1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 4, Open-label, Single-arm Study Evaluating the Effectiveness and Safety of Suzetrigine As Part of Multimodal Therapy for Acute Pain After Aesthetic or Reconstructive Surgeries

Vertex Study Number: VX24-548-113

[redacted]

Date of Protocol: 07 February 2025 (Version 2.0)

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2 PROTOCOL SYNOPSIS

Title A Phase 4, Open-label, Single-arm Study Evaluating the Effectiveness and Safety of Suzetrigine As Part of Multimodal Therapy for Acute Pain After Aesthetic or Reconstructive Surgeries

Brief Title A Single-Arm Study Evaluating the Effectiveness and Safety of Suzetrigine (SUZ) for Acute Pain After Aesthetic or Reconstructive Surgeries

Clinical Phase and Clinical Study Type Phase 4, effectiveness and safety

Objectives

Primary Objective

- To evaluate the effectiveness of SUZ as part of multimodal therapy (MMT) in treating acute postoperative pain

[redacted]

Endpoints

Primary Endpoint

- Proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA) for pain control at the end of treatment

[redacted]

Number of Subjects Approximately 100 subjects

Study Population Male and female subjects 18 years of age or older who are undergoing aesthetic or reconstructive surgery that would be typically treated with opioid therapy for at least 72 hours postoperatively.

Investigational Drug Active substance: SUZ

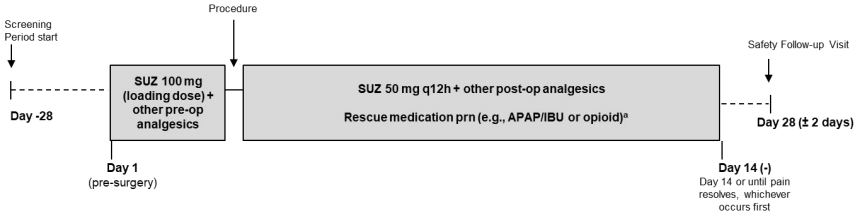
Activity: voltage-gated sodium channel 1.8 (Nav1.8) inhibitor

Strength and route of administration: 50-mg tablets for oral administration

Study Duration Excluding the Screening Period, each subject will participate in the study for 28 ± 2 days, including up to 14 days of treatment with SUZ.

Study Design This is a Phase 4, open-label, single-arm study evaluating the effectiveness and safety of SUZ in treating acute pain as part of MMT after aesthetic or reconstructive surgery (Figure 2-1).

Figure 2-1 VX24-548-113 Study Design



APAP: acetaminophen; ATC: around the clock; IBU: ibuprofen; NSAID: nonsteroidal anti-inflammatory drug; prn: as needed; post-op: postoperative; pre-op: preoperative; q12h: every 12 hours; SUZ: suzetrigine

Notes: Other preoperative analgesics, if utilized, should be administered at approximately the same time as the loading dose of SUZ. Pre-, intra- and postoperative analgesics will be administered by the subject's physician based on the standard of care for the surgical procedure (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg]). Figure is not drawn to scale.

[a] The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC), however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate in the study and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

Approximately 100 subjects will be enrolled to receive SUZ (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will receive study drug (SUZ) for 14 days or until their pain resolves, whichever occurs first. Pain is considered to be resolved if a subject decides they no longer need study drug for pain relief and discontinues further dosing. Subjects will be encouraged to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution.

On Day 1, subjects will undergo the procedure. The first (loading) dose of SUZ (100 mg) will be administered preoperatively. Postoperatively, subjects will start

the maintenance dose of SUZ (50 mg q12h; starting 12 hours after the first dose of SUZ).

All perioperative analgesics (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg], nerve block, local anesthetic infiltration) except SUZ will be administered at the discretion of the subject's physician based on standard of care for the surgical procedure (within study restrictions, Section 9.4).

Preoperative analgesics include any agent (including SUZ) that is administered on Day 1, prior to the subject undergoing the procedure. Intraoperative analgesics include analgesic medications administered by the anesthesiologists through the end of surgery (i.e., incision closed and surgery deemed complete). Postoperative standing analgesics include any agent that is administered on an around the clock (ATC) basis (including SUZ) from the end of surgery for a specified duration (e.g., 48 hours) by the physician. A rescue medication is any analgesic that is used as needed postoperatively (in addition to the physician-directed postoperative standing analgesics, including SUZ) if a subject does not experience pain relief that is acceptable to them and requires additional pain medication. Rescue medication may be used at any time postoperatively.

The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC); however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

All subjects should be informed that they are encouraged to wait at least 60 minutes after taking a dose of first-tier rescue medication before use of the opioid rescue.

MMT is considered complete after the end of SUZ treatment (i.e., at latest Day 14). Analgesics used after the end of SUZ treatment (postoperative standing analgesics or prn medications) are not considered MMT or rescue medication.

Assessments

Effectiveness: PGA, [redacted]

Safety: AEs; clinical laboratory assessments; and clinical evaluation of vital signs, standard 12-lead ECGs, and physical examinations

Statistical Analyses

Descriptive analyses will be performed [redacted]

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 and Table 3-2.

Table 3-1 Study VX24-548-113: Screening

Event/Assessment[a]	Day -28 to Day -1 Screening Visit	Comments
Informed consent	X	Must be obtained before performing any study-related procedures. Remote consent may be used if permitted- by local regulations; Section 13.2.3.
Clinic visit	X	
Demographics	X	Section 11.1
Medical and surgical history	X	Section 11.1
History of drug and alcohol use	X	Section 8.2
Prior use of opioid medications	X	Any use within 12 months before the Screening Visit through intake for surgery will be recorded; Section 9.5.
Vital signs	X	Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes and before blood sampling; Section 11.3.3.
Standard 12-lead ECG	X	Performed in triplicate after the subject has been at rest (supine) for at least 5 minutes; 12-lead ECGs will be done before any procedures that may affect heart rate (e.g., blood sampling); Section 11.3.4.
Complete PE	X	Section 11.3.3
Weight, height, and BMI	X	
Serum β-hCG	X	All biologically female subjects; Section 11.3.2
Serum FSH	X	All biologically female subjects; Section 11.3.2
Serum chemistry	X	Section 11.3.2
Hematology	X	
Coagulation	X	
Drug test	X	Urine; Section 11.3.2
Research subject responsibilities and assessment trainings	X	Section 9.1.1
Medications review	Continuous from signing of ICF through completion of study participation	All medications taken within 14 days before the Screening Visit and selected prior medications taken earlier; Section 9.5.
Nonpharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation	All nonpharmacological treatments and procedures starting from the Screening Visit.
Adverse events	Continuous from signing of ICF through completion of study participation	Section 11.3.1

β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; FSH: follicle-stimulating hormone; ICF: informed consent form; PE: physical examination

[a] When assessment time points coincide, vital signs and 12-lead ECG assessments should be performed before blood sample collection.

