1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of VX-548 for Acute Pain

Vertex Study Number: VX22-548-107

IND Number: 146185

Date of Protocol: 09 November 2022 (Version 2.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.1, 21 September 2022) was amended to create the current version (Version 2.0, 09 November 2022). The protocol history is below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.1, 21 September 2022	Original version
Version 2.0, 09 November 2022	Current version

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Added postdose ECGs at additional study visits and provided instructions on withholding a study drug dose on these days if needed.	Section 3 and Section 9.6
Added exclusion criteria for history of QT prolongation or standard 12-lead ECG demonstrating median QTcF >450 msec at screening or baseline.	Section 8.2, Exclusion Criteria 4 and 30
Added study drug interruption and stopping rules.	Section 9.8
Based on available clinical data from Study VX21-548-011, updated to allow study drug to be taken with or without food after the first dose.	Section 3 (Table 3-4), Section 9.4, and Section 9.6
Added telephone contact on Day 4 to assess the subject's status, any adverse events, concomitant medications, treatments, and procedures at an additional time point.	Section 3 (Table 3-4)
Updated End of Dosing Visit to occur as soon as possible after pain resolution criteria are met instead of as soon as possible after the subject decides to stop study drug treatment.	Section 3 (Table 3-4)
Clarified that discharge assessments should be completed for all surgical subjects and for any non-surgical subjects who required inpatient admission.	Section 3 (Table 3-4)
Clarified that PGA should still be completed even if a study drug dose is missed (e.g., forgotten).	Section 3 (Table 3-4) and Section 11.5.4
Clarified definition of study drug treatment completion for subjects who stop less than 48 hours before the last scheduled dose of study drug.	Section 9.1
Added a requirement for medical monitor to authorize all cases of screening assessment repetition.	Section 9.1.1.1
Updated rescue medication documentation such that subjects will continue documentation through Study Day 14 or the End of Dosing Visit, whichever occurs first.	9.4.1.2
Updated such that documentation of all medications administered in-clinic, including prior medications, will include the time of each administration. Also specified that non-surgical subjects should provide the estimated time of administration for any medications taken on Day 1 before arriving at the medical facility.	Section 9.4.2

Change and Rationale	Affected Sections
Updated study drug dosing window of ± 1 hour around q12h to be with respect to the most recent dose rather than based on the first dose of study drug.	Section 9.6
Clarified procedures for ECG safety monitoring after the first dose of study drug and added a window for postdose ECGs.	Section 11.5.4
Updated the contraception requirements to use of at least 1 acceptable method of contraception based on supporting nonclinical data; updated requirements for suspected postmenopausal subjects with pending FSH data, accordingly.	Section 11.5.6.1; Section 3 (Table 3-3) and Section 11.5.2
Updated list of representative ineligible surgical procedures.	Appendix A

PGA: patient global assessment; q12h: every 12 hours

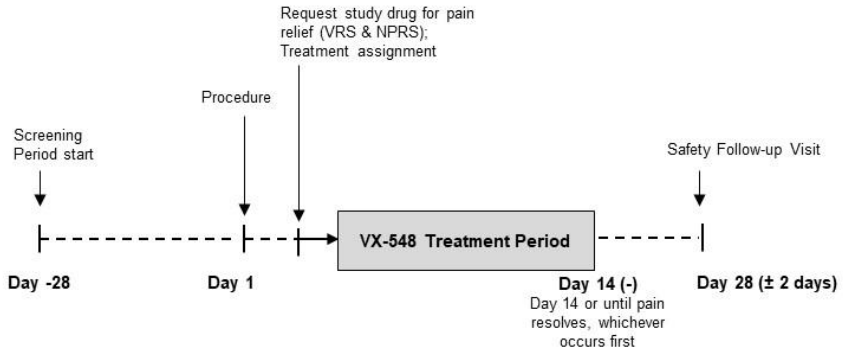
Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title	A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of VX-548 for Acute Pain
Brief Title	A Single-arm Study to Evaluate Safety and Effectiveness of VX-548 for Acute Pain
Clinical Phase and Clinical Study Type	Phase 3, safety and effectiveness
Objectives	Primary Objective To evaluate the safety and tolerability of VX-548 Secondary Objective To evaluate the effectiveness of VX-548 in treating acute pain
Endpoints	Primary Endpoint Safety and tolerability based on treatment-emergent adverse events (TEAEs), laboratory test results, vital signs, and ECGs Secondary Endpoint Subject perception of VX-548 effectiveness in treating pain at the end of treatment as measured by the proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA)
Number of Subjects	Approximately 250 subjects
Study Population	Male and female subjects between the ages of 18 and 80 years, inclusive, with pain that is moderate or severe on a verbal categorical rating scale (VRS) and ≥4 on a numeric pain rating scale (NPRS) resulting from any of the protocol-defined representative ambulatory surgical procedures (e.g., inguinal hernia repair, hemorrhoidectomy, or shoulder arthroscopy) or non-surgical conditions (e.g., traumatic acute musculoskeletal pain), with pain that is expected to last for at least 72 hours and that is expected to require no more than a short-term (i.e., <24-hour) admission, if any.
Investigational Drug	Active substance: VX-548 Activity: voltage-gated sodium channel 1.8 ($Na_V1.8$) 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 VX-548.

