.97, 1.09)	1.00 (0.94, 1.06)
	Moderate-fat meal 60 min predose	20 ^c	24.0 (3.00, 48.0)	0.410 (16.5)	45.3 (35.8)	0.92 (0.87, 0.97)	1.05 (0.99, 1.12)

Source: Adapted from Clinical Study Report VX21-548-016, Tables 11-5 and 11-6

Note: Both meals were given 90 minutes predose and completed within 30 minutes.

^a N = 16 in M6-SUZ Fasted group; 8 subjects were excluded from M6-SUZ fasted analysis due to carryover.

^b Five subjects excluded from M6-SUZ low-fat meal analysis due to carryover.

^c Four subjects excluded from M6-SUZ moderate-fat meal analysis due to carryover.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from the time of dosing extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GLSM, geometric least-squares mean; h, hour; N, total sample size; PK, pharmacokinetics; SUZ, suzetrigine; T_{max}, time to maximum concentration

Reviewer Analysis of Food Effect

SUZ is for an acute pain indication; hence, the attainment of sufficient initial concentrations after dosing is expected for the onset of pain relief. In the phase 3 studies of SUZ (Studies 104, 105 and 107), the first dose (100 mg) was administered under fasting conditions and subsequent doses were administered without regard to food. The median time to onset of perceptible pain relief in abdominoplasty (Study 105) was 34 minutes, while in bunionectomy (Study 104), time to onset was 60 minutes. (b) (4)

The Applicant conducted two food-effect studies, 011 and 016. Study 011 evaluated the effect of a high-fat meal on the PK of SUZ and M6-SUZ versus fasted state. Study 016 evaluated various meal types (low-fat, moderate-fat, and high-fat) and timings of meal administration (60 minutes predose, at 0h, and 60 minutes postdose⁴) on SUZ and M6-SUZ PK versus fasted state.

The effect of food on the first dose of 100 mg and the subsequent doses of 50 mg from 12 hours onwards was evaluated separately. (b) (4)

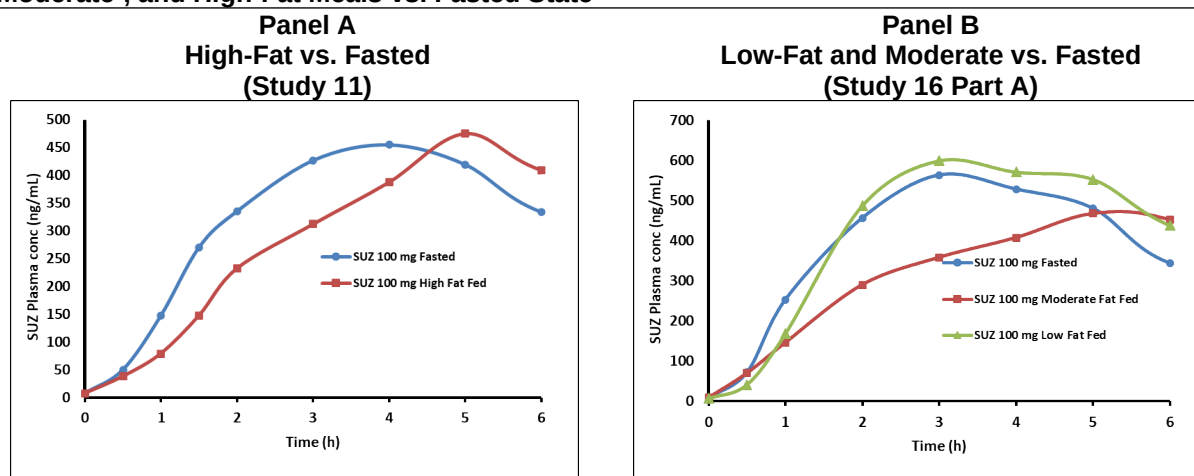
First Dose With Regard to Food

To evaluate the effect of administering SUZ after consuming low-, moderate-, and high-fat meals at 0h (allowing 30 minutes for meal consumption) in comparison to the fasted state, the plasma concentration-time profiles of SUZ in the initial hours (0 to 6 hours) were compared [Figure 17 Panel A (Study 011), and Panel B (Study 016, Part A)].

There was a considerable decrease in SUZ concentrations at the initial time points after dosing with moderate-fat meals and high-fat meals (Figure 17). The individual PK profiles after a high-fat meal versus fasted condition and moderate-fat (standard-fat) meal versus fasted condition are shown in Figure 18 and Figure 19, respectively. This decrease in initial concentrations was well-represented in individual-level PK data, wherein multiple subjects showed very low concentrations for the first 2 to 3 hours postdose in the fed state versus fasted state (Figure 18 and Figure 19). Individual profile data showing low early concentrations in the fed state raised concerns about potential delay in onset of pain relief. The difference in exposure between fed and fasted states for various meals was further evaluated using the partial area under the concentration-time curve (pAUC) ratios of low-, moderate-, and high-fat meals versus fasted conditions. In comparison to the fasted state, taking SUZ with high-fat meals or moderate-fat meals resulted in considerable decreases in SUZ pAUCs for up to 2 to 3 hours postdose, while for the low-fat meals, the exposure was low for up to 1 hour postdose (Figure 20). These results can also be seen when one evaluates differences in T_{max} .

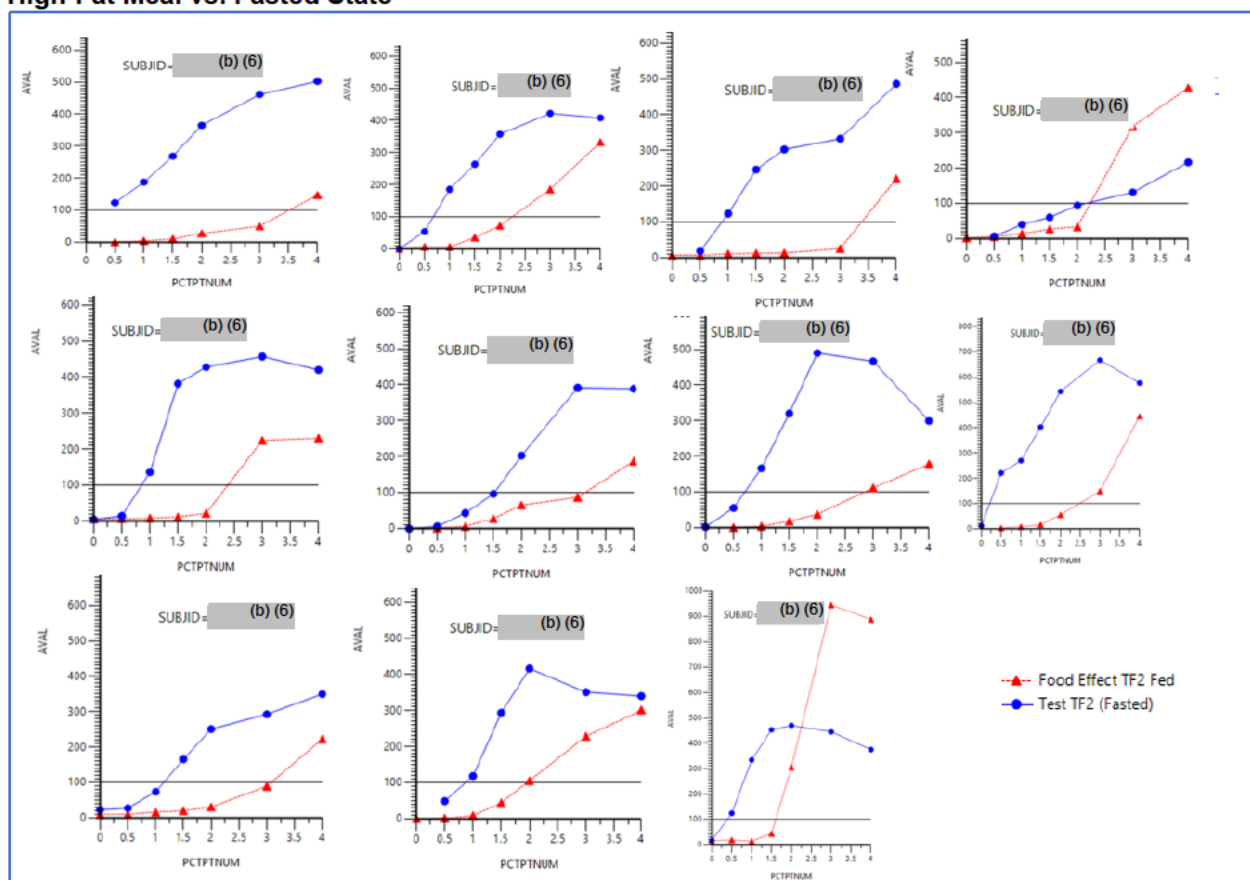
For SUZ 100 mg, both high-fat and moderate-fat meals resulted in delays in T_{max} of similar magnitude (Table 137 and Table 138); however, the Applicant only suggested to avoid high-fat meals for the first dose. The high-fat and moderate-fat meals delayed the median T_{max} of SUZ from 3 hours in the fasted state to 5 hours in the fed state, and M6-SUZ from 8 to 10 hours in the fasted state to 24 hours in the fed state. The C_{max} and AUC of SUZ and M6-SUZ were not affected by any of the meal conditions (Table 137, Table 138, Table 139, and Table 140).

Figure 17. Plasma PK Profiles of SUZ Following a Single Dose of 100 mg SUZ After Low-, Moderate-, and High-Fat Meals vs. Fasted State



Source: Reviewer's analysis
Abbreviations: conc, concentration; PK, pharmacokinetic; SUZ, suzetrigine

Figure 18. Individual Plasma PK Profiles of SUZ Following a Single Dose of 100 mg SUZ After a High-Fat Meal vs. Fasted State



Source: Reviewer's analysis

Abbreviations: AVAL, Concentration (ng/mL); PCTPTNUM, Time (h); PK, pharmacokinetic; SUBJID, subject ID; SUZ, suzetrigine; TF2, tablet formulation 2 (50-mg tablets)

Figure 19. Individual Plasma PK Profiles of SUZ Following a Single Dose of 100 mg SUZ After a Moderate-Fat Meal (Standard Meal) vs. Fasted State

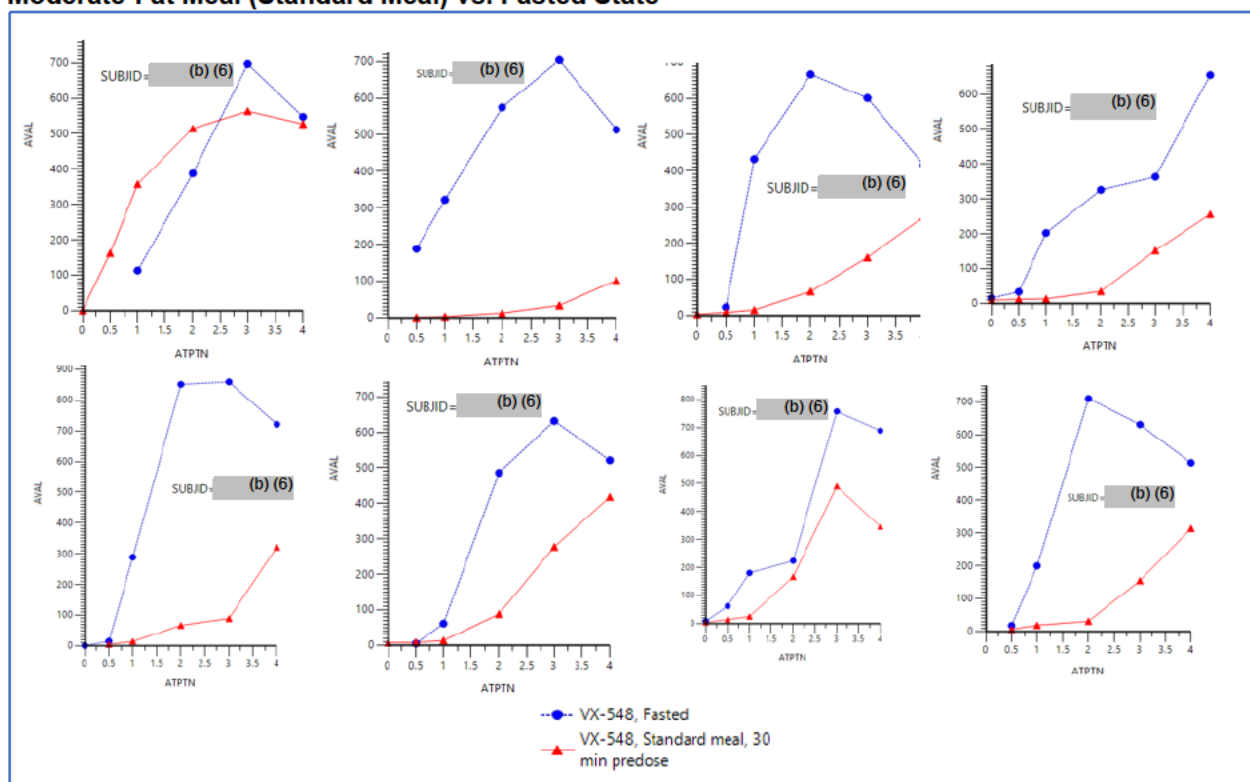
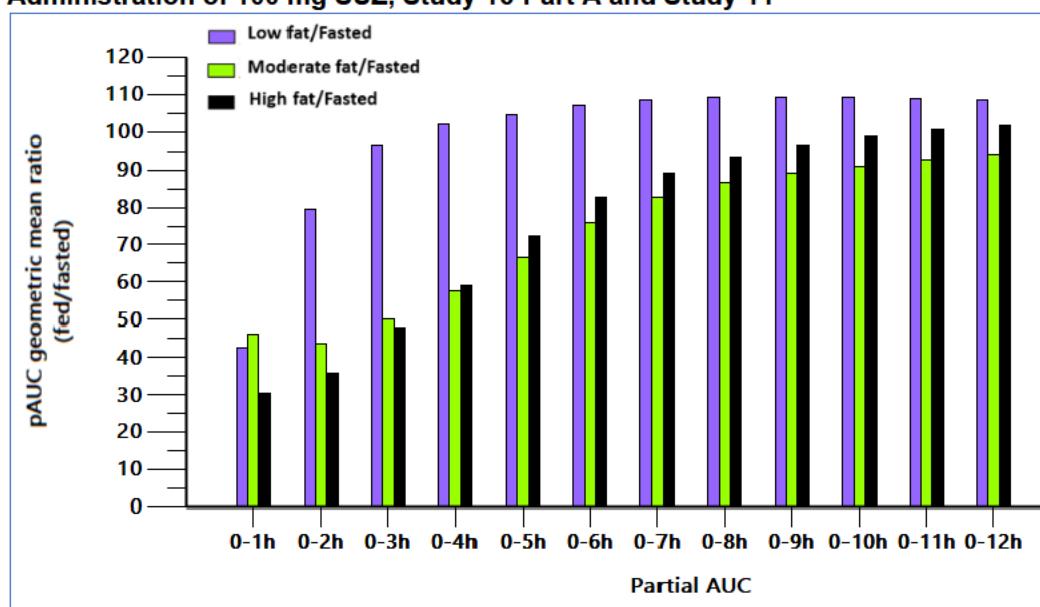


Figure 20. pAUC Ratios Under High-, Moderate-, and Low-Fat Meals at 0h vs. Fasted State After Administration of 100 mg SUZ, Study 16-Part A and Study 11

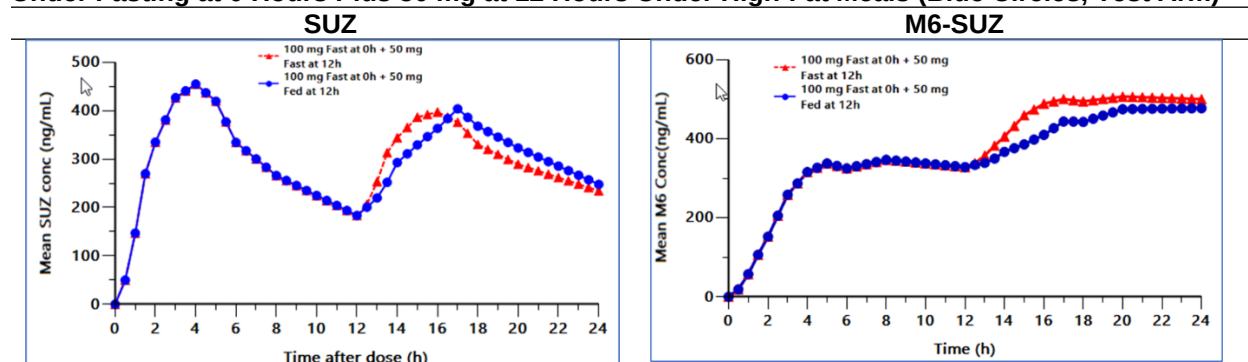


Administration of Subsequent Doses, i.e., 2nd Dose With Regard to Food

The Applicant proposed that after the first dose of 100 mg, the subsequent doses of 50 mg (doses at 12h, 24h, 36h...) can be taken without regard to meals (the same conditions employed in the pivotal phase 3 trials that provided evidence of effectiveness). Since the first dose of SUZ has considerable food effect, the food effect on the second dose, 50 mg at 12h, was evaluated under a high-fat meal condition in comparison to a fasted condition. Since there are no direct data for this evaluation, and SUZ follows linear kinetics at a 50-mg dose, nonparametric superposition simulations were conducted using the Study 011 data. For these simulations, the first dose of 100 mg was administered in a fasting state and the second dose of 50 mg at 12h was administered in two scenarios: 1) under fasting conditions (reference) and 2) under fed conditions (test). The SUZ and M6-SUZ PK profiles of these simulations are shown in [Figure 21](#) (reference [red triangles]: 100-mg first dose at 0 hours under fasting plus 50 mg at 12 hours under fasting; test [blue circles]: 100-mg first dose under fasting at 0 hours plus 50 mg at 12 hours under high-fat meals). From the simulated PK profiles, it can be noted that for the second dose (50 mg at 12 hours), the PK profiles (12 to 24 hours) are not different when taken with or without food. In addition, it can be noted that at 12 hours postdose, there are sufficient trough concentrations from the first dose (100 mg) on top of which the second dose of 50 mg at 12 hours is administered.

Further, the partial areas of the predicted PK profiles were evaluated ([Table 141](#) and [Table 142](#)). There were no differences in predicted SUZ pAUCs, AUC_{0-12h} , or AUC_{0-24h} between test and reference arms. The SUZ partial areas of the second dose, $pAUC_{12-14h}$ and $pAUC_{12-16h}$, were 15% lower under high-fat meals, which is not considered significant. There was no difference in C_{max} values after the second dose between test and reference arms. The median T_{max} after the second dose in the reference arm was 15h, while median T_{max} in the test arm was 17h. Similar to SUZ, there was no difference in partial areas or C_{max} between test and reference arms for M6-SUZ. The median T_{max} of M6-SUZ after the second dose in the reference arm was 22h, while median T_{max} in the test arm was 24h ([Table 141](#) and [Table 142](#)).

Figure 21. Simulated Plasma PK Profiles of SUZ and M6-SUZ Following 100 mg SUZ Under Fasting at 0 Hours Plus 50 mg at 12 Hours Under Fasting (Red Triangles, Reference Arm) and 100 mg SUZ Under Fasting at 0 Hours Plus 50 mg at 12 Hours Under High-Fat Meals (Blue Circles, Test Arm)



Source: Reviewer's analysis

Note: For the first 12 hours the blue circles and red triangles overlap since the loading dose at 0h is 100 mg SUZ under fasting for both treatment arms.

Abbreviations: conc, concentration; h, hours; PK, pharmacokinetic; SUZ, suzetrigine

Table 141. Simulated PK Parameters of SUZ Following 100 mg SUZ Under Fasting at 0 Hours Plus 50 mg at 12 Hours Under Fasting (Test Arm) or 50 mg at 12h Under High-Fat Meals (Reference Arm)

PK Parameter*	Geometric Mean (GM)		Test/Ref GM Ratio (90%CI)
	Test: 100 mg Fasting at 0h+50 mg Fed at 12h	Reference: 100 mg Fasting at 0h +50 mg Fast at 12h	
AUC _{12-24h}	3.62	3.58	101.1 (97.2-105.1)
AUC _{0-24h}	7.01	6.95	100.8 (98.8-102.9)
pAUCs after 2nd dose at 12h			
AUC _{12-14h}	0.42	0.50	85.1 (76.5-94.6)
AUC _{12-16h}	1.05	1.23	84.8 (76.2-94.5)
AUC _{12-18h}	1.81	1.96	92.5 (86.3-99.2)
C _{max} , 2 nd dose	0.427	0.420	101.9 (95.2-109.0)
T _{max} , 2 nd dose	17 (14-20)	15 (13.5-17)	

Source: Reviewer's analysis

* Units: C_{max}, µg/mL; pAUCs and AUC_{0-∞}, µg·h/mL; T_{max}, median (range)

Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean; h, hours; pAUC, partial AUC; PK, pharmacokinetic; ref, reference; ref, reference; SUZ, suzetrigine; T_{max}, time to C_{max}

Table 142. Simulated PK Parameters of M6-SUZ Following 100 mg SUZ Under Fasting at 0 Hours Plus 50 mg at 12 Hours Under Fasting (Test Arm) or 50 mg at 12h Under High-Fat Meals (Reference Arm)

PK Parameter*	Geometric Mean (GM)		Test/Ref GM Ratio (90%CI)
	Test: 100 mg Fasting at 0h +50 mg Fed at 12h	Reference: 100 mg Fasting at 0h +50 mg Fast at 12h	
AUC _{12-24h}	5.10	5.59	91.2 (87.9-94.6)
AUC _{0-24h}	8.38	8.87	94.5 (92.4-96.7)
pAUCs after 2nd dose at 12h			
AUC _{12-14h}	0.68	0.72	94.3 (90.5-98.3)
AUC _{12-16h}	1.44	1.62	88.8 (83.7-94.2)
AUC _{12-18h}	2.30	2.60	88.3 (84.1-92.8)
C _{max} , 2 nd dose	0.487	0.510	95.5 (92.4-96.7)
T _{max} , 2 nd dose	24 (20-24)	22 (16-24)	

Source: Reviewer's analysis

* Units: C_{max}, µg/mL; pAUCs and AUC_{0-∞}, µg·h/mL; T_{max}, median (range)

Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean; h, hours; pAUC, partial AUC; PK, pharmacokinetic; ref, reference; SUZ, suzetrigine; T_{max}, time to C_{max}

Recommendation for Food Effect

Based on these analyses, the review team does not agree with the Applicant's proposal of (b) (4) of SUZ.

The review team's labeling recommendation for the first dose of JOURNAVX is, "Avoid consuming food from 2 hours before until 1 hour after the first dose of JOURNAVX to avoid delay in onset of pain relief. Subsequent doses of JOURNAVX can be taken with or without food." Taking the first dose with food may result in delayed onset of pain relief.

Phase 2 Studies With PK

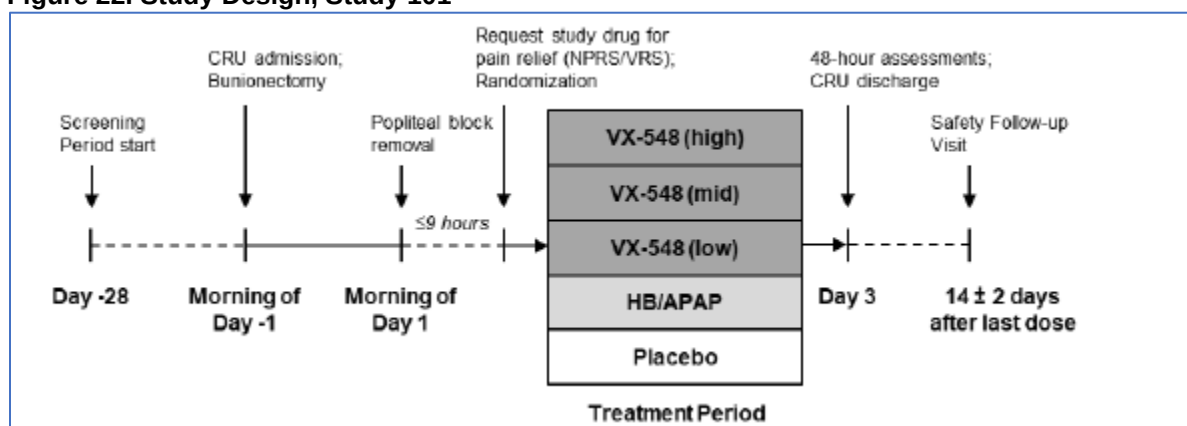
Study 101 (Phase 2 Bunionectomy)

Study 101 was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of SUZ for acute pain after a bunionectomy. Subjects were randomized 2:2:1:2:2 to 5 treatment groups:

- SUZ 100 mg loading dose (LD)/50 mg q12h for 36h (N= 54)
- SUZ 60 mg LD /30 mg q12h for 36h (N= 54)
- SUZ 20 mg LD /10 mg q12h for 36h (N= 27)
- Hydrocodone bitartrate/acetaminophen (HB/APAP) 5/325 q6h for 36h (N= 54)
- Placebo (N= 54)

Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 48 hours postdose.

Figure 22. Study Design, Study 101



Source: Adapted from Clinical Study Report VX21-548-101 Figure 9-1

Abbreviations: CRU, Clinical Research Unit; HB/APAP, hydrocodone bitartrate/acetaminophen; NPRS, numerical pain rating scale; VRS, verbal rating scale; VX-548, suzetrigine

PK parameters ([Table 143](#)):

- $C_{\max}$ and AUC_{0-12h} were approximately dose-proportional.
- Mean SUZ $C_{\max}$ and AUC_{0-12h} values were similar on Day 1 (following the 100-mg loading dose) and Day 2 (following 50-mg maintenance dosing).
- Mean M6-SUZ $C_{\max}$ and AUC_{0-12h} were approximately 2-fold higher on Day 2 compared to Day 1.
- Median $T_{\max}$ for SUZ was approximately 2 hours on Day 1 and Day 2 in all SUZ dose groups.
- Mean SUZ AUC_{0-12h} ranged from 0.650 to 2.95 $\mu\text{g}\cdot\text{h/mL}$ on Day 1 and from 0.885 $\mu\text{g}\cdot\text{h/mL}$ to 3.72 $\mu\text{g}\cdot\text{h/mL}$ on Day 2 across SUZ dose groups.

- Mean M6-SUZ AUC_{0-12h} ranged from 0.845 µg·h/mL to 3.53 µg·h/mL on Day 1 and from 1.94 µg·h/mL to 8.27 µg·h/mL on Day 2 across SUZ dose groups.

Table 143. PK Parameters of SUZ and M6-SUZ After Administration of SUZ in Bunionectomy

Analyte	SUZ Dose	Day	N	Median (Range)	Mean (%CV)	
				T _{max} (h)	C _{max} (µg/mL)	AUC _{0-12h} (µg·h/mL)
SUZ	100 mg/ 50 mg q12h	1	58	2.09 (1.00, 6.03)	0.523 (36.8)	2.95 (25.2)
		2	57	2.00 (0.67, 5.98)	0.503 (25.1)	3.72 (23.5)
	60 mg/ 30 mg q12h	1	58	2.17 (1.00, 5.98)	0.311 (27.8)	1.84 (24.5)
		2	55	1.97 (0.85, 6.00)	0.337 (28.3)	2.54 (28.7)
	20 mg/ 10 mg q12h	1	31	2.20 (0.97, 6.00)	0.119 (45.2)	0.650 (26.7)
		2	29	1.93 (0.87, 7.87)	0.118 (35.9)	0.885 (28.0)
M6-SUZ	100 mg/ 50 mg q12h	1	58	6.02 (1.92, 12.1)	0.385 (29.6)	3.53 (32.0)
		2	57	4.20 (1.70, 12.0)	0.787 (26.7)	8.27 (26.1)
	60 mg/ 30 mg q12h	1	58	5.95 (2.00, 12.2)	0.234 (33.3)	2.23 (33.7)
		2	55	4.28 (1.00, 12.0)	0.483 (27.0)	5.12 (27.5)
	20 mg/ 10 mg q12h	1	31	6.00 (1.08, 12.0)	0.093 (39.0)	0.845 (39.9)
		2	29	5.88 (1.00, 8.05)	0.183 (28.4)	1.94 (29.8)

Source: Adapted from Clinical Study Report VX21-548-101, Tables 11-1

"Day 1" indicates 0 to <24 hours after the first dose. "Day 2" indicates ≥24 to <48 hours after the first dose.

Abbreviations: AUC_{0-12h}, area under the concentration-time curve from the time of dosing 0 to 12h; C_{max}, maximum plasma concentration; CV, coefficient of variation; h, hour; N, total sample size; PK, pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine; T_{max}, time to maximum concentration

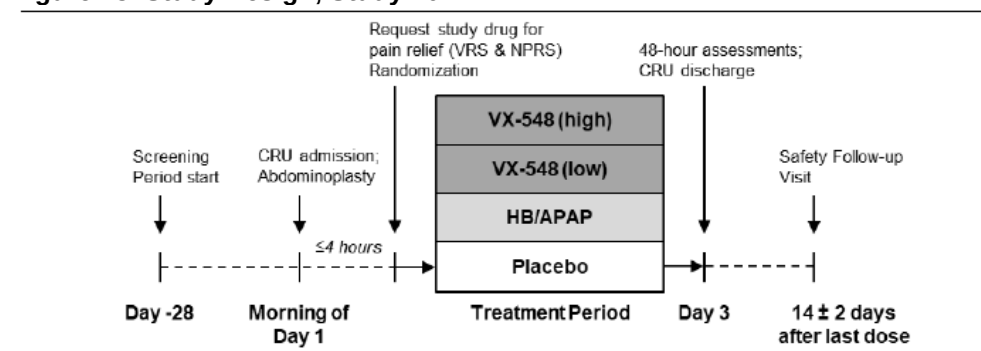
Study 102 (Phase 2 Abdominoplasty)

Study 102 was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of SUZ for acute pain after an abdominoplasty. Subjects were randomized to 1:1:1:1 to 4 treatment groups:

- SUZ 100 mg LD/50 mg q12h for 36h (N=76)
- SUZ 60 mg LD /30 mg q12h for 36h (N=74)
- HB/APAP 5/325 q6h for 36h (N=76)
- Placebo (N=77)

Serial blood samples for the PK analysis of SUZ and M6-SUZ were collected up to 48 hours postdose.

Figure 23. Study Design, Study 102



Source: Adapted from Clinical Study Report VX21-548-102 Figure 9-1

Abbreviations: CRU, Clinical Research Unit; HB/APAP, hydrocodone bitartrate/acetaminophen; NPRS, numerical pain rating scale; VRS, verbal rating scale; VX-548, suzetrigine

PK parameters ([Table 144](#)):

- The median T_{max} for SUZ was approximately 6 hours on Day 1 and approximately 2 hours on Day 2 in both SUZ dose groups.
- Mean SUZ AUC_{0-12h} ranged from 1.13 to 1.64 $\mu\text{g}\cdot\text{h}/\text{mL}$ on Day 1 and from 2.51 to 4.03 $\mu\text{g}\cdot\text{h}/\text{mL}$ on Day 2 across both SUZ dose groups.
- Mean M6-SUZ AUC_{0-12h} ranged from 1.08 to 1.54 $\mu\text{g}\cdot\text{h}/\text{mL}$ on Day 1 and from 4.61 to 7.43 $\mu\text{g}\cdot\text{h}/\text{mL}$ on Day 2 across both SUZ dose groups.

Table 144. PK Parameters of SUZ and M6-SUZ After Administration of SUZ in Abdominoplasty

Analyte	SUZ Dose	Day	N	Median (Range)	Mean (%CV)	
				T_{max} (h)	C_{max} ($\mu\text{g}/\text{mL}$)	AUC_{0-12h} ($\mu\text{g}\cdot\text{h}/\text{mL}$)
SUZ	100 mg/ 50 mg q12h	1	71	6.13 (1.05, 12.1)	0.266 (46.8)	1.64 (43.9)
		2	70	2.11 (0.62, 12.0)	0.481 (26.4)	4.03 (25.2)
	60 mg/ 30 mg q12h	1	68	6.00 (1.92, 12.2)	0.195 (41.4)	1.13 (33.8)
		2	66	2.02 (0.63, 11.7)	0.305 (33.0)	2.51 (26.9)
M6-SUZ	100 mg/ 50 mg q12h	1	71	12.0 (5.95, 12.3)	0.232 (38.0)	1.54 (51.1)
		2	70	7.98 (1.33, 12.1)	0.711 (22.3)	7.43 (22.4)
	60 mg/ 30 mg q12h	1	68	12.0 (1.92, 13.0)	0.160 (34.0)	1.08 (44.7)
		2	66	5.96 (1.53, 12.2)	0.443 (26.2)	4.61 (26.7)

Source: Adapted from Clinical Study Report VX21-548-102, Tables 11-1

"Day 1" indicates 0 to <24 hours after the first dose. "Day 2" indicates ≥ 24 to <48 hours after the first dose.

Abbreviations: AUC_{0-12} , area under the concentration-time curve from the time of dosing 0 to 12h; C_{max} , maximum plasma concentration; CV, coefficient of variation; h, hour; N, total sample size; PK, pharmacokinetic; SUZ, suzetrigine; T_{max} , time to maximum concentration

Comparison of PK Parameters of Suzetrigine and M6-SUZ Between Bunionectomy (Phase 2 Study 101) and Abdominoplasty (Phase 2 Study 102)

The PK parameters in abdominoplasty and bunionectomy on Day 1 and Day 2 after administration of SUZ 100-mg loading dose/50 mg q12h for 36h are shown in [Table 145](#).

On Day 1, exposures of SUZ and M6-SUZ were lower and T_{max} was delayed in the abdominoplasty subjects compared to the bunionectomy subjects. On Day 1, the median SUZ T_{max} was approximately 2 hours in bunionectomy, while it was approximately 6 hours in the abdominoplasty. For doses administered after the first dose, exposures of SUZ and M6-SUZ

were similar between abdominoplasty and bunionectomy. On Day 2, median SUZ T_{max} is similar between bunionectomy and abdominoplasty (approximately 2 hours). The slower absorption observed after the first dose in abdominoplasty is likely due to decreased gastrointestinal motility postoperatively due to abdominal surgery. This difference in exposure between the two surgical procedures did not result in a clinically meaningful difference in efficacy, as the primary efficacy endpoint was met for both procedures.

Table 145. PK Parameters of SUZ and M6-SUZ in Bunionectomy and Abdominoplasty After Administration of SUZ 100 mg/50 mg q12h for 36 Hours

Procedure	Analyte	Day ^a	N	Median (Range)	Mean (%CV)	
				T_{max} (h)	C_{max} (µg/mL)	AUC_{0-12h} (µg·h/mL)
Bunionectomy	SUZ	1	58	2.09 (1.00, 6.03)	0.523 (36.8)	2.95 (25.2) ^b
		2	57	2.00 (0.67, 5.98)	0.503 (25.1)	3.72 (23.5)
	M6-SUZ	1	58	6.02 (1.92, 12.1)	0.385 (29.6)	3.53 (32.0) ^b
		2	57	4.20 (1.70, 12.0)	0.787 (26.7)	8.27 (26.1) ^c
Abdominoplasty	SUZ	1	71	6.13 (1.05, 12.1)	0.266 (46.8)	1.64 (43.9) ^d
		2	70	2.11 (0.62, 12.0)	0.481 (26.4)	4.03 (25.2) ^e
	M6-SUZ	1	71	12.0 (5.95, 12.3)	0.232 (38.0)	1.54 (51.1) ^d
		2	70	7.98 (1.33, 12.1)	0.711 (22.3)	7.43 (22.4) ^f

Source: Compiled by reviewer from Table 11-1 of Study Reports of VX21-548-101 and 102.

^a "Day 1" indicates 0 to <24 hours after the first dose. "Day 2" indicates ≥24 to <48 hours after the first dose.

^b N=57

^c N=56

^d N=70

^e N=69

^f N=67

Abbreviations: AUC_{0-12} , area under the concentration-time curve from the time of dosing 0 to 12h; C_{max} , maximum plasma concentration; h, hour; CV, coefficient of variation; N, total sample size; PK, pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine; T_{max} , time to maximum concentration

14.3. Bioanalytical Method Validation and Performance

For the determination of plasma SUZ and M6-SUZ concentrations, the Applicant used a liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. The Applicant submitted bioanalytical method life cycle information to support SUZ and M6-SUZ quantification in human plasma from various clinical studies (validation reports Q136, Q137, Q222, R116, and T411).

To quantify SUZ and M6-SUZ from plasma samples, a 50-µL aliquot of plasma sample is fortified with 50-µL stable labeled internal standard working solution. The analytes are isolated through liquid/liquid extraction. The solvent is evaporated under nitrogen, then reconstituted with acetonitrile:water (50:50, v/v). The final extract is analyzed via high-performance liquid chromatography with MS/MS detection using positive ion electrospray. The concentration of the samples was determined from a linear regression of the standard curve with $1/x^2$ weighting. This method was developed (b) (4)

A summary of the validation parameters is presented in [Table 146](#).

Table 146. Summary of SUZ and M6-SUZ Plasma Bioanalytical Assay

Validation Parameter	Result
Analyte	VX-548 (SUZ) and M6-SUZ
Biological Matrix	Human plasma (K ₂ EDTA)
Internal Standard	SUZ: VRT-1890537 M6-SUZ: VRT-1890710
Calibration curve	SUZ and M6-SUZ 0.300, 0.600, 3.00, 15.0, 60.0, 210, 270 and 300 ng/mL
LLOQ concentration	SUZ and M6-SUZ: 0.3 ng/mL
ULOQ concentration	SUZ and M6-SUZ: 300 ng/mL
QC concentrations	0.3, 0.9, 10, 150, 240, 1000 and 6000 ng/mL
Calibration curve accuracy %RE from LLOQ to ULOQ	SUZ: Range -1.33 to 2.0% M6-SUZ: Range -2.67 to 2.83%
Calibration curve precision (% CV) from LLOQ to ULOQ	SUZ: Range: 3.82 to 5.74% M6-SUZ: 2.44 to 8.79%
Performance of QCs during accuracy and precision runs	Intrarun (%RE): SUZ -2.00 to 3.00%; M6-SUZ -1.25 to 4.33% Interbatch (%CV): SUZ 4.48 to 9.60%; M6-SUZ: 5.09 to 10.19%
Selectivity & matrix effect	Selectivity evaluated at LLOQ: 6 lots of matrix blanks, 1 Lot of 3% hemolyzed matrix, 1 Lot of lipemic matrix for SUZ No significant interference.
Lipemic effect	One lot of lipemic human plasma tested at QC Low and QC High levels with SUZ and M6-SUZ. The runs met acceptance criteria, %CV<15% and matrix factors were within 0.8 to 1.2
Hemolysis Effect	One lot of 3% hemolyzed human plasma tested matrix effect and matrix factor at QC Low and QC High levels with SUZ and M6-SUZ. The runs met acceptance criteria, %CV<15% and matrix factors were within 0.8 to 1.2
Freeze-thaw stability	5 cycles at -20°C and at -70°C
Long-term storage	459 days -20°C and 756 days at -70°C The longest actual sample storage time prior to analysis is 55 days.
Carryover	No carryover observed for SUZ and M6-SUZ.
Bench-top Stability	25 hours at room temperature
Incurred samples analysis (ISR)	9.4% (120 out of 1280) study samples were analyzed for ISR. 96.61% of SUZ and 98.33% M6-SUZ of ISR samples met the acceptance criteria.