Table 3-2 Study VX24-548-113: Treatment Period and Safety Follow-up- Visit

Event/Assessment[a]	Day 1 (pre-op)[b]	Day 1 (op and post-op)	Day 2	Day 3	Day 4	Day 7 (± 1 day)	Day 10	Day 14 (+3 days)	EDV[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Intake for surgery (e.g., hospital or ambulatory surgical center)	X										
Research subject responsibilities and assessment trainings	X										
SUZ dosing	X (100 mg)	50 mg q12h through Day 14 or until pain resolves, whichever occurs first (note: subjects are encouraged to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution)									**Day 1 pre-procedure:** Subject will be administered first (loading) dose (100 mg). **Day 1, starting 12 hours after first dose:** Subject will take SUZ 50 mg q12h. Subjects will record the date and time of each post-procedure dose administration in an electronic or paper diary. Section 9.6.

[a] Questionnaires must be completed before any other assessments scheduled at relevant visits, with the PGA being completed first, followed by TSQM-9. When assessment time points coincide, vital signs and 12-lead ECG assessments should be performed before blood sample collection. Assessments that coincide with study drug administration will be performed before dosing unless noted otherwise.

[b] On Day 1, drug, alcohol, and pregnancy testing, vital signs, and 12-lead ECGs (if applicable) should be completed to determine eligibility before enrollment.

[c] If a subject discontinues or completes study drug treatment for any reason (except withdrawal of consent, or meeting any of the postoperative stopping criteria described in Section 9.8) before Day 14, including AEs (considered treatment discontinuation) or reaching pain resolution (considered treatment completion), an EDV should be scheduled to occur as soon as possible after treatment discontinuation or after treatment completion due to pain resolution (as applicable), and the Day 14 Visit will not be required. If the EDV occurs on or before Day 10, the Day 10 telephone contact will also not be required. If the EDV occurs within or prior to the Day 7 visit window, the Day 7 Visit will also not be required. Subjects who discontinue dosing due to meeting postoperative stopping criteria will not have an EDV. All subjects who discontinue or complete study drug treatment before Day 14, including subjects who met postoperative stopping criteria, will be required to complete the Safety Follow-up Visit.

Table 3-2 Study VX24-548-113: Treatment Period and Safety Follow-up- Visit

Event/Assessment[a]	Day 1 (pre-op)[b]	Day 1 (op and post-op)	Day 2	Day 3	Day 4	Day 7 (± 1 day)	Day 10	Day 14 (+3 days)	EDV[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Other scheduled analgesics					X						Preoperative analgesics include any agent (including SUZ) that is administered on Day 1, prior to the subject undergoing the procedure. Intraoperative analgesics include analgesic medications administered by the anesthesiologists through the end of surgery (i.e., incision closed and surgery deemed complete). Postoperative standing analgesics include any agent that is administered on an ATC basis (including SUZ) from the end of surgery for a specified duration (e.g., 48 hours) by the physician. Other preoperative and postoperative analgesics in addition to SUZ will be prescribed and/or ordered by the subject's physician based on standard of care for the surgical procedure (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg]) and the prescription and/or order will be recorded. Preoperative analgesics (if utilized) should be administered at approximately the same time as the loading dose of SUZ. Subjects will record the date and time of each post-procedure administration, and the dose in an electronic or paper diary. Section 9.6.
Procedure		X									Section 9.1 and Appendix A

Rescue medication use		X		A rescue medication is any analgesic that is used at any time postoperatively (in addition to the physician-directed ATC postoperative standing analgesics, including SUZ) if a subject does not experience pain relief that is acceptable to them and requires additional pain medication. Subjects will record the date and time of each administration, and dose, in an electronic or paper diary. The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC); however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate in the study and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. Section 9.4.1.

Table 3-2 Study VX24-548-113: Treatment Period and Safety Follow-up- Visit

Event/Assessment[a]	Day 1 (pre-op)[b]	Day 1 (op and post-op)	Day 2	Day 3	Day 4	Day 7 (± 1 day)	Day 10	Day 14 (+3 days)	EDV[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Inpatient (e.g., hospital or ambulatory surgical center), if required, or leaving medical facility		X	(X)	(X)							Subjects may or may not require inpatient admission. Discharge/leaving will be per clinical judgement. Additional details are in Section 9.1.2.
Discharge (e.g., from hospital or ambulatory surgical center), if required, or leaving medical facility		X									
Telephone contact					X		X				Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Clinic visit						X		X	X	X	
PGA				X		X		X	X		Recorded in the electronic or paper diary; Section 11.2.1 Subjects should still complete the PGA even if the specified dose is not taken. **Day 3:** Should be completed after the first study drug dose on that day. **Day 7:** Should be completed after the first study drug dose on Study Day 7 (whether or not this coincides with the date of the Day 7 Visit). **Day 14 or EDV:** Should be completed after final study drug dose for subjects still taking study drug on Day 14. Subjects who have discontinued or completed study drug treatment should complete the PGA at home within approximately 24 hours after the last dose of study drug rather than waiting for their scheduled visit.

Table 3-2 Study VX24-548-113: Treatment Period and Safety Follow-up- Visit

Event/Assessment[a]	Day 1 (pre-op)[b]	Day 1 (op and post-op)	Day 2	Day 3	Day 4	Day 7 (± 1 day)	Day 10	Day 14 (+3 days)	EDV[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
[redacted]											
Vital signs	X	X (post-procedure but before discharge or before leaving medical facility, as applicable)				X		X	X	X	Vital signs will be collected after a ≥5-minute rest (seated or supine) and before blood sampling; Section 11.3.3.
Standard 12-lead ECG	(X)							X	X	(X)	Refer to Section 11.3.4 for information whether Day 1 pre-op ECG may be needed. Required at SFU only if any clinically significant abnormalities were noted on a prior ECG during the Treatment Period, or if the subject discontinued due to meeting postoperative stopping criteria (Section 9.8). Standard 12-lead ECGs will be performed in triplicate after a ≥5-minute rest (supine) and before any procedures that may affect heart rate (e.g., blood sampling); Section 11.3.4.
Symptom-directed PE	As applicable									X	Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator; Section 11.3.3.
Urine β-hCG	X					X		X	X	X	All female subjects of childbearing potential; Section 11.3.2. Assessed by staff onsite.
Drug testing	X							X	X		Urine; Section 11.3.2. Testing kit assessed by staff onsite.
Alcohol testing	X										Urine, blood, or breath. Assessed by staff onsite. Section 11.3.2

Table 3-2 Study VX24-548-113: Treatment Period and Safety Follow-up- Visit

Event/Assessment[a]	Day 1 (pre-op)[b]	Day 1 (op and post-op)	Day 2	Day 3	Day 4	Day 7 (± 1 day)	Day 10	Day 14 (+3 days)	EDV[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Serum chemistry		X (post-procedure but before discharge or before leaving medical facility, as applicable)						X	X	(X)	Required at SFU only if a clinical finding during the Treatment Period requires follow up; Section 11.3.2
Hematology		X (post-procedure but before discharge or before leaving medical facility, as applicable)						X	X	(X)	
Study drug count						X		X	X		
Adverse events	Continuous from signing of ICF through completion of study participation										Section 11.3.1
Medications review	Continuous from signing of ICF through completion of study participation										All medications taken within 14 days before the Screening Visit, and selected prior medications taken earlier, through completion of study participation; Section 9.5
Nonpharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation										All nonpharmacological treatments and procedures starting from the Screening Visit.