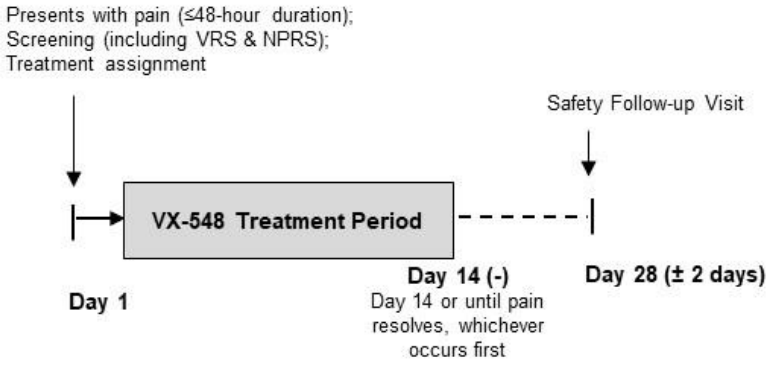
Study Design This is a Phase 3, single-arm study evaluating the safety and effectiveness of VX-548 in treating acute pain (Figure 2-1 [surgical subjects] and Figure 2-2 [non-surgical subjects]).

Figure 2-1 VX22-548-107 Study Design (Surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale
Notes: After surgery completion, a subject will be assigned to treatment if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS, and (3) the subject's pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within the protocol-specified, procedure-specific time period, the subject will not be eligible for this study. Figure is not drawn to scale.

Figure 2-2 VX22-548-107 Study Design (Non-surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale
Notes: After completion of screening assessments and confirmation of eligibility, a subject will be assigned to treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. Figure is not drawn to scale.

Surgical Subjects

On Day 1, subjects will undergo a scheduled ambulatory surgical procedure with pain that is expected to last for at least 72 hours and that is expected to require no more than a short-term (i.e., <24-hour) admission. After surgery completion, a subject will be assigned to treatment if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS, and (3) the subject's pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within the protocol-specified time period for the surgical procedure they underwent (e.g., 4 hours for most procedures), the subject will not be eligible for this study.

Non-surgical Subjects

On Day 1, after completion of screening assessments and confirmation of eligibility, a subject will begin treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. For a subject to be eligible, their pain must have been ongoing for ≤48 hours at presentation.

All Subjects

Approximately 250 subjects will receive VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will continue to receive VX-548 for 14 days or until their pain resolves, whichever occurs first. An acetaminophen/ibuprofen combination may be used as a rescue medication for pain relief as needed (prn), starting any time after the first dose of study drug through Day 14, completion of study drug treatment due to pain resolution, or study drug discontinuation, whichever occurs first. Subjects will be permitted to take acetaminophen 650 mg/ibuprofen 400 mg every 6 hours (q6h) prn, up to a maximum of 2600 mg/1600 mg in any 24-hour period.

The following approach will be used to define pain resolution and completion of study drug treatment:

1. Pain is considered to be resolved and the study drug treatment will be considered completed if
    a. a subject takes no study drug during a 48-hour period (i.e., skipped at least 4 consecutive doses due to pain resolution); and
    b. a subject takes no more than 1 dose of acetaminophen/ibuprofen during each 24-hour period within the 48-hour period (i.e., no more than 2 doses in 48 hours).
2. If a subject stops taking study drug per Criterion 1a but does not meet Criterion 1b, they will be instructed to restart study drug (and prn rescue medication).
3. If a subject stops and restarts study drug (Criterion 2 above) and subsequently believes their pain is resolving and stops study drug a second time, they will be instructed to **not** restart study drug, regardless of whether the above criteria are met.
4. If a subject stops study drug a second time after the restart of dosing (Criterion 3 above) and then fulfills both Criterion 1a and 1b, the pain is considered resolved and study drug treatment will be considered completed. If the subject fulfills only Criterion 1a but not Criterion 1b after the restart of dosing, the pain is considered not resolved and study drug will be considered discontinued.