Source: Applicant's Method Validation Report (136)

Abbreviations: CV, coefficient of variation; ISR, incurred sample reanalysis; K₂EDTA, dipotassium ethylenediaminetetraacetic acid; LLOQ, lower limit of quantification; QC, Quality Control; SUZ, suzetrigine; ULOQ, upper limit of quantification; VX-548, suzetrigine

For all studies, the cumulative accuracy (% bias) was less than $\pm 15\%$ and precision (%CV) was less than 15% for quality control samples and calibration curves used in the LC-MS/MS bioanalytical assay of SUZ and M6-SUZ. The results of incurred sample reanalysis were within acceptable limits.

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

Not applicable.

14.5. Pharmacometrics Assessment

This section is a review of Applicant's pharmacometrics analyses including: (1) population pharmacokinetic (popPK) analysis of SUZ and its major metabolite, M6-SUZ; (2) exposure-response (E-R) analyses; (3) dose adjustment for moderate hepatic impairment; and (4) dose adjustment for coadministration of moderate CYP3A inhibitors.

14.5.1. Applicant's Analyses

PopPK Analyses

Objectives

To characterize the PK disposition of SUZ and M6-SUZ.

Data

The popPK analyses were conducted using plasma concentrations of SUZ and M6-SUZ from studies 001, 002, 005, 007, 008, 011, 013, 016, 101, 102, 104, and 105. A brief description of these studies is provided in [Table 147](#).

The PK data consisted of 19,788 evaluable concentrations of SUZ and 19,788 evaluable concentrations of M6-SUZ from 1,435 subjects, including healthy volunteers, subjects with HI, and subjects treated for postsurgical pain.

The baseline demographics for the continuous and categorical variables for these subjects are provided in [Table 148](#).

Table 147. Summary of Studies Included in the PopPK Analysis

Protocol/Title	Subject Population	Treated/Planned (n)	Dosing Description
VX19-548-001 Phase 1 FIH, SAD, and PK Study, US	Healthy adult subjects (18-55 yrs)	40 subjects (32 SUZ and 8 placebo)	7.5, 22.5, 45 mg (fasted or fed) solution and 65 mg suspension
VX20-548-002 Phase 1 MAD, PK, PD, DDI, relative BA, and food effect study, US	Healthy adult subjects (18-55 yrs)	Part A: 36 subjects (29 SUZ and 7 placebo) Part B: 24 subjects	Part A: 5,15, or 65 mg qd 45 mg qd w/or midazolam 5 mg (fasted) Part B: 40-mg tablet or capsule (single doses, fasted then fed)
VX21-548-005 Phase 1, Safety and PK, US	Healthy adult subjects (18-55 yrs)	Part A: 50 subjects (40 SUZ and 10 placebo) Part B: 30 subjects (24 SUZ and 6 placebo)	90,115,171,256,295 mg (fasted, SAD) 90,115/57.5(q12h),178 mg (q24h) (fasted, MAD)
VX21-548-007 Phase 1, Hepatic impairment (PK and safety), US	Healthy/mild/moderate HI adult subjects (18-75 yrs)	Mild HI: 9/ Matched healthy: 9 Moderate HI: 9/ Matched healthy: 9	50/20 mg q12h fasted

Protocol/Title	Subject Population	Treated/Planned (n)	Dosing Description
VX21-548-008 Phase 1, open-label, fixed-sequence, crossover, DDI, US	Healthy adult subjects (18-55 yrs)	14 subjects	Itraconazole 200 mg qd for 12 days; and/or SUZ 20 mg (single doses, (1 before itraconazole dosing and 1 coadministered with itraconazole))
VX21-548-011 Phase 1, relative BA and food effect, US	Healthy adult subjects (18-55 yrs)	24 subjects	Single doses on 3 dosing occasions (12-day washout period) • SUZ 10-mg tablet (reference formulation) • SUZ 50-mg tablet (test formulation) • SUZ 100 mg (single doses)
VX21-548-013 Phase 1, Open-label, fixed-sequence, DDI, Australia	Healthy adult subjects (18-55 yrs)	Part A:15 subjects Part B:16 subjects	Part A: omeprazole 40 mg qd for 4 days and/or 100 mg SUZ Part B: rifampin 600 mg qd for 18 days and/or 100 mg SUZ
VX22-548-016 Phase 1, Randomized, open-label, 3-period crossover study, US	Healthy adult subjects (18-65 yrs)	Part A: 24 subjects Part B: 25 subjects Part C: 24 subjects	Single doses on 3 dosing occasions (SUZ 50 mg or 100 mg single doses with a 14-day washout period under fasted or fed conditions)
VX22-548-101 Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study, US	Male and female subjects, with moderate or severe pain after a bunionectomy (18-75 yrs)	274 subjects (155 SUZ, 60 HB/APAP, and 59 placebo)	SUZ 100, 60, or 20 mg loading dose followed by 50, 30, or 10 mg q12h, respectively; or HB/APAP 5 mg/325 mg q6h; or matched placebo for 48 hours
VX22-548-102 Phase 2, randomized, double-blind, placebo-controlled, multidose, efficacy and safety study, US	Male and female subjects, with moderate or severe pain after an abdominoplasty (18-75 yrs)	303 subjects (150 SUZ, 76 HB/APAP, and 77 placebo)	• SUZ 10-mg tablet • HB/APAP 5-mg/325-mg capsule SUZ 100 or 60 mg loading dose followed by 50 or 30 mg q12h, respectively; or HB/APAP 5 mg/325 mg q6h; or matched placebo
VX22-548-104 Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study, US	Male and female Subjects, with moderate or severe pain after a bunionectomy (18-80 yrs)	1073 subjects (426 SUZ, 431 HB/APAP, and 216 placebo)	• SUZ 50-mg tablet • HB/APAP 5-mg/325-mg capsule • SUZ 100 mg loading dose followed by 50 mg q12h; or HB/APAP 5 mg/325 mg q6h; or matched placebo for 48 hours
VX22-548-105 Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study, US	Male and female subjects, with moderate or severe pain after an abdominoplasty (18-80 yrs)	1118 subjects (447 SUZ, 448 HB/APAP, and 223 placebo)	• SUZ 50-mg tablet • HB/APAP 5-mg/325-mg capsule SUZ 100 mg loading dose followed by 50 mg q12h; or HB/APAP 5 mg/325 mg q6h; or matched placebo for 48 hours

Source: Adapted from the Applicant's 5.2 Tabular Listing of All Clinical Studies.

Abbreviations: BA, bioavailability; DDI, drug-drug interaction; FIH, first-in-human; HB/APAP, hydrocodone bitartrate/acetaminophen; MAD, multiple ascending dose; n, number of patients; PD, pharmacodynamic; PK, pharmacokinetic; popPK, population pharmacokinetic; q12h, once every 12h; q24h, once every 24h; qd, once daily; SAD, single ascending dose; SUZ, suzetrigine; US, United States

Table 148. Summary Statistics of the Final PopPK Analysis Datasets

Baseline Characteristics	Summary
Age (years)	42 (18,75)
Weight (kg)	76.2 (44.0,128.0)
BMI (kg/m ²)	27.8 (18.1,39.7)
Race	
White	1004 (70.0%)
Black	346 (24.1%)
Asian	29 (2.0%)
Other	56 (3.9%)
Sex	
Female	335 (23.3%)
Male	1100 (76.7%)
eGFR (mL/min/1.73 m ²)	106.0 (34.5,167.6)
POP	
Abdominoplasty	111 (22.9%)
Bunionectomy	3 (0.6%)
Healthy	84 (17.3%)

Source: Adapted from the Applicant's popPK report U049, page 33, Table 7.3.

For continuous variables, median (minimum, maximum) values are provided.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; popPK, population pharmacokinetic; POP, population

Method

Nonlinear mixed effects modeling was used to characterize the time course of SUZ and M6-SUZ concentrations using NONMEM[®] 7.5. All data manipulations, summarizations, and graphical outputs were performed using R[®] (version 4.1.1 or higher).

The base population PK model was developed from prior modeling results using a two-compartment model for SUZ and a three-compartment model for M6-SUZ. The prior model was parameterized for SUZ and M6-SUZ, including clearance (CLP, CLM), volumes of distribution (V2P, V2M, V3P, V3M, V4M), and intercompartmental clearances (Q3P, Q3M, Q4M). Absorption was modeled using both zero- and first-order processes, with a lag time (ALAG) from the depot compartment and relative bioavailability (F1).

In abdominoplasty subjects, reduced F1 and slower absorption were observed following the first dose; therefore, a separate absorption model was estimated for these subjects. This model included an estimated time (MTIME) at which the reduced absorption parameters—early absorption rate (KAD), early absorption duration (D1D), and reduced bioavailability (F1D)—transitioned to the standard absorption parameters (KA, D1, F1) used for all other subjects. Dose-dependent absorption was modeled by including a dose-level covariate on KA, D1, and F1.

The base model was chosen after evaluating various compartmental structures with different parameterizations for absorption (including first- and zero-order, dose-dependent absorption, and bioavailability) and autoinduction (using linear, maximum effect [$E_{\max}$], and sigmoidal $E_{\max}$ models).

Interindividual variability was modeled as multiplicative exponential random effects, and residual variability was assessed using a combined error model with both additive and proportional error, including a logarithmic transformation of concentrations due to the large range of SUZ/M6-SUZ concentrations.

Covariates were assessed for inclusion in the final model using stepwise covariate modeling, with multiplicative effects on population parameters. Body weight was used to allometrically scale PK parameters based on graphical assessment of individual PK parameters and body size (weight and BMI) before stepwise covariate modeling analysis. A stepwise covariate selection (forward p-value of 0.05 or Δ OFV of 3.84, backward p-value of 0.001 or Δ OFV of 10.83) was conducted to assess statistical significance, and covariates were selected based on biological plausibility, diagnostic plots, and statistical tests. The effects of age, baseline BMI, baseline eGFR, sex, and race on CLP, and sex and race on V2P, V2M, V3P, and V3M were tested. After covariate inclusion, model refinement was performed based on goodness-of-fit diagnostics, standard errors of parameter estimates, and clinical relevance of the covariate effects.

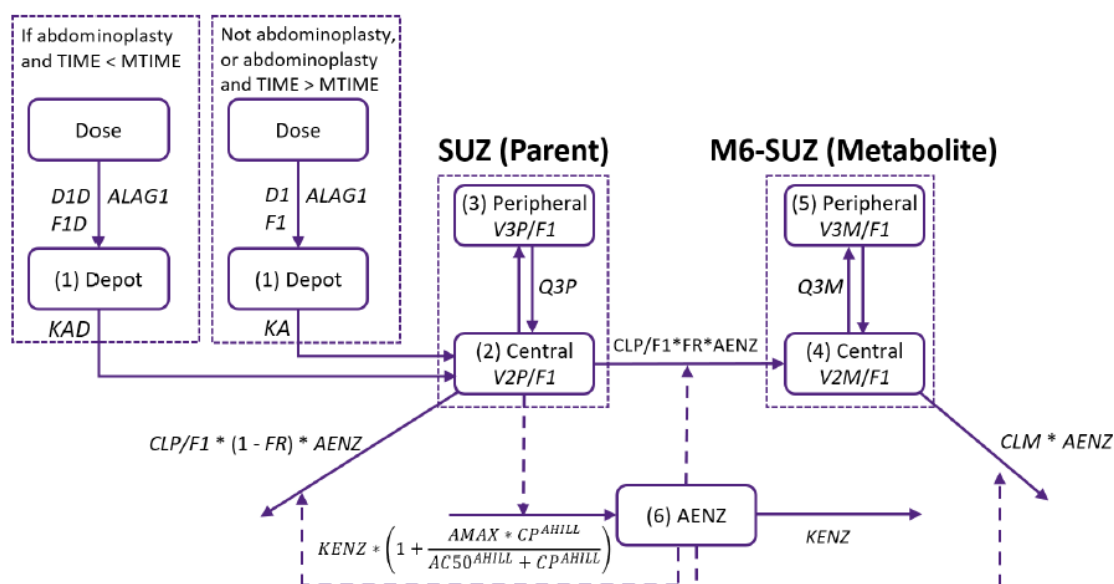
Results

The population PK of SUZ and M6-SUZ were best described in a joint model with SUZ and M6-SUZ concentrations modeled simultaneously ([Figure 24](#)). SUZ disposition included zero-order depot entry, lag time, first-order absorption, distribution, and nonlinear clearance due to autoinduction. M6-SUZ followed first-order formation from SUZ, distribution, and clearance with autoinduction. A second M6-SUZ peripheral compartment was excluded for simplicity. SUZ metabolism to M6-SUZ was fixed at 80%, based on nonclinical data.

Covariates in the model included the effects of body weight on the distribution volumes of SUZ and M6-SUZ and effects of BMI and sex on SUZ clearance.

The population PK parameter estimates from the final PK models are provided in [Table 149](#). The PK models adequately characterize the observed data, as shown in [Figure 25](#), [Figure 26](#), [Figure 27](#), and [Figure 28](#).

Figure 24. Schematics of the Final Population PK Model of SUZ/M6-SUZ



Source: The Applicant's popPK report U049, Page 42, Figure 7.7.

Abbreviations: AC50, autoinduction potency; AENZ, autoinduction effect; AHILL, autoinduction sigmoidal hill coefficient; ALAG1, absorption lag time; AMAX, maximum autoinduction; CLM, M6-SUZ clearance; CLP/F1, apparent clearance for SUZ; CP, plasma concentration of the parent drug in the central compartment; D1, zero-order absorption duration; D1D, D1 for early absorption after first dose in abdominoplasty subjects; F1, relative bioavailability; F1D, relative bioavailability, first absorption period in abdominoplasty subjects; FR, fraction of parent converted to metabolite; KA, absorption rate; KAD, absorption rate of first absorption period dose in abdominoplasty subjects; KENZ, induced enzyme formation and degradation rate; MTIME, estimated model time; PK, pharmacokinetic; popPK, population pharmacokinetic; SUZ, suzetrigine; Q3M, intercompartmental transport for M6-SUZ; Q3P, intercompartmental transport for SUZ; V2M/F1, apparent volume of central compartment for M6-SUZ; V2P/F1, apparent volume of central compartment for SUZ; V3M/F1, apparent volume of peripheral compartment for M6-SUZ; V3P/F1, apparent volume of peripheral compartment for SUZ; SUZ, suzetrigine

Table 149. Parameter Estimates of the Applicant's Final PopPK Model (Model 2822)

		Estimate (RSE%) [CV% or Corr%]	95% Confidence Interval
Structural model parameters			
θ_1^*	Parent clearance, CLP (L/h)	5.56 (0.8%)	[5.4,5.7]
θ_2^*	Parent volume of central compartment, V2P (L)	103 (0.3%)	[100,110]
θ_3^*	Parent volume of peripheral compartment, V3P (L)	204 (0.2%)	[200,210]
θ_4^*	Parent intercompartmental transport, Q3P (L/h)	19 (0.5%)	[18,20]
θ_6^*	Absorption rate, KA (1/h)	2.02 (15.5%)	[1.6,2.5]
θ_8^*	Zero-order absorption duration (suspension), D1 (h)	0.0561 (6.7%)	[0.038,0.082]
θ_{11}^*	Lag time, ALAG1 (h)	0.182 (1.7%)	[0.17,0.19]
θ_{14}^*	Metabolite clearance relative to CLP, CLM (L/h)	0.273 (0.3%)	[0.27,0.28]
θ_{15}^*	Metabolite volume of central compartment, V2M (L)	1.7 (13.5%)	[1.5,2]
θ_{16}^*	Metabolite volume of peripheral compartment, V3M (L)	29.5 (0.4%)	[29,30]
θ_{17}^*	Metabolite intercompartmental clearance, Q3M (L/h)	8.75 (0.6%)	[8.5,9]
θ_{20}^*	Enzymatic synthesis and consumption, KENZ (1/h)	0.00939 (1.9%)	[0.0079,0.011]
θ_{21}^*	Maximum autoinduction, AMAX	0.811 (48.6%)	[0.66,0.99]
θ_{22}^*	Autoinduction potency, AC50 (ng/mL)	432 (0.7%)	[400,470]
θ_{23}	Autoinduction sigmoidal hill coefficient, AHILL	10 (fixed)	-
θ_{26}^*	Zero-order absorption duration (tablet), D1TAB (h)	1.1 (63.8%)	[0.98,1.2]
Parameters related to abdominoplasty			
θ_5^*	Duration of first absorption period (ABD), MTIME (h)	8.12 (0.1%)	[8.1,8.1]
θ_7^*	Absorption rate of first absorption period (ABD), KAD (1/h)	0.511 (14.3%)	[0.42,0.62]
θ_9^*	Zero-order absorption duration, first absorption period (ABD), D1D (h)	2.83 (7.4%)	[2.4,3.3]
θ_{10}	Relative F1, first absorption period (ABD), F1D	0.778 (0.9%)	[0.76,0.79]
Covariate effects			
θ_{24}	F1 for tablet relative to suspension	0.88 (fixed)	-
θ_{25}^*	Tablet effect on KA	2.24 (9.6%)	[1.9,2.6]
θ_{27}^*	Dose at half-maximal effect on F1 (mg)	162 (0.7%)	[150,170]
θ_{28}^*	Maximal effect of dose on F1	0.419 (6.3%)	[0.38,0.47]
θ_{29}	Dose effect on F1 sigmoidal hill coefficient	5 (fixed)	-
θ_{30}^*	Dose at half-maximal effect on KA	36 (14.9%)	[13,100]
θ_{31}^*	Maximal effect of dose on KA	0.895 (42.0%)	[0.82,0.98]
θ_{32}	Dose effect on KA sigmoidal hill coefficient	1 (fixed)	-
θ_{33}	Body weight effect on V2P	1 (fixed)	-
θ_{34}	Body weight effect on V3P	1 (fixed)	-
θ_{35}	Body weight effect on V3M	1 (fixed)	-
θ_{36}	Body weight effect on V2M	1 (fixed)	-
θ_{37}	BMI effect on CLP	-0.605 (9.7%)	[-0.72,-0.49]
θ_{38}^*	MALE effect on CLP	1.21 (11.2%)	[1.2,1.3]
Inter-individual variances			
$\Omega_{1,1}$	Between-subject variability on CLP	0.133 [38%] (4.8%)	[0.12,0.15]
$\Omega_{2,2}$	Between-subject variability on V2P	0.154 [41%] (5.7%)	[0.14,0.17]
$\Omega_{3,3}$	Between-subject variability on V3P	0.0878 [30%] (7.1%)	[0.076,0.1]
$\Omega_{4,4}$	Between-subject variability on V3M	0.121 [36%] (6.8%)	[0.1,0.14]
$\Omega_{5,5}$	Between-subject variability on KA	1.03 [135%] (9.9%)	[0.83,1.2]
$\Omega_{6,6}$	Between-subject variability on D1	1.27 [160%] (8.5%)	[1.1,1.5]
$\Omega_{7,7}$	Between-subject variability on V2M	0.786 [109%] (14.0%)	[0.57,1]
$\Omega_{8,8}$	Between-subject variability on KAD	3.4 [537%] (8.8%)	[2.8,4]
$\Omega_{9,9}$	Between-subject variability on D1D	2.29 [298%] (7.6%)	[1.9,2.6]

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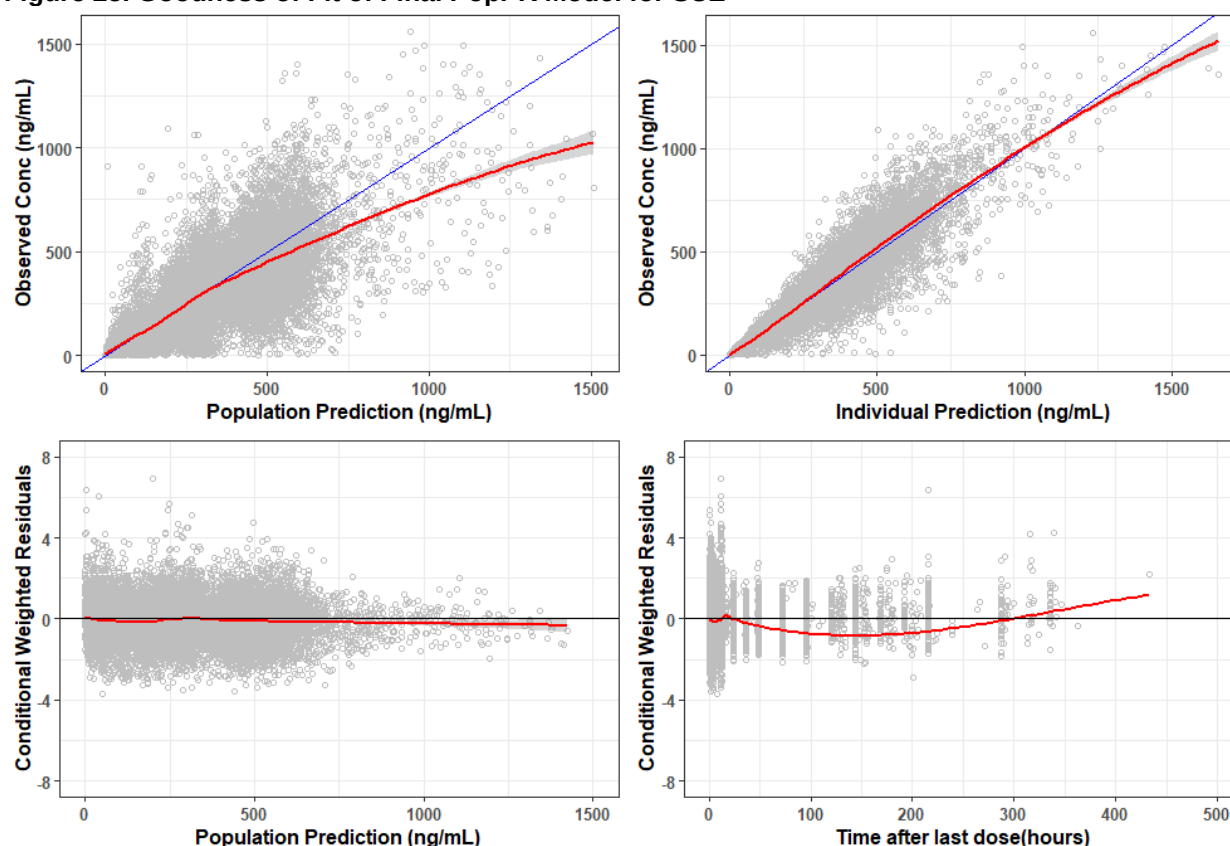
		Estimate (RSE%) [CV% or Corr%]	95% Confidence Interval
Inter-individual covariances			
$\Omega_{2,1}$	Covariance of BSV on CLP and V2P	0.0864 [60%] (6.9%)	[0.075,0.098]
$\Omega_{3,1}$	Covariance of BSV on CLP and V3P	0.018 [17%] (22.7%)	[0.01,0.026]
$\Omega_{3,2}$	Covariance of BSV on V2P and V3P	-0.00504 [-4%] (106.3%)	[-0.016,0.0055]
$\Omega_{4,1}$	Covariance of BSV on CLP and V3M	0.0256 [20%] (20.2%)	[0.015,0.036]
$\Omega_{4,2}$	Covariance of BSV on V2P and V3M	0.0243 [18%] (27.5%)	[0.011,0.037]
$\Omega_{4,3}$	Covariance of BSV on V3P and V3M	0.0281 [27%] (16.3%)	[0.019,0.037]
Residual error standard deviation			
θ_{12}	Parent additive error (SD) (ng/mL)	0.279 (12.5%)	[0.21,0.35]
θ_{13}	Parent proportional error (%CV)	24.2% (0.6%)	[0.24,0.25]
θ_{18}	Metabolite additive error (SD) (ng/mL)	8.2 (3.3%)	[7.7,8.7]
θ_{19}	Metabolite proportional error (%CV)	13.2% (0.8%)	[0.13,0.14]

Source: The Applicant's popPK report 049, page 54-55, Table 7.9.

* Parameter was estimated in the log domain and back-transformed for clarity. RSE: Relative Standard Error on the scale where the parameter was estimated.

Abbreviations: ABD, absorption period; AC50, autoinduction potency; AHILL, autoinduction sigmoidal hill coefficient; ALAG1, lag time; AMAX, maximum autoinduction; BSV, between subject variability; CLM, metabolite clearance relative to CLP; CLP, parent clearance; Corr%, correlation percentage; CV, coefficient of variation; D1, zero-order absorption duration (suspension); D1D, zero-order absorption duration of first ABD; D1TAB, zero-order absorption duration (tablet); F1, bioavailability; F1D, relative F1, first ABD; KA, absorption rate; KAD, absorption rate of first ABD; KENZ, enzymatic synthesis and consumption; MTIME, duration of first ABD; popPK, population pharmacokinetics; Q3M, metabolite intercompartmental transport; Q3P, parent intercompartmental transport; RSE, relative standard error; SD, standard deviation; V2M, metabolite volume of central compartment; V2P, parent volume of central compartment; V3M, metabolite volume of peripheral compartment; V3P, parent volume of peripheral compartment

Figure 25. Goodness of Fit of Final PopPK Model for SUZ

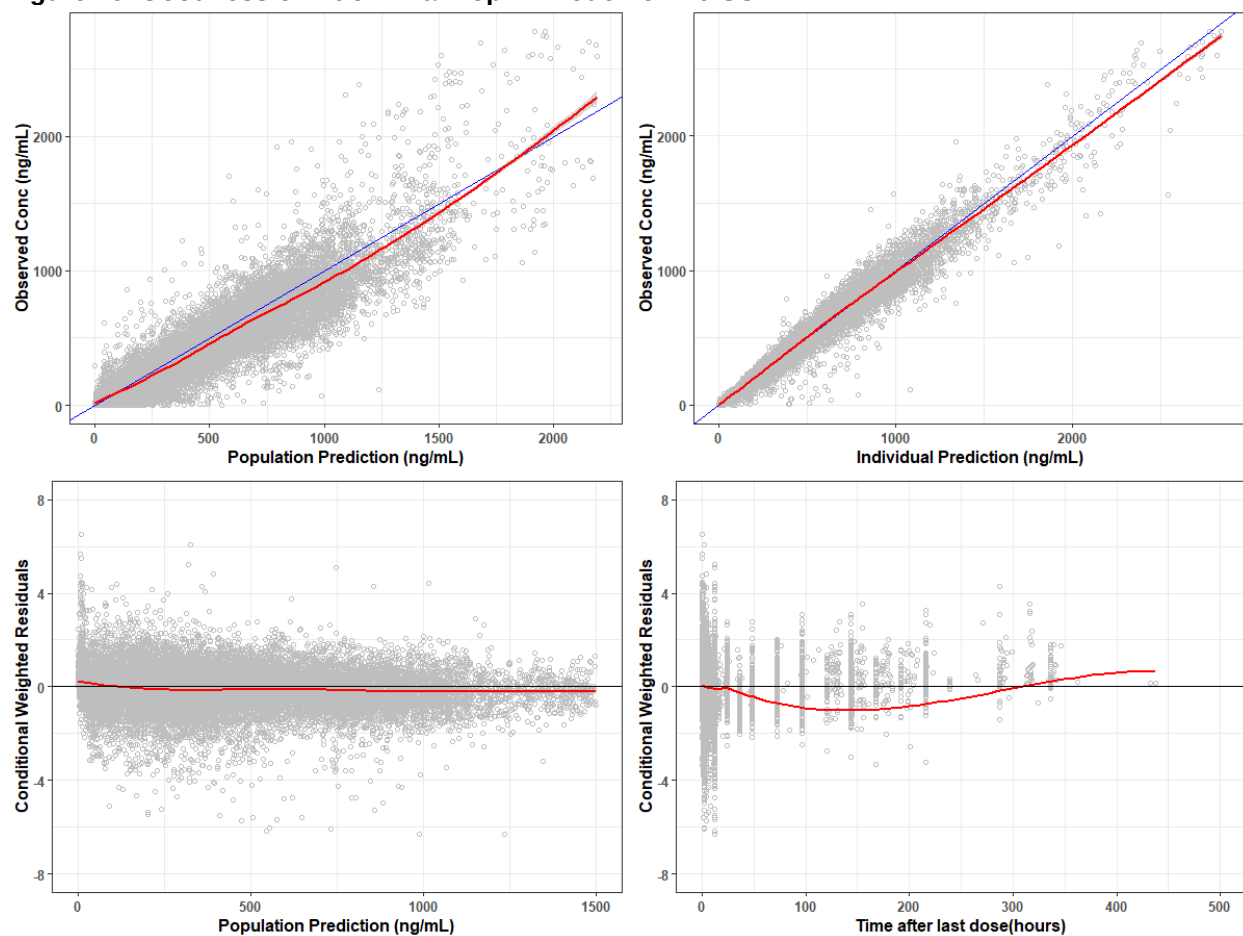


Source: Generated by an FDA reviewer.

Blue solid line represents line of unity.

Abbreviations: Conc, concentration; popPK, population pharmacokinetic; SUZ, suzetrigine

Figure 26. Goodness of Fit of Final PopPK Model for M6-SUZ

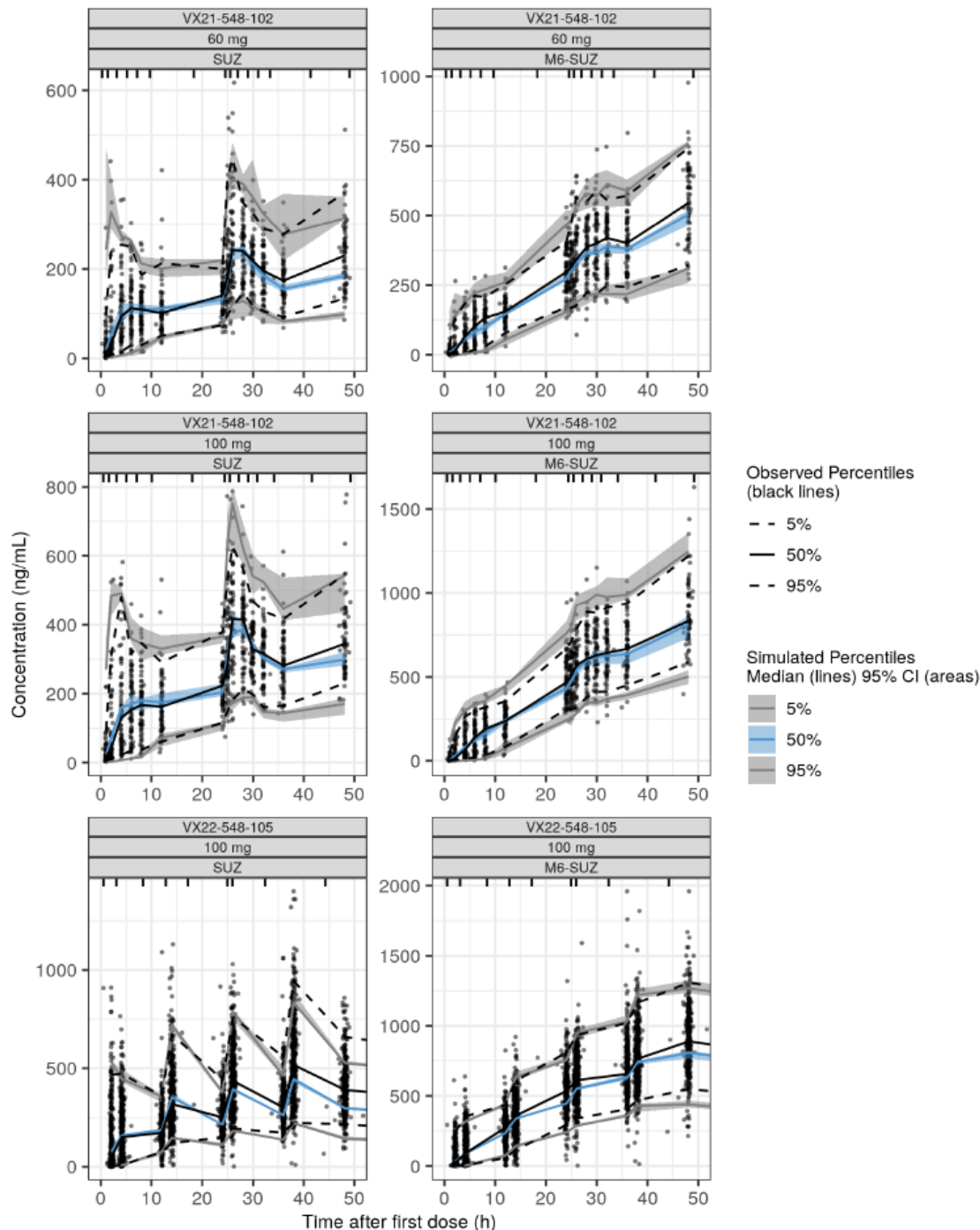


Source: Generated by an FDA reviewer.

Blue solid line represents line of unity.

Abbreviations: Conc, concentration; popPK, population pharmacokinetic; SUZ, suzetrigine

Figure 27. Visual Predictive Check of Final PopPK Model (Model 2822) Stratified by Dose for Abdominoplasty Subjects, Phase 2 and 3 Studies



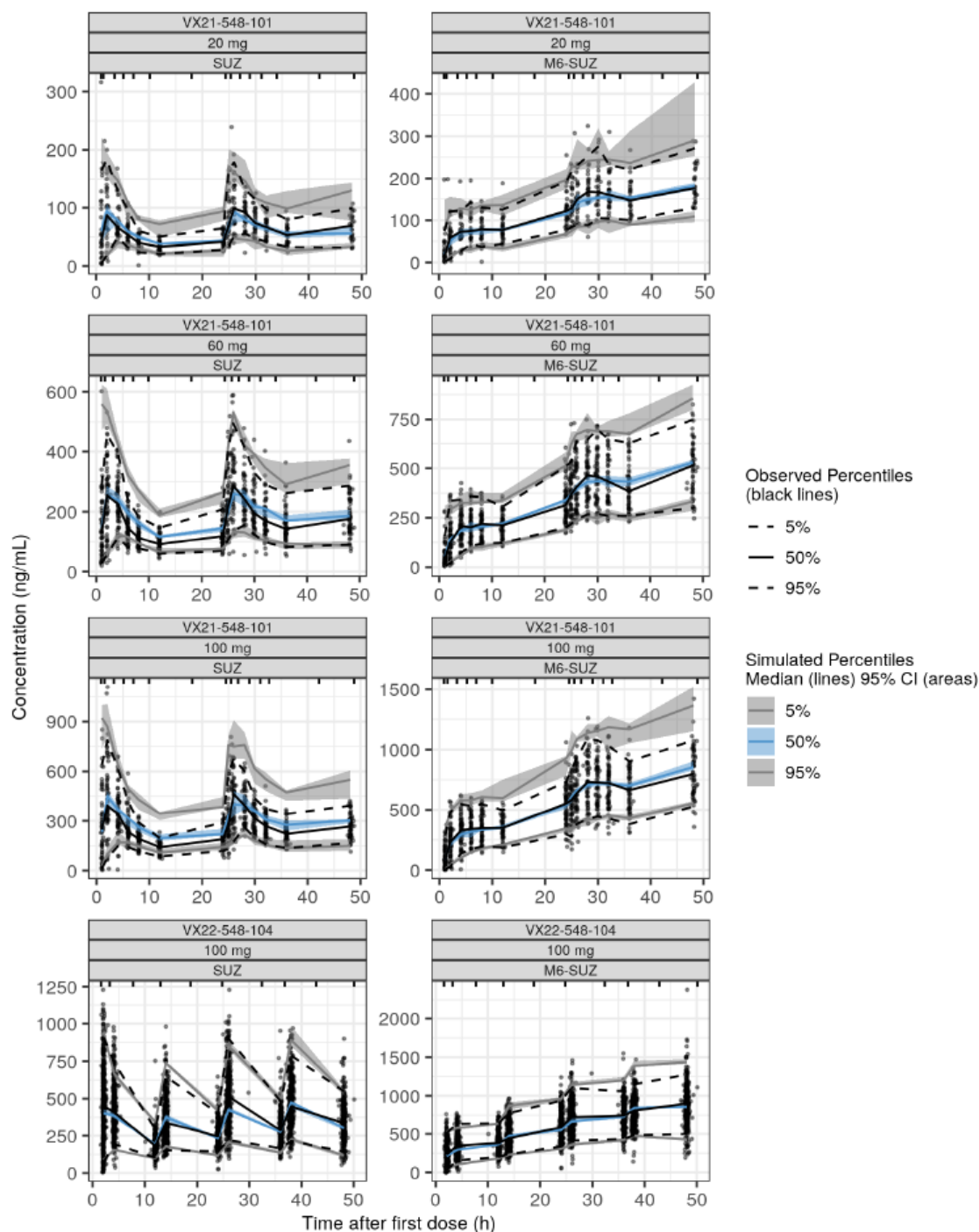
Source: The Applicant's popPK report (049), page 62, Figure 7.19.

Note: The median and 5th and 95th percentiles of the observed data (grey dots) are indicated with the black solid curve and the dashed curves, respectively. 95% confidence intervals of predictions are displayed as areas in light blue (median) and grey (5th and 95th percentiles). 500 simulated replicates.

The doses listed in each figure panel correspond to the loading dose for the regimen shown (60 mg = 60 mg loading, 30 mg q12h; 100 mg = 100 mg loading, 50 mg q12h).

Abbreviations: CI, confidence interval; popPK, population pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine

Figure 28. Visual Predictive Check of Final Model (Model 2822) Stratified by Dose for Bunionectomy Subjects, Phase 2 and 3 Studies



Source: The Applicant's popPK report (049), page 63, Figure 7.20.

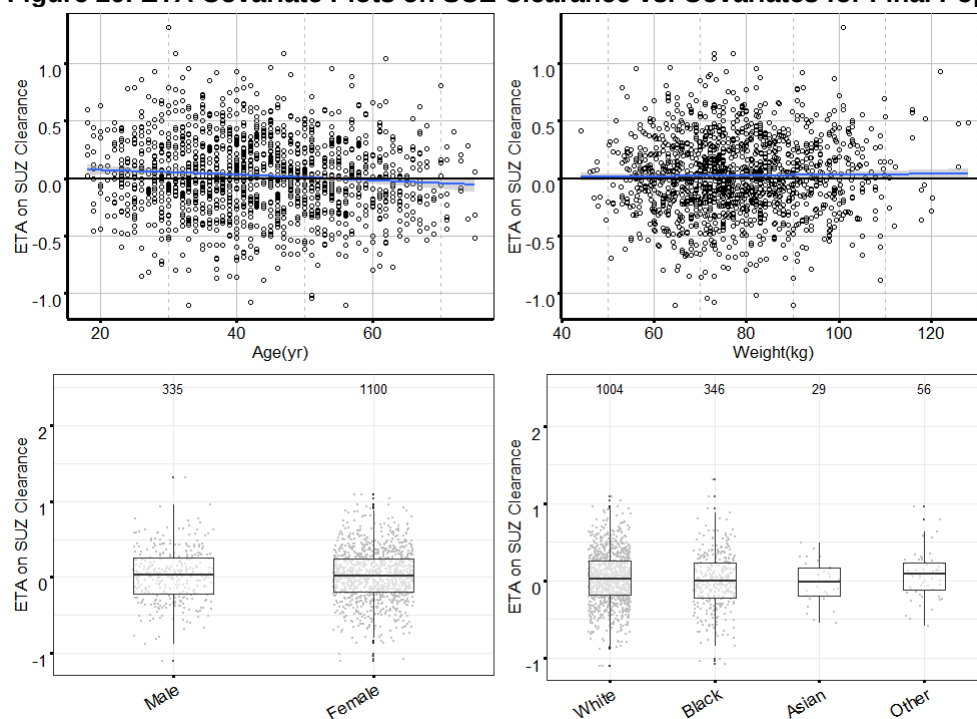
Note: The median and 5th and 95th percentiles of the observed data (grey dots) are indicated with the black solid curve and the dashed curves, respectively. 95% confidence intervals of predictions are displayed as areas in light blue (median) and grey (5th and 95th percentiles). 500 simulated replicates.