AE: adverse event; APAP: acetaminophen; ATC: around the clock; β-hCG: beta-human chorionic gonadotropin; EDV: End of Dosing Visit; IBU: ibuprofen; ICF: informed consent form; MMT: multimodal therapy; NSAID: nonsteroidal anti-inflammatory drug; op: operation; PE: physical examination; PGA: patient global assessment; post-op: postoperative; pre-op: preoperative; prn: as needed; q12h: every 12 hours; SFU: Safety Follow-up; SUZ: suzetrigine; TSQM: Treatment Satisfaction Questionnaire for Medication

Note: Assessments denoted by "(X)" are performed in the situations defined in the Comments column.

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine transaminase
APAP	acetaminophen
AST	aspartate transaminase
ATC	around the clock
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIEP	deep inferior epigastric perforator flap
ECG	electrocardiogram
EDC	electronic data capture
EDV	End of Dosing Visit
eGFR	estimated glomerular filtration rate
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
IBU	ibuprofen
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	institutional review board
IV	intravenous
MAC	monitored anesthesia care
max	maximum value
min	minimum value
MMT	multimodal therapy
NA	not applicable
Na_V	voltage-gated sodium channel
NSAID	nonsteroidal anti-inflammatory drug
op	operation

Abbreviation	Definition
PE	physical examination
PGA	patient global assessment
post-op	postoperative
pre-op	preoperative
prn	as needed
q12h	every 12 hours
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFU	Safety Follow-up
SUSARs	suspected, unexpected, serious adverse reactions
SUZ	suzetrigine
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TRAM	transverse rectus abdominis muscle
[redacted]	
ULN	upper limit of normal
US	United States
USA	United States of America

5 INTRODUCTION

5.1 Background

Pain is one of the most common symptoms for which patients seek medical attention. Current treatment options for pain are limited by poor efficacy and high rates of adverse events (AEs), leaving many patients without adequate pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) pose a potentially serious risk of gastrointestinal toxicity with acute and chronic use, hematologic toxicity with acute use, and nephrotoxicity with chronic use.[1] Opioids are significantly limited by safety and tolerability issues and have a high abuse liability. Opioid associated deaths have increased in frequency over the past 2 decades.[2] Opioids were involved in approximately 80,000 overdose deaths in the US in 2022 and in approximately 74% of fatal drug overdoses in the EU in 2021.[3, 4]

Given the limited treatment options, combined with the risks and constrained utility of current treatments, the development of new analgesics with improved efficacy and safety profiles is vital for better pain management and patient health outcomes. Despite the need for new analgesics, clinical development has exhibited a considerable lack of recent progress and innovation of new medications to treat pain.[5] Over the last decade, the majority of approved analgesic drugs either act on the opioid receptor system or are NSAIDs[6]; few new molecular entities for moderate to severe pain have been approved.[7, 8] The majority of research activity focuses on developing abuse deterrent reformulations of existing narcotic pain drugs, or combinations with NSAIDs. The resultant compounds do not have substantially improved- efficacy or safety. Suzetrigine (SUZ) represents a proposed new pharmacological class of non-opioid analgesics, known as selective pain signal inhibitors.

Supporting evidence for the role of voltage-gated sodium channel 1.8 ($Na_V1.8$) in pain signaling[9-11] includes: (1) $Na_V1.8$ is selectively expressed in human peripheral nociceptors where its role is to transmit action potentials[12-19], (2) Human $Na_V1.8$ gain-of-function mutations increase pain sensitivity[20, 21], (3) Loss or reduction of $Na_V1.8$ gene expression in animals reduces pain sensation[22-25], and (4) $Na_V1.8$ inhibitors reduce pain sensation in animal studies and human clinical trials of different pain models.[26-28] In addition, because $Na_V1.8$ is expressed in peripheral nociceptors but not in the human brain[29-33], $Na_V1.8$ inhibitors are not expected to be associated with side effects observed with less selective sodium channel modulators and do not have the central nervous system (CNS) side effects and abuse liability associated with centrally acting opioid therapies. Therefore, targeting an underlying mechanism of pain signaling in the peripheral nervous system through selective $Na_V1.8$ inhibition represents a novel scientific approach to analgesic drug development with the potential to address an unmet need for safe and effective pain therapies.

A pivotal Phase 3 program in adult subjects with moderate to severe acute pain was conducted with SUZ, a potent and highly selective inhibitor of $Na_V1.8$ that specifically inhibits the transmission of pain signals (action potentials) in pain-sensing neurons (nociceptors) of peripheral sensory nerves. The Phase 3 program showed that SUZ is an efficacious treatment for moderate to severe acute pain and was generally safe and well tolerated, and SUZ, as Journavx™, is approved for the treatment of moderate to severe acute pain in adults in the US.

5.2 Study Rationale

This study will evaluate the effectiveness and safety of SUZ in treating acute pain as part of multimodal therapy (MMT) after aesthetic or reconstructive surgeries.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the effectiveness of SUZ as a part of MMT in treating acute postoperative pain

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA) for pain control at the end of treatment

[redacted]

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible.

8.1 Inclusion Criteria

1. Subject will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (male and female) 18 years of age or older.
4. Body mass index (BMI) of ≥18.0 to ≤40.0 kg/m^2.
5. Scheduled to undergo an aesthetic or reconstructive surgical procedure that would typically be treated with opioid therapy for at least 72 hours postoperatively. Additional details on eligible and ineligible procedures are provided in Appendix A.

8.2 Exclusion Criteria

1. History of a prior surgical procedure in the same region of the body that resulted in any perioperative complications or that, in the opinion of the investigator or medical monitor, would preclude participation in the study.
2. 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. This may include, but is not limited to, history of relevant drug or food allergies; history of significant respiratory, cardiovascular, metabolic, hematologic, neurologic, or psychiatric disease; history or presence of clinically significant pathology; and history of cancer. Note that this criterion does not apply to squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma (i.e., no adjudication by the investigator is needed), so long as there has been no recurrence for the last 5 years.
3. Cardiac dysrhythmias requiring anti-arrhythmic 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 in biological males or >470 msec in biological females at the Screening Visit.
4. History of significant hepatic disease, including but not limited to hepatic cirrhosis, portal hypertension, or moderate or severe hepatic impairment (defined as Child Pugh Class B or C[34]).
5. Alanine transaminase (ALT) or aspartate transaminase (AST) values >3 × upper limit of normal (ULN).
6. History of severe renal impairment defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated using the subject's measured serum creatinine; the suggested calculation method for eGFR is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