Note: If subject stops study drug due to pain resolution less than 48 hours before the last scheduled dose of study drug (i.e., stops after the second dose on Day 12) and therefore cannot meet Criterion 1a by Day 14, the subject will be considered to have completed study drug dosing as long as they also meet Criterion 1b.

Assessments

Safety: adverse events (AEs); clinical laboratory assessments; clinical evaluation of vital signs, standard 12-lead ECGs, and physical examinations; and Columbia-Suicide Severity Rating Scale (C-SSRS)

Effectiveness: PGA of study drug

Other: use of rescue medications

Statistical Analyses	Sample size: Approximately 250 subjects are planned to be enrolled. With 250 subjects, there is a 92% probability of observing an AE in at least 1 subject if the true incidence is 1% and a 99% probability of observing an AE in at least 1 subject if the true incidence is 2%. Descriptive summary analyses will be performed.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 (surgical subjects), Table 3-2 (surgical subjects), Table 3-3 (non-surgical subjects), and Table 3-4 (all subjects).

Table 3-1 Study VX22-548-107: Screening Through Admission (Surgical Subjects)

Event/Assessment[a]	Day -28 to Day -1 Screening	Day 1 Pre-procedure	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 or home health visit	X		Subjects will have the option to complete this visit in the clinic or to have a home health visit. Home health visits are only an option if permitted by local regulations; Section 9.1.1.
Telemedicine video conference or telephone contact	(X)		A consultation between the subject and investigator or qualified delegate (LIP) must be **performed within 2 business days after the home health visit** (must be within screening window) and may also include a separate follow-up with the study coordinator. Required only for subjects who have a home health visit; not required for subjects who have a clinic visit; Section 9.1.6.
Admission for surgery (e.g., hospital or ambulatory surgical center)		X	Upon completion of pre-procedure eligibility assessments; Section 8.
Demographics	X		Section 11.1
Medical and surgical history	X		Section 11.1
History of drug and alcohol use	X		Section 8.2
Vital signs	X	X	Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes and before any 12-lead ECG assessment or blood sampling; Section 11.5.3.
Standard 12-lead ECG	X	X	Performed in triplicate after the subject has been at rest (supine) for at least 5 minutes; 12-lead ECGs will be done after taking vital signs and before any procedures that may affect heart rate (e.g., blood sampling); Section 11.5.4.
PE	X	(X)	Section 11.5.3 **Screening Visit:** A complete PE will be performed if the visit occurs in clinic. An abbreviated PE will be performed if the visit occurs via home health. **Day 1:** A complete PE will be performed only if the Screening Visit occurs via home health. Otherwise, no PE is required.
Weight, height, and BMI	X		Weight and height will be measured with shoes off.
C-SSRS		X	Section 11.5.5
Serology (HBsAg, HCV Ab, HCV RNA, and HIV-1/HIV-2 Abs)	X		Section 11.5.2
Serum β-hCG	X		All biologically female subjects; Section 11.5.2.

Table 3-1 Study VX22-548-107: Screening Through Admission (Surgical Subjects)

Event/Assessment[a]	Day -28 to Day -1 Screening	Day 1 Pre-procedure	Comments
Serum FSH	X		Suspected postmenopausal female subjects only; Section 11.5.2
Serum chemistry	X		Section 11.5.2
Hematology	X		
Coagulation	X		
Urinalysis	X		
Drug test	X	X	Urine; Section 11.5.2 **Day 1:** Testing kit assessed by staff onsite.
Urine β-hCG		X	All female subjects of childbearing potential. Assessed by staff onsite; Section 11.5.2.
Alcohol test		X	Urine, blood, or breath. Assessed by staff onsite; Section 11.5.2.
Research subject responsibilities and pain assessment trainings	X	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 through completion of study participation; Section 9.4.2.
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 11.5.1

β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; C-SSRS: Columbia-Suicide Severity Rating Scale; FSH: follicle-stimulating hormone; HbsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; LIP: licensed independent practitioner; PE: physical examination

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

[a] When assessment time points coincide, assessments will be performed in the following order: vital signs, 12-lead ECG, PE, and blood sample collection.