The doses listed in each figure panel correspond to the loading dose for the regimen shown (60 mg = 60 mg loading, 30 mg q12h; 100 mg = 100 mg loading, 50 mg q12h).

Abbreviations: CI, confidence interval; popPK, population pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine

The impact of age, body weight, sex, and race/ethnicity on PK parameters of SUZ and M6-SUZ was evaluated across each group ([Figure 29](#) and [Figure 30](#)).

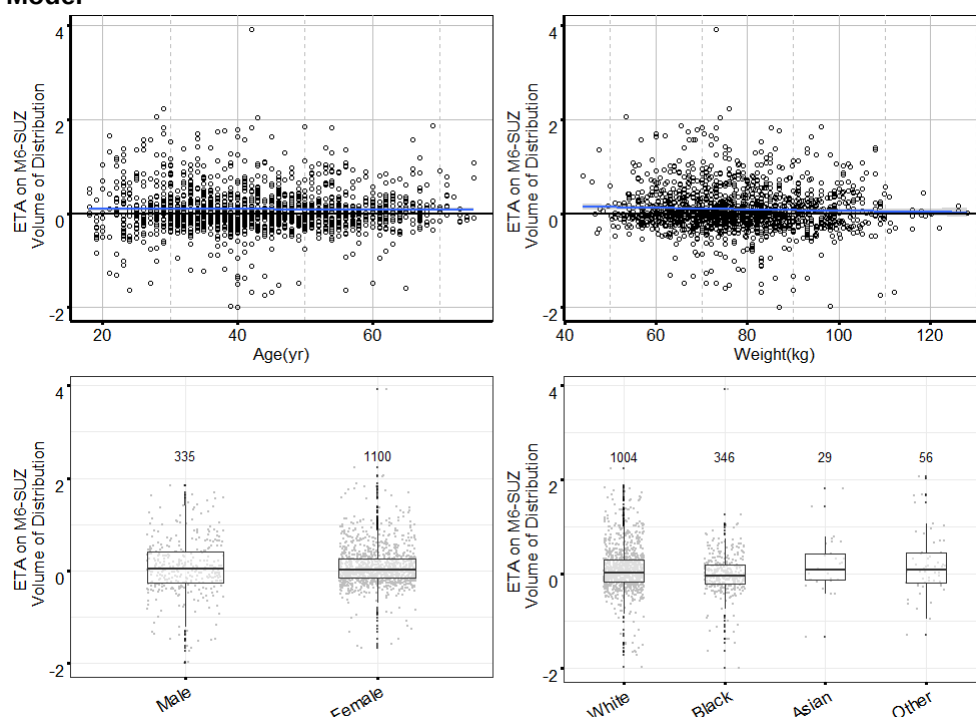
Figure 29. ETA Covariate Plots on SUZ Clearance vs. Covariates for Final PopPK Model



Source: Generated by an FDA reviewer.

Abbreviations: ETA, interindividual random effect; popPK, population pharmacokinetic; SUZ, suzetrigine; yr, years

Figure 30. ETA Covariate Plots on M6-SUZ Volume of Distribution vs. Covariates for Final PopPK Model



Source: Generated by an FDA reviewer.

Abbreviations: ETA, interindividual random effect; popPK, population pharmacokinetic; yr, years; SUZ, suzetrigine

The Applicant conducted simulations using the final popPK model to predict exposures over the first 48 hours and at steady state (Day 30) following administration of SUZ 100 mg/50 mg q12h and to compare to prior clinical experience. Over the first 48 hours, differences in absorption parameters (relative bioavailability) for the first dose following an abdominoplasty result in slightly lower predicted exposures for abdominoplasty than for bunionectomy. At steady state, the predicted exposures for abdominoplasty and bunionectomy are similar (within 2%) and therefore a pooled analysis was conducted. A summary of key PK parameters and properties for the proposed dosing regimen is provided in [Table 150](#).

Table 150. Pharmacokinetic Parameters of SUZ and M6-SUZ

Parameter		SUZ	M6-SUZ
General Information			
Mean (CV%) AUC, $\mu\text{g}\cdot\text{h/mL}$	AUC _{0-48h} ^a	15.8 (25.9%)	27.1 (31.2%)
	Steady-state	11.5 (25.6%)	34.7 (25.6%)
	AUC _{0-24h} ^a		
Mean (CV%) C _{max} , $\mu\text{g/mL}$	First 48 hours ^a	0.558 (31.7%)	0.914 (27.5%)
	Steady state ^a	0.623 (27.7%)	1.52 (24.5%)
Time to steady state, days		16	21
Time to 90% of steady state, days		3	5
Mean (CV%) accumulation ratio ^b		3.37 (30.2%)	4.49 (30.6%)
Absorption			
Median T _{max} (range), hours		3.0 hours (1.50, 5.03)	10.01 hours (4.00, 48.08)
Effect of acid-reducing agents		No clinically meaningful effect	No clinically meaningful effect

Parameter	SUZ	M6-SUZ
Distribution		
Mean (CV%) apparent volume of distribution, L	495 (25.0%)	NA
Protein binding	99%	96%
Elimination		
Mean (CV%) effective half-life, hours ^b	23.6 (36.2%)	33.0 (34.9%)
Mean (CV%) terminal half-life, hours	Single dose Steady state ^c	55.3 (37.0%) 62.6 (51.9%)
Mean (CV%) apparent clearance, L/h	Single dose Steady state ^c	29.5 (40.8%) 32.5 (31.3%)
Mean (CV%) apparent clearance, L/h	Single dose Steady state ^c	7.01 (39.7%) 13.9 (37.5%)
Mean (CV%) apparent clearance, L/h	Single dose Steady state ^c	NA NA
Metabolism		
Primary pathway	CYP3A	CYP3A
Excretion		
CYP3A primary pathway	Feces: 49.9% (primarily as metabolites; unchanged parent and M6-SUZ <10%) Urine: 44% (primarily as metabolites; unchanged parent and M6-SUZ undetectable in urine)	

Source: The Applicant's Summary of Clin Pharm, page 81, Table 20.

^a Pooled abdominoplasty & bunionectomy

^b Based on simulations of a dose of 50 mg q12h

^c At Day 14 (near steady state)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450, NA, not applicable; q12h, every 12 hours; SUZ, suzetrigine; T_{max}, time to maximum plasma concentration

Exposure-Response Analysis

Objectives

To evaluate the correlation between the PK exposure of SUZ and its active metabolite M6-SUZ with the efficacy endpoint (time-weighted sum of the pain intensity difference as recorded on the numerical pain rating scale (NPRS) from 0 to 48 hours [SPID48] response) in subjects administered SUZ after abdominoplasty or bunionectomy.

Data

PK data (individual concentrations of SUZ and M6-SUZ) and efficacy response (SPID48) from phase 2 (VX21-548-101 and VX21-548-102) and phase 3 (VX22-548-104 and VX22-548-105) studies in subjects who underwent bunionectomy or abdominoplasty were used to develop the E-R models.

A total of 1,725 subjects who underwent abdominoplasty (N=875) or bunionectomy (N=850) were included in the E-R analysis. Of these 1,725 subjects, 574 received placebo, 33 were administered a loading dose of 20 mg SUZ followed by 10 mg SUZ every 12 hours, 134 received a loading dose of 60 mg SUZ followed by 30 mg SUZ every 12 hours, and 984 were dosed with a loading dose of 100 mg SUZ followed by 50 mg SUZ every 12 hours. The covariate characteristics of the data are provided in [Table 151](#).

Table 151. Summary Statistics of Continuous and Categorical Covariates for Subjects Undergoing Abdominoplasty or Bunionectomy

Continuous Covariates	Total Number of Patients (N=1725)
Baseline NPRS	
Mean (SD)	7.04 (1.79)
Median [Min, Max]	7.00 [4.00, 10.0]
Baseline BMI (kg/m²)	
Mean (SD)	28.7 (4.49)
Median [Min, Max]	28.6 [18.1, 41.5]
Age (years)	
Mean (SD)	44.8 (11.8)
Median [Min, Max]	44.0 [18.0, 75.0]

Categorical Covariates	Total Number of Patients (N=1725)
Sex	
Male (%)	133 (7.7%)
Female (%)	1592 (92.3%)
Race	
White (%)	1207 (70.0%)
Non-white (%)	518 (30.0%)

Source: The Applicant's popPK report (U058), page 49, Table 26.

Abbreviations: BMI, body mass index; N, number of subjects; NPRS, numeric pain rating scale score; SD, standard deviation; popPK, population pharmacokinetic

Methods

The endpoint evaluated in the E-R analysis was SPID48. The E-R dataset consisted of mean SUZ and M6-SUZ concentrations, along with SPID48, for 875 subjects who underwent an abdominoplasty and 850 subjects who underwent a bunionectomy.

Several structural forms of the E-R model were evaluated to characterize the E-R relationship for SUZ. Linear, power, and sigmoidal E-R model structures were investigated to describe the relationship between SPID48 response and SUZ/M6-SUZ mean concentrations over 48 hours.

Baseline NPRS, baseline BMI, race, age, sex, and type of surgery (abdominoplasty versus bunionectomy) were evaluated as covariates.

Results

A power model was identified as the most suitable structural model. Models were also developed for the abdominoplasty and bunionectomy datasets individually. The results were similar to those obtained when estimating a single E-R relationship for SUZ using the combined abdominoplasty and bunionectomy dataset.

Parameter estimates for the final E-R model are presented in [Table 152](#). Baseline NPRS was identified as the only clinically relevant covariate. Age was also found to be a significant covariate; however, its effect on efficacy (SPID48) was small and not clinically meaningful (<20%, [Figure 31](#)), with slightly higher SPID48 values in older subjects.

Mean predictions from the E-R models are overlaid on individual observed SPID48 values from Studies 101, 102, 104, and 105 in [Figure 32](#). The largest SPID48 response was predicted at the

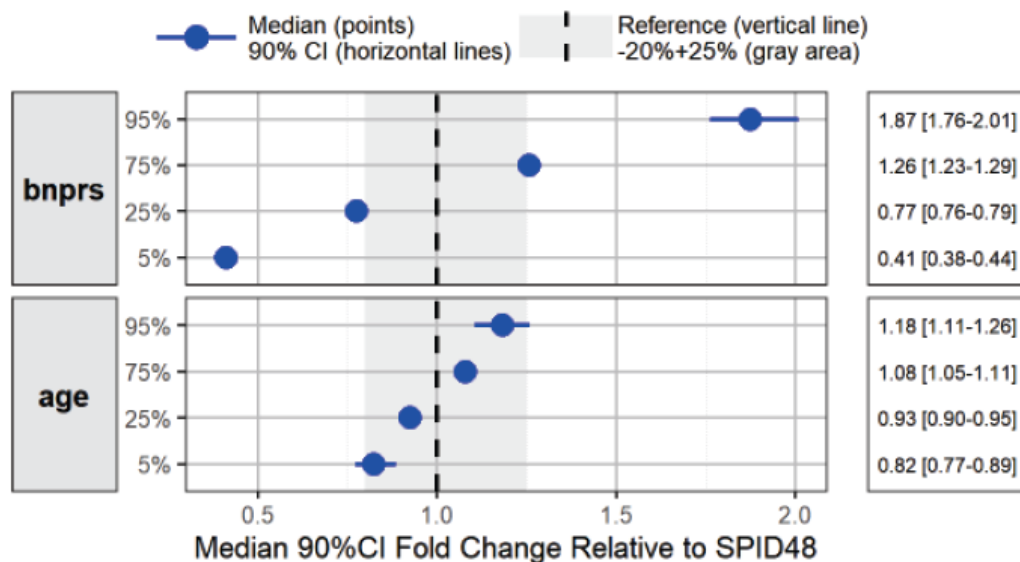
exposures resulting from the 100 mg/50 mg q12h dose, with a consistent response predicted across the entire exposure range at this dose, supporting its selection as the proposed dosing regimen.

Table 152. Parameter Estimates of Final Power Model for Subjects Undergoing an Abdominoplasty or a Bunionectomy

Final Power model: $SPID48 = E_0 \cdot bnprsg^1 \cdot age^{g2} + C[g \cdot (bnprsg^3)]$						
Parameters	Estimates	RSE (%)	p-value	95% CI	Bootstrap Estimates	Bootstrap 95% CI
E_0 (NPRS* h)	67.5	6.01	<2e-16	(59.5, 75.4)	67.3	(61.0, 73.9)
g	0.557	3.29	<2e-16	(0.521, 0.593)	0.557	(0.527, 0.581)
$g1$	1.67	13.9	9.64e-13	(1.22, 2.13)	1.66	(1.35, 2.00)
$g2$	0.635	18.6	8.02e-08	(0.404, 0.866)	0.642	(0.399, 0.878)
$g3$	0.464	26.4	1.54e-04	(0.224, 0.704)	0.465	(0.317, 0.658)
Residual standard error	92				91.8	(89.2, 94.3)

Source: The Applicant's popPK report (U058), page 51, Table 28.
Abbreviations: -2LL, -2* loglikelihood; AIC, Akaike information criteria; bnprs, baseline numeric pain rating scale score; CI, confidence interval; E_0 , baseline SPID48; $g1$, effect of bnprs on E_0 ; $g2$, effect of age on E_0 ; $g3$, effect of bnprs on g ; g , exponent of power model; NPRS, numeric pain rating scale score; popPK, population pharmacokinetics; RSE, relative standard error; SPID48, time-weighted sum of the pain intensity difference over 48 hours

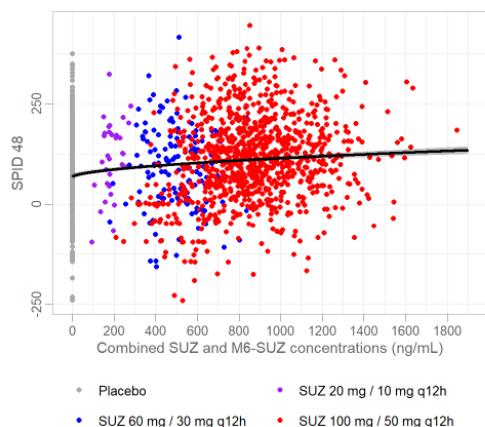
Figure 31. Impact of Covariates of Final Power Model on Predicted SPID48 for Subjects Receiving an Abdominoplasty or a Bunionectomy



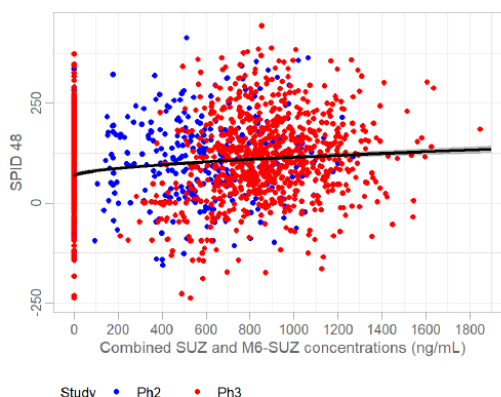
Source: The Applicant's popPK report (U058), page 53, Figure 15.
Notes: Reference subject is a 44-year-old white female with a bnprs of 7 and a BMI of 28.6 kg/m² receiving a bunionectomy. Blue dots denote the change in SPID48 from the reference value of 1, the horizontal bars represent the confidence interval of predicted SPID48, and the gray area denotes a change in SPID48 of 80%-125% relative to the reference.
Abbreviations: BMI, body mass index; bnprs, baseline numeric pain rating scale score; popPK, population pharmacokinetics; SPID48, time-weighted sum of the pain intensity difference over 48 hours

Figure 32. Exposure-Response Models for SPID48, Studies 101, 102, 104, and 105

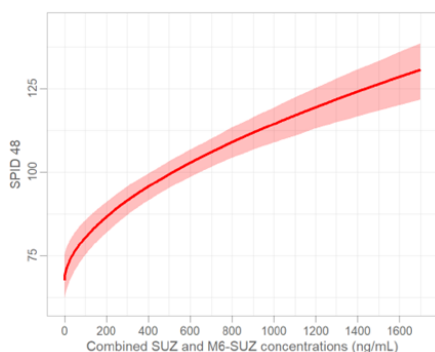
A. Scatterplot by SUZ Dosing Regimen and 95% CI



B. Scatterplot by Study Phase and 95% CI



C. Median and 95% CI



Source: The Applicant's popPK report (U058), page 51, Figure 13.

Notes: Across all panels, the solid line denotes the final model median predicted SPID, and the shaded area represents the 5% to 95% confidence intervals of model-predicted SPID48.

Abbreviations: CI, confidence interval; Ph2, phase 2; Ph3, phase 3; popPK, population pharmacokinetics; q12h, every 12 hours; SPID48, time-weighted sum of the pain intensity difference over 48 hours; SUZ, suzetrigine

Dose Adjustment for Special Populations

Objective

To evaluate the appropriateness of adjusting the SUZ dosage in subjects with HI, coadministered a moderate CYP3A inhibitor, or missing doses.

Method

The Applicant simulated SUZ and M6-SUZ exposures using the phase 3 popPK model (Report U049) based on data from healthy volunteers and phase 2/3 acute pain studies.

To predict exposure ranges in acute pain patients receiving the phase 3 SUZ regimen (100-mg loading dose followed by 50 mg q12h), the model simulated a typical subject and 1,000 virtual subjects. Results were compared to simulations in subjects with hepatic impairment and those coadministered SUZ with a CYP3A inhibitor, using both phase 3 and reduced SUZ dosing regimens.

Simulation of SUZ PK in Subjects With HI

The Applicant modified the phase 3 popPK model to simulate subjects with HI. A separate popPK model (Report U036) estimated the relative bioavailability ratio of SUZ and SUZ/M6-SUZ clearances in subjects with moderate HI compared to matched healthy subjects ([Table 153](#)). These parameters were then integrated into the phase 3 model to simulate subjects with moderate HI.

Table 153. Scaling Parameters and Demographic Covariates of Different Simulation Populations, Hepatic Impairment

Population	Scaling Parameters			Mean Age (years)	Covariates		
	Clearance Ratio (SUZ)	Clearance Ratio (M6-SUZ)	Bioavailability Ratio		Mean baseline BMI (kg/m^2)	Mean baseline weight (kg)	% Males
Acute Pain	1.00	1.00	1.00	47.71	28.02	75.54	14.80
Mild Hepatic Impairment	0.90	1.10	1.01	61.68	26.19	74.90	49.80
Moderate Hepatic Impairment	0.65	0.85	1.00	63.35	31.21	93.44	56.78

Source: The Applicant's popPK report (U50), page 13, Table 6.1.

DDI-HI model (report U036) estimated effects for moderate HI were used to scale SUZ and M6-SUZ clearances and bioavailability in the simulation.

Abbreviations: BMI, body mass index; DDI, drug-drug interaction; HI, hepatic impairment; popPK, population pharmacokinetic; SUZ, suzetrigine

Simulations of SUZ PK in Subjects Coadministered SUZ and a Moderate CYP3A Inhibitor

The Applicant modified the phase 3 popPK model to simulate subjects coadministered SUZ and a CYP3A inhibitor. As the effect of moderate CYP3A inhibitors on SUZ and M6-SUZ PK was not clinically studied, a physiologically based pharmacokinetic (PBPK) model was developed to predict this effect. The PBPK model predicted the relative bioavailability ratio of SUZ in subjects coadministered SUZ and a CYP3A inhibitor to that of subjects receiving SUZ alone (Report T415), as well as the ratios of SUZ and M6-SUZ clearances in these subjects ([Table 154](#)). These parameters were then incorporated into the phase 3 popPK model to simulate coadministration of SUZ and a CYP3A inhibitor in subjects with acute pain.

Table 154. Scaling Parameters and Demographic Covariates of Different Simulation Populations, CYP3A Inhibitors

Population	Scaling Parameters			Mean Age (years)	Covariates		
	Clearance Ratio (SUZ)	Clearance Ratio (M6-SUZ)	Bioavailability Ratio		Mean baseline BMI (kg/m^2)	Mean baseline weight (kg)	% Males
Acute Pain	1.00	1.00	1.00	47.80	28.05	75.59	14.70
Verapamil	0.45	0.46	1.12	48.05	28.22	76.13	14.32
Erythromycin	0.39	0.39	1.12	47.71	27.96	75.43	14.32
Fluconazole	0.32	0.39	1.09	47.76	28.04	75.52	14.12

Source: The Applicant's popPK report (U50), page 14, Table 6.2.

For SUZ coadministered with moderate CYP3A inhibitors, clearance scale for SUZ=1/PBPK model estimated clearance-ratio for SUZ; clearance scale for M6-SUZ=1/(AUC Ratio for M6-SUZ/ F-ratio) for example, in case of verapamil, it is $1/(2.43/1.12)=0.46$.

Abbreviations: AUC, area under the plasma concentration-time curve; BMI, body mass index; CYP, cytochrome P450; F, clearance; PBPK, physiologically-based pharmacokinetics; popPK, population pharmacokinetics; SUZ, suzetrigine

Simulation of Missed-Doses Scenarios

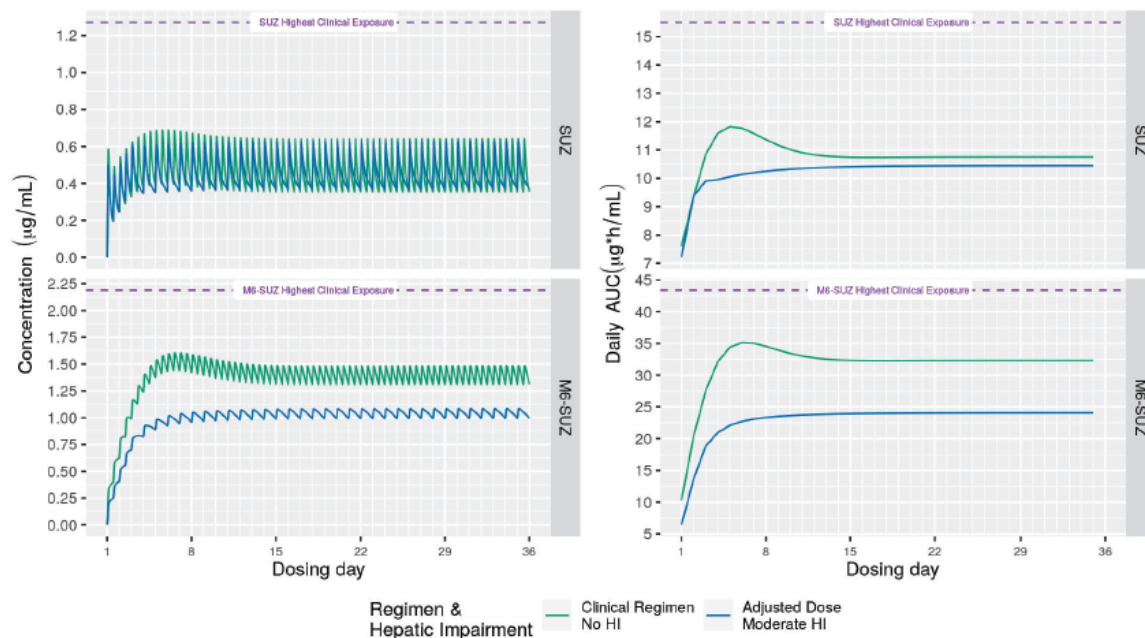
The Applicant conducted simulations using the final model to evaluate the impact of missed doses on SUZ and M6-SUZ exposure in subjects administered the standard SUZ regimen and in special-population subjects administered a reduced SUZ dose (100-mg loading dose, 50 mg q12h for the next 3 doses, followed by 50 mg qd for all subsequent doses). Simulations of the standard-SUZ-regimen scenarios were performed where one or two doses were missed, and a make-up dose (50 mg or 100 mg) was taken with the next scheduled dose. A 50-mg dose was given for one missed dose, and a 100-mg dose for more than one missed.

Results

Hepatic Impairment

The Applicant conducted a dedicated study (Study 007) to evaluate the PK and safety of multiple doses of SUZ in subjects with mild or moderate hepatic impairment, as well as in matched healthy subjects, refer to Section 14.2. Based on the increased SUZ exposure, a reduced dose is recommended in subjects with moderate hepatic impairment: 100 mg for the initial (loading) dose, followed by 50 mg q12h for the next 3 doses, then 50 mg qd for all subsequent doses. This adjusted regimen will result in SUZ exposure levels similar to those in subjects without hepatic impairment. However, M6-SUZ exposures are lower in subjects with hepatic impairment (Figure 33 and Figure 34).

Figure 33. Plots of C_{max} and AUC Values of SUZ and M6-SUZ After Dose Adjustment in Subjects With Moderate HI Against Day After First Dose

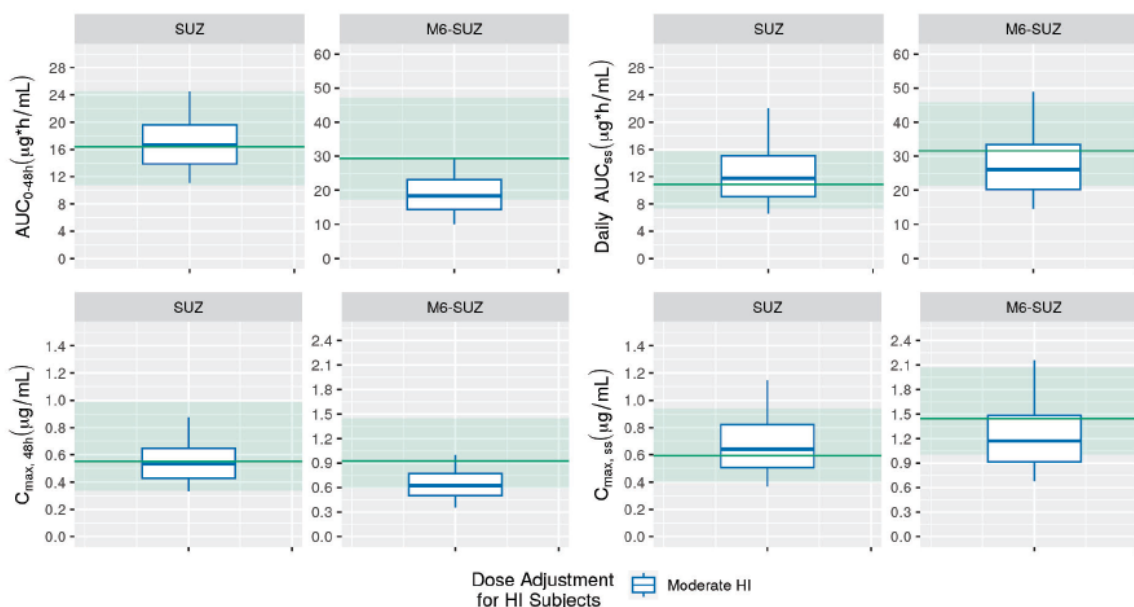


Source: The Applicant's popPK report (U50), page 18, Figure 7.3

Notes: Green line represents phase 3 clinical regimen administered in a typical subject without HI; blue line represents a typical subject with HI receiving adjusted dose. Purple dotted lines (highest clinical exposure) represent mean C_{max} and mean AUC observed after 200 mg once-daily dosing of SUZ in study VX21-548-009.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; HI, hepatic impairment; popPK, population pharmacokinetic; SUZ, suzetrigine

Figure 34. Boxplots of SUZ and M6-SUZ After Dose Adjustment in Subjects With Moderate HI



Source: The Applicant's popPK report (U50), page 19, Figure 7.4

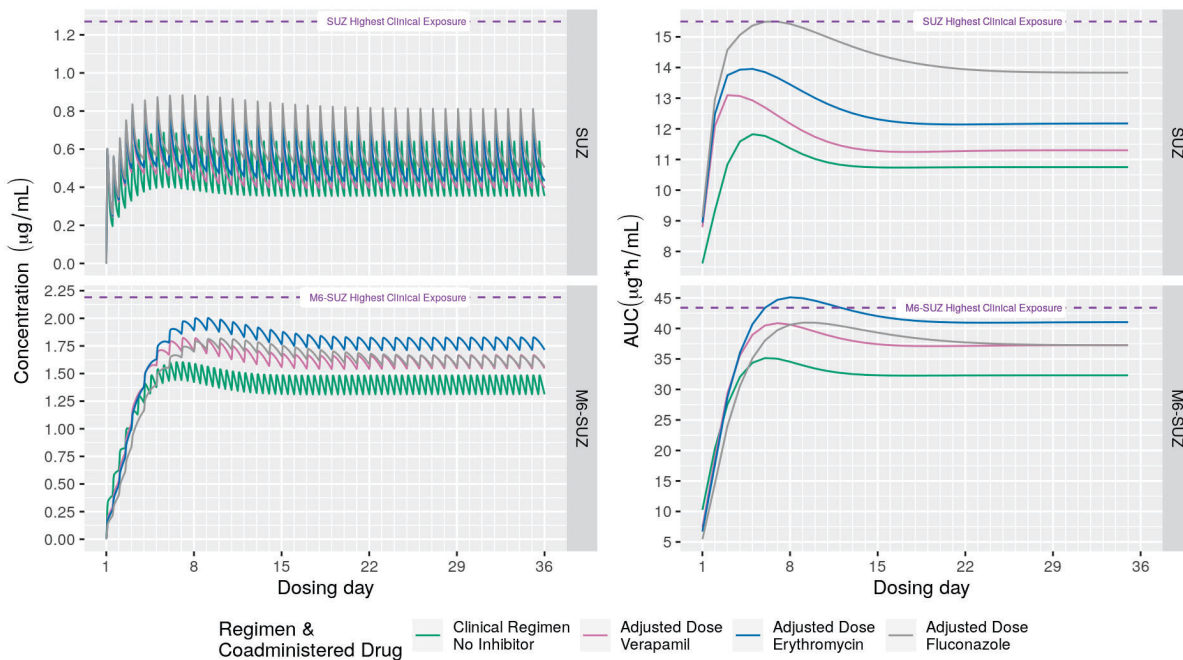
Notes: The box plots represent 25%, median and 75% interquartile ranges of the predictions and the whiskers represent the 90% PI. The solid green line and the shaded area represent median and the 90% PI of exposure in acute pain subjects receiving clinical regimen, respectively.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; HI, hepatic impairment; PI, prediction interval; popPK, population pharmacokinetic; ss, steady state; SUZ, suzetrigine

Coadministered SUZ and Moderate CYP3A Inhibitor

The effects of moderate CYP3A inhibitors fluconazole, erythromycin, and verapamil on the PK of SUZ and M6-SUZ were predicted using PBPK modeling (refer to Section 14.7). Based on the predicted increase in SUZ exposure when coadministered with moderate CYP3A inhibitors, a reduced SUZ dosing regimen is recommended: 100 mg for the initial (loading) dose followed by 50 mg q12h for the next 3 doses, and then 50 mg qd for all subsequent doses. In subjects coadministered a moderate CYP3A inhibitor, this adjusted dose will lead to higher SUZ and M6-SUZ exposures than when no DDI is present, but will not exceed the maximum exposure levels at the highest clinical doses (Figure 35 and Figure 36).

Figure 35. Plots of C_{max} and AUC Values of SUZ and M6-SUZ vs. Dosing Day After Dose Adjustment in Subjects Coadministered With Moderate CYP3A Inhibitors

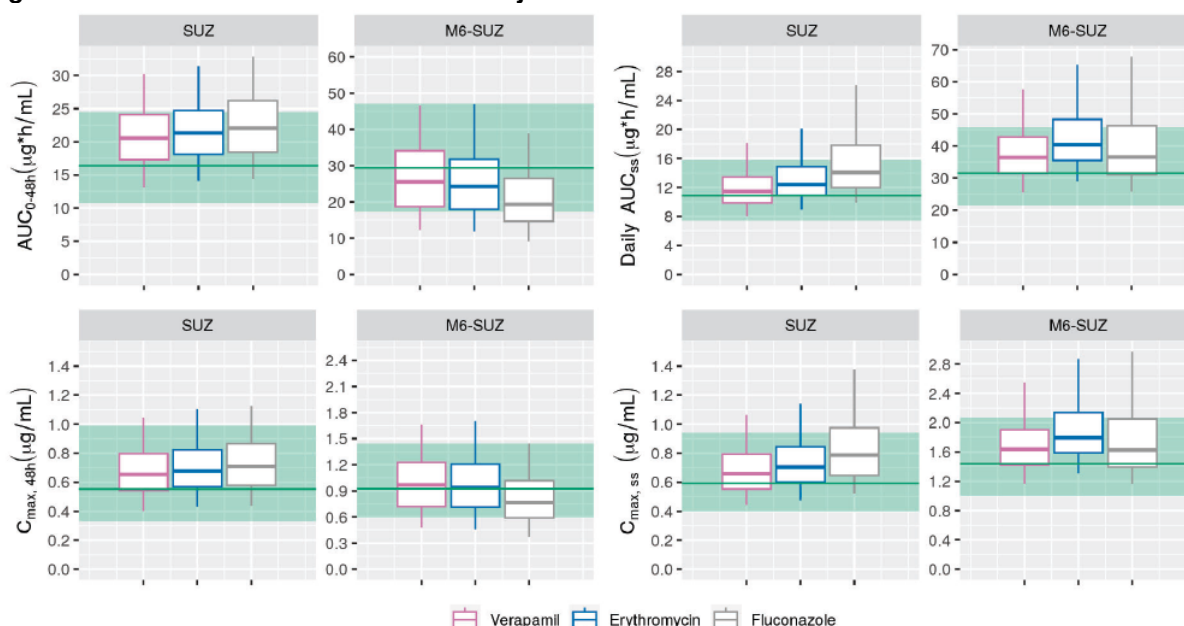


Source: The Applicant's popPK report (U50), page 22, Figure 7.9

Notes: Green line represents phase 3 clinical regimen administered in a typical subject without CYP3A inhibitor; grey, blue, and purple lines represent a typical subject receiving clinical regimen concurrently with fluconazole, erythromycin, and verapamil, respectively. Purple dashed lines (highest clinical exposure) represent mean C_{max} and mean AUC observed after 200 mg once-daily dosing of SUZ in study VX21-548-009.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max} , maximum plasma concentration; CYP, cytochrome P450; popPK, population pharmacokinetic; SUZ, suzetrigine

Figure 36. SUZ and M6-SUZ After Dose Adjustment in Moderate CYP3A Inhibitor-Mediated DDI



Source: The Applicant's popPK report (U50), page 22, Figure 7.8

Notes: The box plots represent 25%, median and 75% interquartile ranges of the predictions and the whiskers represent the 90% PI. The solid green line and the shaded area represent median and the 90% PI of exposure in acute pain subjects receiving clinical regimen, respectively.

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome p450; DDI, drug-drug interaction; PI, prediction interval; popPK, population pharmacokinetic; SUZ, suzetrigine

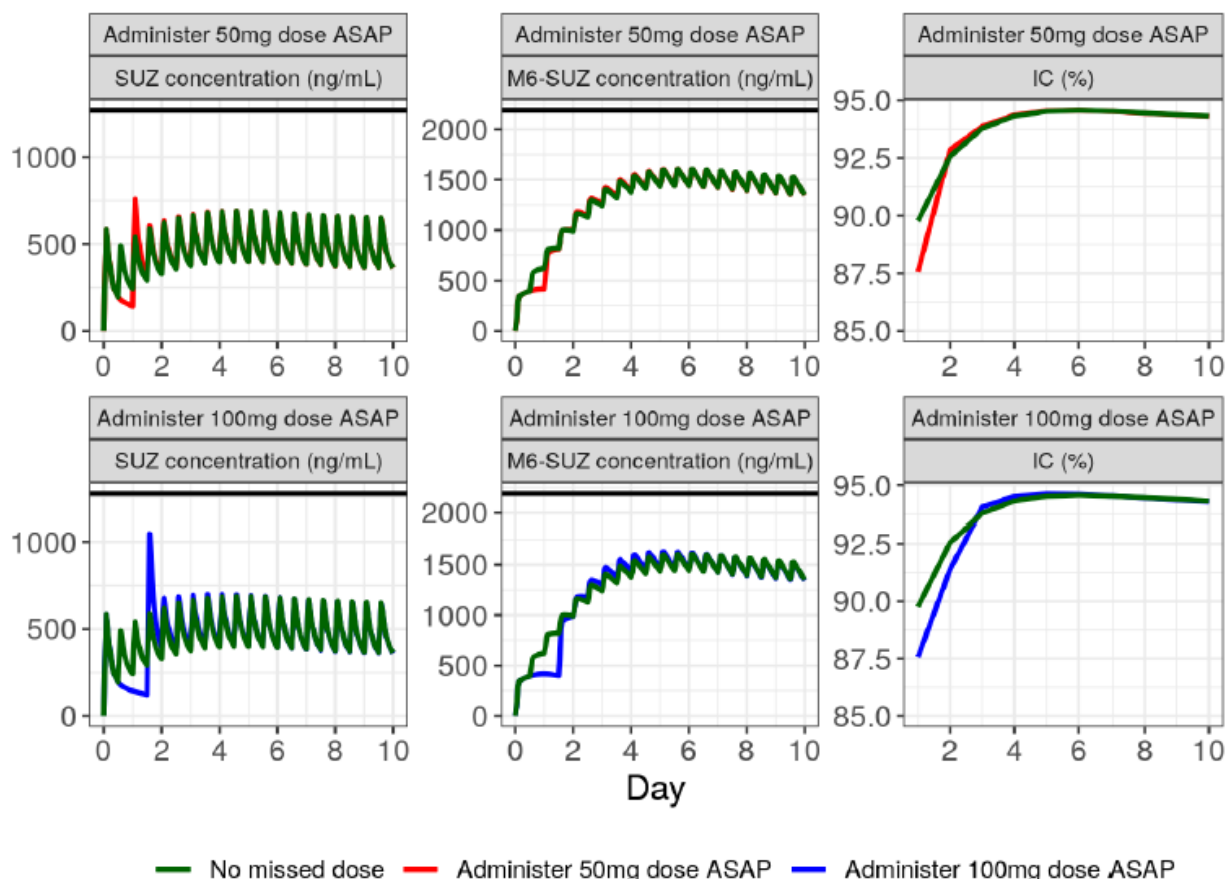
Missed Dose Simulations

The Applicant conducted simulations for a 50-mg make-up dose following a single missed dose or a 100-mg make-up dose following two or more missed doses for subjects receiving the standard regimen. The worst case was simulated, where the make-up dose was administered together with the next scheduled dose.

As an example of a missed dosing scenario in the subjects on the standard regimen, [Figure 37](#) illustrates the simulated concentration-time profiles where the scheduled dose(s) at 12 hours (top) or 12 and 24 hours (bottom) were missed, and make-up doses (either 50 mg for one missed dose or 100 mg for two missed doses) were taken at the same time as the next regularly scheduled dose.

If a dose is missed, it is recommended to take the missed dose as soon as possible and resume the original schedule. If two or more doses are missed, it is recommended to take a loading dose of 100 mg and then resume the original schedule. The Applicant's recommendation for missed dose management is appropriate; refer to [Section 14.5.2](#).