7. Any abnormal laboratory results indicative of significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study.
8. History of any sensory abnormality that, in the opinion of the investigator, may confound the ability of the subject to assess postoperative pain.
9. Subjects who have a painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain.
10. A known or clinically suspected active infection with human immunodeficiency virus or hepatitis B or C viruses.
11. Any prior surgery within 1 month before the first study drug dose unless approved by the medical monitor.
12. American Society of Anesthesiologists physical status classification of ≥3.
13. Analgesic use as follows:
    a. Chronic use of any opioids (pure agonists, agonist/antagonists, partial agonists, antagonists) within the past 12 months before the procedure.
    b. Dose escalation of chronically administered NSAIDs within 30 days before the procedure.
    c. Unwilling or unable to stop all analgesics at least 5 half-lives or 2 days (whichever is longer) before the procedure.
14. Subjects who have started any new non-analgesic medications that have not been at a stable dose for at least 14 days before the first dose of study drug.
15. Subjects unwilling to receive SUZ or any analgesics (e.g., acetaminophen [APAP], fentanyl, orally administered opioids).
16. Subjects with a history of allergy or significant AE to any study-related medicine that, in the opinion of the investigator, would significantly increase the chance of AEs from medicines used in the study.
17. 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.
18. For biologically female subjects: Pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last dose of study drug.

    For biologically male subjects: With a biologically female partner who is pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last dose of study drug.
19. Participated in another investigational study within 30 days of the first dose of study drug.
20. Evidence of misuse, aberrant use, or addiction to alcohol or a drug of abuse in the past 3 years, or a positive test for drugs of abuse as defined in Section 11.3.2.
    - A positive drug test for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.

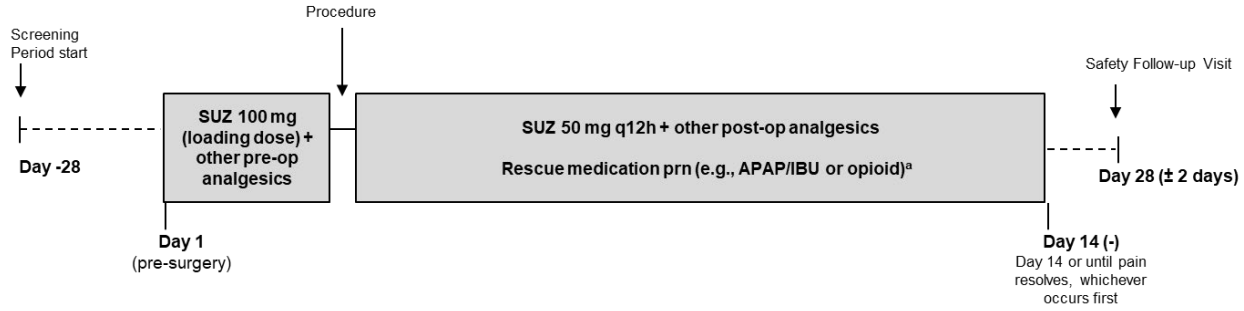
21. Use of the substances, activities, or devices as indicated in Table 9-1, during the specified times.
22. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.
23. Participated in a previous study with SUZ or received Journavx™.
24. History of a clinical atherosclerotic event, such as myocardial infarction or stroke, within the past 12 months before the Screening Visit.

9 STUDY IMPLEMENTATION

9.1 Study Design

is a Phase 4, open-label, single-arm study evaluating the effectiveness and safety of SUZ in treating acute pain as part of MMT after aesthetic or reconstructive surgery (Figure 9-1).

Figure 9-1 VX24-548-113 Study Design



APAP: acetaminophen; ATC: around the clock; IBU: ibuprofen; NSAID: nonsteroidal anti-inflammatory drug; prn: as needed; post-op: postoperative; pre-op: preoperative; q12h: every 12 hours; SUZ: suzetrigine

Notes: Other preoperative analgesics, if utilized, should be administered at approximately the same time as the loading dose of SUZ. Pre-, intra- and postoperative analgesics will be administered by the subject's physician based on the standard of care for the surgical procedure (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg]). Figure is not drawn to scale.

[a] The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC), however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate in the study and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

Approximately 100 subjects will be enrolled to receive SUZ (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will receive study drug (SUZ) for 14 days or until their pain resolves, whichever occurs first. Pain is considered to be resolved if a subject decides they no longer need study drug for pain relief and discontinues further dosing. Subjects are encouraged

to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution.

On Day 1, subjects will undergo the procedure. The first (loading) dose of SUZ (100 mg) will be administered preoperatively. Postoperatively, subjects will start the maintenance dose of SUZ (50 mg q12h; starting 12 hours after the first dose of SUZ).

All perioperative analgesics (e.g., APAP, NSAIDs, dexamethasone, gabapentin [≤600 mg], nerve block, local anesthetic infiltration) except SUZ will be administered at the discretion of the subject's physician based on standard of care for the surgical procedure (within study restrictions, Section 9.4).

Preoperative analgesics include any agent (including SUZ) that is administered on Day 1, prior to the subject undergoing the procedure. Intraoperative analgesics include analgesic medications administered by the anesthesiologists through the end of surgery (i.e., incision closed and surgery deemed complete). Postoperative standing analgesics include any agent that is administered on an around the clock (ATC) basis (including SUZ) from the end of surgery for a specified duration (e.g., 48 hours) by the physician. A rescue medication is any analgesic that is used as needed postoperatively (in addition to the physician-directed postoperative standing analgesics, including SUZ) if a subject does not experience pain relief that is acceptable to them and requires additional pain medication. Rescue medication may be used at any time postoperatively.

The recommended postoperative standing analgesics (in addition to SUZ) are APAP and IBU (administered together ATC); however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician. If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and IBU (administered together prn). If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication). A subject for whom IBU is contraindicated may participate and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication. For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication. If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.

All subjects should be informed that they are encouraged to wait at least 60 minutes after taking a dose of first-tier rescue medication before use of the opioid rescue.

MMT is considered complete after the end of SUZ treatment (i.e., at latest Day 14). Analgesics used after the end of SUZ treatment (postoperative standing analgesics or prn medications) are not considered MMT or rescue medication.

9.1.1 Screening

Screening assessments are listed in Table 3-1.

Screening will occur within 28 days before the scheduled surgical procedure. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject in person or remotely (Section 13.2.3) before performing any study-related procedure. If

needed, screening assessments may be performed at multiple visits provided that these visits occur within the screening period.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.4).

Subjects will be instructed during screening on appropriate expectations around their participation in a clinical study. At the Screening Visit, subjects will receive trainings on clinical study participation, and use of the electronic or paper diary for recording study drug administration, rescue medication use, the PGA, [redacted] Additional review of these educational materials may be repeated for some or all subjects, as needed.

9.1.1.1 Repetition of Screening Assessment(s)

Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error (e.g., hemolysis of sample, equipment error) or unless otherwise specified (screening ECG; Section 11.3.4). The medical monitor must authorize retesting except in cases where no result was obtained.