Figure 37. Example Simulated Concentration Time Profiles for SUZ and M6-SUZ With Either a Single Missed Dose at 12 Hours (Top) or Missed Doses at 12 and 24 Hours (Bottom) in Subjects on the Standard Regimen Over the First 10 Days of Dosing



Source: The Applicant's popPK report (U49), page 97, Figure 7.38

Note: The horizontal black line at the top of each concentration-time plot represents the maximum mean clinical experience (from TQT Study VX21-548-009 [7]): SUZ C_{max} = 1270 (ng/mL), M6-SUZ C_{max} = 2190 (ng/mL).
Abbreviations: SUZ, suzetrigine; ASAP, as soon as possible; IC, inhibition constant; popPK, population pharmacokinetic; TQT, thorough QT; C_{max} , maximum plasma concentration

14.5.2. Reviewer's Analyses

Objectives

- Evaluate the popPK model.
- Assess the effect of intrinsic and extrinsic factors based on popPK analyses.
- Evaluate the exposure-response relationship.
- Evaluate the proposed dose for subjects with HI, coadministered with a moderate CYP3A inhibitor, or missing doses.

Data

Table 155. Dataset Used for the Reviewer's Analysis

Study	Dataset(s)
VX19-548-001;	PK_suz_nda_v03.csv
VX21-548-101;	vx548er.csv
VX21-548-102;	
VX21-548-103;	
VX22-548-104;	
VX22-548-105;	
VX21-548-011;	
VX22-548-013;	
VX22-548-014;	
VX22-548-016;	
VX20-548-002;	
VX21-548-004;	
VX21-548-005;	
VX21-548-007;	
VX21-548-008	

Source: Generated by an FDA reviewer.

Abbreviation: FDA, Food and Drug Administration

Software

PopPK model fitting was performed in NONMEM 7.5 and Pirana 2.9.9. Exploratory E-R analysis and plotting were performed in R 4.0.0.

Models

The reviewer utilized the Applicant's final popPK model for SUZ and M6-SUZ. SUZ disposition was described by a two-compartment model, with zero-order entry into the depot compartment, followed by first-order absorption from the depot compartment into the central compartment, first-order distribution to and from a peripheral compartment, and parallel linear clearances (metabolism and elimination) from the central compartment. The disposition of the major metabolite (M6-SUZ) was described by a two-compartment model, with formation by nonreversible, first-order creation from SUZ, first-order distribution to and from the peripheral compartment, and clearance from its central compartment with nonlinearity due to autoinduction.

Additionally, the reviewer evaluated the E-R relationship and evaluated the appropriateness of the proposed dose regimen for subjects with moderate hepatic impairment, coadministered with a moderate CYP3A inhibitor, or missing doses. Typical-subject simulations were performed to evaluate the impact of those intrinsic or extrinsic factors.

Results

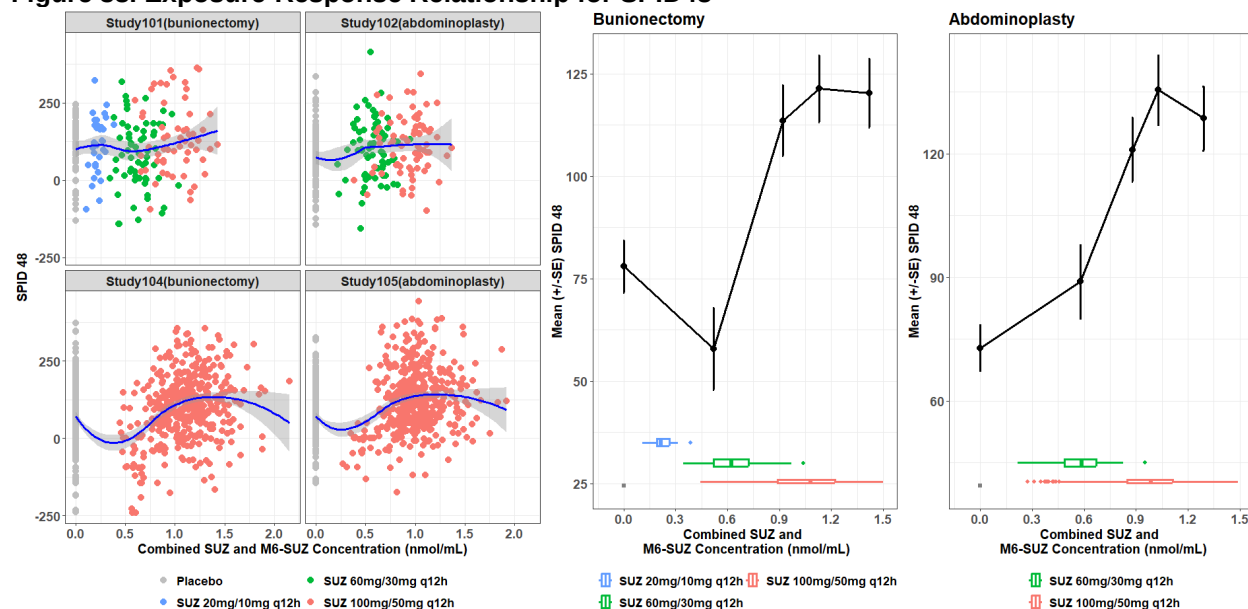
PopPK and E-R Analysis

The reviewer was able to reproduce the Applicant's popPK model and obtain the E-R analysis results.

The relationship between SPID48 and average combined SUZ and M6-SUZ concentration is shown in [Figure 38](#). Overall, maximum SPID48 response was observed at the exposures

associated with the 100 mg/50 mg q12h dosing regimen. This supported the efficacy of SUZ at a dose of 100 mg/50 mg q12h.

Figure 38. Exposure-Response Relationship for SPID48



Source: Generated by an FDA reviewer.

Left: SPID 48 versus Combined SUZ and M6-SUZ Concentration across Different Studies. Right: Mean±SE SPID 48 versus Quantiles of Combined SUZ and M6-SUZ Concentration across Indications

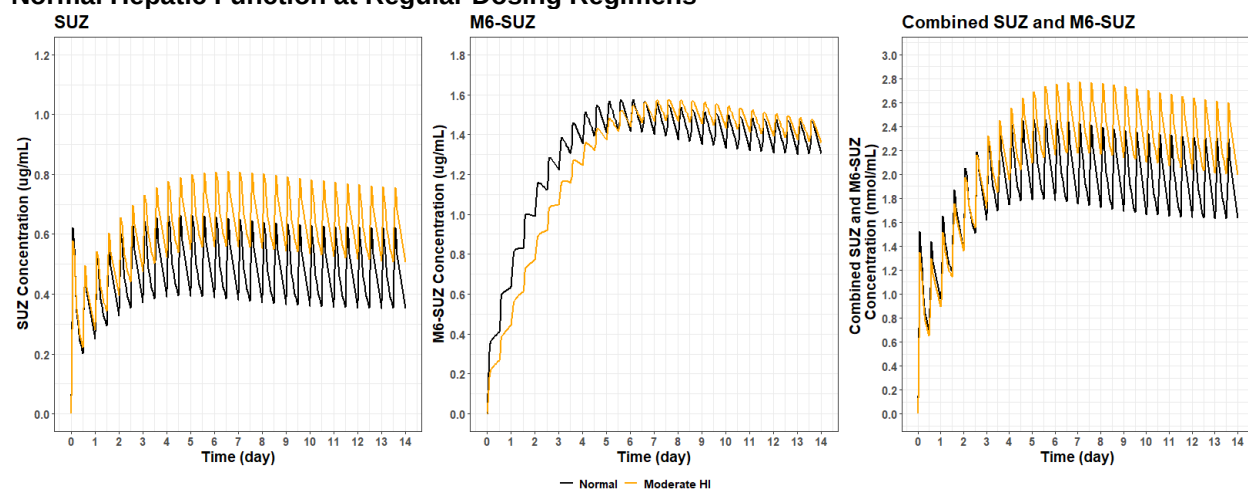
Abbreviations: FDA, Food and Drug Administration; SE, standard error; SPID48, time-weighted sum of the pain intensity difference over 48 hours; SUZ, suzetrigine

Dose Adjustment for Special Population

Hepatic Impairment

[Figure 39](#) and [Figure 40](#) present PK profiles of typical subjects with normal hepatic function or moderate hepatic impairment, who received the regular or a modified dose regimen, respectively.

Figure 39. Simulated PK Profiles in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function at Regular Dosing Regimens



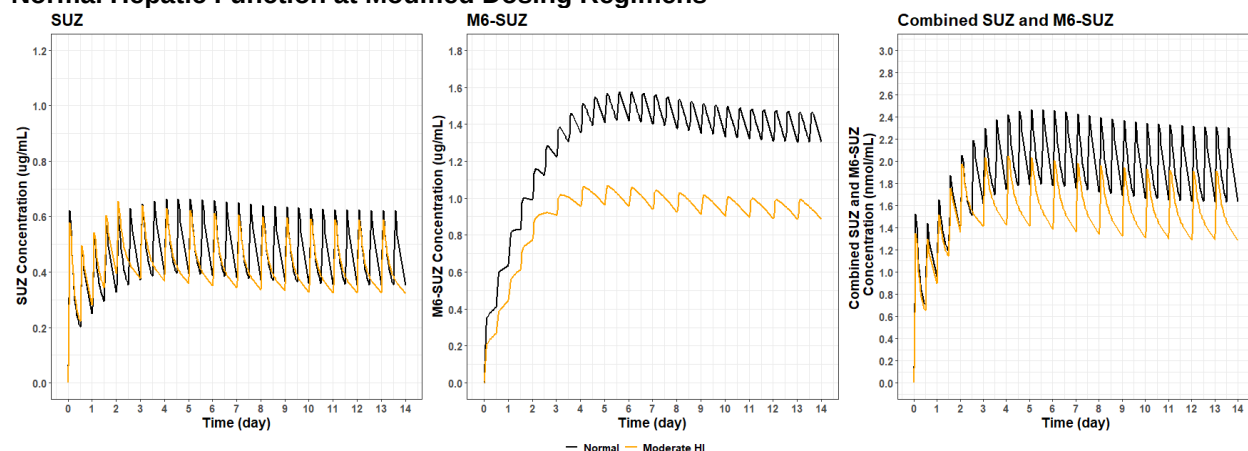
Source: Generated by an FDA reviewer.

Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Regular dosing regimen: 100-mg Loading Dose, Followed by 50 mg q12h
Subject with normal hepatic function: BMI: 27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy

Subject with moderate hepatic impairment: BMI: 29.6 kg/m², WT: 81.3 kg, Age: 61.5 yrs old, male, under bunionectomy
Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; HI, hepatic impairment; popPK, population pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine; WT, weight

Figure 40. Simulated PK Profiles in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function at Modified Dosing Regimens



Source: Generated by an FDA reviewer.

Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Modified dosing regimens: 100-mg loading dose, followed by 50 mg q12h for the next 3 doses followed by 50 mg qd for all subsequent doses

Subject with normal hepatic function: BMI:27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy

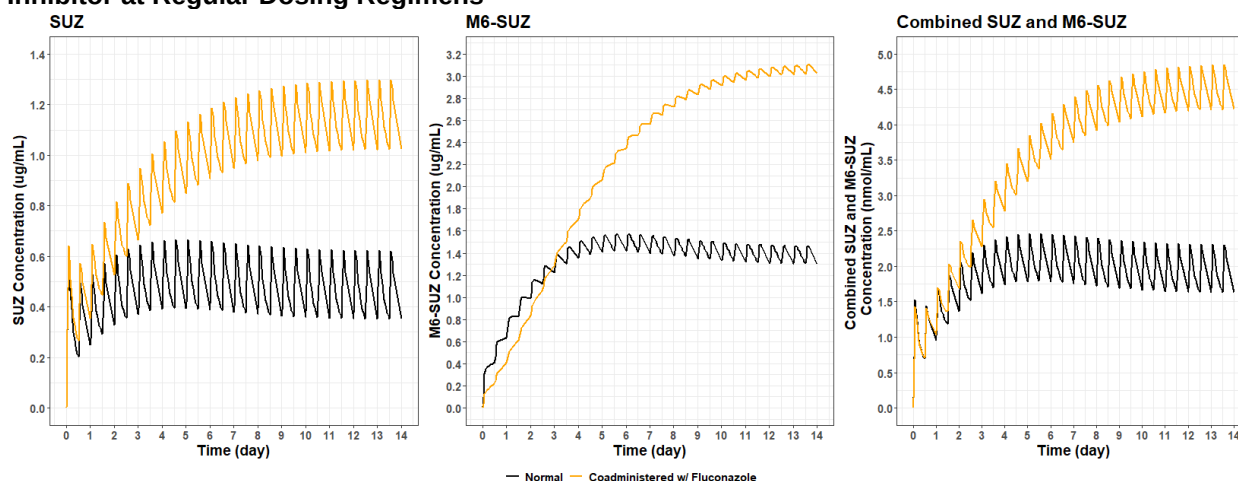
Subject with moderate hepatic impairment: BMI:29.6 kg/m², WT: 81.3 kg, Age: 61.5 yrs old, male, under bunionectomy

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; HI, hepatic impairment; popPK, population pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine; WT, weight

Coadministration w/ Moderate CYP3A Inhibitor

[Figure 41](#) and [Figure 42](#) present PK profiles of typical subjects coadministered with or without a moderate CYP3A inhibitor (fluconazole) who received the regular or a modified dose regimen, respectively.

Figure 41. Simulated PK Profiles in Subjects Coadministered With or Without Moderate CYP3A Inhibitor at Regular Dosing Regimens



Source: Generated by an FDA reviewer.

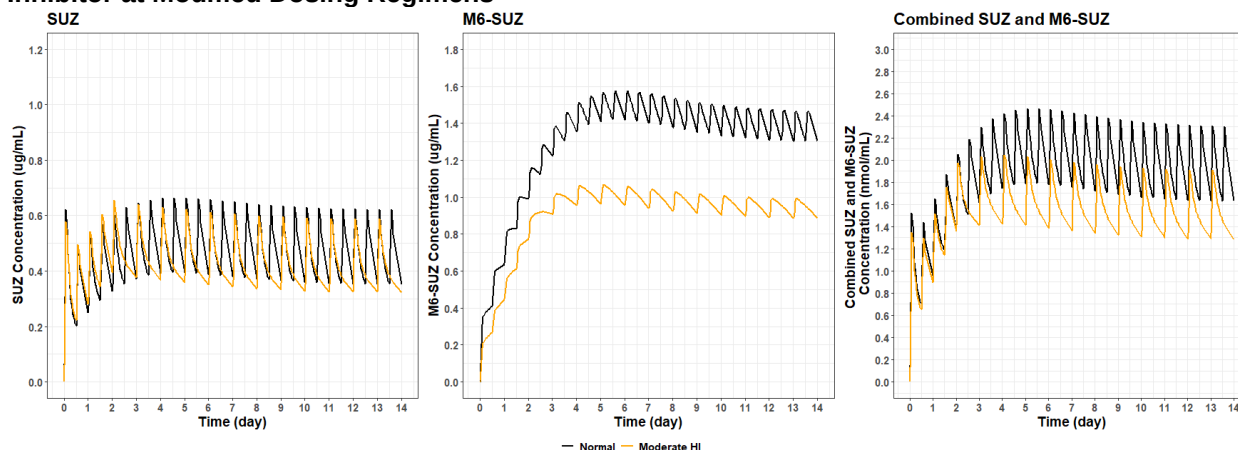
Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Regular dosing regimen: 100-mg loading dose, followed by 50 mg q12h

Subject receiving SUZ alone: Normal hepatic function, BMI:27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy.
Subject coadministered w/ Fluconazole: Normal hepatic function, BMI:27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy.

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; HI, hepatic impairment; popPK, population pharmacokinetic; SUZ, suzetrigine; q12h, every 12 hours; WT, weight

Figure 42. Simulated PK Profiles in Subjects Coadministered With or Without Moderate CYP3A Inhibitor at Modified Dosing Regimens



Source: Generated by an FDA reviewer.

Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Modified dosing regimens: 100-mg loading dose, followed by 50 mg q12h for the next 3 doses followed by 50 mg qd for all subsequent doses.

Subject receiving SUZ alone: Normal hepatic function, BMI:27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy.
Subject coadministered w/ Fluconazole: Normal hepatic function, BMI:27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy.

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; HI, hepatic impairment; popPK, population pharmacokinetic; q12h, every 12 hours; SUZ, suzetrigine; WT, weight

[Table 156](#) and [Table 157](#) show the comparison of PK exposure metrics across different dose regimens in subjects who underwent bunionectomy or abdominoplasty. The Applicant's proposed adjusted dosing regimen for subjects with moderate hepatic impairment would result in

approximately a 20% reduction in PK metrics, including a 17% reduction in maximum plasma concentration at steady state ($C_{max,ss}$), a 22% reduction in trough plasma concentration at steady state ($C_{trough,ss}$), and a 23% reduction in daily AUC_{ss} . For subjects coadministered a moderate CYP3A4 inhibitor, the proposed adjusted dose regimen would lead to a 25% increase in $C_{max,ss}$ and 27% increases in both $C_{trough,ss}$ and daily AUC_{ss} . These changes in the PK metrics are unlikely to impact efficacy ([Figure 43](#)).

Table 156. Comparison of PK Metrics Across Different Dose Regimens in Subjects Who Underwent Bunionectomy

Dose Regimen	$C_{max,ss}$ (nmol/mL)	$C_{trough,ss}$ (nmol/mL)	Daily AUC_{ss} (nmol·h/mL)	$C_{max,ss}$ Ratio	$C_{trough,ss}$ Ratio	Daily AUC_{ss} Ratio
20 mg/10 mg q12h	0.65	0.50	13.5	0.27	0.29	0.29
60 mg/30 mg q12h	1.76	1.32	36.12	0.74	0.77	0.77
100 mg/50 mg q12h	2.38	1.66	47.1	1	1	1
Reduced dose in moderate HI	1.97	1.31	36.62	0.83	0.78	0.77
Reduced dose w/fluconazole	2.97	2.24	59.6	1.25	1.27	1.27

Source: Generated by an FDA reviewer.

Abbreviations: FDA, Food and Drug Administration; HI, hepatic impairment; PK, pharmacokinetic; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; AUC_{ss} , area under the plasma concentration-time curve at steady state

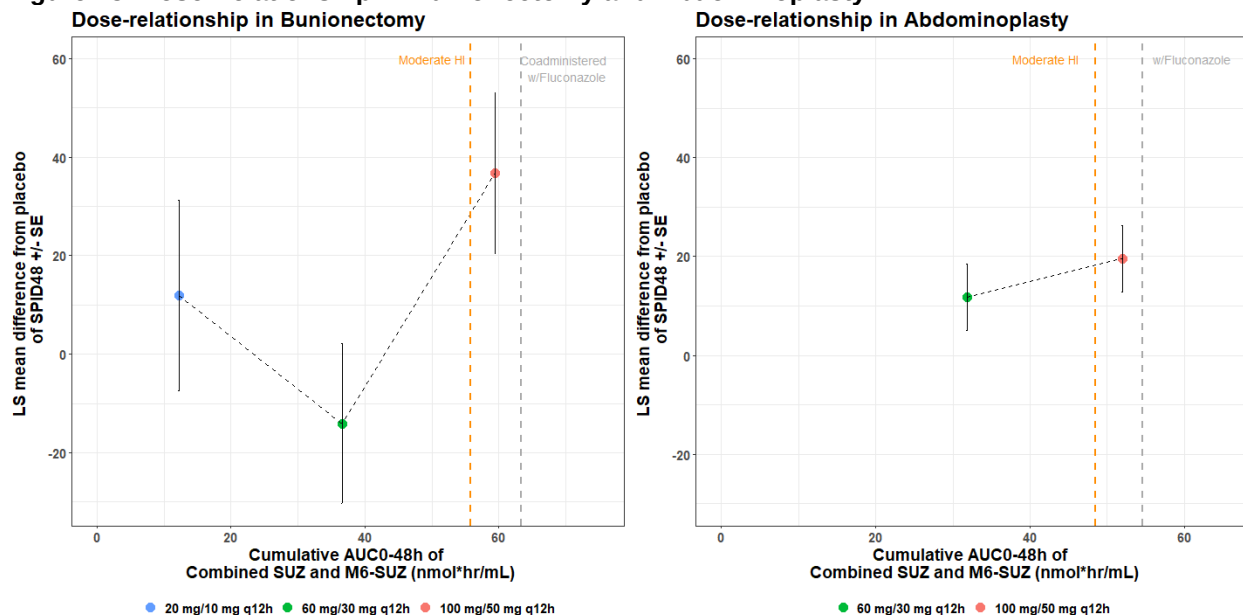
Table 157. Comparison of PK Metrics Across Different Dose Regimens in Subjects Who Underwent Abdominoplasty

Dose Regimen	$C_{max,ss}$ (nmol/mL)	$C_{trough,ss}$ (nmol/mL)	Daily AUC_{ss} (nmol·h/mL)	$C_{max,ss}$ Ratio	$C_{trough,ss}$ Ratio	Daily AUC_{ss} Ratio
20 mg/10 mg q12h	0.65	0.50	13.5	0.27	0.29	0.23
60 mg/30 mg q12h	1.76	1.32	36.2	0.74	0.77	0.77
100 mg/50 mg q12h	2.38	1.66	47.1	1	1	1
Reduced dose in moderate HI	1.97	1.31	36.8	0.83	0.79	0.78
Reduced dose w/fluconazole	2.97	2.24	59.6	1.25	1.27	1.27

Source: Generated by an FDA reviewer.

Abbreviations: AUC_{ss} , area under the plasma concentration-time curve at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{trough,ss}$, trough plasma concentration at steady state; FDA, Food and Drug Administration; HI, hepatic impairment; PK, pharmacokinetic

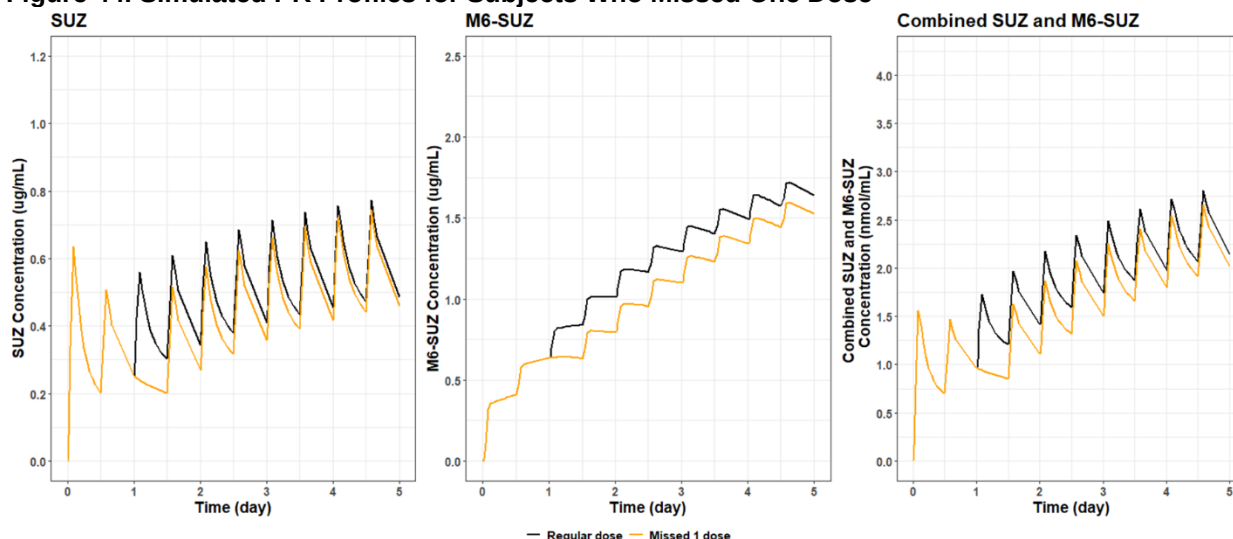
Figure 43. Dose Relationship in Bunionectomy and Abdominoplasty



Missed Dose Management

The reviewer was able to derive simulation result consistent with the Applicant's findings, as shown in [Figure 44](#) and [Figure 45](#). After resuming the make-up dose, within 3-4 dosing intervals, SUZ plasma concentration returns to the same level as with the regular dosing regimen without missed doses.

Figure 44. Simulated PK Profiles for Subjects Who Missed One Dose



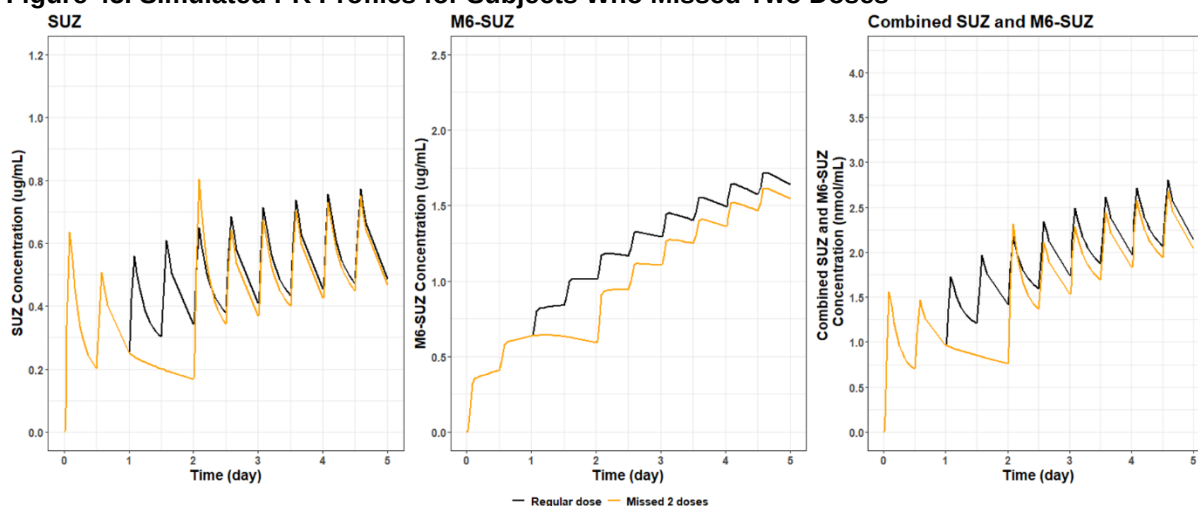
Source: Generated by an FDA reviewer.

Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Typical subjects who received regular dose and missed one dose: Normal hepatic function, BMI: 27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; PK, pharmacokinetic; popPK, population pharmacokinetic; SUZ, suzetrigine; WT, weight

Figure 45. Simulated PK Profiles for Subjects Who Missed Two Doses



Source: Generated by an FDA reviewer.

Note: The simulation was conducted in typical subjects using final popPK model (model 2822) with autoinduction. The combined SUZ and M6-SUZ concentration was calculated by adjusting for potency, M6-SUZ being ~ 1/3 as potent as SUZ.

Typical subjects who received regular dose and missed two doses: Normal hepatic function, BMI: 27.7 kg/m², WT: 73.3 kg, Age: 48 yrs old, male, under bunionectomy.

Abbreviations: BMI, body mass index; FDA, Food and Drug Administration; popPK, population pharmacokinetic; PK, pharmacokinetic; SUZ, suzetrigine; WT, weight

Conclusion

The Applicant's proposed dose regimen for subjects with moderate hepatic impairment, coadministration with a moderate CYP3A inhibitor, and missed doses is acceptable.

Table 158. Listing of Analysis Codes and Output Files

File Name	Description
pk_analysis_Suzetrigine.R	Exploratory PK analysis
Simulation_2822.R	Simulation

Source: Generated by an FDA reviewer.
Abbreviations: FDA, Food and Drug Administration; PK, pharmacokinetic

14.6. Pharmacogenetics

Not applicable.

14.7. Physiologically Based Pharmacokinetic Modeling

The objective of this review is to evaluate the adequacy of the Applicant’s PBPK analyses to predict impact of weak or moderate CYP3A inhibitors or inducers on the PK of SUZ and its primary metabolite, M6-SUZ.

The Division of Pharmacometrics has reviewed the PBPK report (Reports S313 and T415), modeling files, and modeling files and Response to FDA’s Information Request (IR) received on June 28, July 7, July 24, September 10, and October 1, 2024. The reviewers concluded that the final PBPK model can be used to simulate the DDI effect of moderate CYP3A inhibitors or inducers on the PK of suzetrigine and M6-SUZ.

The Applicant has developed PBPK models (Reports S313 and T415) for SUZ using Simcyp version 22 software. The PBPK modeling objectives were to 1) predict the impact of hepatic impairment on the steady-state exposure parameters (e.g., AUC₀₋₂₄ and C_{max}) of SUZ and M6-SUZ; 2) predict the impact of weak or moderate CYP3A inhibitors or inducers on the PK of suzetrigine and its primary metabolite, M6-SUZ.

The DDI simulation results indicated that:

- The AUC and C_{max} for SUZ increase approximately 3.0-and 1.2-fold, respectively, when coadministered with a moderate CYP3A4 inhibitor (such as fluconazole).
- SUZ AUC and C_{max} increased approximately 1.5-fold and 1.4-fold, respectively, when an alternative SUZ dosing regimen was implemented to manage the DDI with fluconazole, compared to the default SUZ dosing.
- The AUC and C_{max} for M6-SUZ increase approximately 2.6-fold and 0.7-fold, respectively, when coadministered with a moderate CYP3A4 inhibitor (such as fluconazole).
- M6-SUZ AUC and C_{max} increased approximately 1.2-fold and 1.1-fold, respectively, when an alternative SUZ dosing regimen was implemented to manage the DDI with fluconazole, compared to the default SUZ dosing.
- The AUC and C_{max} for SUZ would decrease approximately by 60% and 30%, respectively, when coadministered with a moderate CYP3A4 inducer (such as efavirenz).

- The AUC and $C_{\max}$ for M6-SUZ would decrease approximately 60% and increase approximately 1.3-fold, respectively, when coadministered with a moderate CYP3A4 inducer (such as efavirenz).
- Weak CYP3A inhibitors and weak CYP3A inducers would have minor effects on SUZ and M6-SUZ exposure.

Background

The suzetrigine (JOURNAVX) dosing regimen is a loading dose of 100 mg in a fasted state (b) (4) followed by a maintenance dosing regimen of 50 mg twice daily (BID) (b) (4). Food restriction is not required during the maintenance dosing time frame.

Apparent volume of distribution based on the terminal phase (V_z/F) of SUZ is 495 L. Plasma protein binding was 99% for SUZ and 96% for M6-SUZ. Both albumin and alpha-1 acid glycoprotein contribute to SUZ and M6-SUZ binding in human plasma. The in vitro blood-to-plasma concentration ratio was approximately 0.6 for both SUZ and M6-SUZ in humans. SUZ is not a substrate for transporters (P-gp, BCRP, OATP1B1 or OATP1B3). M6-SUZ is a substrate for P-gp, but not other transporters.

Following [^{14}C]SUZ oral administration, ~94% of the administered dose was recovered, out of which ~50% was recovered in feces (primarily as metabolites, with 9.1% unchanged parent and <0.9% unchanged M6-SUZ) and ~44% in urine (as metabolites). The mean plasma apparent clearance is 13.9 L/h. Effective half-lives of SUZ and M6-SUZ are 24 hours and 33 hours, respectively. SUZ and M6-SUZ are primarily metabolized by CYP3A, with minor contributions from CYP2C9, CYP2C19, and CYP2C8. SUZ was mainly cleared by oxidative metabolism. After a single oral dose of [^{14}C]SUZ, 44.0% and 49.9% of the dose was excreted in urine and feces, respectively.

Based on in vitro data, SUZ and M6-SUZ are not expected to result in clinically significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes. SUZ decreased the AUC of midazolam (a sensitive CYP3A substrate) by 48% and $C_{\max}$ by 37% (Study 010). Compared to CYP3A, SUZ has lesser potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19 based on the in vitro data. SUZ does not induce CYP1A2 according to the in vitro data. SUZ has no significant effect on the PK of levonorgestrel and ethinyl estradiol.

A clinical DDI study (Study 010) showed that SUZ did not affect the PK of digoxin (P-gp substrate). Based on in vitro data, SUZ and M6-SUZ do not inhibit transporters (OATP1B1, OATP1B3, OAT3 BCRP OAT1, organic cation transporter (OCT) 2, multidrug and toxin extrusion protein [MATE] 1, and MATE2/K).

The Applicant also used PBPK analysis to assess the effects of hepatic impairment. At the current stage, the application of PBPK analysis to assess the effects of hepatic impairment without clinical data is considered exploratory. The Applicant's PBPK analysis for severe hepatic impairment was not reviewed.

Methods

Model Development

The PBPK analyses were performed using the PBPK software Simcyp® V22 (Simcyp Ltd., Sheffield, UK).

The suzetrigine PBPK model was developed based on physicochemical properties and preclinical and clinical PK data. The SUZ 50-mg (b) (4) tablet is an immediate-release tablet with a (b) (4) film coating (b) (4). However, absorption for the SUZ (b) (4) tablet was described using (b) (4) dissolution, absorption, and metabolism model under the fasted state. It allows simulating an increased solubilization of SUZ in small intestine, where the solubility (b) (4) is higher than in the stomach. Human effective permeability ($P_{eff,man}$) (12×10^{-4} cm/s) was estimated from Caco-2 permeability by using the SIMCYP built-in calculator and the in vitro permeability data in Madin-Darby canine kidney – knockout (MDCK-KO) cells ($P_{app} = 12.25 \times 10^{-6}$ cm/s) calibrated with propranolol's P_{app} value of 12.43×10^{-6} cm/s (Study FDD-36383). The values of Q_{gut} (nominal flow through gut model) and unbound fraction in enterocytes ($f_{u,gut}$) were optimized based on using PK data from VX19-548-001 (single ascending dose study), VX20-548-002 (multiple ascending dose study), and VX21-548-008 (DDI study with itraconazole).

The full PBPK distribution model was utilized, and steady-state volume of distribution (V_{ss}) was predicted via Method 2 in Simcyp software. Furthermore, a tissue-to-plasma partitioning coefficient scalar (Kp scalar) of 0.55 was applied to fit the observed SUZ PK data from the following clinical studies: VX21-548-008 (itraconazole DDI study), VX22-548-013 (rifampin DDI study), VX21-548-011 (relative bioavailability study).

SUZ intravenous clearance (CL_{iv}) was set as 5.8 L/h based on the PBPK model-predicted bioavailability value (F) and the observed apparent oral CL values in Study VX21-548-011 and VX22-548-013, assuming minimal first-pass elimination in the gut (Response to the IR received on July 24, 2024). SUZ's fm (fraction metabolized) values for CYP3A4, CYP2C19, and CYP2C9 were set to 0.85, 0.10, and 0.05, respectively, based on CYP reaction phenotyping studies in recombinant CYP enzymes in human liver microsomes (Report R161). M6-SUZ's fm values for CYP3A4 and CYP2C9 were set to 0.85 and 0.15, respectively, according to Report R184. These fmCYP (fraction of hepatic clearance of the substrate mediated by an individual CYP enzyme) values were confirmed by two DDI study results with rifampin (VX22-548-013) or itraconazole (VX21-548-008).

Additionally, the CYP3A4 induction E_{max} value of 12.92, half-maximal effective concentration (EC_{50}) value of 1.097 and fraction of unbound drug ($f_{u,inc}$) value of $0.63 \mu M$ were incorporated into the PBPK model for SUZ. These values are the average values of the calibrated fold mRNA E_{max} and EC_{50} from data of three hepatocyte lots in Report P169.

An absorption process using the first-order absorption model for the active primary metabolite, M6-SUZ, is included in the PBPK model, although the gastrointestinal absorption process does not occur for a metabolite. A full PBPK distribution model predicted the V_{ss} via Method 2 in Simcyp software. A Kp scalar of 0.2 was applied to fit the observed M6-SUZ PK data. The CL_{iv} value of M6-SUZ was set to 2.23 L/h. M6-SUZ's fmCYP3A4 and fmCYP2C9 values were set to be 0.85 and 0.15, respectively, based on results in human liver microsomes (Report R184). These

fmCYP values were confirmed by two DDI study results with rifampin (VX22-548-013) or itraconazole (VX21-548-008).

Additionally, the CYP3A4 induction $E_{\max}$ value of 9.63, EC_{50} value of 4.115 and $f_{u,inc}$ value of 0.73 μ M were incorporated into the PBPK model for M6-SUZ. These values are the average values of the calibrated fold mRNA $E_{\max}$ and EC_{50} from data of three hepatocyte lots in Report P169. The CYP3A induction parameters for SUZ and M6-SUZ were confirmed by matching the observed midazolam PK data in Study VX21-548-010, where 2 mg midazolam was dosed after SUZ PK reached steady state.

In response to the FDA's IR, the Applicant stated that the (b) (4) fasted-state simulated intestinal fluid (FaSSIF) was used to represent the intrinsic solubility of the compound in the PBPK model, (b) (4)

(b) (4) A solubility value of 0.036 mg/mL (b) (4) FaSSIF was used in the model (Report T415); for comparison, the solubility of (b) (4) FaSSIF is <0.002 mg/mL. Reviewers noted that the intrinsic solubility refers to the solubility of the compound itself. The (b) (4) bile salt, therefore, should not be integrated. The Applicant stated that the human ADME study (VX21-548-008) results indicated a fraction absorbed more than 0.9 following an 80-mg single dose in capsules. Furthermore, the Applicant estimated the dose-normalized AUC across clinical study cohorts following a single dose of 100 mg and compared them to the dose-normalized AUC value after an 80-mg dose in the human absorption, metabolism, and excretion study (VX21-548-006). The resultant ratio was in the range of 0.97 to 1.2. These results implicitly demonstrated a high fraction absorbed (Fa) following a 100-mg single dose in the (b) (4) formulation.

Model Verification

PK Performance

- A single 100-mg SUZ dose in healthy subjects (Study VX22-548-013, VX21-548-011)
- Multiple dosing (50 mg q12h) in healthy subjects (VX21-548-007)

Victim DDI Potential of SUZ as a CYP3A Substrate

- Verification of the contribution of CYP-mediated metabolic pathways using the clinical DDI data with the strong CYP3A inhibitor itraconazole (Study VX21-548-008) in healthy subjects
- Verification of the contribution of CYP-mediated metabolic pathways using the clinical DDI data with the strong CYP3A inhibitor rifampin (Study VX21-548-013) in healthy subjects

DDI Potential of SUZ as a CYP3A Inducer

- Verification of SUZ and M6-SUZ's CYP3A induction parameters using the DDI data of midazolam with 100 mg SUZ (VX21-548-010) in healthy subjects

Model Application

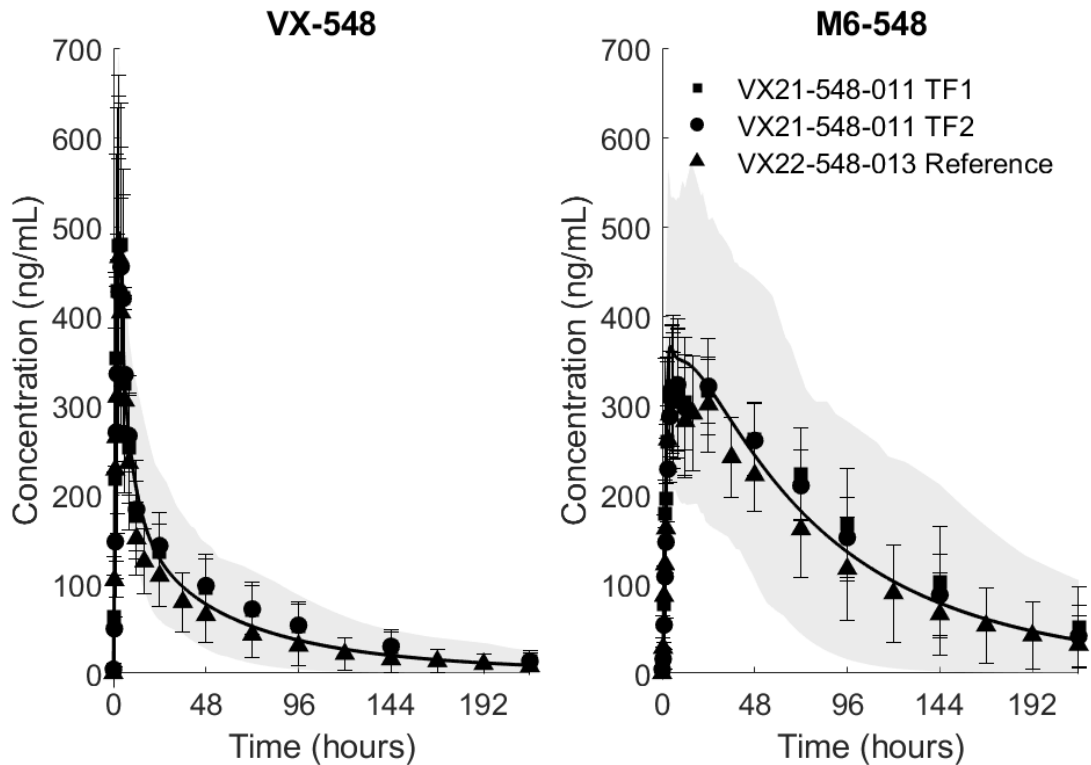
- Prediction of the effect of a moderate CYP3A inhibitor on SUZ and M6-SUZ's PK: Simulation: SUZ 100-mg single dose (on Day 8), administered with fluconazole (200 mg BID for 28 days) in healthy volunteers, fasted state
- Prediction of the effect of a weak CYP3A inhibitor on SUZ and M6-SUZ's PK: SUZ 100-mg single dose (on Day 4), administered with cimetidine (400 mg BID Days 1 through 24) in healthy volunteers, fasted state
- Prediction of the effect of a moderate CYP3A inducer on SUZ and M6-SUZ's PK: SUZ 100-mg single dose (on Day 28), administered with phenobarbital (100 mg qd Days 1 through 37) in healthy volunteers, fasted state
- Prediction of the CYP3A induction effect of a moderate CYP3A inducer on SUZ and M6-SUZ PK: SUZ 100-mg single dose (on Day 12), administered with efavirenz (600 mg qd Days 1 through 21) in healthy volunteers, fasted state
- Prediction of the CYP3A induction effect of a weak CYP3A inducer on SUZ and M6-SUZ PK: SUZ 100-mg single dose (on Day 9), administered with modafinil (200 mg qd Days 1 through 18) in healthy volunteers, fasted state
- Prediction of the effect of a moderate CYP3A inhibitor on the PK of SUZ or M6-SUZ following the modified dosing regimen in healthy volunteers, fasted state

Results

Q1. Can the PBPK model adequately describe the PK profiles of SUZ and M6-SUZ?

Yes, the PBPK model of SUZ adequately described SUZ or M6-SUZ PK following administration of a single 100-mg dose ([Figure 46](#)) and multiple dosing (50 mg BID) in healthy subjects ([Figure 47](#) and [Table 159](#)).

Figure 46. Predicted and Observed Plasma PK Profiles of SUZ and M6-SUZ After a Single 100-mg Dose in Healthy Subjects

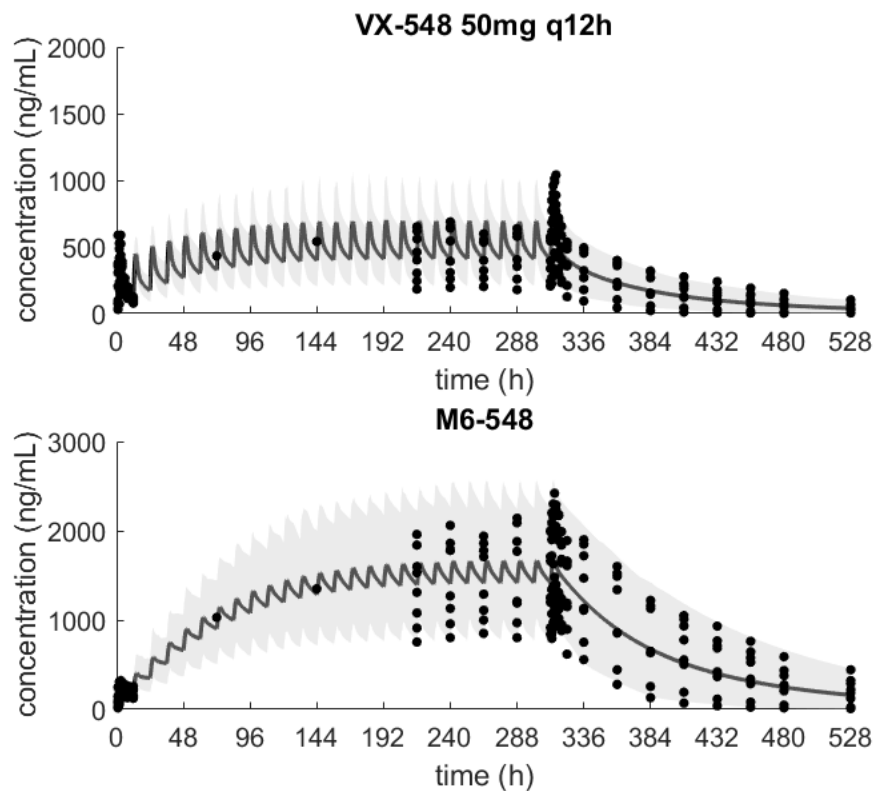


Source: Report #T415

Notes: VX-548 is SUZ and M6-548 is M6-SUZ. Solid symbols represent the observed data (mean $\pm$ standard deviation) from study VX21-548-011 and VX-22-548-013 (VX21-548-011 CSR and VX-22-548-013 CSR). Solid lines represent simulated mean and shaded areas represent area between the 5th and 95th percentile of the virtual population. TF1 is the reference tablet formulation (supplied as 10-mg tablets) and TF2 is the test tablet formulation (supplied as 50-mg tablets).

Abbreviations: CSR, clinical study report; PK, pharmacokinetic; SUZ, suzetrigine; TF1, tablet formulation 1; TF2, tablet formulation 2

Figure 47. Observed and Predicted SUZ and M6-SUZ Plasma Concentration-Time Profile Following 50 mg BID



Source: Report #T415
Notes: VX-548 is SUZ and M6-548 is M6-SUZ. Solid circles represent the individual observed data from study VX21-548-007 (VX21-548-007 CSR). Solid lines represent simulated mean and shaded areas represent area between the 5th and 95th percentile of the virtual population.
Abbreviations: BID, twice daily; CSR, clinical study report; PK, pharmacokinetics; SUZ, suzetrigine; q12h, every 12 hours

Table 159. Summary of Observed and Predicted Exposure PK Parameters of SUZ and M6-SUZ Following 50 mg BID Regimen

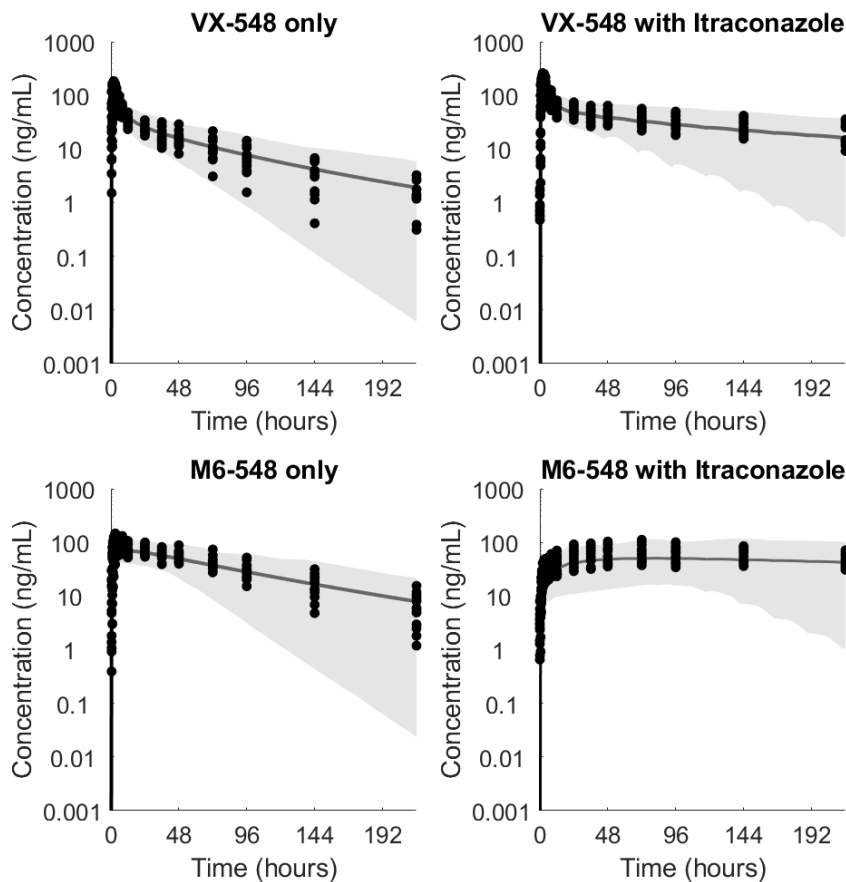
Parameter		SUZ		M6-SUZ	
		Day 1	Day 14	Day 1	Day 14
C _{max} (µg/mL)*	Observed	0.451 (25.5)	0.787 (30.1)	0.236 (22.7)	1.72 (29.3)
	Predicted	0.403 (18.1)	0.733 (25.5)	0.235 (30.8)	1.70 (29.0)
AUC _{0-12h} (µg·hr/mL)*	Observed	2.36 (19.3)	6.32 (33.6)	2.18 (26.2)	18.0 (30.9)
	Predicted	2.12 (16.4)	6.10 (31.8)	2.05 (30.1)	18.4 (32.0)

Source: Report #T415
Source of the observed data: VX21-548-007 CSR
* Mean (%CV)
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; SUZ, suzetrigine

Q2. Can PBPK analyses predict the effect of a strong CYP3A inhibitor on the PK of SUZ or M6-SUZ?

Yes, the PBPK model adequately simulated SUZ and M6-SUZ PK profiles and exposure parameters following a single 20-mg SUZ dose, with or without itraconazole, as shown in [Figure 48](#) and [Table 160](#).

Figure 48. Predicted and Observed SUZ and M6-SUZ Concentrations in Plasma vs. Time Profiles After a Single 20-mg Dose in Healthy Subjects, Without or With Itraconazole



Source: Report #T415
Notes: VX-548 is SUZ and M6-548 is M6-SUZ, Solid circles represent the individual observed data from study VX21-548-008 (VX21-548-008 CSR). Solid lines represent simulated mean and shaded areas represent area between the 5th and 95th percentile of the virtual population.
Abbreviations: CSR, clinical study report; SUZ, suzetrigine

Table 160. Summary of Observed and Predicted PK Exposure Parameters of SUZ and M6-SUZ With or Without Itraconazole

Condition	Parameter		SUZ	M6-SUZ
SUZ alone	C_{max} (µg/mL), mean (%CV)	Observed	0.140 (20.9)	0.0936 (26.0)
		Predicted	0.181 (16.8)	0.0903 (29.2)
	AUC_{inf} (µg·hr/mL), mean (%CV)	Observed	2.59 (27.6)	7.91 (20.7)
		Predicted	2.90 (50.1)	7.74 (57.7)
SUZ and itraconazole	C_{max} (µg/mL), mean (%CV)	Observed	0.204 (18.2)	0.0662 (37.6)
		Predicted	0.217 (16.4)	0.0653 (53.5)
	AUC_{inf} (µg·hr/mL), mean (%CV)	Observed	12.9 (42.5)	32.3 (30.3)
		Predicted	17.6 (60.1)	52.4 (149)

Condition	Parameter		SUZ	M6-SUZ
PK exposure parameter comparison: SUZ + itraconazole versus SUZ alone	$C_{\max}$ ratio, geomean (90%CI)	Observed ^a	1.47(1.32 – 1.64)	0.683(0.611 – 0.764)
		Predicted ^b	1.20 (1.19 – 1.22)	0.662 (0.616 – 0.711)
	AUC _{inf} ratio, geomean (90% CI)	Observed ^a	4.79 (4.28 – 5.35)	4.42 (3.64 – 5.37)
		Predicted ^b	4.68 (4.27 – 5.13)	4.23 (3.45 – 5.17)

Source: Report #T415

Observed data source: VX21-548-008 CSR

^a Geometric least squares mean (GLSM) ratio (90% CI for the GLSM)

^b Geometric mean of ratios (90% CI around geometric mean of ratios).

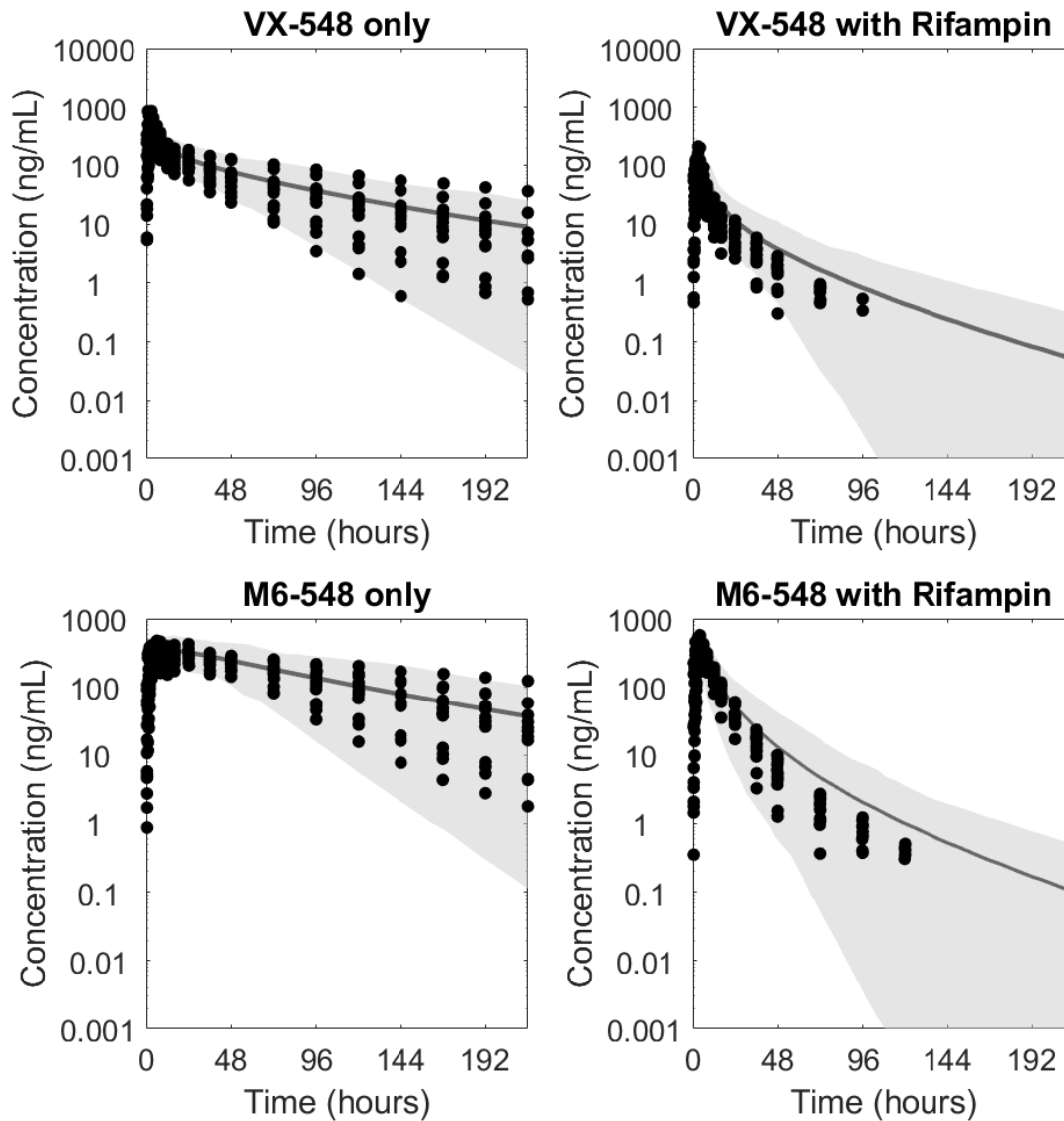
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; $C_{\max}$, maximum plasma concentration; geomean, geometric mean; GLSM, geometric least-squares mean; CV, coefficient of variation; PK, pharmacokinetic; SUZ, suzetrigine

The predicted AUC or $C_{\max}$ value after a single 20-mg dose was similar to the observed value in study VX21-548-008. Likewise, the predicted AUC or $C_{\max}$ value after a single 20-mg dose in the presence of itraconazole was similar to the observed value in the study. The corresponding AUC ratio or $C_{\max}$ ratio predicted by the PBPK model was comparable to the observed value. The simulation results for the itraconazole DDI study confirmed the fmCYP3A4 value of 85% for SUZ or M6-SUZ incorporated in the PBPK model.

Q3. Can PBPK analyses predict the effect of a strong CYP3A inducer on the PK of SUZ or M6-SUZ?

Yes, the PBPK model adequately simulated SUZ and M6-SUZ PK profiles and exposure parameters following a single 100-mg SUZ dose, with or without rifampin, as shown in [Figure 49](#) and [Table 161](#).

Figure 49. Predicted and Observed SUZ and M6-SUZ Concentrations in Plasma vs. Time Profiles After a Single 100-mg Dose in Healthy Subjects, Without or With Rifampin



Source: the Applicant's report T415.

Notes: VX-548 is SUZ and M6-548 is M6-SUZ. Solid circles represent the individual observed data from study VX22-548-013 (VX22-548-013 CSR). Solid lines represent simulated mean and shaded areas represent area between the 5th and 95th percentile of the virtual population.

Abbreviations: CSR, clinical study report; SUZ, suzetrigine

Table 161. Summary of Observed and Predicted PK Exposure Parameters of SUZ and M6-SUZ With or Without Rifampin

Condition	Parameter		SUZ	M6-SUZ
SUZ alone	C_{max} (µg/mL), mean (%CV)	Observed	0.559 (33.4)	0.344 (21.4)
		Predicted	0.547 (20.3)	0.413 (28.7)
	AUC_{inf} (µg·hr/mL), mean (%CV)	Observed	11.4 (50.6)	29.2 (28.8)
		Predicted	13.9 (49.6)	37.1 (57.1)
SUZ and rifampin	C_{max} (µg/mL), mean (%CV)	Observed	0.118 (39.4)	0.447 (20.3)
		Predicted	0.206 (36.7)	0.548 (26.9)
	AUC_{inf} (µg·hr/mL), mean (%CV)	Observed	0.763 (33.3)	4.40 (19.0)
		Predicted	1.60 (52.9)	5.37 (62.1)
PK exposure parameter comparison: SUZ + rifampin versus SUZ alone	C_{max} ratio, geomean (90% CI)	Observed ^a	0.205 (0.166 – 0.252)	1.29 (1.14 – 1.46)
		Predicted ^b	0.359 (0.341 – 0.378)	1.34 (1.27 – 1.41)
	AUC_{inf} ratio, geomean (90% CI)	Observed ^a	0.0727 (0.0602 – 0.0879)	0.153 (0.136 – 0.173)
		Predicted ^b	0.113 (0.106 – 0.121)	0.142 (0.134 – 0.150)

Source: Report #T415

Observed data source: VX21-548-013 CSR

^a Geometric least squares mean (GLSM) ratio (90% CI for the GLSM).

^b Geometric mean of ratios (90% CI around geometric mean of ratios).

Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max} , maximum plasma concentration; CV, coefficient of variation; geomean, geometric mean; GLSM, geometric least-squares mean; PK, pharmacokinetic; SUZ, suzetrigine

Q4. Can PBPK analyses predict the effect of a weak or moderate CYP3A modulator on the PK of SUZ or M6-SUZ following a single SUZ dose?

Yes, the PBPK model adequately predicted the effect of a weak or moderate CYP3A modulator on the PK of SUZ and M6-SUZ after a single SUZ dose. The Applicant conducted the DDI simulation for a single 20-mg SUZ dose (not the proposed therapeutic dose) as a CYP3A substrate administered 2 hours after CYP3A inhibitor dosing in a 23- to 52-year-old population (not the intended patient population age range). The Applicant responded to the agency that the SUZ dose, dosing time, and the participants' age range in the itraconazole DDI study (VX21-548-008) were applied to the DDI simulations for SUZ as a CYP3A substrate with weak to moderate CYP3A inhibitors. The Applicant conducted the DDI simulation for a single 100-mg SUZ dose as a CYP3A substrate after CYP3A inducer dosing in 23- to 52-year-old population. Hence, the reviewer performed a DDI simulation for a single 100-mg dose in an 18- to 65-year-old population. The simulation results are summarized in [Table 162](#).

1. After a single 100-mg SUZ dose coadministered with the moderate CYP3A inhibitor fluconazole (200 mg qd Days 1 through 28), SUZ's geometric mean AUC and C_{max} ratio was predicted to be 3.0 (90% CI: 2.9, 3.1) and 1.2 (90% CI: 1.2, 1.2), whereas for M6-SUZ, the predicted AUC and C_{max} ratio was 2.6 (90% CI: 2.5, 2.6) and 0.74 (90% CI: 0.72, 0.77).
2. The geometric mean PK exposure ratio was predicted to be ~1.1 after a single 100-mg SUZ dose in the presence of a weak CYP3A inhibitor, such as cimetidine (400 mg BID).
3. SUZ's and M6-SUZ's geometric mean AUC ratios (90% CI) were 0.37 (0.35, 0.39) and 0.40 (0.38, 0.42), and geometric mean C_{max} ratio (90% CI) were 0.71 (0.68, 0.73) and 1.32 (1.28, 1.36) following a single 100-mg SUZ dose in the presence of a moderate CYP3A inducer (e.g., efavirenz 600 mg qd). The Applicant recommend avoiding concomitant use of SUZ with moderate CYP3A inducers, as coadministration with a moderate CYP3A inducer (e.g.,

efavirenz) results in an approximate 40% decrease in SUZ exposure. The reviewer did not assess the effect of a moderate CYP3A inducer following multidosing SUZ.

4. SUZ's and M6-SUZ's exposure ratio for AUC and C_{max} were ~0.8-1.0 after a single 100-mg SUZ dose in the presence of a weak CYP3A inducer (e.g., modafinil).

Table 162. Summary of the Predicted Effects of a Moderate CYP3A Inducer or Inhibitor on Suzetrigine and M6-SUZ PK

Substrate (Dosing Regimen)	Perpetrator (Dosing Regimen)	Suzetrigine		M6-SUZ	
		AUC Ratio ^a	C_{max} Ratio ^a	AUC Ratio ^a	C_{max} Ratio ^a
Suzetrigine (a single dose of 100 mg)	Fluconazole (200 mg qd)	3.0 (2.9-3.1)	1.2 (1.2-1.2)	2.6 (2.5-2.6)	0.74 (0.72-0.77)
Suzetrigine (a single dose of 100 mg)	Cimetidine (400 mg BID)	1.1 (1.1-1.1)	1.1 (1.1-1.1)	1.1 (1.1-1.1)	0.92 (0.91-0.93)
Suzetrigine (a single dose of 100 mg)	Efavirenz (600 mg qd)	0.37 (0.35-0.39)	0.71 (0.68-0.73)	0.40 (0.38-0.42)	1.32 (1.28-1.36)
Suzetrigine (a single dose of 100 mg)	Modafinil (200 mg qd)	0.84 (0.83-0.86)	0.96 (0.95-0.96)	0.83 (0.82-0.85)	1.0 (1.0-1.0)

Source: FDA reviewer's PBPK analysis results

PBPK simulation results performed by the reviewer

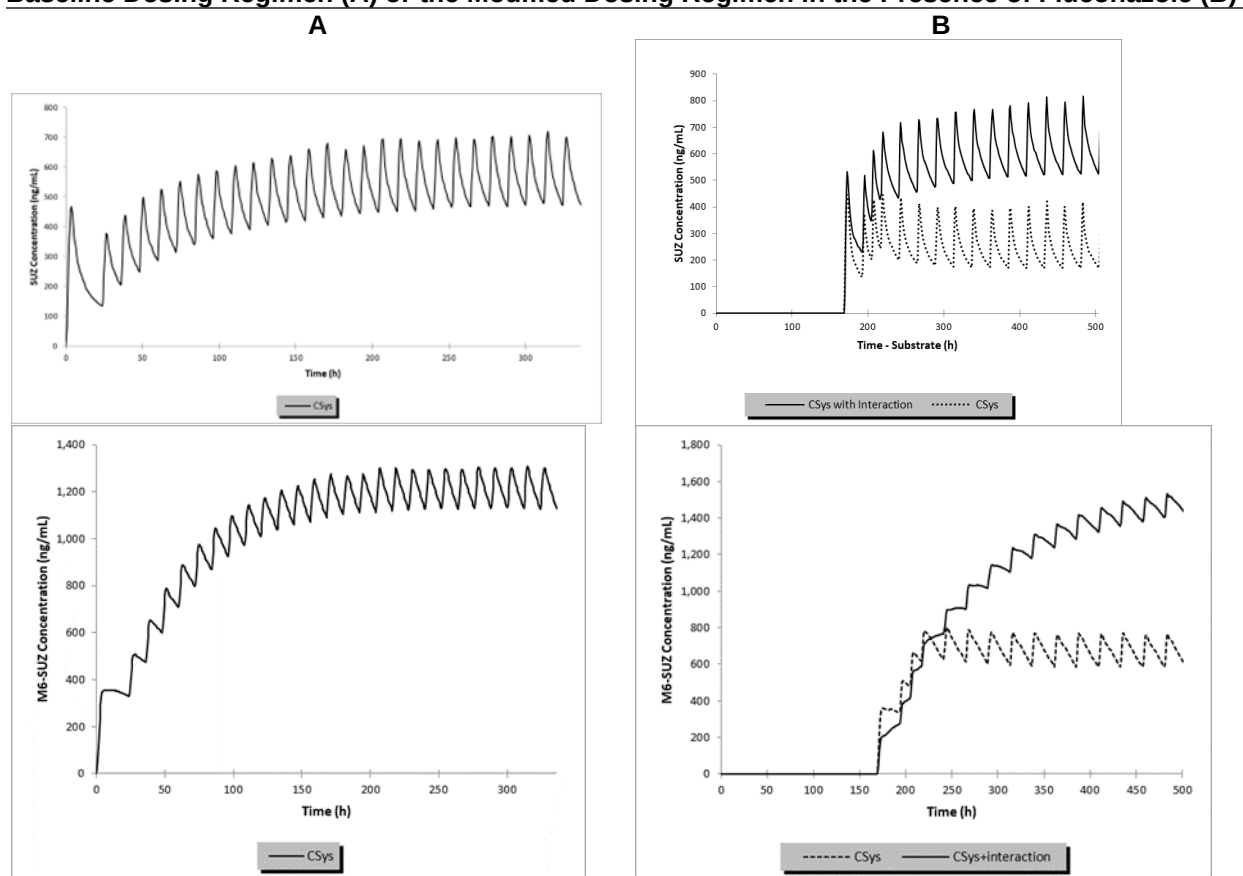
^a Values as geometric mean (GM) (90% CI)

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; C_{max} , maximum plasma concentration; CYP, cytochrome p450; GM, geometric mean; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; SUZ, suzetrigine; qd, once daily

Q4. Can PBPK analyses predict the effect of a moderate CYP3A inhibitor on the PK of SUZ or M6-SUZ following the modified dosing regimen?

The reviewer conducted DDI simulations to assess the effect of fluconazole on SUZ and M6-SUZ's PK following the modified dosing regimen (i.e., 100 mg on Day 1 + 50 mg every 12 hours for three doses, followed by 50 mg qd on Days 4 to 14, in the presence of a moderate CYP3A inhibitor), and compared the predicted exposure PK parameters with the baseline dosing regimen (i.e., 100 mg on Day 1 + 50 mg BID on Days 2 to 14). The simulation using the modified dosing regimen is needed for the following reasons: 1) the appropriate dose metrics at PK steady state are more relevant than those estimated after a single dose of SUZ in the presence of a moderate CYP modulator, 2) SUZ is a weak-to-moderate CYP3A inducer and would have decreased PK exposure after multiple doses. Therefore, a straightforward dose adjustment using the AUC ratio derived from the single-dose DDI simulation is not suitable. In the virtual DDI trial setting, 200 mg fluconazole qd was set from Day 1 to Day 28, and the modified SUZ dosing regimen was set to start on Day 8. The PBPK-predicted effect of a moderate CYP3A inhibitor on the PK of SUZ or M6-SUZ following the modified dosing regimen was that the AUC and C_{max} ratio for SUZ or M6-SUZ was ≤ 1.5 on Day 14 when compared to the baseline dosing regimen (Figure 50, Table 163).

Figure 50. Predicted SUZ and M6-SUZ Concentration in Plasma vs. Time Profiles Following the Baseline Dosing Regimen (A) or the Modified Dosing Regimen in the Presence of Fluconazole (B)



Source: Analysis conducted by the Agency's reviewer.
Abbreviations: SUZ, suzetrigine; CSys, systemic concentration

Table 163. Summary of the Predicted SUZ and M6-SUZ PK Exposure Parameters on Day 14 Following the Baseline Dosing Regimen or the Modified Dosing Regimen in the Presence of Fluconazole (200 mg qd)

Analyte	AUC _{0-24h} (ng/mL·h)		C _{max} (ng/mL)		AUC Ratio	C _{max} Ratio
	Baseline Dosing Regimen	Modified Dosing Regimen + Fluconazole	Baseline Dosing Regimen	Modified Dosing Regimen + Fluconazole		
SUZ	9414	13857	599	861	1.5	1.4
M6-SUZ	27252	33126	1294	1479	1.2	1.1

Source: The analysis was conducted by the Agency's reviewer.
Geometric mean value reported for AUC_{0-24h} and C_{max} on Day 14 following the baseline dosing regimen or the modified dosing regimen in the presence of fluconazole. As it is not a cross-over population simulation, the 90% confidence interval for PK parameters is not reported. The AUC ratio or the C_{max} ratio is the simulated AUC or C_{max} value following the modified dosing regimen versus the simulated AUC or C_{max} value following the baseline dosing regimen.
Baseline SUZ dosing regimen: 100 mg on Day 1 + 50 mg BID every 12h and onward to Day 14.
Modified SUZ dosing regimen: 100 mg on Day 1 + 50 mg BID every 12h for 3 doses followed by 50 mg qd on Day 4 and onward to Day 14.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration, PK, pharmacokinetic; qd, once daily; SUZ, suzetrigine

15. Study / Trial Design

This section describes in detail the designs of the two phase 3 double-blind, placebo-controlled studies (Studies 104 and 105) that were submitted as evidence of safety and efficacy. In addition, this section briefly describes Study 107, a phase 3, open-label, longer term safety and efficacy study.

15.1. Study of Bunionectomy Pain, VX22-548-104 (Study 104)

15.1.1. Study Design, Study 104

Overview and Objective

The primary objective of Study 104 was to evaluate the efficacy of SUZ in treating acute pain after a bunionectomy.

Study Design

Study 104 was a randomized, double-blind, placebo-controlled, three-arm, parallel-group study evaluating the efficacy and safety of SUZ in treating acute pain after a bunionectomy. The study took place at 21 clinical sites in the United States.

Subjects were randomized 2:2:1 to the SUZ, HB/APAP, or placebo treatment groups, respectively. The sample size was 1,073 subjects with 216 subjects in the placebo arm, 431 subjects in the HB/APAP arm, and 426 subjects in the SUZ arm (full analysis set).

The treatment arms consisted of placebo, SUZ 100 mg for the first dose followed by 50 mg every 12 hours, and HB/APAP 5/325 mg every 6 hours. All subjects received the same number of tablets and capsules every 6 hours in a double-dummy design.

The surgery was performed under regional anesthesia (Mayo and popliteal sciatic block) with intravenous sedation. A continuous popliteal sciatic block infusion was started after surgery and remained in place until approximately 3 a.m., but no later than 5 a.m., on post-operative Day 1. Subjects were on a clear liquid diet (≤ 8 fluid ounces per hour) starting 2 hours before block removal through 2 hours after the first dose of study drug. After this period, study drug could be taken with or without food.

The duration of treatment was 48 hours. The safety follow-up visit took place 14 ± 2 days after the last dose of study drug.

Ibuprofen (400 mg orally every 6 hours as needed) was permitted as a rescue medication starting any time after the first dose of study drug through 48 hours after the first dose of study drug. All other medications with analgesic properties, except for those permitted for perioperative pain management, were prohibited for five half-lives or 2 days (whichever was longer) before admission through completion of 48-hour assessments (or after early discontinuation, if applicable).

In the postoperative period, supplemental analgesic medications were permitted before the time of popliteal block removal. This included acetaminophen (975 to 1,000 mg every 6 hours as needed) until 6 hours before removal of the popliteal block for subjects with NPRS score of 4 through 6, intravenous fentanyl citrate (12.5 to 25 µg every 2 hours as needed) until 1.5 hours before removal of the popliteal block for subjects with NPRS score of 7 or above, and ropivacaine boluses and/or infusion rate changes as needed prior to removal of the popliteal block for subjects with NPRS score of ≥ 4 . Boluses were not to be used at the time of block removal.

Administration of study drug began once the subject's eligibility had been confirmed by their request for the first dose of study drug for pain relief and postoperative pain that was reported as moderate or severe on the verbal rating scale (VRS) and ≥ 4 on the NPRS within 9 hours after removal of the popliteal sciatic block. The first dose of study drug was required to be administered within 25 minutes after randomization.

Other key inclusion criteria included the following: 1) male or female between the ages of 18 and 80 years, inclusive; 2) BMI of 18 to 40 kg/m², inclusive; 3) had undergone a primary unilateral bunionectomy with distal first metatarsal osteotomy (i.e., Austin procedure) and internal fixation under regional anesthesia (Mayo and popliteal sciatic block); 4) lucid and able to follow commands; 5) all analgesic guidelines were followed during and after the bunionectomy.

The key exclusion criteria included the following:

- Before surgery:
 - Prior history of bunionectomy or other foot surgery on the index foot or bunionectomy on the opposite foot as part of this study.
 - History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
 - Cardiac dysrhythmias requiring antiarrhythmic treatment(s) within the last 2 years; history or evidence of abnormal study ECGs that, in the opinion of the investigator or medical monitor, would preclude the subject's participation in the study; or history of QT prolongation or standard 12-lead ECG (performed in triplicate) demonstrating median corrected QT interval, Fridericia's calculation (QTcF) >450 msec at the screening visit or on Day -1 (preprocedure).
 - Presence of an automated implantable cardioverter defibrillator, cardiac resynchronization therapy device, or pacemaker.
 - History of significant hepatic disease.
 - Alanine transaminase or aspartate transaminase values $>2.5\times$ upper limit of normal.
 - History of severe renal impairment defined as eGFR of <30 mL/min/1.73m² calculated using the subject's measured serum creatinine.
 - History of any sensory abnormality that, in the opinion of the investigator, may confound the ability of the subject to assess postoperative pain.
 - Subjects who have a painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain.

- Any prior surgery within 1 month before the first study drug dose, unless approved by the medical monitor.
- American Society of Anesthesiologists physical status classification of ≥ 3 .
- Chronic use of opioids (pure agonists, agonist/antagonists, partial agonists, antagonists) or nonsteroidal anti-inflammatory drugs (NSAIDs) with dose escalation within 30 days before admission or unwillingness or inability to stop analgesics at least five half-lives or 2 days (whichever is longer) before admission.
- Subjects who have started new medications that have not been at a stable dose for at least 14 days prior to the scheduled bunionectomy procedure and before dosing with investigational product.
- Subjects with sleep apnea and/or on a home positive airway pressure device.
- History of peptic ulcer disease or gastrointestinal bleeding that, in the opinion of the investigator or medical monitor, would preclude the subject's participation in the study.
- Evidence of misuse, aberrant use, or addiction to alcohol or an illicitly used drug of abuse in the past 3 years, or a positive test for drugs of abuse.
 - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.
- After surgery:
 - Subject had a type 3 deformity requiring a base wedge osteotomy, concomitant surgery such as hammertoe repair, or any surgical complications during the bunionectomy.
 - Subject had a medical complication during the bunionectomy that, in the opinion of the investigator, should preclude randomization.
 - Standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at baseline (Day 1 predose).

NDA 219209
Journavx (Suzetrigine; VX-548)

Table 164. Schedule of Assessments (Screening Visit Through Admission), Study 104

Event/Assessment	Day -28 to Day -2	Day -1
	Screening Visit	Pre-procedure
Informed consent	X	
Clinic or home health visit	X	
Telemedicine video conference or telephone contact	(X)	
Admission		X
Demographics	X	
Medical and surgical history	X	
History of drug and alcohol use	X	
Prior use of opioid medications	X	X
Vital signs	X	X
Standard 12-lead ECG	X	X
PE	X	(X)
Weight, height, and BMI	X	
Serology (HbsAg, HCV Ab, HCV RNA, HIV-1/HIV-2 Ab/Ag, and HIV-1/HIV-2 RNA)	X	
Serum β -hCG	X	
Serum FSH	X	
Serum chemistry	X	
Hematology	X	
Coagulation	X	
Urinalysis	X	
Urine β -hCG		X
Drug test	X	X
Alcohol test		X
Research subject responsibilities, placebo, and pain assessment trainings	X	X
Medications review	Continuous from signing of ICF through completion of study participation	
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation	
Adverse events	Continuous from signing of ICF through completion of study participation	

Source: Applicant's Submission of Protocol VX22-548-104 (April 12, 2023; Version 4.0, pages 7-8)

Abbreviations: β -hCG, beta human chorionic gonadotropin; Ab, antibody; Ag, antigen; BMI, body mass index; ECG, electrocardiogram; FSH, follicle stimulating hormone; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICF, informed consent form; PE, physical examination

Table 165. Schedule of Assessments (Procedure Through Randomization), Study 104

Event/Assessment	Day -1	Day 1
	Procedure and Post-procedure	Block Removal Through Randomization / Predose ^a
Inpatient period	X	X
Bunionectomy	X	
Record supplemental analgesic medication	X	X
Clear liquid diet		X
Removal of popliteal sciatic block (block removal)		X
Vital signs		X
Standard 12-lead ECG		X
Blood sampling for PK		X
VRS		X
NPRS	X	X
Randomization		X
Medications review	Continuous from signing of ICF through completion of study participation	
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation	
Adverse events	Continuous from signing of ICF through completion of study participation	

Source: Applicant's Submission of Protocol VX22-548-104 (April 12, 2023; Version 4.0, page 9)

Abbreviations: ECG, electrocardiogram; ICF, informed consent form; NPRS, numeric pain rating scale; PK, pharmacokinetics; VRS, verbal rating scale

Table 166. Schedule of Assessments (Treatment Period and Safety Follow-Up), Study 104

Event/ Assessment ^a	Hours After First Dose of Study Drug																				SFU ^b
	0 ^c	0.5	1	1.5	2	3	4	5	6	8	12	14	16	18	20	24	26 to 32	36	38 to 44	48	
Inpatient period	Continuous from admission through completion of 48-hour assessments																				
Discharge																					X
Clinic or home health visit																					X
Telemedicine video conference or telephone contact																					(X)
PGA of study drug																				X	
Vital signs					X		X									X				X	X
Standard 12-lead ECG							X					X					26 h		38 h		
Complete PE																					(X)
Focused PE																				X	X
NPRS		X	X	X	X	X	X	X	X	X	X		X		X	X	28 h 32 h	X	40 h 44 h	X	
Blood sampling for PK					X		X				X	X				X	26 h	X	38 h	X	
DNA blood sample (optional)	X																				
Serum chemistry																					X
Hematology																					X
Coagulation																					X
Urinalysis																					X
Clear liquid diet	X																				
Study drug administration	X								X		X			X		X	30 h	X	42 h		
Rescue medication use	Ibuprofen 400 mg orally q6h prn (upon request) after first dose of study drug																				
Medications review	Continuous from signing of ICF through completion of study participation																				
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation																				
Adverse events	Continuous from signing of ICF through completion of study participation																				

Source: Applicant's Submission of Protocol VX22-548-104 (April 12, 2023; Version 4.0, pages 10-11)

^a Assessments that coincide with study drug administration will be performed before dosing, unless noted otherwise.