9.1.1.2 Rescreening

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions:

- Subjects who met all eligibility criteria but had an intercurrent illness (e.g., upper respiratory infection with fever) in the 5 days before the first dose of study drug that was properly evaluated and which resolved fully
- Subjects who met all eligibility criteria but were not able to obtain required documentation within the allotted screening window
- Subjects who met all eligibility criteria but transiently (for personal reasons) are unable to commit to all study procedures
- Subjects who met all eligibility criteria but are not enrolled for administrative reasons (e.g., study drug is not available at the study site)
- Subjects who were screened under a prior version of the protocol and did not meet any exclusion criterion, with the exception of a criterion that was updated in a subsequent version of the protocol

Any subject who is rescreened for any of the exceptions listed above may have the screening window extended by 1 week before needing to undergo any rescreening assessments. If more than 35 days have elapsed from the Screening Visit before first dose of study drug, all screening assessments need to be repeated. The medical monitor must approve all rescreening and/or screening window extension requests before these occur.

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2.

All study periods will be conducted as described in Section 9.1.

Subjects will receive preoperative analgesia, including the first (loading) dose of SUZ, as described in Section 9.1.

Use of drains for all relevant procedures will be at the discretion of the surgical team. Surgeries may be performed with a combination of nerve block, intravenous (IV) sedation, monitored anesthesia care (MAC), or general anesthesia. In the perioperative period, anesthesia and pain management agents will be administered by the subject's physician based on standard of care for the surgical procedure (Section 9.4).

Subjects will receive postoperative analgesia and rescue medication as described in Section 9.1, unless they meet any of the postoperative stopping criteria outlined in Section 9.8.

Subjects who complete or prematurely discontinue study drug treatment before Day 14 will remain in the study from the time of stopping study drug treatment through the last scheduled study visit and complete assessments for all required study visits, as described in Section 9.1.4.

9.1.3 Follow-up

Subjects will have a Safety Follow-up Visit approximately 28 days after the first dose of study drug (Day 28 ± 2 days). Safety Follow-up Visit assessments are listed in Table 3-2.

9.1.4 Study Drug Treatment Completion or Discontinuation

Subjects will receive SUZ for 14 days or until their pain resolves, whichever occurs first, where pain is considered to be resolved if a subject decides they no longer need study drug for pain relief and discontinues further dosing. Subjects may also choose to discontinue study drug for other reasons. The reason for, date, and time of study drug discontinuation will be recorded for all subjects who discontinue study drug. Subjects are encouraged to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution.

If a subject discontinues or completes study drug treatment for any reason (except withdrawal of consent, or meeting any of the postoperative stopping criteria described in Section 9.8) before Day 14, including AEs (considered treatment discontinuation) or reaching pain resolution (considered treatment completion), an End of Dosing Visit (EDV) should be scheduled as soon as possible after the subject decides to stop study drug treatment, and the Day 14 Visit will not be required. If the EDV occurs on or before Day 10, the Day 10 telephone contact will also not be required. If the EDV occurs within or prior to the Day 7 visit window, the Day 7 Visit will also not be required. The EDV should be scheduled to occur as soon as possible after treatment discontinuation or after treatment completion due to pain resolution (as applicable). Subjects who discontinue treatment due to meeting postoperative stopping criteria will not have an EDV.

All subjects who discontinue study drug treatment or complete treatment due to pain resolution before Day 14, including subjects who met postoperative stopping criteria, will be required to complete the Safety Follow-up Visit (Section 9.1.3).

If a subject withdraws consent for the study, no further assessments will be performed; refer to Section 9.10 for information on the use of study data and samples already collected.

9.1.5 Completion of Study Participation

Completion of study participation for each individual subject is defined as one of the following:

- For enrolled subjects who have a Safety Follow-up Visit: the date of the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit: the date of last contact

The end of study is defined in Section 13.2.9.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label and single-arm study.

9.3 Rationale for Study Elements

9.3.1 Study Design

This study is designed to evaluate the effectiveness and safety of SUZ in treating acute pain as part of MMT after aesthetic or reconstructive surgeries. Subjects will receive SUZ both before and after surgery. As this is a Phase 4 study to collect additional information on SUZ beyond the registrational studies, an open-label, single-arm study design is appropriate.

The procedures and pre- and postoperative care, including methods for acute pain management, will be at the discretion of the subject's physician and based on standard of care.

IBU and APAP were selected as the recommended postoperative standing analgesics and/or rescue medications because they are commonly used, short-acting, standard-of-care treatments for acute pain.

9.3.2 Study Drug Dose and Duration

The SUZ dosing regimen is 100 mg first dose (loading dose), then 50 mg q12h will be administered. This is the dosing regimen that was evaluated in Phase 3 studies of SUZ and is the approved commercial regimen.

The dosing duration for each subject will be determined by the clinical need for postoperative analgesic therapy. In current practice, analgesics are used as needed for at least several days and up to approximately 2 weeks for acute pain.

9.3.3 Rationale for Study Assessments

PGA of study drug: The PGA captures subjects' perceptions of pain control using a validated, single-item questionnaire.[35] This study will use a 5-point Likert scale (poor, fair, good, very good, or excellent) for the PGA evaluation.[36]

[redacted]

9.4 Study Restrictions

Study restrictions are summarized in Table 9-1. Additional details on study restrictions will be

provided in the Study Reference Manual.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction	
	Start	**Stop**
Other investigational drugs or devices	30 days before first dose of study drug, 5 half-lives before first dose of study drug, or time determined by local requirements (whichever is longest)	Completion of SFU assessments
Analgesic medications	5 half-lives or 2 days (whichever is longer) before intake for surgery	Until intake for surgery
Analgesic medications other than as directed by the subjects physician[b]	Intake for surgery	Until last dose of study drug is taken
Oral, intravenous, or injectable corticosteroids except as outlined in Section 9.4.1[b]	5 half-lives or 2 days (whichever is longer) before intake for surgery	Until last dose of study drug is taken
Medications, herbal and dietary supplements (including St. John's wort) known to be moderate or strong inducers of CYP3A	14 days before first dose of study drug	Completion of SFU assessments
Medications, herbal and dietary supplements known to be moderate or strong inhibitors of CYP3A	7 days before first dose of study drug	Completion of SFU assessments
Grapefruit or grapefruit juice; pomelos, star fruit, and Seville oranges or their juices	7 days before first dose of study drug	Completion of SFU assessments
Alcohol	24 hours before first dose of study drug	At the discretion of the investigator

SFU: safety follow-up; SUZ: suzetrigine

[a] See Section 9.5 for guidance on concomitant medications.

[b] SUZ is an inducer of CYP3A. Some medications, including certain opioids, are CYP3A substrates and have warnings and precautions regarding co-administration with CYP3A inducers. If considering use of SUZ with opioids (e.g., as rescue medication), refer to the opioid prescribing information for appropriate co-administration. Dose adjustment of the concomitant CYP3A substrate may be required, including when initiating or discontinuing SUZ. See also Section 9.5.

All pre-, intra-, and postoperative standard-of-care agents are allowed at the discretion of surgical and anesthesia teams except those which are on the restricted medication list (Table 9-1). Gabapentin (if applicable) should be administered at a dose ≤600 mg.