^b All subjects will have a SFU Visit 14±2 days after the last dose of study drug, including those who prematurely discontinue study drug dosing.

^c Time 0 hours is defined as the time of administration for the first dose of study drug, which must occur within 25 minutes after randomization (ideally within 15 minutes).

Abbreviations: ECG, electrocardiogram; ICF, informed consent form; NPRS, numeric pain rating scale; PE, physical examination; PGA, Patient Global Assessment; PK, pharmacokinetics; q6h, every 6 hours; SFU, safety follow-up

Study Endpoints

The primary efficacy endpoint was SPID48 compared to placebo.

The key secondary efficacy endpoints included the following:

- SPID48 compared to HB/APAP
- Time to ≥ 2 -point reduction in NPRS from baseline compared to placebo

Other secondary efficacy endpoints included the following:

- Time to ≥ 1 -point reduction in NPRS from baseline compared to placebo
- Proportion of subjects reporting good or excellent on the Patient Global Assessment (PGA) at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- SPID24 compared to placebo
- Rescue medication use from 0 to 48 hours compared to placebo:
 - Time to first use
 - Proportion of subjects with use
 - Total usage

Other endpoints included the following:

- SPID36 and SPID12 compared to placebo
- Proportion of subjects with $\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 24 hours compared to placebo
- Time to first use of rescue medication in the first 12 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 12 hours and 24 to 48 hours compared to placebo
- PK parameter estimates of SUZ and its metabolite, M6-SUZ

The safety endpoints were the incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, vital signs, and ECGs.

Pain Intensity Assessment

Pain intensity assessment was obtained by a subject's report on the NPRS. Before removal of the popliteal sciatic block, an unscheduled NPRS was completed before administration of supplemental analgesic medication. After removal of the popliteal sciatic block, NPRS was completed after VRS only if the subject's pain was rated moderate or severe on the VRS. During the treatment period, subjects reported their pain intensity on the NPRS at each scheduled time point through 48 hours after the first dose of study drug. In addition, pain intensity was recorded on an unscheduled NPRS immediately before each administration of rescue medication.

Table 167. Protocol Amendments, Study 104

Protocol Version	Date	Reason for Change	Summary of Changes
2.0	10/12/2022	In response to FDA's 10/3/2022 comments	- Added exclusion criteria for history of QT prolongation or standard 12-lead ECG demonstrating median QTcF >450 msec at screening or baseline. - Added study drug interruption and stopping rules. - Clarified procedures for ECG safety monitoring after the first dose of study drug.
3.0	11/9/2022	Applicant states that results from Study VX21-548-011 supported administering the first SUZ dose in phase 3 acute pain studies under fasted conditions and subsequent doses with or without food. They also state that supporting nonclinical data justifies revision of the contraception requirements	- Permitted study drug to be taken with or without food after the first dose. - Updated the contraception requirement to the use of at least 1 acceptable method of contraception based on supporting nonclinical data. - Specified that NPRS responder endpoints will be compared to placebo. - Expanded NPRS window at 48 hours to ± 15 min for operational feasibility. - Added a requirement for medical monitor to authorize all cases of screening assessment repetition. - Restricted inhalational anesthetics use from admission through discharge. - Clarified that documentation of all medications administered in-clinic, including prior medications, will include the time of each administration.

Continued

Table 167, continued

Protocol Version	Date	Reason for Change	Summary of Changes
4.0	4/12/2023	Applicant's decision	- Moved the last key secondary endpoint, "time to ≥ 1-point reduction in NPRS from baseline compared to placebo", to other secondary endpoints. - Simplified the order of assessments for operational feasibility. - Added an exception for Vertex personnel or vendor(s), who are not part of the study team, to be unblinded for the analysis of pharmacokinetic (PK)/population PK data to support interactions with regulatory authorities, as applicable. - Clarified viral load sample collection and reflex testing for human immunodeficiency viruses 1 and 2. - Clarified that Exclusion Criterion 3 applies to standard 12-lead ECGs performed at the Screening Visit and on Day -1 (preprocedure). - Clarified the restrictions on analgesic medications, inhalational anesthetics, and steroids. - Clarified that the timing of meals relative to dosing is only required to be recorded in the source for the first dose of study drug.

Source: Adapted from Applicant's submission; Protocol VX22-548-104 Clinical Study Report Version 1.0, Table 9-5, p. 30
Abbreviations: ECG, electrocardiogram; NPRS, numeric pain rating scale; QTcF, corrected QT interval, Fridericia's calculation; SUZ, suzetrigine

15.2. Study of Abdominoplasty Pain, VX22-548-105 (Study 105)

15.2.1. Study Design, Study 105

Overview and Objective

The primary objective of Study 105 was to evaluate the efficacy of SUZ in treating acute pain after an abdominoplasty.

Study Design

Study 105 was a randomized, double-blind, placebo-controlled, three-arm, parallel-group study evaluating the efficacy and safety of SUZ in treating acute pain after an abdominoplasty. The study took place at 12 clinical sites in the United States.

Subjects were randomized 2:2:1 to the SUZ, HB/APAP, or placebo treatment groups, respectively. The sample size was 1,118 subjects with 223 subjects in the placebo arm, 448 subjects in the HB/APAP arm, and 447 subjects in the SUZ arm (full analysis set).

The treatment arms consisted of placebo, SUZ 100 mg for the first dose followed by 50 mg every 12 hours, and HB/APAP 5/325 mg every 6 hours. All subjects received the same number of tablets and capsules every 6 hours in a double-dummy design.

The surgery was performed under intravenous general anesthesia. Subjects abstained from all food and drink (except ≤ 8 fluid ounces per hour of water) from the time of surgery completion through 4 hours after the first dose of study drug. After this period, study drug could be taken with or without food.

The duration of treatment was 48 hours. The safety follow-up visit took place 14 ± 2 days after the last dose of study drug.

Ibuprofen (400 mg orally every 6 hours as needed) was permitted as a rescue medication starting any time after the first dose of study drug through 48 hours after the first dose of study drug. All other medications with analgesic properties, except for those permitted for perioperative pain management, were prohibited for five half-lives or 2 days (whichever was longer) before admission through completion of 48-hour assessments (or after early discontinuation, if applicable).

Intravenous fentanyl citrate (12.5 to 25 μg as needed) was permitted as postoperative supplemental analgesic medication in the postanesthesia care unit if a subject was not lucid enough for randomization but deemed to be in severe pain per clinical judgement and/or was unable to swallow oral medications. Randomization was not permitted until at least 15 minutes after the last administration of supplemental analgesic medication.

Administration of study drug began once a subject's eligibility had been confirmed by their request for the first dose of study drug for pain relief and postoperative pain that was reported as moderate or severe on the VRS and ≥ 4 on the NPRS within 4 hours after surgery completion. The first dose of study drug was required to be administered within 25 minutes after randomization.

Other key inclusion criteria included the following: 1) male or female between the ages of 18 and 80 years, inclusive; 2) BMI of 18 to 40 kg/m^2 , inclusive; 3) had undergone a standard ("full") abdominoplasty procedure; 4) lucid, able to follow commands, and able to swallow oral medications; 5) all analgesic guidelines were followed during and after the abdominoplasty; 6) abdominoplasty procedure duration ≤ 3 hours.

The key exclusion criteria included the following:

- Before surgery:
 - Prior history of abdominoplasty.
 - History of intra-abdominal and/or pelvic surgery that resulted in any complications or, in the opinion of the investigator or medical monitor, would preclude participation in the study.
 - History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.

- Cardiac dysrhythmias requiring antiarrhythmic treatment(s) within the last 2 years; history or evidence of abnormal study ECGs that in the opinion of the investigator or medical monitor would preclude the subject's participation in the study; or history of QT prolongation or standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at the screening visit or on Day -1 (preprocedure).
- Presence of an automated implantable cardioverter defibrillator, cardiac resynchronization therapy device, or pacemaker.
- History of significant hepatic disease.
- Alanine transaminase or aspartate transaminase values >2.5× upper limit of normal.
- History of severe renal impairment defined as an eGFR of <30 mL/min/1.73m² calculated using the subject's measured serum creatinine.
- History of any sensory abnormality that, in the opinion of the investigator, may confound the ability of the subject to assess postoperative pain.
- Subjects who have a painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain.
- Any prior surgery within 1 month before the first study drug dose unless approved by the medical monitor.
- American Society of Anesthesiologists physical status classification of ≥3.
- Chronic use of opioids (pure agonists, agonist/antagonists, partial agonists, antagonists) or NSAIDs with dose escalation within 30 days before admission or unwillingness or inability to stop analgesics at least five half-lives or 2 days (whichever is longer) before admission.
- Subjects who have started new medications that have not been at a stable dose for at least 14 days prior to the scheduled abdominoplasty procedure and before dosing with investigational product.
- Subjects with sleep apnea and/or on a home positive airway pressure device.
- History of peptic ulcer disease or gastrointestinal bleeding that, in the opinion of the investigator or medical monitor, would preclude the subject's participation in the study.
- Evidence of misuse, aberrant use, or addiction to alcohol or an illicitly used drug of abuse in the past 3 years, or a positive test for drugs of abuse.
 - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.
- After surgery:
 - Subject had a nonstandard abdominoplasty, collateral procedures during the abdominoplasty, or any surgical complications during the abdominoplasty.
 - Subject had a medical complication during the abdominoplasty that, in the opinion of the investigator, should preclude randomization.

- Standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at baseline (Day 1 predose).

Table 168. Schedule of Assessments (Screening Visit Through Admission), Study 105

Event/Assessment	Day -28 to Day -1	Day 1
	Screening Visit	Pre-procedure
Informed consent	X	
Clinic or home health visit	X	
Telemedicine video conference or telephone contact	(X)	
Admission		X
Demographics	X	
Medical and surgical history	X	
History of drug and alcohol use	X	
Prior use of opioid medications	X	X
Vital signs	X	X
Standard 12-lead ECG	X	X
PE	X	(X)
Weight, height, and BMI	X	
Serology (HBsAg, HCV Ab, HCV RNA, HIV-1/HIV-2 Ab/Ag, and HIV-1/HIV-2 RNA)	X	
Serum β -hCG	X	
Serum FSH	X	
Serum chemistry	X	
Hematology	X	
Coagulation	X	
Urinalysis	X	
Urine β -hCG		X
Drug test	X	X
Alcohol test		X
Research subject responsibilities, placebo, and pain assessment trainings	X	X
Blood sampling for PK		X
Medications review	Continuous from signing of ICF through completion of study participation	
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation	
Adverse events	Continuous from signing of ICF through completion of study participation	

Source: Applicant's Submission of Protocol VX22-548-105 (April 12, 2023; Version 4.0, p. 7-8)

Abbreviations: Ab, antibody; Ag, antigen; BMI, body mass index; ECG, electrocardiogram; FSH, follicle stimulating hormone; HbsAg, hepatitis B surface antigen; β -hCG, beta human chorionic gonadotropin; HCV, hepatitis C virus; ICF, informed consent form; PE, physical examination; PK, pharmacokinetics

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Table 169. Schedule of Assessments (Procedure Through Randomization), Study 105

Event/Assessment	Day 1
	Procedure Through Randomization / Predose ^a
Inpatient period	X
Abdominoplasty	X
Fasting period	X
Record supplemental analgesic medication	X
Vital signs	X
Standard 12-lead ECG	X
VRS	X
NPRS	X
Randomization	X
Medications review	Continuous from signing of ICF through completion of study participation
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation
Adverse events	Continuous from signing of ICF through completion of study participation

Source: Applicant's Submission of Protocol VX22-548-105 (April 12, 2023; Version 4.0, p. 9)

^a Subject must complete all Day 1 predose assessments before the first dose of study drug is administered.

Abbreviations: ECG, electrocardiogram; ICF, informed consent form; NPRS, numeric pain rating scale; VRS, verbal rating scale

Table 170. Schedule of Assessments (Treatment Period and Safety Follow-Up), Study 105

Event/ Assessment ^a	Hours After First Dose of Study Drug																				Optional PK Visit ^b	SFU ^c
	0 ^d	0.5	1	1.5	2	3	4	5	6	8	12	14	16	18	20	24	26 to 32	36	38 to 44	48		
Inpatient period	Continuous from admission through completion of 48-hour assessments																					
Discharge																					X	
Clinic visit																						X
Clinic or home health visit																					(X)	
Telemedicine video conference or telephone contact																					(X)	
PGA of study drug																					X	
Vital signs					X		X									X					X	X
Standard 12-lead ECG							X					X					26 h		38 h			
Complete PE																						X
Focused PE																					X	X
NPRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	28 h 32 h	X	40 h 44 h	X		
Blood sampling for PK					X		X				X	X			X		26 h	X	38 h	X	(X)	
DNA blood sample (optional)	X																					
Serum chemistry																					X	
Hematology																					X	
Coagulation																					X	
Urinalysis																					X	
Fasting period	0 to 4 h																					
Study drug administration	X								X	X			X	X			30 h	X	42 h			
Rescue medication use	Ibuprofen 400 mg orally q6h prn (upon request) after first dose of study drug																					
Medications review	Continuous from signing of ICF through completion of study participation																					
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation																					
Adverse events	Continuous from signing of ICF through completion of study participation																					

^a Assessments that coincide with study drug administration will be performed before dosing, unless noted otherwise.

^b Approximately 375 subjects enrolled in the study will have an additional PK sample collected between 5 to 8 days after the last dose of study drug, either in the clinic or through a home health visit (Section 11.2.1). Vertex will manage the allocation of the subjects providing this additional PK sample across study sites.

^c All subjects will have a SFU Visit 14 ± 2 days after the last dose of study drug (Section 9.1.3), including those who prematurely discontinue study drug dosing (Section 9.1.4).

^d Time 0 hours is defined as the time of administration for the first dose of study drug, which must occur within 25 minutes after randomization (ideally within 15 minutes).

Source: Applicant's Submission of Protocol VX22-548-105 (April 12, 2023; Version 4.0, p. 10-11)

Abbreviations: ECG, electrocardiogram; ICF, informed consent form; NPRS, numeric pain rating scale; PGA, Patient Global Assessment; PE, physical examination; PK, pharmacokinetics; q6h, every 6 hours; SFU, safety follow-up; VRS, verbal rating scale

Study Endpoints

The primary efficacy endpoint was the SPID48 compared to placebo. The key secondary efficacy endpoints included the following:

- SPID48 compared to HB/APAP
- Time to ≥ 2 -point reduction in NPRS from baseline compared to placebo

Other secondary efficacy endpoints included the following:

- Time to ≥ 1 -point reduction in NPRS from baseline compared to placebo
- Proportion of subjects reporting good or excellent on the PGA at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- SPID24 compared to placebo
- Rescue medication use from 0 to 48 hours compared to placebo:
 - Time to first use
 - Proportion of subjects with use
 - Total usage

Other endpoints included the following:

- SPID36 and SPID12 compared to placebo
- Proportion of subjects with $\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 24 hours compared to placebo
- Time to first use of rescue medication in the first 12 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 12 hours and 24 to 48 hours compared to placebo
- PK parameter estimates of SUZ and its metabolite, M6-SUZ

The safety endpoints were the incidence and type of AEs, changes from baseline in clinically significant laboratory test results, vital signs, and ECGs.

Pain Intensity Assessment

Pain intensity assessment was obtained by a subject's report on the NPRS. In the postoperative period before randomization, NPRS was completed after VRS only if the subject's pain was rated moderate or severe on the VRS. During the treatment period, subjects reported their pain intensity on the NPRS at each scheduled time point through 48 hours after the first dose of study drug. In addition, pain intensity was recorded on an unscheduled NPRS immediately before each administration of rescue medication.

Table 171. Protocol Amendments, Study 105

Protocol Version	Date	Reason for Change	Summary of Changes
2.0	10/12/2022	In response to FDA's 10/3/2022 comments	- Added exclusion criteria for history of QT prolongation or standard 12-lead ECG demonstrating median QTcF >450 msec at screening or baseline. - Added study drug interruption and stopping rules. - Clarified procedures for ECG safety monitoring after first dose of study drug.
3.0	11/9/2022	Applicant reported that results from Study VX21-548-011 supported administering the first SUZ dose in phase 3 acute pain studies under fasted conditions and subsequent doses with or without food. They also reported that supporting nonclinical data justified revision of the contraception requirements	- Permitted study drug to be taken with or without food after the first dose. - Updated the contraception requirement to the use of at least 1 acceptable method of contraception based on supporting nonclinical data. - Specified that NPRS responder endpoints would be compared to placebo. - Expanded NPRS window at 48 hours to ± 15 minutes for operational feasibility. - Clarified details of the abdominoplasty procedure. - Added a requirement for medical monitor to authorize all cases of screening assessment repetition. - Restricted inhalational anesthetic use from admission through discharge. - Clarified that documentation of all medications administered in-clinic, including prior medications, would include the time of each administration.
4.0	4/12/2023	Applicant's decision	- Moved the last key secondary endpoint, "time to ≥ 1-point reduction in NPRS from baseline compared to placebo", to other secondary endpoints. - Simplified the order of assessments for operational feasibility. - Added an exception for Vertex personnel or vendor(s), who are not part of the study team, to be unblinded for PK/population PK data analysis. - Clarified viral load sample collection and reflex testing for human immunodeficiency viruses 1 and 2. - Clarified that Exclusion Criterion 4 applies to standard 12-lead ECGs performed at the Screening Visit and on Day 1 (preprocedure). - Clarified the restrictions on analgesic medications, inhalational anesthetics, and steroids. - Clarified that the timing of meals relative to dosing is only required to be recorded in the source for the first dose of study drug.

Source: Adapted from Applicant's submission; Protocol VX22-548-105 Clinical Study Report Version 1.0, Table 9-5, p. 30
Abbreviations: ECG, electrocardiogram; NPRS, numeric pain rating scale; PK, pharmacokinetics; QTcF, corrected QT interval, Fridericia's calculation; SUZ, suzetrigine

15.3. Longer-Term Phase 3 Study, VX22-548-107 (Study 107)

Study 107 was a single-arm study evaluating the safety and effectiveness of SUZ in treating acute pain. The study took place at 13 clinical sites in the United States. The study population consisted of subjects with a variety of surgical and nonsurgical conditions resulting in pain that was moderate or severe on a VRS and ≥ 4 on an NPRS. Surgical subjects had to have had pain that was expected to last for at least 72 hours and was expected to require no more than a short-term (i.e., < 24 hours) admission, if any. Nonsurgical subjects had to have had pain for a duration of ≤ 48 hours. The sample size was 256 subjects (full analysis set).

The treatment consisted of SUZ 100 mg for the first dose then 50 mg every 12 hours. Subjects continued to receive SUZ for up to 14 days or until their pain resolved, whichever occurred first. Acetaminophen 650 mg/ibuprofen 400 mg every 6 hours as needed, up to a maximum of 2,600 mg/1,600 mg in any 24-hour period, was permitted as a rescue medication.

Pain was considered to be resolved if a subject took no study drug during a 48-hour period and took no more than one dose of acetaminophen/ibuprofen during each 24-hour period within the 48-hour period.

The safety assessments included adverse event monitoring, clinical laboratory assessments, vital sign measurement, standard 12-lead ECGs, physical examinations, and the Columbia-Suicide Severity Rating Scale. The efficacy assessment was PGA of the study drug.

15.4. Overall Assessment of the Phase 3 Study Designs

The phase 3 controlled studies (Study 104 and Study 105) were appropriately designed to meet their stated objectives. As described in the draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* ([February 2022](#)), the randomized, double-blind, repeat-dose design of these superiority studies was acceptable for evaluating the safety and efficacy of a nonopioid analgesic intended for the treatment of acute pain. The primary efficacy endpoint of sum of the pain intensity difference (SPID) as recorded on the NPRS from 0 to 48 hours compared to placebo is acceptable. Bunionectomy and abdominoplasty are established models for bony and soft tissue pain, respectively. The inclusion and exclusion criteria were appropriate to select a representative patient population with moderate-to-severe acute pain. Appropriate monitoring for potential safety signals of interest was included in these protocols.

The design of the phase 3 single-arm study (Study 107) was acceptable for providing supportive data regarding the safety profile of SUZ, especially for longer term use given the treatment period of up to 14 days. However, the lack of a comparator in this study limits the conclusions that can be drawn from these data. The usefulness of the efficacy data generated in this study is limited from a regulatory decision-making standpoint given its single-arm design and the use of PGA, rather than a measure of pain intensity, as the efficacy assessment.

16. Efficacy

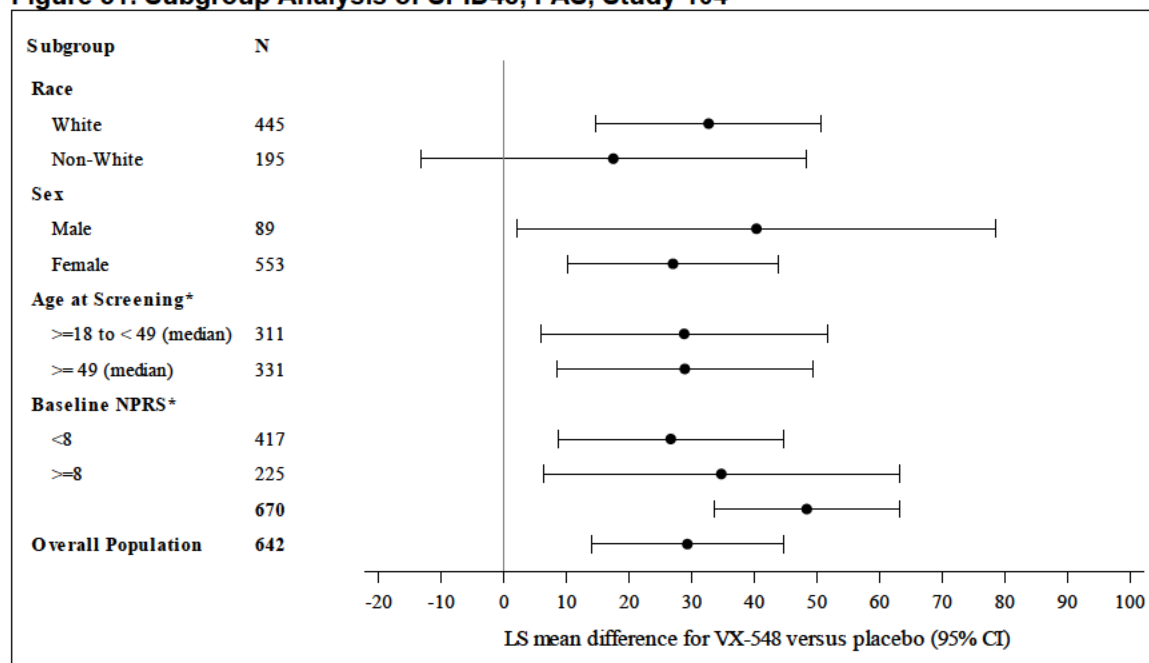
Prespecified clinical efficacy results from Studies 104 and 105 were presented in Section 6.2.2.4. In the current section, the presented exploratory analyses were not planned to formally test the specified hypotheses given their exploratory aims.

16.1. Subgroup Analyses for the Primary Endpoint

The same analysis of covariance model and imputation methods as described in Section 6.2.2.3 were used, but it was fit separately for each subgroup.

Results from subgroup analyses for the primary endpoint are shown in Figure 51 for Study 104 and Figure 52 for Study 105. In both studies, due to low numbers of subjects in the group of ≥ 65 years of age, the Applicant performed ad-hoc subgroup analyses with age groups categorized by median age instead of the originally planned age groups (≥ 18 to < 65 years of age or ≥ 65 years of age). Additionally, in Study 105, the Applicant did not include results from subgroup analysis by sex in the original submission.

Figure 51. Subgroup Analysis of SPID48, FAS, Study 104

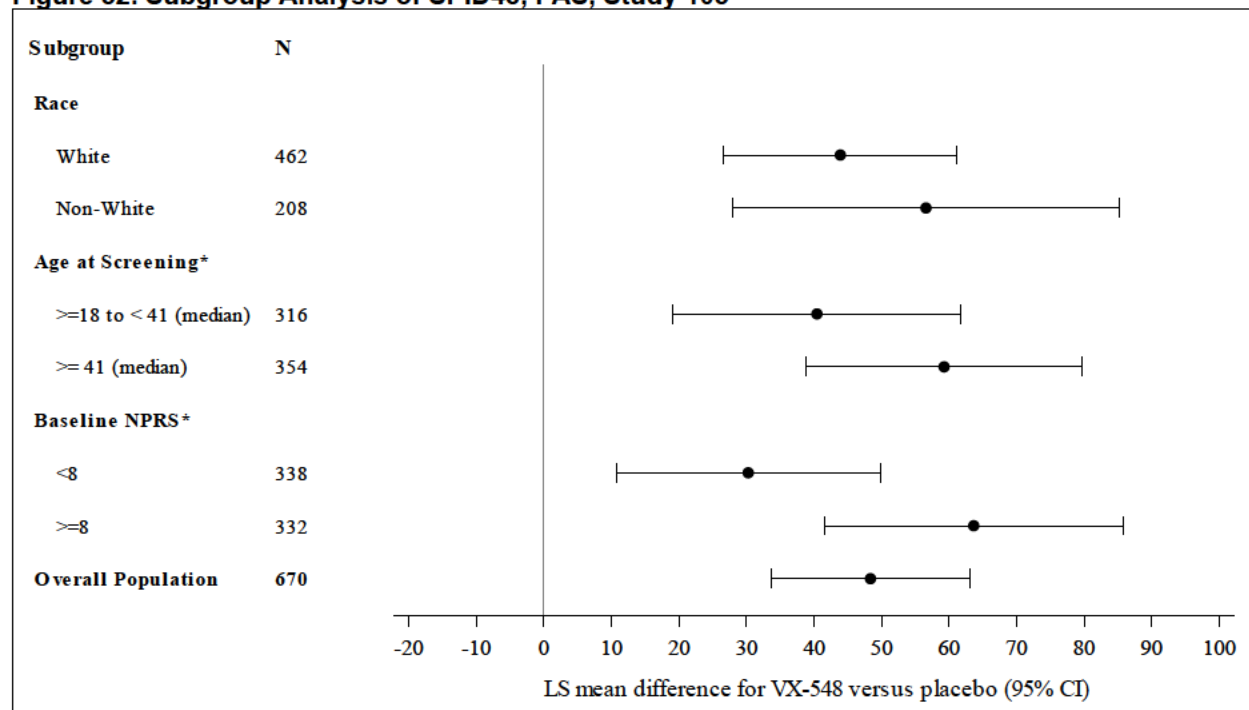


Source: Figure 14.2.2.4, page 203 of Applicant's Clinical Study Report of VX22-548-104

Notes: Asterisk (*) indicates ad hoc analyses. Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Analyses were performed using the same imputation scheme as for the primary analysis (Table 9-3). Non-White consisted of race of Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other, and multiple.

Abbreviations: ANCOVA, analysis of covariance; FAS, full analysis set; LS, least-squares; N, number of subjects; NPRS, numerical pain rating scale; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; VX-548, suzetrigine

Figure 52. Subgroup Analysis of SPID48, FAS, Study 105



Source: Figure 14.2.2.4, page 199 of Applicant's Clinical Study Report of VX22-548-105

Notes: Asterisk (*) indicates ad hoc analyses. Estimates were obtained from an ANCOVA model with SPID48 as the dependent variable, treatment as a fixed effect, and with site and baseline NPRS as covariates. Analyses were performed using the same imputation scheme as for the primary analysis (Table 9-3). Non-White consisted of race of Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other, and multiple.

Abbreviations: ANCOVA, analysis of covariance; FAS, full analysis set; LS, least-squares; N, number of subjects; NPRS, numerical pain rating scale; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; VX-548, suzetrigine

Per Agency request, the Applicant provided the summary of SPID48 by age groups (≥ 18 to < 65 years of age or ≥ 65 years of age) for both studies and the summary of SPID48 by sex for Study 105 as shown in [Table 172](#) and [Table 173](#) below.

Table 172. Summary of SPID48 by Age at Screening, FAS, Study 104

Statistic	Placebo N=216	HB/APAP N=431	SUZ N=426
Age at screening: ≥ 18 to < 65			
N	193	397	383
Mean (SD)	63.6 (107.1)	118.0 (103.5)	93.2 (109.7)
Median	58.0	124.0	98.5
Min, max	-240, 373	-191, 424	-240, 355
Age at screening: ≥ 65			
N	23	34	43
Mean (SD)	136.2 (101.3)	155.0 (87.6)	147.6 (86.2)
Median	104.5	165.8	146.8
Min, max	2, 348	-36, 322	-85, 339

Source: Tables 8, page 10 of Applicant's response to FDA Information Request dated July 1, 2024

Notes: The same imputation methods were used as for the primary analysis.

Abbreviations: FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; N, number of subjects in the analysis set; NPRS, numerical pain rating scale; SD, standard deviation; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

Table 173. Summary of SPID48 by Age and Sex at Screening, FAS, Study 105

Statistic	Placebo N=223	HB/APAP N=448	SUZ N=447
Age at screening: ≥ 18 to < 65			
N	223	359	443
Mean (SD)	72.4 (93.1)	112.2 (108.7)	117.2 (104.7)
Median	66.0	118.0	112.0
Min, max	-144, 326	-239, 401	-174, 444
Age at screening: ≥ 65			
N	0	1	4
Mean (SD)	--	-26.0 (--)	107.8 (26.8)
Median	--	-26	114.8
Min, max	--	-26, -26	70, 132
Sex: Male			
N	3	7	10
Mean (SD)	56.2 (26.5)	129.9 (83.0)	90.0 (81.6)
Median	60.0	162.0	86.8
Min, max	28, 81	5, 249	-48, 232
Sex: Female			
N	220	441	437
Mean (SD)	72.7 (93.7)	111.6 (109.1)	117.7 (104.7)
Median	66.5	116	113.5
Min, max	-144, 326	-239, 401	-174, 444

Source: Tables 9, page 10 of Applicant's response to FDA Information Request dated July 1, 2024

Notes: The same imputation methods were used as for the primary analysis.

Abbreviations: FAS, full analysis set; HB/APAP, hydrocodone bitartrate/acetaminophen; n, number of subjects; N, number of subjects in the analysis set; NPRS, numerical pain rating scale; SD, standard deviation; SPID48, time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

16.2. Exploratory Result for the Second Key Secondary Endpoint

Because both studies failed on the first key secondary endpoint, any analysis of the second key secondary endpoint (i.e., SUZ versus placebo on time to a ≥ 2 -point reduction in NPRS from baseline) was considered exploratory.

In Study 104, the median time to ≥ 2 -point reduction in NPRS from baseline was 240 minutes (95% CI: 117, 477) for SUZ, 90 minutes (95% CI: 85, 110) for HB/APAP, and 480 minutes (95% CI: 476, 716) for placebo. In Study 105, the median time to ≥ 2 -point reduction in NPRS from baseline was 119 minutes (95% CI: 90, 180) for SUZ, 475 minutes (95% CI: 236, 480) for HB/APAP, and 480 minutes (95% CI: 477, 705) for placebo.

17. Clinical Safety

17.1. Consultative Review, Interdisciplinary Review Team for Cardiac Safety Studies

The Applicant conducted a thorough QT study (Study VX21-548-009). Based on this study, SUZ is not associated with significant QTc prolongation up to two times exposure of the maximum recommended dose. The interdisciplinary review team for Cardiac Safety Studies Consultative Review dated July 31, 2024, including recommended revisions to labeling, is excerpted below:

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 (C_{max}) 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

QT assessment pathway	☒ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☐ Alternative QT study when a thorough QT study is not feasible (6.1)																			
Clinical QT study findings	- The high clinical exposure scenario for VX-548 and M6-548 is expected in subjects with severe hepatic impairment. The predicted mean ratios for C_{max} 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>					ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)	ΔΔQTcF	200 mg QD Day 6	1251.7 ng/mL	-0.70	(-3.83, 2.42)	ΔΔQTcF	200 mg QD Day 10	1163.8 ng/mL	0.66	(-3.75, 2.44)
ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)																
ΔΔQTcF	200 mg QD Day 6	1251.7 ng/mL	-0.70	(-3.83, 2.42)																
ΔΔQTcF	200 mg QD Day 10	1163.8 ng/mL	0.66	(-3.75, 2.44)																
In vitro and In vivo findings	Integrated nonclinical risk assessment was not performed.																			

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 from the CS-IRT [cardiac safety interdisciplinary review team].

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)

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](#)).

In the aforementioned review, the interdisciplinary review team for Cardiac Safety Studies also commented on cardiac safety events (per ICH harmonized tripartite guideline *E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* ([May 2005](#))) in the controlled phase 3 trials. They found that the incidence of cardiac safety events in the SUZ group was similar to that in the active control or placebo groups. The relevant section from their review is excerpted below:

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.

In the completed phase 3 trials, the incidence of cardiac safety events (per ICH E14 ([May 2005](#))) in the SUZ group was similar to that of the active control or placebo.

17.2. Safety Review of Individual Phase 3 Controlled Studies

17.2.1. Safety Results, Study VX22-548-104 (Study 104)

17.2.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study 104

There were no deaths, serious adverse events (SAEs), or AEs leading to discontinuation. The incidence of any AE was lower in the SUZ treatment arm than in both the HB/APAP and placebo arms. The majority of these AEs were mild in severity.

Table 174. Overview of Adverse Events, Safety Population, Study 104

Event Category	SUZ N=426 n (%)	HB/APAP N=431 n (%)	Placebo N=216 n (%)
SAE	0	0	0
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0
AE leading to dose modification of study drug	0	0	0
AE leading to interruption of study drug	0	0	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Any AE	132 (31.0)	180 (41.8)	76 (35.2)
Severe and worse	1 (0.2)	4 (0.9)	0
Moderate	27 (6.3)	42 (9.7)	15 (6.9)
Mild	104 (24.4)	134 (31.1)	61 (28.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.1.2. Deaths, Study 104

There were no deaths.

17.2.1.3. Serious Treatment-Emergent Adverse Events, Study 104

There were no SAEs.

17.2.1.4. Adverse Events Leading to Treatment Discontinuation, Study 104

There were no AEs leading to discontinuation.

17.2.1.5. Treatment-Emergent Adverse Events, Study 104

[Table 175](#) presents the common AEs by preferred term (PT) and system organ class (SOC) in Study 104 that occurred in at least 0.3% of subjects in any arm. There was a lower percentage of subjects with any AEs in the SUZ treatment arm than in the HB/APAP and placebo arms.

There was a substantially higher percentage of subjects who had AEs that were within the SOC of musculoskeletal and connective tissue disorders in the SUZ arm (3.1%) than in the placebo arm (0.5%). The risk difference by SOC is depicted in [Figure 53](#). This imbalance is primarily driven by the PT of muscle spasms.

Table 175. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.3% of Subjects in Any Arm, Safety Population, Study 104

System Organ Class Preferred Term	SUZ N=426 n (%)	HB/APAP N=431 n (%)	Placebo N=216 n (%)
Any AE	132 (31.0)	180 (41.8)	76 (35.2)
Ear and labyrinth disorders (SOC)	3 (0.7)	0	1 (0.5)
Tinnitus	2 (0.5)	0	1 (0.5)
Eye disorders (SOC)	0	1 (0.2)	2 (0.9)
Blindness	0	0	1 (0.5)
Vision blurred	0	0	1 (0.5)
Gastrointestinal disorders (SOC)	54 (12.7)	95 (22.0)	41 (19.0)
Diarrhoea	2 (0.5)	2 (0.5)	3 (1.4)
Abdominal pain upper	0	0	1 (0.5)
Gastrooesophageal reflux disease	0	0	2 (0.9)
Haematochezia	0	0	1 (0.5)
Dyspepsia	1 (0.2)	3 (0.7)	1 (0.5)
Constipation	15 (3.5)	22 (5.1)	9 (4.2)
Vomiting	7 (1.6)	19 (4.4)	6 (2.8)
Nausea	35 (8.2)	62 (14.4)	23 (10.6)
General disorders and administration site conditions (SOC)	9 (2.1)	10 (2.3)	3 (1.4)
Oedema peripheral	3 (0.7)	0	2 (0.9)
Medical device site reaction	2 (0.5)	1 (0.2)	0
Infusion site haemorrhage	0	0	1 (0.5)
Infusion site pruritus	0	1 (0.2)	1 (0.5)
Fatigue	0	2 (0.5)	0
Peripheral swelling	0	2 (0.5)	1 (0.5)
Infections and infestations (SOC)	5 (1.2)	11 (2.6)	4 (1.9)
Urinary tract infection	2 (0.5)	0	0
Postoperative wound infection	3 (0.7)	3 (0.7)	1 (0.5)
Nasopharyngitis	0	0	1 (0.5)
Post procedural infection	0	0	1 (0.5)
COVID-19	0	1 (0.2)	1 (0.5)

System Organ Class Preferred Term	SUZ N=426 n (%)	HB/APAP N=431 n (%)	Placebo N=216 n (%)
Injury, poisoning and procedural complications (SOC)	7 (1.6)	10 (2.3)	3 (1.4)
Fall	2 (0.5)	0	0
Skin abrasion	2 (0.5)	1 (0.2)	1 (0.5)
Post procedural erythema	1 (0.2)	0	1 (0.5)
Suture related complication	0	0	1 (0.5)
Post procedural pruritus	0	2 (0.5)	0
Investigations (SOC)	11 (2.6)	9 (2.1)	5 (2.3)
Blood creatine phosphokinase increased	5 (1.2)	2 (0.5)	0
Lipase increased	2 (0.5)	1 (0.2)	0
Blood pressure increased	0	0	1 (0.5)
Body temperature increased	0	0	1 (0.5)
White blood cells urine positive	0	0	1 (0.5)
Gamma-glutamyltransferase increased	0	1 (0.2)	1 (0.5)
Alanine aminotransferase increased	2 (0.5)	5 (1.2)	2 (0.9)
Aspartate aminotransferase increased	2 (0.5)	5 (1.2)	1 (0.5)
Metabolism and nutrition disorders (SOC)	1 (0.2)	3 (0.7)	0
Musculoskeletal and connective tissue disorders (SOC)	13 (3.1)	8 (1.9)	1 (0.5)
Muscle spasms	9 (2.1)	4 (0.9)	1 (0.5)
Pain in extremity	0	2 (0.5)	0
Nervous system disorders (SOC)	40 (9.4)	73 (16.9)	31 (14.4)
Somnolence	1 (0.2)	1 (0.2)	2 (0.9)
Presyncope	0	0	1 (0.5)
Paraesthesia	3 (0.7)	4 (0.9)	1 (0.5)
Hypoaesthesia	1 (0.2)	2 (0.5)	1 (0.5)
Syncope	1 (0.2)	7 (1.6)	1 (0.5)
Dizziness	15 (3.5)	23 (5.3)	11 (5.1)
Headache	21 (4.9)	45 (10.4)	20 (9.3)
Renal and urinary disorders (SOC)	0	3 (0.7)	0
Reproductive system and breast disorders (SOC)	3 (0.7)	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders (SOC)	5 (1.2)	5 (1.2)	5 (2.3)
Dyspnoea	2 (0.5)	0	0
Epistaxis	2 (0.5)	0	0
Nasal congestion	0	0	1 (0.5)
Sinus congestion	0	0	1 (0.5)
Sneezing	0	0	1 (0.5)
Throat irritation	0	0	1 (0.5)
Cough	1 (0.2)	2 (0.5)	0
Oropharyngeal pain	1 (0.2)	2 (0.5)	1 (0.5)
Skin and subcutaneous tissue disorders (SOC)	28 (6.6)	29 (6.7)	12 (5.6)
Dermatitis contact	6 (1.4)	3 (0.7)	3 (1.4)
Rash	6 (1.4)	5 (1.2)	1 (0.5)
Blister	2 (0.5)	1 (0.2)	1 (0.5)
Pruritus	13 (3.1)	13 (3.0)	3 (1.4)
Acanthosis nigricans	0	0	1 (0.5)
Cold sweat	0	0	1 (0.5)
Epidermolysis	0	0	1 (0.5)
Skin irritation	1 (0.2)	2 (0.5)	0
Hyperhidrosis	0	2 (0.5)	0
Erythema	0	6 (1.4)	1 (0.5)

System Organ Class Preferred Term	SUZ N=426 n (%)	HB/APAP N=431 n (%)	Placebo N=216 n (%)
Vascular disorders (SOC)	6 (1.4)	2 (0.5)	4 (1.9)
Hypertension	3 (0.7)	1 (0.2)	1 (0.5)
Orthostatic hypotension	2 (0.5)	0	1 (0.5)
Hot flush	0	0	1 (0.5)
Hypotension	0	0	1 (0.5)

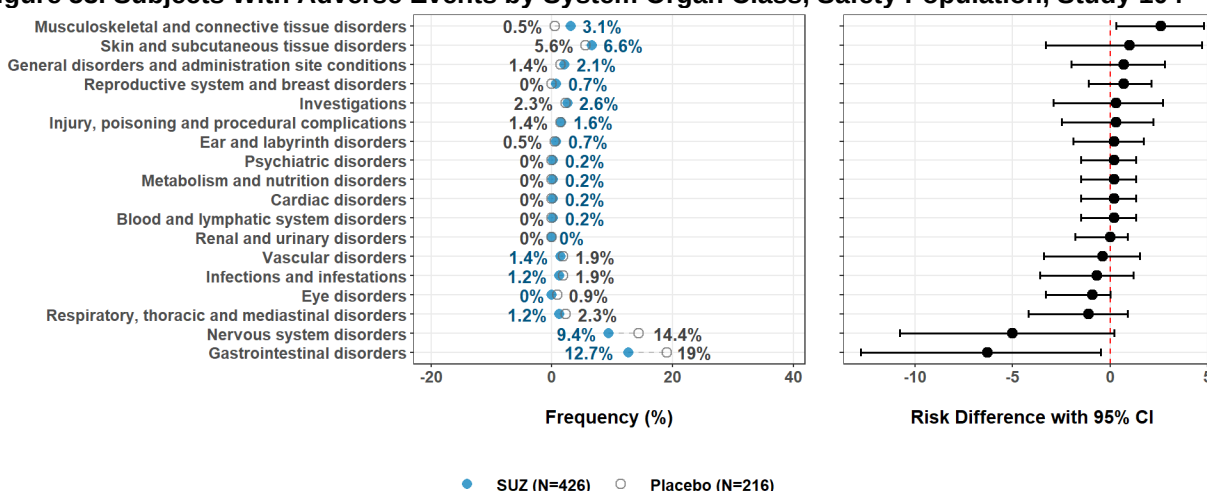
Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Figure 53. Subjects With Adverse Events by System Organ Class, Safety Population, Study 104



Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.1.6. Laboratory Findings, Study 104

Analyses of laboratory data did not raise significant clinically meaningful safety concerns. Median changes from baseline to the end of treatment were similar between the treatment arms for the majority of the laboratory assessments conducted.

There were some laboratory parameters with notable imbalances between the SUZ treatment arm and the HB/APAP and placebo treatment arms. [Table 176](#) and [Table 177](#) demonstrate that a higher percentage of subjects in the SUZ treatment arm had creatine phosphokinase (CPK) and eGFR values exceeding certain threshold levels than did subjects in the other treatment arms. [Table 178](#) demonstrates that the mean changes in CPK and creatinine from baseline were higher and the mean change in eGFR from baseline was lower in the SUZ treatment arm at 48 hours. However, the magnitude of these changes was relatively small and unlikely to be clinically significant.

Table 176. Subjects With CPK Values Exceeding Specified Levels, Safety Population, Study 104

Laboratory Parameter	SUZ N=426 n/N _w (%)	HB/APAP N=431 n/N _w (%)	Placebo N=216 n/N _w (%)
CPK, high (U/L)			
Level 1 (>3× ULN)	10/423 (2.4)	4/419 (1.0)	1/209 (0.5)
Level 2 (>5× ULN)	4/423 (0.9)	1/419 (0.2)	0/209 (0)
Level 3 (>10× ULN)	2/423 (0.5)	1/419 (0.2)	0/209 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 48 hours.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CPK, creatine phosphokinase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

Table 177. Subjects With eGFR Values Exceeding Specified Levels, Safety Population, Study 104

Laboratory Parameter	SUZ N=426 n/N _w (%)	HB/APAP N=431 n/N _w (%)	Placebo N=216 n/N _w (%)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥25% decrease)	13/412 (3.2)	4/415 (1.0)	1/209 (0.5)
Level 2 (≥50% decrease)	0/412 (0)	1/415 (0.2)	0/209 (0)
Level 3 (≥75% decrease)	0/412 (0)	1/415 (0.2)	0/209 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 48 hours.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: eGFR, estimated glomerular filtration rate; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 178. Selected Chemistry Assessments and Changes From Baseline at 48 Hours, Study 104

Laboratory Parameter	SUZ N=426	HB/APAP N=431	Placebo N=216
Creatine kinase (U/L)			
N	418	414	208
Mean (SD)	5.5 (230.7)	-18.5 (897.6)	-13.4 (95.5)
Median	-9.0	-9.0	-10.5
Creatinine (μmol/L)			
N	418	416	208
Mean (SD)	1.2 (10.2)	-3.1 (20.1)	-3.7 (9.8)
Median	0.0	0.0	0.0
Glomerular filtration rate, estimated (mL/min/1.73 m ²)			
N	418	416	208
Mean (SD)	-0.8 (11.3)	3.6 (11.0)	3.1 (10.2)
Median	0.0	0.0	0.0

Source: Modified from Protocol VX22-548-104 CSR, Table 14.3.4.1, Pages 9, 10, 13

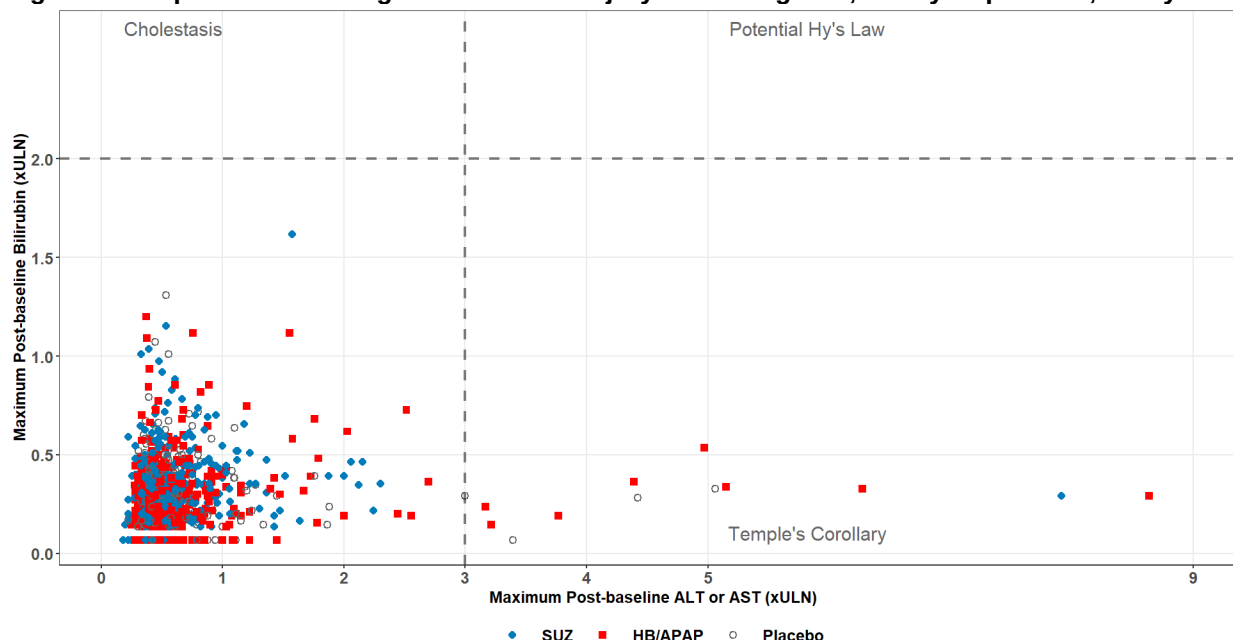
Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: CSR, clinical study report; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.1.7. Assessment of Drug-Induced Liver Injury, Study 104

[Figure 54](#) shows a screening assessment for potential cases of serious drug-induced liver injury (DILI). There were no subjects in any treatment arm in the Cholestasis and Potential Hy's Law quadrants. There was a lower percentage of subjects in the SUZ treatment arm (0.2%) in the Temple's Corollary quadrant than in the HB/APAP (1.9%) and placebo (1.9%) treatment arms. These findings do not suggest a significant relationship between SUZ and drug-induced liver injury.

Figure 54. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 104



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

17.2.1.8. Vital-Sign and ECG Analyses, Study 104

Review of the vital-sign data and ECG parameters did not reveal significant clinically meaningful safety concerns associated with SUZ. As depicted in [Table 179](#) and [Table 180](#), during the treatment period, there were larger decreases from baseline in the mean systolic and diastolic blood pressures in the SUZ arm than in the placebo arm. However, the magnitude of this difference was small and unlikely to be clinically significant.

Table 179. Systolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Study 104

Time Point	Statistics	SUZ N=426	HB/APAP N=431	Placebo N=216
2 hours	n	426	431	215
	Mean (SD)	0.7 (13.3)	-2.9 (13.7)	1.5 (11.8)
	Median	0.0	-3.0	1.0
4 hours	n	423	429	215
	Mean (SD)	-1.1 (13.8)	-3.1 (13.7)	0.4 (13.4)
	Median	-1.0	-3.0	-1.0
24 hours	n	418	419	210
	Mean (SD)	-5.3 (14.9)	-3.6 (13.6)	-1.5 (13.7)
	Median	-4.5	-4.0	-1.0
48 hours	n	419	417	210
	Mean (SD)	-4.1 (14.6)	-2.7 (14.1)	-2.6 (13.9)
	Median	-4.0	-3.0	-2.0
Safety follow-up	n	418	419	207
	Mean (SD)	-0.1 (16.7)	1.6 (15.5)	2.2 (15.1)
	Median	1.0	0.0	3.0

Source: Modified from Protocol VX22-548-104 CSR, Table 14.3.5.1, Pages 1-2

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects evaluated; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 180. Diastolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Study 104

Time Point	Statistics	SUZ N=426	HB/APAP N=431	Placebo N=216
2 hours	n	426	431	215
	Mean (SD)	0.2 (9.4)	-2.1 (10.4)	0.7 (7.9)
	Median	0.0	-3.0	1.0
4 hours	n	423	429	215
	Mean (SD)	-1.7 (9.3)	-2.7 (10.0)	-0.9 (8.0)
	Median	-2.0	-3.0	-1.0
24 hours	n	418	419	210
	Mean (SD)	-3.2 (10.1)	-2.0 (9.9)	-1.1 (9.0)
	Median	-3.0	-2.0	-2.0
48 hours	n	419	417	210
	Mean (SD)	-2.0 (10.3)	-0.9 (9.9)	-0.9 (10.3)
	Median	-2.0	-1.0	-1.0
Safety follow-up	n	418	419	207
	Mean (SD)	4.1 (10.6)	5.0 (11.2)	5.2 (10.9)
	Median	5.0	4.0	5.0

Source: Modified from Protocol VX22-548-104 CSR, Table 14.3.5.1, Pages 3-4

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects evaluated; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.1.9. Subgroup Analyses, Study 104

[Table 181](#) depicts the number of subjects in each specific subgroup among the different treatment arms. The finding of a lower incidence of AEs in the SUZ arm than in the HB/APAP and placebo arms was generally consistent across subgroups. However, there were notable imbalances in terms of the number of subjects between subgroup categories, which limited the

conclusions that can be drawn from these data. There were significantly fewer males, subjects ≥ 65 years of age, and subjects of races other than Black, African American, or White exposed to SUZ.

Table 181. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study 104

Characteristic	SUZ N=426 n/N _s (%)	HB/APAP N=431 n/N _s (%)	Placebo N=216 n/N _s (%)
Sex			
Female	114/366 (31.1)	164/359 (45.7)	66/187 (35.3)
Male	18/60 (30.0)	16/72 (22.2)	10/29 (34.5)
Age group, years			
≥ 18 to <65	119/383 (31.1)	168/397 (42.3)	67/193 (34.7)
≥ 65	13/43 (30.2)	12/34 (35.3)	9/23 (39.1)
Race			
American Indian or Alaska Native	1/4 (25.0)	6/7 (85.7)	0/0 (NA)
Asian	4/9 (44.4)	5/7 (71.4)	5/8 (62.5)
Black or African American	34/116 (29.3)	34/96 (35.4)	15/48 (31.2)
Multiple	4/6 (66.7)	2/3 (66.7)	0/0 (NA)
Native Hawaiian or other Pacific Islander	0/1 (0)	0/1 (0)	0/0 (NA)
Other	1/3 (33.3)	0/2 (0)	0/0 (NA)
White	87/285 (30.5)	132/314 (42.0)	56/160 (35.0)
Missing	1/2 (50.0)	1/1 (100)	0/0 (NA)
Ethnicity			
Hispanic or Latino	30/131 (22.9)	75/149 (50.3)	29/84 (34.5)
Not Hispanic or Latino	102/295 (34.6)	105/282 (37.2)	47/132 (35.6)

Source: adae.xpt; Software: R

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2. Safety Results, Study VX22-548-105 (Study 105)

17.2.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 105

There were no deaths in subjects treated with SUZ. The incidence of SAEs and AEs leading to discontinuation of the study drug was low overall, and there were no substantial differences between the treatment arms. The incidence of any AE was lower in the SUZ arm than in both the HB/APAP and placebo arms.

Table 182. Overview of Adverse Events, Safety Population, Study 105

Event Category	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
SAE	11 (2.5)	7 (1.6)	5 (2.3)
SAEs with fatal outcome	0	0	1 (0.5)
Life-threatening SAEs	2 (0.4)	2 (0.4)	0
SAEs requiring hospitalization	7 (1.6)	6 (1.3)	4 (1.8)
SAEs resulting in substantial disruption of normal life functions	2 (0.4)	1 (0.2)	1 (0.5)
Other	6 (1.3)	2 (0.4)	3 (1.4)
AE leading to permanent discontinuation of study drug	5 (1.1)	5 (1.1)	1 (0.5)
AE leading to dose modification of study drug	0	1 (0.2)	0
AE leading to interruption of study drug	0	1 (0.2)	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Any AE	224 (50.0)	272 (60.7)	125 (56.3)
Severe and worse	10 (2.2)	11 (2.5)	7 (3.2)
Moderate	83 (18.5)	112 (25.0)	46 (20.7)
Mild	131 (29.2)	149 (33.3)	72 (32.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.2. Deaths, Study 105

There was one death in the placebo group due to an SAE of pulmonary embolism. There were no deaths in subjects treated with SUZ.

17.2.2.3. Serious Treatment-Emergent Adverse Events, Study 105

There was no substantial difference in the overall incidence of SAEs experienced by subjects in the SUZ arm compared to the HB/APAP and placebo arms. The majority of SAEs were experienced by only one subject in any given treatment arm. There were no substantial differences between the treatment arms for any specific SAE. No SAEs were considered related or possibly related to the study drug by the study investigators. Most of these SAEs were known risks associated with surgical procedures and were not unexpected considering the surgical acute pain model used.

Table 183. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 105

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Any SAE	11 (2.5)	7 (1.6)	5 (2.3)
Blood and lymphatic system disorders (SOC)	1 (0.2)	0	1 (0.5)
Anaemia	1 (0.2)	0	0
Disseminated intravascular coagulation	0	0	1 (0.5)

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Cardiac disorders (SOC)	0	0	1 (0.5)
Cardiogenic shock	0	0	1 (0.5)
Gastrointestinal disorders (SOC)	1 (0.2)	2 (0.4)	0
Small intestinal obstruction	1 (0.2)	0	0
Intra-abdominal haematoma	0	1 (0.2)	0
Volvulus	0	1 (0.2)	0
General disorders and administration site conditions (SOC)	1 (0.2)	0	0
Impaired healing	1 (0.2)	0	0
Immune system disorders (SOC)	0	0	1 (0.5)
Drug hypersensitivity	0	0	1 (0.5)
Infections and infestations (SOC)	2 (0.4)	1 (0.2)	0
Infected seroma	1 (0.2)	0	0
Medical device site infection	1 (0.2)	0	0
Pneumonia	0	1 (0.2)	0
Injury, poisoning and procedural complications (SOC)	2 (0.4)	3 (0.7)	3 (1.4)
Post procedural haematoma	2 (0.4)	1 (0.2)	2 (0.9)
Post procedural haemorrhage	0	0	1 (0.5)
Anaemia postoperative	0	2 (0.4)	0
Nervous system disorders (SOC)	1 (0.2)	0	0
Syncope	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	3 (0.7)	2 (0.4)	1 (0.5)
Hypoxia	1 (0.2)	0	0
Pulmonary embolism	2 (0.4)	2 (0.4)	1 (0.5)
Vascular disorders (SOC)	0	0	1 (0.5)
Hypotension	0	0	1 (0.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 48 hours.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.4. Adverse Events Leading to Treatment Discontinuation, Study 105

There was no substantial difference in the incidence of any AE leading to discontinuation in the SUZ arm compared to the HB/APAP and placebo arms. The majority of AEs leading to discontinuation were experienced by only one subject in any given treatment arm.

There were no substantial differences between the treatment arms for any specific AE leading to discontinuation. Similar to the SAEs described in Section [17.2.2.3](#), many of the AEs leading to discontinuation were known to be associated with surgical procedures and were not unexpected considering the surgical acute pain model used.

Table 184. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study 105

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Any AE leading to discontinuation	5 (1.1)	5 (1.1)	1 (0.5)
Cardiac disorders (SOC)	0	0	1 (0.5)
Tachycardia	0	0	1 (0.5)
Gastrointestinal disorders (SOC)	0	1 (0.2)	0
Intra-abdominal haematoma	0	1 (0.2)	0
Nausea	0	1 (0.2)	0
General disorders and administration site conditions (SOC)	0	1 (0.2)	0
Pyrexia	0	1 (0.2)	0
Injury, poisoning and procedural complications (SOC)	2 (0.4)	0	0
Post procedural haematoma	2 (0.4)	0	0
Nervous system disorders (SOC)	1 (0.2)	1 (0.2)	0
Syncope	1 (0.2)	0	0
Migraine	0	1 (0.2)	0
Vascular disorders (SOC)	2 (0.4)	2 (0.4)	1 (0.5)
Hypotension	2 (0.4)	1 (0.2)	1 (0.5)
Orthostatic hypotension	0	1 (0.2)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.5. Treatment-Emergent Adverse Events, Study 105

[Table 185](#) presents the common AEs by PT and SOC in Study 105 that occurred in at least 0.3% of subjects in any arm. There was a lower percentage of subjects with any AEs in the SUZ treatment arm than in the HB/APAP and placebo arms. No AEs by PT occurred more frequently in the SUZ group than in the placebo group by $\geq 1.0\%$. Notable imbalances in AEs between the treatment arms were generally favorable for the safety profile of SUZ.

Table 185. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.3% of Subjects in Any Arm, Safety Population Study 105

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Any AE	224 (50.0)	272 (60.7)	125 (56.3)
Blood and lymphatic system disorders (SOC)	4 (0.9)	5 (1.1)	2 (0.9)
Coagulopathy	2 (0.4)	1 (0.2)	0
Blood loss anaemia	0	0	1 (0.5)
Disseminated intravascular coagulation	0	0	1 (0.5)
Anaemia	2 (0.4)	3 (0.7)	0
Cardiac disorders (SOC)	4 (0.9)	9 (2.0)	7 (3.2)
Bradycardia	2 (0.4)	1 (0.2)	1 (0.5)
Cardiogenic shock	0	0	1 (0.5)
Tachycardia	1 (0.2)	7 (1.6)	5 (2.3)

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Eye disorders (SOC)	1 (0.2)	2 (0.4)	0
Gastrointestinal disorders (SOC)	142 (31.7)	192 (42.9)	82 (36.9)
Constipation	47 (10.5)	39 (8.7)	24 (10.8)
Diarrhoea	3 (0.7)	1 (0.2)	0
Gastrooesophageal reflux disease	4 (0.9)	2 (0.4)	0
Toothache	0	0	1 (0.5)
Flatulence	10 (2.2)	11 (2.5)	5 (2.3)
Abdominal discomfort	0	2 (0.4)	0
Abdominal distension	0	2 (0.4)	2 (0.9)
Dyspepsia	8 (1.8)	12 (2.7)	3 (1.4)
Vomiting	10 (2.2)	18 (4.0)	3 (1.4)
Nausea	85 (19.0)	147 (32.8)	56 (25.2)
General disorders and administration site conditions (SOC)	8 (1.8)	9 (2.0)	6 (2.7)
Medical device site erythema	1 (0.2)	0	1 (0.5)
Medical device site vesicles	1 (0.2)	0	1 (0.5)
Injection site haematoma	0	0	1 (0.5)
Pyrexia	3 (0.7)	5 (1.1)	3 (1.4)
Immune system disorders (SOC)	0	0	1 (0.5)
Drug hypersensitivity	0	0	1 (0.5)
Hypersensitivity	0	0	1 (0.5)
Infections and infestations (SOC)	14 (3.1)	7 (1.6)	4 (1.8)
Conjunctivitis	2 (0.4)	0	0
Medical device site infection	3 (0.7)	1 (0.2)	0
Pharyngitis	3 (0.7)	1 (0.2)	0
Postoperative wound infection	3 (0.7)	1 (0.2)	2 (0.9)
Bacteriuria	0	0	1 (0.5)
Urinary tract infection	0	0	1 (0.5)
COVID-19	0	2 (0.4)	0
Injury, poisoning and procedural complications (SOC)	14 (3.1)	20 (4.5)	15 (6.8)
Procedural nausea	1 (0.2)	0	2 (0.9)
Skin abrasion	1 (0.2)	0	1 (0.5)
Fall	0	0	1 (0.5)
Muscle strain	0	0	1 (0.5)
Post procedural oedema	0	0	1 (0.5)
Postoperative wound complication	0	0	1 (0.5)
Vascular access site haemorrhage	0	0	1 (0.5)
Incision site pruritus	1 (0.2)	1 (0.2)	1 (0.5)
Post procedural haematoma	2 (0.4)	2 (0.4)	2 (0.9)
Post procedural haemorrhage	1 (0.2)	2 (0.4)	1 (0.5)
Wound dehiscence	1 (0.2)	2 (0.4)	0
Anaemia postoperative	2 (0.4)	8 (1.8)	4 (1.8)

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Investigations (SOC)	19 (4.2)	25 (5.6)	12 (5.4)
Blood pressure increased	2 (0.4)	0	0
Body temperature increased	2 (0.4)	0	0
Blood creatine increased	0	0	1 (0.5)
Electrocardiogram T wave inversion	0	0	1 (0.5)
Glomerular filtration rate decreased	0	0	1 (0.5)
Lipase increased	0	0	1 (0.5)
Neutrophil count increased	0	0	1 (0.5)
Urinary squamous epithelial cells increased	0	0	1 (0.5)
White blood cell count increased	0	0	1 (0.5)
Blood creatine phosphokinase increased	5 (1.1)	5 (1.1)	2 (0.9)
Bacterial test positive	0	1 (0.2)	1 (0.5)
Hepatic enzyme increased	1 (0.2)	2 (0.4)	3 (1.4)
Red blood cells urine positive	0	1 (0.2)	1 (0.5)
White blood cells urine positive	0	1 (0.2)	1 (0.5)
Blood urine present	0	2 (0.4)	0
Aspartate aminotransferase increased	3 (0.7)	11 (2.5)	3 (1.4)
Gamma-glutamyltransferase increased	1 (0.2)	9 (2.0)	2 (0.9)
Alanine aminotransferase increased	4 (0.9)	13 (2.9)	3 (1.4)
Metabolism and nutrition disorders (SOC)	2 (0.4)	3 (0.7)	2 (0.9)
Dehydration	0	0	1 (0.5)
Hypernatraemia	0	0	1 (0.5)
Musculoskeletal and connective tissue disorders (SOC)	11 (2.5)	8 (1.8)	7 (3.2)
Back pain	4 (0.9)	1 (0.2)	2 (0.9)
Pain in extremity	4 (0.9)	3 (0.7)	2 (0.9)
Musculoskeletal chest pain	0	0	1 (0.5)
Muscle spasms	2 (0.4)	2 (0.4)	1 (0.5)
Arthralgia	0	1 (0.2)	1 (0.5)
Nervous system disorders (SOC)	45 (10.0)	62 (13.8)	29 (13.1)
Syncope	6 (1.3)	2 (0.4)	4 (1.8)
Presyncope	4 (0.9)	1 (0.2)	0
Tremor	0	0	1 (0.5)
Paraesthesia	2 (0.4)	2 (0.4)	0
Migraine	0	3 (0.7)	0
Dizziness	18 (4.0)	24 (5.4)	17 (7.7)
Headache	19 (4.2)	32 (7.1)	11 (5.0)
Renal and urinary disorders (SOC)	2 (0.4)	7 (1.6)	6 (2.7)
Proteinuria	0	0	1 (0.5)
Urinary retention	1 (0.2)	3 (0.7)	3 (1.4)
Haematuria	0	4 (0.9)	2 (0.9)
Reproductive system and breast disorders (SOC)	4 (0.9)	0	1 (0.5)
Vaginal discharge	0	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	18 (4.0)	19 (4.2)	9 (4.1)
Cough	4 (0.9)	2 (0.4)	4 (1.8)
Oropharyngeal pain	4 (0.9)	3 (0.7)	2 (0.9)
Asthma	0	0	1 (0.5)
Dyspnoea	2 (0.4)	2 (0.4)	1 (0.5)
Pulmonary embolism	2 (0.4)	2 (0.4)	1 (0.5)
Hypoxia	6 (1.3)	8 (1.8)	1 (0.5)

System Organ Class Preferred Term	SUZ N=448 n (%)	HB/APAP N=448 n (%)	Placebo N=222 n (%)
Skin and subcutaneous tissue disorders (SOC)	23 (5.1)	33 (7.4)	11 (5.0)
Rash	4 (0.9)	1 (0.2)	1 (0.5)
Blister	3 (0.7)	1 (0.2)	0
Urticaria	2 (0.4)	1 (0.2)	1 (0.5)
Hyperhidrosis	3 (0.7)	3 (0.7)	5 (2.3)
Epidermolysis	1 (0.2)	2 (0.4)	0
Dermatitis contact	2 (0.4)	4 (0.9)	0
Ecchymosis	1 (0.2)	3 (0.7)	0
Ischaemic skin ulcer	0	2 (0.4)	0
Pruritus	5 (1.1)	17 (3.8)	4 (1.8)
Vascular disorders (SOC)	14 (3.1)	21 (4.7)	17 (7.7)
Superficial vein thrombosis	2 (0.4)	0	0
Orthostatic hypotension	0	1 (0.2)	2 (0.9)
Flushing	0	2 (0.4)	0
Hot flush	0	2 (0.4)	0
Hypotension	11 (2.5)	16 (3.6)	15 (6.8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the time from the first dose of study drug in the Treatment Period to the Safety Follow-up Visit or to the completion of study participation, whichever occurred first.

Duration is 48 hours.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.6. Laboratory Findings, Study 105

Analyses of laboratory data did not raise significant clinically meaningful safety concerns. Median changes from baseline to the end of treatment were similar between the treatment arms for the majority of the laboratory assessments conducted.

There were some laboratory parameters with notable imbalances between the SUZ treatment arm and the HB/APAP and placebo treatment arms. [Table 186](#) demonstrates that a higher percentage of subjects in the SUZ treatment arm had CPK values exceeding certain threshold levels than did subjects in the other treatment arms. [Table 187](#) demonstrates that the mean changes in CPK and creatinine from baseline were higher and the mean change in eGFR from baseline was lower in the SUZ treatment arm at 48 hours. However, the magnitude of these changes was relatively small and unlikely to be clinically significant.

Table 186. Subjects With CPK Values Exceeding Specified Levels, Safety Population, Study 105

Laboratory Parameter	SUZ N=448 n/N _w (%)	HB/APAP N=448 n/N _w (%)	Placebo N=222 n/N _w (%)
CPK, high (U/L)			
Level 1 (>3× ULN)	15/443 (3.4)	5/441 (1.1)	4/216 (1.9)
Level 2 (>5× ULN)	5/443 (1.1)	1/441 (0.2)	1/216 (0.5)
Level 3 (>10× ULN)	2/443 (0.5)	0/441 (0)	0/216 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 48 hours.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CPK, creatine phosphokinase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

Table 187. Selected Chemistry Assessments and Changes From Baseline at 48 Hours, Study 105

Laboratory Parameter	SUZ N=448	HB/APAP N=448	Placebo N=222
Creatine kinase (U/L)			
N	438	438	214
Mean (SD)	66.8 (212.4)	45.8 (120.1)	43.3 (158.7)
Median	22.0	16.0	21.0
Creatinine (μmol/L)			
N	440	439	215
Mean (SD)	-1.2 (11.4)	-5.1 (10.4)	-3.3 (32.1)
Median	0.0	-8.8	-8.8
Glomerular filtration rate, estimated (mL/min/1.73 m ²)			
N	440	439	215
Mean (SD)	1.1 (12.8)	4.6 (11.0)	3.9 (15.9)
Median	0.0	4.0	4.0

Source: Modified from Protocol VX22-548-105 CSR, Table 14.3.4.1, Pages 9, 10, 13

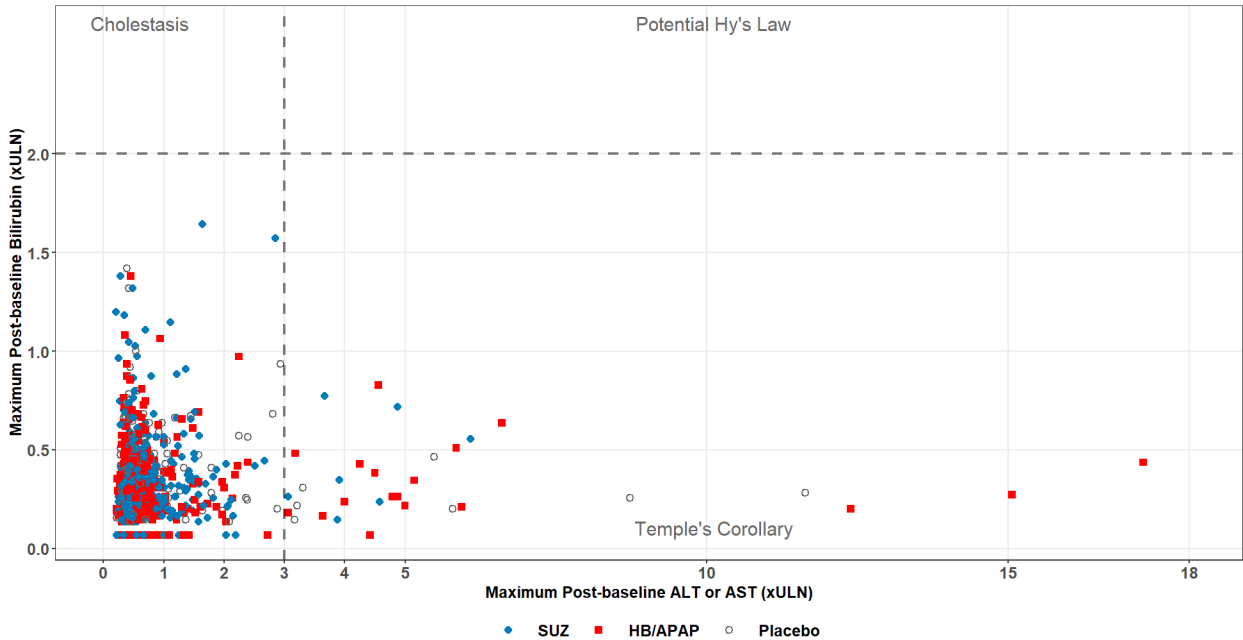
Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects evaluated; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.7. Assessment of Drug-Induced Liver Injury, Study 105

[Figure 55](#) shows a screening assessment for potential cases of serious DILI. There were no subjects in any treatment arm in the Cholestasis and Potential Hy's Law quadrants. There was a lower percentage of subjects in the SUZ treatment arm (1.8%) in the Temple's Corollary quadrant than in the HB/APAP (4.1%) and placebo (3.2%) treatment arms. These findings do not suggest a significant relationship between SUZ and drug-induced liver injury.

Figure 55. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 105



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours; ULN, upper limit of normal

17.2.2.8. Vital-Sign and ECG Analyses, Study 105

Review of the vital sign data and ECG parameters did not reveal significant clinically meaningful safety concerns associated with SUZ. As depicted in [Table 188](#) and [Table 189](#), during the treatment period, there were larger decreases from baseline in the mean systolic and diastolic blood pressures in the SUZ arm than in the placebo arm. However, the magnitude of this difference was small and unlikely to be clinically significant.

Table 188. Systolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Study 105

Time Point	Statistic	SUZ N=448	HB/APAP N=448	Placebo N=222
2 hours	n	448	447	221
	Mean (SD)	-4.8 (17.2)	-3.1 (17.4)	-0.4 (17.9)
	Median	-5.0	-2.0	1.0
4 hours	n	448	447	219
	Mean (SD)	-5.0 (17.4)	-4.0 (18.2)	-2.8 (16.1)
	Median	-5.5	-4.0	-2.0

Time Point	Statistic	SUZ N=448	HB/APAP N=448	Placebo N=222
24 hours	n	444	442	218
	Mean (SD)	-9.6 (17.2)	-7.9 (17.9)	-4.9 (17.2)
	Median	-9.0	-7.0	-5.0
48 hours	n	443	441	216
	Mean (SD)	-6.7 (18.6)	-4.4 (18.4)	-3.8 (18.2)
	Median	-7.0	-4.0	-5.0
Safety follow-up	n	424	427	205
	Mean (SD)	-4.5 (19.4)	-3.4 (18.6)	-3.7 (19.2)
	Median	-3.0	-3.0	-4.0

Source: Modified from Protocol VX22-548-105 CSR, Table 14.3.5.1, Pages 1-2

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

Table 189. Diastolic Blood Pressure (mm Hg) and Changes From Baseline by Visit, Study 105

Change From Baseline at	Statistic	SUZ N=448	HB/APAP N=448	Placebo N=222
2 hours	n	448	447	221
	Mean (SD)	-1.5 (11.9)	-0.8 (12.4)	-0.7 (12.4)
	Median	-2.0	-1.0	-1.0
4 hours	n	448	447	219
	Mean (SD)	-2.4 (12.1)	-1.8 (12.6)	-1.3 (11.6)
	Median	-3.0	-2.0	-2.0
24 hours	n	444	442	218
	Mean (SD)	-5.4 (12.0)	-4.7 (13.0)	-2.3 (13.6)
	Median	-6.0	-5.0	-3.0
48 hours	n	443	441	216
	Mean (SD)	-2.7 (13.0)	-1.6 (13.5)	-0.9 (13.4)
	Median	-4.0	-1.0	-2.0
Safety follow-up	n	424	427	205
	Mean (SD)	2.6 (13.4)	2.8 (12.9)	1.9 (14.3)
	Median	2.0	3.0	2.0

Source: Modified from Protocol VX22-548-105 CSR, Table 14.3.5.1, Pages 3-4

Baseline value is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects evaluated; SD, standard deviation; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.2.2.9. Subgroup Analyses, Study 105

[Table 190](#) depicts the number of subjects in each specific subgroup among the different treatment arms. The finding of a lower incidence of AEs in the SUZ arm than in the HB/APAP and placebo arms was generally consistent across subgroups. However, there were notable imbalances in terms of the number of subjects between subgroup categories, which limited the conclusions that could be drawn from these data. There were significantly fewer males, subjects ≥65 years of age, and subjects of races other than Black, African American, or White exposed to SUZ.

Table 190. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study 105

Characteristic	SUZ N=448 n/N _s (%)	HB/APAP N=448 n/N _s (%)	Placebo N=222 n/N _s (%)
Sex			
Female	220/438 (50.2)	268/441 (60.8)	123/219 (56.2)
Male	4/10 (40.0)	4/7 (57.1)	2/3 (66.7)
Age group, years			
≥18 to <65	224/444 (50.5)	271/447 (60.6)	125/222 (56.3)
≥65	0/4 (0)	1/1 (100)	0/0 (NA)
Race			
American Indian or Alaska Native	1/5 (20.0)	0/0 (NA)	0/1 (0)
Asian	5/7 (71.4)	6/9 (66.7)	0/0 (NA)
Black or African American	53/123 (43.1)	56/114 (49.1)	31/62 (50.0)
Multiple	2/2 (100)	2/4 (50.0)	1/2 (50.0)
Native Hawaiian or other Pacific Islander	1/3 (33.3)	3/5 (60.0)	1/1 (100)
Other	0/0 (NA)	0/0 (NA)	2/2 (100)
White	162/308 (52.6)	205/316 (64.9)	90/154 (58.4)
Ethnicity			
Hispanic or Latino	77/150 (51.3)	99/157 (63.1)	39/73 (53.4)
Not Hispanic or Latino	147/298 (49.3)	171/288 (59.4)	86/149 (57.7)
Missing	0/0 (NA)	2/3 (66.7)	0/0 (NA)

Source: adae.xpt; Software: R

Abbreviations: HB/APAP, hydrocodone bitartrate/acetaminophen 5/325 mg every 6 hours; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SUZ, suzetrigine 100 mg loading dose followed by 50 mg every 12 hours

17.3. Major Safety Findings, Phase 2 and 3 Studies

Summaries of narratives for the major safety findings in subjects treated with SUZ in the phase 2 and 3 clinical studies are provided below.

Phase 2 Studies

Study VX21-548-101

There were no deaths, no SAEs, and no AEs leading to study drug interruption or discontinuation.

Study VX21-548-102

There were no deaths. One subject in the SUZ 60 mg/30 mg q12h group experienced an SAE. Two subjects in the SUZ 60 mg/30 mg q12h group experienced an AE leading to treatment discontinuation. There were no AEs leading to treatment interruption.

1. Subject (b) (6) (SAE - pulmonary embolism): This was a 53-year-old female status post (s/p) abdominoplasty surgery. The subject was randomized to SUZ 60 mg/30 mg q12h. On Study Day 1, before the first dose of study drug, the subject had an AE of mild hypoxia. Treatment included oxygen and this AE was considered resolved the next day. The subject completed treatment with the study drug. On Study Day 10, the subject had worsening tachycardia, hypertension, and hypoxia. The subject was subsequently hospitalized for an

SAE of pulmonary embolism. Treatment included apixaban and oxygen therapy. The subject was discharged from the hospital on Study Day 14. The SAE of pulmonary embolism was considered resolved approximately 10 weeks after the start of this SAE.