9.4.1 Rescue Medication

Rescue medication for pain relief may be used at any time postoperatively per the following guidelines and as outlined in Table 9-2:

- APAP and IBU (administered together ATC) are recommended as postoperative standing analgesics, however, alternative postoperative standing analgesics may be prescribed at the discretion of the subject's physician.

- If a subject is not taking either APAP or IBU as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be APAP and/or IBU (administered together prn).
- If a subject is taking either APAP or IBU (but not both) as part of physician-directed postoperative standing analgesia, the recommended first-tier rescue medication will be whichever medication was not included (e.g., if a subject was taking APAP as part of postoperative standing analgesia, IBU would be used as first-tier rescue medication).
- A subject for whom IBU is contraindicated may participate and take APAP alone. For these subjects, if APAP is already included as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.
- For subjects who use APAP and/or IBU as first-tier rescue medication, an orally administered opioid may be used as second-tier rescue medication.
- If a subject is taking both APAP and IBU as part of physician-directed postoperative standing analgesia, then an orally administered opioid may be used as first-tier rescue medication.
- A record (date and time of administration, and dose) will be kept of all rescue medication use. Subjects will continue to document rescue medication use through Study Day 14 or the EDV, whichever occurs first.
- All subjects should be informed that they are encouraged to wait at least 60 minutes after taking a dose of non-opioid rescue medication before use of the opioid rescue.
- Analgesics used after end of SUZ treatment (i.e., at latest Day 14) are not considered rescue medication.

Table 9-2 Recommended Rescue Medication

Physician-directed Postoperative Standing Analgesia	Recommended First-tier rescue medication	Recommended Second-tier rescue medication
Does not include APAP or IBU	APAP and/or IBU[a]	Orally administered opioid
Includes APAP, but not IBU	IBU[b]	Orally administered opioid
Includes IBU, but not APAP	APAP	Orally administered opioid
Includes APAP and IBU	Orally administered opioid	NA

APAP: acetaminophen; IBU: ibuprofen; NA: not applicable

[a] A subject for whom IBU is contraindicated may take APAP alone.

[b] For subjects in this scenario for whom IBU is contraindicated, an orally administered opioid may be used as first-tier rescue medication.

9.5 Prior and Concomitant Medications

- Subjects will abstain from all concomitant medications as described in the exclusion criteria (Section 8.2) and study restrictions (Section 9.4).
- SUZ is an inducer of CYP3A. While the use of CYP3A substrates is not prohibited in this study, investigators should refer to the prescribing information of sensitive CYP3A substrates or CYP3A substrates where minimal concentration changes may lead to loss of efficacy for dosing instructions if used concomitantly with SUZ. Dose adjustment of the concomitant CYP3A substrates may be required, including when initiating or discontinuing SUZ.

Concomitant use with SUZ may reduce the exposure of sensitive CYP3A substrates which may decrease the efficacy of these substrates. Discontinuation of SUZ may increase the exposure of sensitive CYP3A substrates.

- All opioid medications taken within 12 months before the Screening Visit through intake for surgery will be recorded with indication, route of administration, and start and stop dates of administration.
- All medications taken within 14 days before the Screening Visit through completion of study participation will be recorded with indication, route of administration, and start and stop dates of administration. In addition, all medications administered in-clinic will also be recorded with the time of each administration, and analgesic concomitant medications will be recorded with the dose. All subjects will be questioned about medications at each visit or telephone contact.
- A female subject of childbearing potential using hormonal contraceptives does not need to stop taking hormonal contraceptives; however, they are not considered an approved form of contraception unless levonorgestrel or norethindrone are the progestin component (Section 11.3.5.1).

9.6 Administration

Additional information is provided in the Pharmacy Manual.

9.6.1 Study Drug (SUZ)

SUZ will be administered orally to all subjects q12h.

Study drug will be administered according to the following guidelines:

- The first (loading) dose will be administered according to the site's preoperative standard of care (e.g., with a sip of water).
- For maintenance doses (i.e., starting from the second dose of study drug), SUZ may be taken with or without food.
- Subjects will swallow the study drug whole and will not chew it before swallowing.
- The date and time of administration of each dose of study drug will be recorded.
- Study drug should be administered approximately q12h. Per investigator discretion, the study drug schedule may be adjusted within the first few days for convenience of the subject.
    - If a subject forgets a dose but remembers within 5 hours, they will take the dose at that time and then resume their normal schedule.
    - If a subject forgets a dose and more than 5 hours have elapsed, they are to skip that dose and then resume their normal schedule.
- Subjects will receive study drug for 14 days or until their pain resolves, whichever occurs first. Subjects are encouraged to have taken at least 6 doses of SUZ postoperatively before deciding to complete treatment due to pain resolution.

9.6.2 Other Scheduled Analgesics

All pre-, intra-, and postoperative analgesics will be administered at the direction of the subject's physician based on standard of care for the surgical procedure (within the study restrictions listed in Section 9.4).

The date, time of administration, and dose of each medication will be recorded.

9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed or required. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.4).

9.8 Individual Stopping Rules and Precautions

Postoperative

The investigator should evaluate subjects for the following stopping criteria after completion of surgery but before discharge/leaving the medical facility, no later than the time of the first maintenance dose of SUZ (i.e., 12 hours after the first [preoperative] dose), before dosing. Dosing of SUZ in an individual subject will be discontinued if any of the following criteria are met:

- The subject is not lucid, is not able to follow commands, or is not able to swallow oral medications.
- The subject had a surgical complication(s) during the procedure that, in the opinion of the investigator, should preclude continued dosing in the study.
- The subject had a medical complication(s) during the procedure that, in the opinion of the investigator, should preclude continued dosing in the study.

Subjects who discontinue dosing due to any of the above stopping criteria will not have an EDV but will be required to complete the Safety Follow-up Visit (Section 9.1.3).

At any time

Dosing of SUZ in an individual subject will be discontinued if the subject has

- a serious adverse event (SAE) of heart failure that is considered related or possibly related to SUZ by the investigator or Vertex; or
- an SAE of ventricular arrhythmia that is considered related or possibly related to SUZ by the investigator or Vertex

The investigator must immediately notify the Vertex medical monitor if either of the above SAEs occur. All SAEs, regardless of the presumed relationship to study drug, must also be reported to Vertex Global Patient Safety (GPS) within 24 hours (Section 13.1.2).

9.9 General Study Drug Interruption and Stopping Rules

Enrollment and dosing will be paused if any of the following events occur and are considered related or possibly related to SUZ by the investigator or Vertex:

- ≥3 SAEs of QTc prolongation
- 1 SAE of Torsades de Pointes
- Death

Vertex will notify regulatory authorities according to applicable regulations. A review of safety data will be conducted by Vertex to determine whether to: (1) continue to pause enrollment and dosing for further evaluation; (2) resume enrollment and dosing without modification to study conduct; (3) resume enrollment and dosing with modification to study conduct; or (4) terminate the study.

9.10 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

Subjects who complete or discontinue study treatment before Day 14 should continue to return for study assessments, as noted in Section 9.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit (see Section 9.1.3), and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

Individual stopping rules and precautions are described in Section 9.8. General study drug interruption and stopping rules are described in Section 9.9.

9.11 Replacement of Subjects

Subjects who withdraw or are withdrawn during the study drug Treatment Period will not be replaced.

10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to SUZ (Section 10.1 through Section 10.7).

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

Tablets will be dispensed at the site to individual dosing containers by a qualified pharmacist or designated study site staff, and following national and local laws and regulations.

10.2 Packaging and Labeling

Vertex will supply the 50-mg SUZ tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for SUZ will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

Study drug supply details are listed in Table 10-1. Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Dosing Form/ Route	Dosage	How Supplied
SUZ	Tablet/ oral	100 mg first dose; all other doses 50 mg	Supplied as 50-mg tablets

SUZ: suzetrigine

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

The principal investigator, study site staff, including pharmacy personnel will assist Vertex with any recall activities (as applicable) and place impacted investigational medicinal product (IMP) in quarantine when requested.

10.6 Compliance

To ensure treatment compliance, the investigator or qualified designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count in the clinic.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject from the study.

10.7 Blinding and Unblinding

This is an open-label study.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1 and Table 3-2.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical and surgical history, height, and weight.

11.2 Effectiveness

11.2.1 Patient Global Assessment of Study Drug

The PGA of study drug is completed after taking a dose of study drug, at the indicated time points. Subjects should still complete the PGA even if the specified dose is not taken (e.g., forgotten dose). Detailed procedures for the administration of the PGA of study drug will be provided in a separate document. Subjects will record their PGA responses in an electronic or paper diary.



11.3 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, standard 12-lead ECGs, and physical examinations (PEs).

11.3.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with current ICH E6 GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs.

11.3.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, unless otherwise specified.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-1.

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Coagulation (Screening Only)
Glucose	Hemoglobin	Activated partial thromboplastin time
Blood urea nitrogen[a]	Platelets	Prothrombin time
Creatinine	Leukocytes	Prothrombin time International Normalized Ratio
Sodium	Differential (percent):	
Potassium	Eosinophils	
Calcium	Basophils	
Chloride	Neutrophils	
Magnesium	Lymphocytes	
Bicarbonate	Monocytes	
Phosphate		
Total bilirubin, direct bilirubin		
Alkaline phosphatase		
Aspartate transaminase		
Alanine transaminase		
Lipase		
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Urate		

[a] If blood urea nitrogen cannot be collected, urea may be substituted.

Clinical laboratory assessments during screening must have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to receive study drug on Day 1.

Additional testing at screening: The following additional tests will be performed at the Screening Visit and/or pre-procedure to assess eligibility:

- Serum follicle-stimulating hormone (FSH) will be tested at the Screening Visit for all biologically female subjects. For a subject to be considered of non-childbearing potential, the serum FSH levels will be within the laboratory's range for postmenopausal females.
- Serum β-human chorionic gonadotropin (β-hCG) test for all biologically female subjects at the Screening Visit. Urine β-hCG for female subjects of childbearing potential (as defined in Section 11.3.5.1) on Day 1; both the serum and urine β-hCG test (as applicable per Table 3-1 and Table 3-2) must be negative to receive study drug. Additional pregnancy tests are described below.
- Drug testing during screening; both screening and additional drug and alcohol tests are described below.

Drug and alcohol testing: Drug testing for opioids, methadone, cocaine, amphetamines/methamphetamines, barbiturates, and benzodiazepines will be assessed by a urine test at the Screening Visit and before enrollment on Day 1. Alcohol testing will be assessed before enrollment on Day 1 by a urine, blood, or breath test. During treatment, drug testing will be performed per Table 3-2. Subjects may also undergo random urine drug testing and alcohol testing if deemed appropriate by the investigator. Drug and alcohol test results must be negative for a subject to receive study drug. A positive drug test for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.

Pregnancy testing for female subjects of childbearing potential (as defined in Section 11.3.5.1):

In addition to the tests before the first dose of study drug, subjects will have urine β-hCG pregnancy tests periodically per Table 3-2. Urine pregnancy tests will be performed and analyzed at the site. During treatment, if a urine pregnancy test is positive, all study drug dosing will stop, and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.3.5.2 will be followed.

Additional evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used, with the following exceptions:

- Drug and alcohol tests and urine β-hCG pregnancy tests (except where otherwise noted) will be assessed by staff onsite.
- Local laboratories may be used to repeat a screening assessment to determine eligibility on Day 1 (pre-procedure) if there is clear evidence of laboratory error (Section 9.1.1.1) in the central laboratory assessment.

Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the

central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.3.3 Physical Examinations and Vital Signs

A complete PE will be performed at screening. A vital signs assessment will be performed at screening and select study visits. A symptom-directed PE will be performed at the Safety Follow-up Visit. At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: general; head, neck, and thyroid; eyes, ears, nose, and throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The symptom-directed PE should include, at a minimum, an assessment of the following body systems: general, cardiovascular system, and respiratory system; skin; and abdomen.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and oxygen saturation (SpO_2). The subject will be instructed to rest (seated or supine) for at least 5 minutes before vital signs are assessed.

11.3.4 Electrocardiograms

Standard 12-lead ECGs will be performed in triplicate using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines. Detailed instructions are provided in the Study Reference Manual.

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest (supine) for at least 5 minutes before having an ECG.
- The test should be performed in the supine position.

An electronic version (or paper backup/printout) of the ECG traces will be made for safety review by the investigator and maintained with source documentation. All traces will be centrally evaluated by a qualified cardiologist. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

If the centrally read ECG at the Screening Visit demonstrates a median QTcF >450 msec in biological males or >470 msec in biological females, the site investigator may obtain 1 additional set of 12-lead ECGs (performed in triplicate) on Day 1 (before SUZ dosing) to determine eligibility

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the median QTcF is increased by >60 msec from the baseline or the median absolute QTcF value is ≥500 msec for any scheduled or unscheduled ECGs (performed in triplicate), 2 additional ECGs (performed in triplicate) will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If the median QTcF values from either of these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), the subject should discontinue dosing. For safety monitoring after discontinuation, a single ECG

will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

11.3.5 Contraception and Pregnancy

The effects of SUZ on conception, pregnancy, and lactation in humans are not known. Refer to the SUZ Investigator's Brochure for additional details.

11.3.5.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below.

Contraception for the couple is waived for the following:

- True abstinence for the subject. The subject must confirm that they will practice true abstinence from the Screening Visit through 30 days after the last dose of study drug. True abstinence is important to differentiate from periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal, which are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen.
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
    - Documented bilateral oophorectomy and/or hysterectomy
- Same biological sex relationships.

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception, as outlined in Table 11-2, is used as a couple from the Screening Visit through 30 days after the last dose of study drug.