2. Subject (b) (6) (AE that led to study drug discontinuation - chest discomfort): This was a 43-year-old female s/p abdominoplasty surgery. The subject was randomized to SUZ 60 mg/30 mg q12h. On Study Day 2, the subject had an AE of moderate chest discomfort (pressure in esophageal area of upper chest). The subject did not receive treatment for this. There were no ECG or oxygen saturation abnormalities at scheduled time points before and after the start of this AE. Study drug dosing was withdrawn due to this event. The subject was lost to follow-up and was considered to have discontinued the study on Study Day 3.
3. Subject (b) (6) (AE that led to study drug discontinuation – anemia): This was a 42-year-old female s/p abdominoplasty surgery. On Study Day 1, before the first dose of study drug, the subject had AEs of moderate hypoxia and mild hypothermia, which were considered resolved that same day. The subject was randomized to SUZ 60 mg/30 mg q12h. Later on Study Day 1, the subject had AEs of moderate anemia and moderate hypotension. The subject also had high output from their surgical drains. The subject was treated with IV fluid. Relevant concomitant medication before or at onset of the AE of anemia included heparin. Study drug dosing was withdrawn due to this AE. On Study Day 2, the subject experienced decreasing hemoglobin/hematocrit laboratory values and hypotension. The subject returned to the operating room for wound exploration, and a venous bleed was identified and treated. The subject had an AE of moderate hypoxia, which was treated with oxygen and considered resolved the next day. The AE of anemia was considered resolved approximately 2.5 weeks after the start of this AE.

Phase 3 Studies

Study VX22-548-104

There were no AEs leading to death, no SAEs, and no AEs that led to treatment discontinuation or interruption in subjects treated with SUZ.

Study VX22-548-105

There were no AEs leading to death in the SUZ group. Eleven (2.5%) subjects in the SUZ group experienced an SAE. Five (1.1%) subjects in the SUZ group experienced an AE leading to treatment discontinuation. There were no subjects in the SUZ group who experienced an AE leading to treatment interruption.

1. Subject (b) (6) (SAE - hypoxia): This was a 61-year-old female s/p abdominoplasty surgery who was found to have an oxygen saturation (SpO₂) of 89% approximately 2 hours after the first dose of study drug. The subject's predose SpO₂ was 97%. No symptoms, such as dyspnea and shortness of breath, were reported but their room air SpO₂ remained low despite regular incentive spirometry, ambulation, deep breaths, and cough. Treatment included supplemental oxygen. The subject also had moderate AEs of anemia postoperative and coagulopathy and a mild AE of dizziness on Study Day 3. The subject completed treatment with the study drug. On Study Day 5, the SAE of hypoxia was considered resolved with a SpO₂ of 95%.

2. Subject [REDACTED] (b) (6) (SAE - anemia): This was a 31-year-old female s/p abdominoplasty surgery who was found to have anemia with hemoglobin of 6.4 g/dL on Study Day 3. Screening laboratory results showed a hemoglobin of 12.2 g/dL. The subject completed treatment with the study drug. Approximately 2.5 weeks after the last dose of study drug, the subject was hospitalized due to the SAE of anemia. Laboratory test results included hemoglobin of 6.3 g/dL. The subject was transfused with a total of two units of packed red blood cells and underwent debridement, which showed infection and a hematoma. Five days after this surgery, the subject's hemoglobin improved to 8.9 g/dL and they were discharged from the hospital.
3. Subject [REDACTED] (b) (6) (SAE - impaired healing): This was a 35-year-old female s/p abdominoplasty surgery. The subject completed treatment with the study drug. On Study Day 15, the subject had an SAE of impaired healing. They reported drainage and described superficial necrosis of the skin at the incision edge, which was confirmed as a wound infection. The subject subsequently underwent debridement, wound packing, and wound care. The SAE of impaired healing was considered resolved approximately 20 weeks after the start of this SAE.
4. Subject [REDACTED] (b) (6) (SAE - pulmonary embolism): This was a 36-year-old female s/p abdominoplasty surgery. On Study Day 1, the subject had a moderate AE of syncope, which resolved after treatment with IV fluids. The subject completed treatment with the study drug. On Study Day 9, the subject had an SAE of pulmonary embolism and was discharged home with apixaban for treatment. On Study Day 10, the subject was hospitalized due to an SAE of pulmonary embolism and presented with right leg pain. Additional treatment included IV heparin and normal saline. The subject's breathing improved, the right lower chest pain was controlled, and the subject was discharged from the hospital on Study Day 12.
5. Subject [REDACTED] (b) (6) (SAE - pulmonary embolism): This was a 36-year-old female s/p abdominoplasty surgery. The subject received her last dose of study drug on Study Day 2 (discontinued due to lack of efficacy). On Study Day 4, the subject was hospitalized due to an SAE of pulmonary embolism after a syncopal episode. The subject also had an AE of moderate ECG ST-T segment abnormal. Computed tomography (CT) angiography showed an acute submassive pulmonary embolism. The subject was treated with alteplase. They started bleeding from lower abdominal drains and went into respiratory failure and shock. The subject had six vessels embolized by interventional radiology to control bleeding. The subject was asymptomatic and was discharged from the hospital on Study Day 13. The SAE of pulmonary embolism was considered resolved approximately 23 weeks after the start of this SAE.
6. Subject [REDACTED] (b) (6) (SAE, AE that led to study drug discontinuation - post procedural hematoma): This was a 29-year-old female s/p abdominoplasty surgery. On Study Day 1, the subject had AEs of moderate nausea and mild dizziness and was hospitalized for an SAE of postprocedural hematoma. The subject underwent incision and drainage of hematoma. Study drug dosing was withdrawn due to this SAE. On the same day, the SAE of postprocedural hematoma and AEs of nausea and dizziness were considered resolved.
7. Subject [REDACTED] (b) (6) (SAE, SAE that led to study drug discontinuation - postprocedural hematoma): This was a 34-year-old female s/p abdominoplasty surgery. The subject had increased drainage and slightly increased swelling at surgical site along with tachycardia and

hemoglobin of 9.4 g/dL. The subject was given a red blood cell transfusion and taken back to the operating room for an abdominal flap exploration, hemostasis, washout, and removal of 700 mL of blood clot. Study drug dosing was withdrawn due to the SAE of postprocedural hematoma. On the same day, the SAE of postprocedural hematoma was considered resolved.

8. Subject (b) (6) (SAE, AE that led to study drug discontinuation - syncope): This was a 27-year-old male s/p abdominoplasty surgery. The subject received only one dose of study drug. On Study Day 1, the subject was found to be hypotensive and sent to the emergency department for evaluation. During evaluation, they had an episode of weakness, lightheadedness, pallor, tachycardia, and diaphoresis with a depressed mental state but without syncope while attempting to stand up. The subject was subsequently admitted for the SAE of syncope and was treated with IV fluids, hydrocodone bitartrate/acetaminophen for pain, and ondansetron for nausea. On the same day, the SAE of syncope was considered resolved. Study drug dosing was withdrawn due to this SAE. The subject was discharged from the hospital on Study Day 2.
9. Subject (b) (6) (SAE - small intestinal obstruction): This was a 37-year-old female s/p abdominoplasty surgery. The subject completed treatment with the study drug. On Study Day 3, the subject was taken by ambulance to a medical center due to complaints of shortness of breath, nausea, and intractable vomiting. A CT scan of the abdomen and pelvis revealed a small bowel obstruction. A nasogastric tube was then placed for bowel decompression. On Study Day 4, the subject was hospitalized for an SAE of small intestinal obstruction. On Study Day 7, this SAE was considered resolved and the subject was discharged from the hospital.
10. Subject (b) (6) (SAE - infected seroma): This was a 34-year-old female s/p abdominoplasty surgery. The subject completed treatment with the study drug. On Study Day 15, the subject presented to the emergency department complaining of pain and fever and was subsequently hospitalized for an SAE of infected seroma. On the same day, the subject had an AE of moderate wound dehiscence. Treatment included incision and drainage with wound packing. On Study Day 17, the subject was discharged from the hospital. At the time of reporting, the SAE of infected seroma and the AE of wound dehiscence were considered not resolved.
11. Subject (b) (6) (SAE - medical device site infection): This was a 20-year-old female s/p abdominoplasty surgery. The subject completed treatment with the study drug. On Study Day 10, the subject presented to the emergency department and was hospitalized for an SAE of medical device site infection (infection of abdominoplasty drainage tubes). On Study Day 12, the subject was discharged from the hospital and their drains were removed two days later. At the time of reporting, the SAE of medical device site infection was considered not resolved.
12. Subject (b) (6) (AE that led to study drug discontinuation – hypotension): This was a 42-year-old female s/p abdominoplasty surgery. The subject's relevant medical history included low baseline blood pressure. The subject received only one dose of study drug. On the same day (Study Day 1), they had AEs of severe hypotension and severe bradycardia. Treatment included IV fluids for hypotension and bradycardia. Additional treatment for the event of bradycardia included placement in the Trendelenburg position, oxygen, and IV

glycopyrronium bromide. Study drug dosing was withdrawn due to the event of hypotension. On Study Day 2, the AEs of nausea, hypotension, and bradycardia were considered resolved.

13. Subject (b) (6) (AE that led to study drug discontinuation - hypotension): This was a 42-year-old female s/p abdominoplasty surgery. On Study Day 1, the subject had AEs of moderate presyncope and moderate hypotension. They also had an AE of mild oxygen saturation decreased. Treatment included IV fluids and oxygen. Study drug dosing was discontinued due to the event of hypotension. On the same day, the AEs of presyncope and oxygen saturation decreased were considered resolved. On Study Day 2, the AE of hypotension was considered resolved.

Study VX22-548-107

There were no AEs leading to death. Two (0.8%) subjects had SAEs. Five (2.0%) subjects had AEs that led to treatment discontinuation. There were no AEs leading to treatment interruption.

1. Subject (b) (6) (SAE - suicidal ideation): This was a 42-year-old female s/p arthroscopic surgery (left ankle) and ligament operation (left ankle ligament repair and removal of Bassett lesion). On Study Day 8, the subject completed study drug treatment due to pain resolution. On Study Day 12, they had an SAE of suicidal ideation. The subject felt that the suicidal ideation was situational, as they were a single parent of multiple children and had recently ended a relationship. An additional struggle was being nonweight-bearing after surgery. The subject had already discussed their feelings with their primary care physician and scheduled therapy. The subject improved over the subsequent weeks and the SAE of suicidal ideation was considered resolved as of approximately 1 month after the start of this SAE.
2. Subject (b) (6) (SAE - cellulitis): This was a 42-year-old female s/p a skin cosmetic procedure (brachioplasty). On Study Day 8, the subject completed study drug treatment due to pain resolution. On Study Day 13, the subject had an AE of moderate cellulitis (right arm). They were treated with antibiotics in an emergency room and discharged home. On Study Day 23, the subject was hospitalized for an SAE of cellulitis (worsening right arm cellulitis). A computerized tomography scan was suggestive of a small abscess within the subcutaneous tissues of the right upper arm. They were treated with antibiotics and discharged from the hospital on Study Day 27. Follow-up information received after database lock indicated that the SAE of cellulitis was considered resolved.
3. Subject (b) (6) (AE that led to study drug discontinuation –somnolence): This was a 32-year-old female s/p abdominoplasty and mammoplasty. On Study Day 2, the subject had an AE of mild somnolence and did not receive treatment for this event. Relevant concomitant medication before onset of this AE included fluoxetine hydrochloride. On Study Day 4, the AE of somnolence was considered resolved. Study drug dosing was withdrawn due to this AE.

4. Subject (b) (6) (AE that led to study drug discontinuation - accidental overdose): This was a 50-year-old female who experienced neck pain (acute cervical pain due to fall). On Study Day 1, the subject had an AE of mild accidental overdose. They took two tablets of SUZ for 11 succeeding doses from Study Day 1 through Study Day 7, when the overdose was discovered at their clinic visit and study drug dosing was withdrawn. On Study Day 5, the subject had an AE of mild dry mouth and did not receive treatment for this event, which was considered resolved on Study Day 9.
5. Subject (b) (6) (AE that led to study drug discontinuation - rash): This was a 56-year-old female who experienced arthralgia (acute left wrist pain). On Study Day 3, the subject had an AE of mild rash (chest) and, on Study Day 4, they had an AE of mild rash (both wrists). Treatment included diphenhydramine hydrochloride for both events. Study drug dosing was withdrawn on Study Day 4 due to these AEs. On Study Day 5, the subject had an AE of mild pruritus and they continued treatment with diphenhydramine hydrochloride. The chest rash, pruritis, and wrist rash were considered resolved on Study Day 7, 8, and 9, respectively.
6. Subject (b) (6) (AE that led to study drug discontinuation - arrhythmia): This was a 38-year-old female s/p a ligament operation (left anterior cruciate ligament repair). The subject's relevant medical history included sinus arrhythmia and cardiac murmur. On Study Day 5, they experienced exacerbation of preexisting arrhythmia. Study drug dosing was withdrawn due to this AE. On Study Day 6, ECG results (performed twice) were normal, with the exception of premature atrial complexes in both readings. At the time of reporting, the adverse event of arrhythmia was considered not resolved.
7. Subject (b) (6) (AE that led to study drug discontinuation - nausea): This was a 65-year-old female who experienced post-traumatic pain (right hip pain from fall). The subject's relevant medical history included Meniere's disease, Crohn's disease, and nausea/vomiting. On Study Day 2, they had an AE of nausea. The subject stated that they took omeprazole to help with nausea/vomiting due to Meniere's disease. However, this medication was prohibited during the study. The subject was not able to tolerate oral intake without omeprazole and decided to stop taking study drug. On Study Day 3, the AE of nausea was considered resolved.

18. Clinical Virology

SUZ is not a therapeutic antiviral drug; therefore, clinical virology data were not required or submitted for this application.

19. Clinical Microbiology

SUZ is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

20. Mechanism of Action/Drug Resistance

Since SUZ is not a therapeutic antimicrobial drug, mechanism of action studies are not needed. Hence, this section is not applicable to SUZ.

21. Other Drug Development Considerations

There are no additional drug development considerations to include here as they have been described in detail in other sections of this review.

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

No significant issues were identified that affected the interpretation of this review. See Section [10](#).

23. Labeling: Key Changes

See the approved prescribing information for the final, agreed-upon language. A summary of the significant changes made to the full prescribing information from the Applicant's proposed label (submitted on January 29, 2024) is shown below in [Table 191](#). Highlights and table of contents were revised for consistency with the rest of the prescribing information (PI). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 191. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
BOXED WARNING	Not Applicable
1 INDICATIONS AND USAGE	In the INDICATIONS AND USAGE section of the HIGHLIGHTS OF PRESCRIBING INFORMATION, the Applicant proposed the language (b) (4) The review team did not agree with the Applicant's proposed established pharmacologic class (EPC) (b) (4) because it is promotional and does not provide clinically meaningful information about the mechanism of action or potential risk profile. The review team recommends the EPC phrase "sodium channel blocker" based on its pharmacology/mechanism of action. During labeling discussions, the Applicant proposed the EPC phrase (b) (4) however, the review team concluded (b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	(b) (4) The review team recommended that the EPC remain less specific (b) (4) 'Blocker' has typically been used for ion channels in the EPC phrase list. (b) (4) The review team and Applicant have agreed on "sodium channel blocker."
2 DOSAGE AND ADMINISTRATION	The Applicant proposed use of JOURNAVX (b) (4) (b) (4) Duration of use is discussed in more detail in Section 7.8.2. During labeling negotiations, the review team proposed replacing (b) (4) with (b) (4) (b) (4) However, the Applicant disagreed with this proposal, citing the favorable safety profile of JOURNAVX, safety data from their chronic pain program, and regulatory precedent. There were also concerns about limiting the use of JOURNAVX, considering the possibility of acute pain lasting more than 14 days and the risks associated with needing to switch to an alternative analgesic, such as opioids. The Applicant proposed deleting (b) (4) and including "use for the shortest duration, consistent with individual patient treatment goals" in Section 2.1. The review team considered this acceptable, with the addition of "use of JOURNAVX for the treatment of acute pain has not been studied beyond 14 days" to inform prescribers about the limitations in safety data. The Applicant proposed (b) (4) (b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	Based on overall data, the review team's recommendation for food effect is, "Avoid consuming food from 2 hours before until 1 hour after the first dose of JOURNAVX to avoid delay in onset of pain relief. Subsequent doses of JOURNAVX can be taken with or without food." Upon further discussion with the Applicant, the Applicant wanted to add consumption of clear liquids with the first dose because this was how the efficacy was conducted. Thus, the following language was agreed upon: Take the starting dose on an empty stomach at least 1 hour before or 2 hours after food to avoid delay in onset of action. Clear liquids may be consumed during this time (e.g., water, apple juice, vegetable broth, tea, black coffee). Avoid food or drink containing grapefruit during treatment with JOURNAVX.
4 CONTRAINDICATIONS	There were originally no contraindications listed. The review team added: "Concomitant use of JOURNAVX with strong CYP3A4 inhibitors is contraindicated" due to the ≥ 5-fold exposure that occurs with SUZ in this setting. See the Drug Interactions section below for further information.
5 WARNINGS AND PRECAUTIONS	There were originally no warnings and precautions. Four subsections were added which included: 1) Increased Risk of Adverse Reactions with Concomitant Use with Strong or Moderate CYP3A Inhibitors, 2) Risk of Drug Interactions with Certain CYP3A Substrates, 3) Risk of Drug Interactions with Certain Hormonal Contraceptives, and 4) Risk of Adverse Reactions in Patients with Moderate and Severe Hepatic Impairment. The rationale for adding these subsections is related to predicted drug interactions through which serious or otherwise clinically significant outcomes may occur, and in the case of hepatic impairment, anticipated adverse reactions. These decisions were made in accordance with guidance for industry <i>Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (October 2011). A warning regarding potential renal impairment was considered but not included. Although mean changes in CPK and creatinine from baseline were higher and the mean change in eGFR from baseline was lower in the SUZ group compared to placebo, the magnitude of these changes were small and unlikely to be clinically significant. Notably, the changes from baseline in these parameters for the SUZ groups were minimal, while the changes from baseline for the placebo groups indicated an overall improvement, possibly attributable to perioperative hydration. Thus, while there is a potential signal that SUZ could counteract the positive impact of perioperative hydration, it cannot be confirmed by these perioperative studies, and ultimately, the observed changes were unlikely to be clinically significant. No warning regarding renal impairment was added.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	In Section 6.1, the Applicant stated (b) (4) The Applicant agreed to describe the imbalances and state that there are insufficient data to detect differences in safety signals between subgroups. The review team initially recommended expanding the common adverse events table to include those occurring in $\geq 1\%$ (from $\geq 2\%$) of JOURNAVX treated patients to provide a more robust representation of the safety profile of this first-in-class drug. However, the table was ultimately revised to reflect adverse reactions in $\geq 1\%$ of JOURNAVX-treated patients. The laboratory abnormalities regarding elevations in creatine phosphokinase and a decrease in estimated glomerular filtration rate were added to Section 6 and not to Section 5 as described above. No clinically significant adverse events were associated with these laboratory abnormalities. The review team also revised the description of Trial 3 (Study 107) from (b) (4) to "open-label study" considering the limitations for evaluation of safety or efficacy in a single-arm trial. The Applicant also proposed including a description of the rescue medication regimen in Trial 3, which was acceptable.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
7 DRUG INTERACTIONS	<u>CYP3A Substrates</u> The Applicant did not have any proposed language for CYP3A substrates. Since SUZ decreases the exposure, it can thereby compromise the efficacy of certain CYP3A substrates. The review team included following labeling recommendations: • Avoid concomitant use of JOURNAVX with CYP3A substrates where minimal concentration changes may lead to loss of efficacy unless otherwise recommended in the Prescribing Information for CYP3A substrates. • When using JOURNAVX with sensitive CYP3A substrates, consider increasing the dose of substrate drugs based on their Prescribing Information if needed or use alternative medications. During labeling negotiations, the Applicant proposed the following language, which was acceptable: Refer to the prescribing information (b) (4) for dosing (b) (4) instructions Suzetrigine is an inducer of CYP3A. Concomitant use with JOURNAVX may reduce the exposure of sensitive CYP3A substrates which may decrease the efficacy of these substrates. Discontinuation of JOURNAVX may increase the exposure of sensitive CYP3A substrates.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	The Applicant initially proposed the following language in section 8.1: (b) (4) (b) (4) However, based on the information submitted under this NDA, the review team could not conclude (b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	(b) (4) Therefore, the review team recommends removing statements (b) (4) The review team informed the Applicant during mid-cycle communication discussions that they had concerns about the proposed statements (b) (4) After the mid-cycle communication, Applicant revised the proposed language to: (b) (4) (b) (4) Overall, the review team cannot conclude that (b) (4) After the late-cycle communication meeting, the Applicant submitted a response (b) (4) However, the Applicant agreed to remove statements (b) (4) and agreed to the Agency's recommended statement 'the relevance to humans is unclear' based on the totality of data given a new drug class that cannot exclude all possible causes affecting reproductive toxicity findings observed in rats. However, the Applicant did not agree to include the sentence, (b) (4) in Sections 8.3 and 17. The Applicant submitted additional information to justify their rationale; however, the information could not be reviewed because it was submitted late in the review cycle. Therefore, this information may be reviewed and addressed in a future labeling supplement submission. Based on pre-/postimplantation loss observed in fertility and EFD studies in rats, the statement regarding potential impact on fertility should be included in the labeling. After significant internal discussion including DPMH and negotiations with the Applicant, the agreed upon language is as follows: "JOURNAVX may reversibly impact the likelihood of females of reproductive potential to become pregnant while on treatment. Patients using contraceptives should continue to use contraceptives."

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	(b) (4) Regarding Section 8.2, based on further review of the information (b) (4) (b) (4) DPMH recommended deleting (b) (4) and its contents (b) (4)
9 DRUG ABUSE AND DEPENDENCE	Not applicable (see Section 7.8)
10 OVERDOSAGE	Overdose potential was not explicitly evaluated during SUZ development in either nonclinical or clinical studies. The label instructs that general supportive measures be provided. Contact information for the Poison Control Center was added.
11 DESCRIPTION	The review team did not agree with the Applicant's proposal to call the drug (b) (4). The review team recommends "sodium channel blocker." Refer to discussion in Section 1 INDICATIONS AND USAGE.
12 CLINICAL PHARMACOLOGY	The review team did not agree with the Applicant's proposal to include the statement (b) (4) (b) (4). It is unclear if the data adequately support the proposed statement and it is promotional and not related to the mechanism of action. The review team also recommended including the following statement about the active major metabolite, M6, as it contributes to the efficacy of the product. "M6 SUZ, a major active metabolite, is a less potent inhibitor of Na_v1.8 than suzetrigine by 3.7 fold. Based on an in vitro electrophysiology assay in human DRG neurons, M6 SUZ is a less potent inhibitor of Na_v1.8 than suzetrigine by 3.7 fold."
13 NONCLINICAL TOXICOLOGY	The Applicant added (b) (4) (b) (4) The review team recommended removing this as this type of information is not appropriate to be included (b) (4) Therefore, language (b) (4) is not appropriate for this section.
14 CLINICAL STUDIES	The Applicant stated that (b) (4) (b) (4) in Sections 14.1 and 14.2. The review team recommended deleting this sentence since it may potentially be misinterpreted (b) (4) Since the first key secondary endpoint failed to demonstrate superiority in both Study 104 and Study 105, the reporting of subsequent endpoints in the label was considered exploratory and was generally avoided. The exception was that of the SPID24 which was considered directly related to the primary

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	efficacy endpoint of SPID48 and was considered useful information for prescribers. Qualifying language was included to indicate that SPID24 was an exploratory analysis. Similarly, information (b) (4) was deleted from both Study 104 and 105. In order to provide context to prescribers for how to interpret the results of the active control group (HB/APAP), the review team and Applicant agreed to include the results of the LS Mean Difference vs. HB/APAP in the table reporting the primary endpoint. The Applicant also agreed to include a footnote describing how to interpret the LS mean.
17 PATIENT COUNSELING INFORMATION	Language pertaining to taking with or without food, and when, was added to this section. Language agreed on for section 2 was included in this section. Advise patients to take the starting dose of JOURNAVX on an empty stomach at least 1 hour before or 2 hours after food to avoid delay in onset of action. Clear liquids may be consumed (such as water, apple juice, vegetable broth, tea or black coffee) during this time. Avoid food and drink containing grapefruit during treatment with JOURNAVX. Subsequent doses of JOURNAVX can be taken with or without food. Language pertaining to "Females of Reproductive Potential" was added to include, "Advise females of reproductive potential that JOURNAVX may reversibly impact the likelihood to become pregnant while on treatment. Patients using contraceptives should continue to use contraceptives [see Use in Specific Populations (8.3)]." Language (b) (4) was removed from this section in alignment with guidance for industry: <i>Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (December 2014).
Product quality sections 3 DOSAGE FORMS and STRENGTHS	No change
11 DESCRIPTION	Change to therapeutic class; minor formatting changes to chemical name; deletion of (b) (4) deletion of (b) (4)
16 HOW SUPPLIED/STORAGE and HANDLING	Addition of dosage form shape; deletion of (b) (4) minor formatting changes to storage temperatures

Source: Generated by the SUZ review team.]

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

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

Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; DPMH, Division of Pediatrics and Maternal Health; DRG, dorsal root ganglion; EFD, embryo-fetal development; EPC, established pharmacologic class; HB/APAP, hydrocodone bitartrate/acetaminophen; MRHD, maximum recommended human dose; NDA, new drug application; NPRS, numerical pain rating scale; pAUC, partial AUC; PI, prescribing information; PK, pharmacokinetics; PR, progesterone receptor; SPID48, sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours; SUZ, suzetrigine

23.1. Approved Labeling Types

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

- Prescribing Information
- Patient Package Insert (PPI)
- Carton Labeling
- Container Labeling (including blister packs)

24. Postmarketing Requirements and Commitments

The following Pediatric Research Equity Act PMRs will be issued at the time of approval. Moderate to severe acute pain affects pediatric patients and, similar to adults, there is a need for non-opioid analgesics in this population. However, given the risks inherent to a new pharmacologic class of medications, the review team favors a conservative approach to the pediatric studies. The study in the oldest age group (12 to <17 years) will be completed before proceeding with the subsequent age group (6 to <12 years) to confirm that the safety data is favorable before exposing younger cohorts. Some overlap, as specified in the Agreed initial Pediatric Study Plan (iPSP), will be allowed between the studies in younger cohorts. Careful consideration was given to balancing the safety of the study subjects with the need for expeditious development of SUZ for use in pediatric patients. Further, the review team thoroughly discussed the dates below with the DAAP Safety team, acknowledging that the overlap of dates is intentional. These are effectively interdependent PMRs which will increase the likelihood that milestone dates may be missed and will need to be re-negotiated.

1. Conduct a randomized, controlled study evaluating the pharmacokinetic, safety, and efficacy of JOURNAVX in pediatric patients aged 12 to less than 17 years with moderate to severe acute pain.

Draft protocol submission: 03/2025

Final protocol submission: 09/2025

Study completion: 06/2027

Final report submission: 12/2027

2. Conduct a randomized, controlled study evaluating the pharmacokinetic, safety, and efficacy of JOURNAVX in pediatric patients aged 6 to less than 12 years with moderate to severe acute pain.

Draft protocol submission: 09/2027

Final protocol submission: 03/2028

Study completion: 03/2030

Final report submission: 09/2030

3. Conduct a randomized, controlled study evaluating the pharmacokinetic, safety, and efficacy of JOURNAVX in pediatric patients aged 1 to less than 6 years with moderate to severe acute pain.

Draft protocol submission: 06/2029

Final protocol submission: 12/2029

Study completion: 12/2031

Final report submission: 06/2032

4. Conduct a randomized, controlled study evaluating the pharmacokinetic, safety, and efficacy of JOURNAVX in pediatric patients from birth to less than 1 year of age with moderate to severe acute pain.

Draft protocol submission: 03/2031

Final protocol submission: 09/2031

Study completion: 09/2033

Final report submission: 03/2034

5. Conduct a juvenile animal study in the rodent model to characterize the impact of JOURNAVX on the developing brain to support clinical studies in pediatric patients from birth to less than 3 years of age.

Draft protocol submission: 03/2027

Final protocol submission: 06/2027

Study completion: 06/2028

Final report submission: 12/2028

6. Conduct a juvenile animal study in the rodent model to characterize the impact of JOURNAVX on the developing brain to support clinical studies in pediatric patients from 3 to less than 12 years of age.

Draft protocol submission: 06/2025

Final protocol submission: 09/2025

Study completion: 09/2026

Final report submission: 03/2027

The following postmarketing requirements (PMRs) are recommended by the Division of Pediatrics and Maternal Health (DPMH) and describe a pregnancy exposure registry study, complementary pregnancy study, and lactation study.

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 United States 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.

Draft protocol submission: 07/2025

Final protocol submission: 01/2026

Interim/Other: 01/2027, 01/2028, 01/2029, 01/2030, 01/2031, 01/2032, 01/2033, 01/2034, 01/2035

Study completion: 01/2036

Final report submission: 07/2036

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).

Draft protocol submission: 07/2025

Final protocol submission: 01/2026

Interim/Other: 01/2028, 01/2030, 01/2032, 01/2034

Study completion: 01/2036

Final report submission: 07/2036

3. Perform a milk-only lactation study in lactating women who have received Journavx 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.

Draft protocol submission: 07/2025

Final protocol submission: 01/2026

Study completion: 01/2028

Final report submission: 07/2028

25. Financial Disclosure

Table 192. Covered Clinical Studies: VX22-548-104, VX22-548-105

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 290		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature

Akopian, AN, V Souslova, S England, K Okuse, N Ogata, J Ure, A Smith, BJ Kerr, SB McMahon, S Boyce, R Hill, LC Stanfa, AH Dickenson, and JN Wood, 1999, The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways, *Nat Neurosci*, 2(6):541-548.

Amato, R, JF Gardin, JA Tooze, and JM Cline, 2022, Organ Weights in Relation to Age and Sex in Cynomolgus Monkeys (*Macaca fascicularis*), *Toxicol Pathol*, 50(5):574-590.

Haruyama, E, M Suda, Y Ayukawa, K Kamura, M Mizutamari, Y Ooshima, and A Tanimoto, 2012, Testicular development in cynomolgus monkeys, *Toxicol Pathol*, 40(6):935-942.

Wiesinger, H, S Klein, A Rottmann, B Nowotny, K Riecke, I Gashaw, M Brudny-Kloppel, R Fricke, J Hochel, and C Friedrich, 2020, The Effects of Weak and Strong CYP3A Induction by Rifampicin on the Pharmacokinetics of Five Progestins and Ethinylestradiol Compared to Midazolam, *Clin Pharmacol Ther*, 108(4):798-807.

Guidance Documents

ICH harmonised guideline *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (April 2023)

NDA 219209

Journavx (Suzetrigine; VX-548)

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

Draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* (February 2022)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

ICH harmonised tripartite guideline *E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (May 2005)

ICH harmonised tripartite guideline *S10 Photosafety Evaluation of Pharmaceuticals* (November 2013)

ICH harmonised guideline *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* (November 2016)

ICH harmonised tripartite guideline *Q3A (R2) Impurities in new drug substances* (October 2006)

Guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

27. Review Team

Table 193. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Rita Joshi, PharmD
Nonclinical reviewer	Irene Surh, PhD
Nonclinical team leader	Misol Ahn, PhD
Nonclinical supervisor	Jay Chang, PhD
OCP reviewer	Suresh Naraharisetti, PhD (primary)
OCP team leader	Deep Kwatra, PhD
OCP / Pharmacometrics	Atul Bhattaram, PhD (primary) / Jie Liu, PhD (secondary)
OCP / PBPK	Wen Li (primary) / Yuching Yang (secondary)
Clinical reviewer	James Yeh, MD
Clinical team leader	Tanya Brescia-Oddo, MD
Associate Director for Therapeutic Review, Pain	Tina Doshi, MD, MHS
Biometrics reviewer	Yunjiang Ge, PhD
Biometrics team leader	Xinyu Tang, PhD
Cross-discipline team leader	Tanya Brescia-Oddo, MD
Assistant Director of Labeling	Lisa Basham, MS
Deputy director (pharm/tox)	Dan Mellon, PhD
Division director (OCP)	Yun Xu, PhD
Deputy director (OB)	Sue-Jane Wang, PhD
Deputy director, Acting (clinical)	Michelle Horner, DO
Office director (or designated signatory authority)	Mary Thanh Hai, MD

Abbreviations: OCP, Office of Clinical Pharmacology; PBPK, Physiologically based pharmacokinetic modeling; OB, Office of Biostatistics

Table 194. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Mariappan Chelliah, MSc, PhD (ATL) / Teicher Agosto, PharmD (RBPM)
Drug Substance	Sharon Kelly, PhD (primary) / Katharine Duncan, PhD (secondary)
Drug Product / Labeling	Eric Bow, PhD (primary) / Mariappan Chelliah, MSc, PhD (secondary: drug product); Julia Pinto, PhD (secondary; labeling)
Manufacturing	Yongming Lu, PhD (primary) / Jingbo Xiao, PhD (secondary)
Biopharmaceutics	Moshe Honick, PharmD, PhD (primary) / Ta-Chen Wu, PhD (secondary)
OPDP	L. Sheneé Toombs, PharmD (primary) / Sam Skariah, PharmD, RAC (secondary)
DMPP	Helen Young, MSN, MPH, CRRN, PHN, RN
OSI	John Lee, MD (primary) / Phillip Kronstein, MD (secondary)
OSE/DEPI	Yan Li, MS, PhD
OSE/DMEPA	Susan Hakeem, PharmD (primary) / Valerie Vaughan, PharmD (secondary)
OSE/DRISK	Carolyn Tieu, PharmD, MPH
DPMH (maternal)	Kerry Shaab, MD (primary) / Tamara Johnson, MD, MS (secondary)
CSS	Greg Hawkins, PhD / Chad Reissig, PhD
CDS	Ling Wang, MS, PhD

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; DMPP, OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPMH, Division of Pediatric and Maternal Health; CSS, Controlled Substance Staff; CDS, Clinical Data Scientist

27.1. Reviewer Signatures

Table 195. Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Tina Tuong-Vi Doshi ON DAAP	Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Tina Tuong-Vi Doshi		Digitally signed by Tina Tuong-Vi Doshi		
		Date: 1/30/2025 11:47 AM EST GUID: 2025130164731		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Sue Jane Wang OB DBI	Sections: 6, 16, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sue Jane Wang		Digitally signed by Sue Jane Wang		
		Date: 1/30/2025 11:47 AM EST GUID: 2025130164754		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
DRISK Team Lead Discipline Secondary Reviewer	Carolyn Tieu OMEPRM DRM	Sections: 7	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Carolyn Tieu		Digitally signed by Carolyn Tieu		
		Date: 1/30/2025 11:48 AM EST GUID: 2025130164815		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Tanya Brescia-Oddo ON DAAP	Sections: 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tanya Brescia-Oddo		Digitally signed by Tanya Brescia-Oddo		
		Date: 1/30/2025 11:50 AM EST GUID: 202513016506		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Venkatesh Bhattaram OCP DPM	Sections: 14.5, 8.1, 8.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Venkatesh Bhattaram Digitally signed by Venkatesh Bhattaram Date: 1/30/2025 11:55 AM EST GUID: 2025130165536				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	James Yeh ON DAAP	Sections: 1-26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: James Yeh Digitally signed by James Yeh Date: 1/30/2025 11:58 AM EST GUID: 202513016586				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Rita Joshi ORO DRON	Sections: 12	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☒ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Rita Joshi		Digitally signed by Rita Joshi		
		Date: 1/30/2025 11:59 AM EST GUID: 202513016591		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Suresh Naraharisetti OCP DNP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Suresh Naraharisetti		Digitally signed by Suresh Naraharisetti		
		Date: 1/30/2025 11:59 AM EST GUID: 2025130165934		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Yunjiang Ge OB DBI	Sections: 6, 16, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Yunjiang Ge		Digitally signed by Yunjiang Ge		
		Date: 1/30/2025 12:00 PM EST GUID: 202513017058		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Lisa Basham ON DAAP	Sections: 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lisa Basham		Digitally signed by Lisa Basham		
		Date: 1/30/2025 12:03 PM EST GUID: 202513017315		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Jie Liu OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Jie Liu		Digitally signed by Jie Liu		
		Date: 1/30/2025 12:05 PM EST GUID: 202513017557		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Xinyu Tang OB DBI	Sections: 6, 16, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xinyu Tang		Digitally signed by Xinyu Tang		
		Date: 1/30/2025 12:08 PM EST GUID: 20251301783		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Wen Lin OCP DPM	Sections: 14.6	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Wen Lin		Digitally signed by Wen Lin		
		Date: 1/30/2025 12:13 PM EST GUID: 2025130171358		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Irene Surh ON DPTN	Sections: 5.1, 7.1, 7.7.3, 8.3, 13, 23, and 24	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Irene Surh		Digitally signed by Irene Surh		
		Date: 1/30/2025 12:28 PM EST GUID: 2025130172848		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Misol Ahn ON DPTN	Sections: Sections 5.1, 7.1, 7.7.3, 8.3, 13, 23, and 24	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Misol Ahn		Digitally signed by Misol Ahn		
		Date: 1/30/2025 12:29 PM EST GUID: 2025130172948		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Yuching Yang OCP DPM	Sections: 14.6	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang		Digitally signed by Yuching Yang		
		Date: 1/30/2025 12:29 PM EST GUID: 2025130172951		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Deep Kwatra OCP DNP	Sections: 2, 5, 8, 14, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Deep Kwatra		Digitally signed by Deep Kwatra		
		Date: 1/30/2025 12:31 PM EST GUID: 2025130173118		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Supervisor / Team Lead	Jay Chang ON DPTN	Sections: 5.1, 7.1, 7.7.3, 8.3, 13, 23, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jay Chang		Digitally signed by Jay Chang		
		Date: 1/30/2025 12:37 PM EST GUID: 2025130173719		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Matthew Sullivan ORO DRON	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Matthew Sullivan		Digitally signed by Matthew Sullivan		
		Date: 1/30/2025 12:51 PM EST GUID: 202513017515		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Richard Mellon ON DPTN	Sections: Nonclinical portions of Section 5.1, 7.1, 7.7.3, 8.3, 13, 23, and 24	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Richard Mellon		Digitally signed by Richard Mellon		
		Date: 1/30/2025 12:54 PM EST GUID: 2025130175451		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hongwu Shen OCP DNP	Sections: 2, 5, 8, 14, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Hongwu Shen		Digitally signed by Hongwu Shen		
		Date: 1/30/2025 1:07 PM EST GUID: 202513018729		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
DRISK Team Lead Discipline Primary Reviewer	Timothy Bernheimer OMEPRM DRM	Sections: not applicable	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Timothy Bernheimer		Digitally signed by Timothy Bernheimer		
		Date: 1/30/2025 1:12 PM EST GUID: 2025130181233		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Suresh Narahariseti OCP DNP	Sections: 2, 5, 8,14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

NDA 219209
Journavx (Suzetrigine; VX-548)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Suresh Naraharisetti Digitally signed by Suresh Naraharisetti Date: 1/30/2025 1:14 PM EST GUID: 2025130181444				

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/

TANYA L BRESCIA-ODDO
01/30/2025 01:09:24 PM

MICHELLE S HORNER
01/30/2025 01:24:12 PM

MARY T THANH HAI
01/30/2025 01:41:35 PM