Table 11-2 Acceptable Methods of Contraception

Subjects and their non-study partners[a]	At least 1 of the following acceptable methods must be used as a couple from the Screening Visit through 30 days after the last dose of study drug: • Male vasectomy 6 months or more previously, with a documented negative post-vasectomy semen analysis for sperm[b] • Female bilateral tubal ligation performed at least 6 months previously • Female continuous use of an intrauterine device for at least 90 days before the first dose of study drug, throughout study drug treatment, and until 30 days after the last dose of study drug • Female hormonal contraceptives with levonorgestrel or norethindrone as the progestin component, if successfully used for at least 60 days before the first dose of study drug, throughout study drug treatment, and until 30 days after the last dose of study drug • Male or female condom (with or without spermicide)[c] • Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide

[a] Applicable to subjects and their non-study partners of the opposite biological sex for whom the contraception requirement is not waived.
[b] Medical record documentation of contraception for non-study partners is not required. The subject must confirm that their partner has documented proof, and the subject's confirmation should be documented.
[c] Female condom cannot be used with male condom due to risk of tearing.

Additional notes:

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in Table 11-2.
- Male subjects must not donate sperm from the first dose of study drug, throughout the study, and for 30 days following the last dose of study drug.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite biological sex.
- Medical record documentation of contraception for non-study partners is not required.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.

Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or designee on an individual basis.

11.3.5.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a subject, or the female partner of a male subject, becomes pregnant while participating in the study, the study drug will be permanently discontinued immediately. The investigator will 1) notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy, and 2) send the Pregnancy Information Collection Form to Vertex GPS.

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy. The infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

12 STATISTICAL ANALYSIS

12.1 Sample Size and Power

Approximately 100 subjects are planned to be enrolled. With a sample size of 100, the half width of the 95% confidence interval for the proportion of subjects reporting good, very good, or excellent in PGA at the end of treatment will be no more than 10%.

12.2 Analysis Sets

The **All Subjects Set** is defined as all subjects who were enrolled (defined as subject having data in the clinical database). The All Subjects Set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set will be used for all safety analyses.

The **Full Analysis Set (FAS)** is defined as all subjects who have received at least 1 dose of study drug. The FAS will be used for effectiveness analyses unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the principal features of the planned statistical analyses. Statistical analysis details will be in the statistical analysis plan (SAP), which will be finalized before clinical database lock.

12.3.1 General Considerations

All enrolled subjects will be presented in individual subject data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max).

Categorical variables will be summarized using counts and percentages.

[redacted]

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECGs, the baseline value will be defined as the average of the nonmissing pretreatment measurements (triplicate) before the first dose of study drug.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Treatment-emergent (TE) Period will include the time from the first dose of study drug to the Safety Follow-up Visit or to the completion of study participation (as defined in Section 9.1.5), whichever occurs first.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, and prior and concomitant medications will be summarized.

12.3.3 Effectiveness Analysis

The subject perception of SUZ effectiveness as part of a multimodal strategy in treating pain as measured via PGA will be summarized descriptively. Additional details will be provided in the SAP.

12.3.4 Safety Analysis

The overall safety profile of SUZ will be assessed in terms of the following:

- Incidence of TEAEs
- Clinical laboratory values (i.e., hematology and serum chemistry)
- Standard 12-lead ECG outcomes
- Vital signs

Safety analysis will be descriptive and based on the Safety Set. Additional details will be provided in the SAP.

12.4 Interim Analysis

Interim analyses may be performed during the study. If these occur, the timing and details of the interim analysis will be documented in the SAP.

12.5 Independent Data Monitoring Committee Analysis

Not applicable

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis,

the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected in source documents from the time the ICF is signed until completion of study participation (Section 9.1.5).

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in source documents. AEs for subjects who are screened but not subsequently enrolled will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed June 2024). The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Description
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to adverse event

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed June 2024)
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

AE: adverse event

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification[a]	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

AE: adverse event
[a] Refer to Sections 9.7, 9.8, and 9.9 for directions regarding what drug actions are permitted per protocol.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/resolved	Resolution of an AE with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not recovered/not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow up)

AE: adverse event

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious", which is based on subject/event outcome or action described above and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent through completion of study participation, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after completion of study participation and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent through completion of study participation, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

[redacted]

SAEs that occur after completion of study participation and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IEC, and participating investigators in accordance with current ICH E2A Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects, if allowed by local regulations.

13.2 Administrative Requirements

13.2.1 Product Complaints

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

13.2.2 Ethical Considerations

The study will be conducted in accordance with the current ICH E6 GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.3 Subject Information and Informed Consent

After the study has been fully explained, informed consent will be obtained from the subject before study participation and before performing any study-related procedures. Remote consent may be used. Remote consent would include a phone call or telemedicine visit between the site and subject for the consent discussion. The method of obtaining and documenting the informed consent and the contents of the consent will comply with current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.4 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.5 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.6 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers will be limited to the site and the study physician and will not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information

to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.7 Record Retention

The investigator will maintain all study records according to current ICH E6 GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.8 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.2.9 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation per current ICH E6 GCP Guidelines.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. The investigator will affirm the completeness and accuracy of the data by signing each casebook before data lock. If applicable, periodic investigator signatures may also be required.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution.

13.4 Monitoring

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines.

The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. The study site monitor will ensure that the study is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to them, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF will be placed in the investigator's study file.

13.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

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13.7.2 Clinical Study Report

A clinical study report, written in accordance with the current ICH E3 Guideline, will be submitted in accordance with local regulations.

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APPENDIX A: GUIDANCE ON SURGICAL PROCEDURES

Representative Eligible and Ineligible Surgical Procedures

Eligible (examples)	Ineligible
Breast • Reduction • Augmentation • Mastopexy • Augmentation-mastopexy • Reconstruction (1st or 2nd stage alloplastic) • Revision of reconstruction Liposuction Abdominoplasty (full or mini) with liposuction Brachioplasty Turbinoplasty (with or without concomitant other nasal surgery) Skin grafts (split-thickness or full)	Surgery in subject with active cancer – curative or palliative Rhinoplasty, septoplasty, septo-rhinoplasty Eye procedures Abdominoplasty (full or mini) without liposuction Autologous breast reconstruction (e.g., latissimus dorsi, TRAM, DIEP) Free-flap repairs

DIEP: deep inferior epigastric perforator flap; TRAM: transverse rectus abdominis muscle

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX24-548-113	Version #: 2.0	Version Date: 07 February 2025
Study Title: A Phase 4, Open-label, Single-arm Study Evaluating the Effectiveness and Safety of Suzetrigine As Part of Multimodal Therapy for Acute Pain After Aesthetic or Reconstructive Surgeries		

This clinical study protocol has been reviewed and approved by the sponsor.

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX24-548-113	Version #: 2.0	Version Date: 07 February 2025
Study Title: A Phase 4, Open-label, Single-arm Study Evaluating the Effectiveness and Safety of Suzetrigine As Part of Multimodal Therapy for Acute Pain After Aesthetic or Reconstructive Surgeries		

I have read Protocol VX24-548-113, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning SUZ and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

_____

Printed Name

_____ _____

Signature Date