Table 3-2 Study VX22-548-107: Procedure Through Treatment Assignment (Surgical Subjects)

Event/Assessment	Day 1 Procedure Through Treatment Assignment/ Predose[a]	Comments
Inpatient (e.g., hospital or ambulatory surgical center)	X	
Procedure	X	Section 9.1 and Appendix A
Fasting period	X	No food or drink (except ≤8 fluid ounces of water per hour) from time of surgery completion through 2 hours after the first dose of study drug; Section 9.4.2.
Record supplemental analgesic medication	X	Pain medications given postoperatively through time subject is assigned to treatment will be recorded. Refer to Section 9.4.1 for permitted pain medication.
Vital signs	X	Performed after surgery completion (at least 1 hour after surgery completion is recommended) before the first dose of study drug. Vital signs will be collected after a ≥5-minute rest (seated or supine) and before any 12-lead ECG assessment or blood sampling; Section 11.5.3.
Standard 12-lead ECG	X	Performed after surgery completion (at least 1 hour after surgery completion is recommended) before the first dose of study drug. Standard 12-lead ECGs will be performed in triplicate after a ≥5-minute rest (supine); these will be done after taking vital signs and before any procedures that may affect heart rate (e.g., blood sampling); Section 11.5.4.
VRS	X	Completed upon request for the first dose of study drug for pain relief after surgery completion; Section 9.1.2.
NPRS	X	Completed immediately after the VRS only if the subject's pain is rated moderate or severe on the VRS; Section 9.1.2.
Medications review	Continuous from signing of ICF through completion of study participation	All medications taken within 14 days before the Screening Visit through completion of study participation; Section 9.4.2.
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 11.5.1

ICF: informed consent form; NPRS: numeric pain rating scale; VRS: verbal categorical rating scale

[a] Subject must complete all Day 1 predose assessments before the first dose of study drug is administered. When assessment time points coincide, assessments will be performed in the following order: vital signs, 12-lead ECG, and blood sample collection.

Table 3-3 Study VX22-548-107: Screening Through Treatment Assignment (Non-surgical Subjects)

Event/Assessment[a]	Screening Visit/Day 1 Screening Through Treatment Assignment	Comments
Presents with pain at medical facility (e.g., hospital, clinic, or ambulatory center)	X	Section 9.1
Informed consent	X	Must be obtained before performing any study-related procedures; Section 13.2.3.
Demographics	X	Section 11.1
Medical and surgical history	X	Section 11.1
History of drug and alcohol use	X	Section 8.2
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 any 12-lead ECG assessment or blood sampling; Section 11.5.3.
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 after taking vital signs and before any procedures that may affect heart rate (e.g., blood sampling); Section 11.5.4.
Complete PE	X	Section 11.5.3
Weight, height, and BMI	X	Weight and height will be measured with shoes off.
C-SSRS	X	Section 11.5.5
Urine β-hCG	X	All biologically female subjects. Assessed by staff onsite; Section 11.5.2.
Serum FSH	X	Suspected postmenopausal female subjects only; Section 11.5.2. A test result is not required for eligibility; however, until the test result is received, a subject will be considered to be of childbearing potential and must follow contraception requirements (Section 11.5.6.1) until postmenopausal status is confirmed.
Serum chemistry	X	Section 11.5.2. Test results are required for eligibility; a local laboratory will be used. Previous test results from the facility's local laboratory may be used to establish eligibility if collected within 2 hours before ICF signing.
Hematology	X	
Coagulation	X	
Urinalysis	X	
Drug test	X	Urine. Testing kit assessed by staff onsite; Section 11.5.2
Alcohol test	X	Urine, blood, or breath. Assessed by staff onsite; Section 11.5.2.
Research subject responsibilities and pain assessment trainings	X	Section 9.1.1
VRS	X	Completed before treatment assignment; Section 9.1.1.
NPRS	X	Completed immediately after the VRS and before treatment assignment only if the subject's pain is rated moderate or severe on the VRS; 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 through completion of study participation; Section 9.4.2.

Table 3-3 Study VX22-548-107: Screening Through Treatment Assignment (Non-surgical Subjects)

Event/Assessment[a]	Screening Visit/Day 1 Screening Through Treatment Assignment	Comments
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 11.5.1

β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; C-SSRS: Columbia-Suicide Severity Rating Scale; FSH: follicle-stimulating hormone; ICF: informed consent form; PE: physical examination

[a] When assessment time points coincide, assessments will be performed in the following order: vital signs, 12-lead ECG, PE, and blood sample collection.

Table 3-4 Study VX22-548-107: Treatment Period and Safety Follow-up Visit (All Subjects)

Event/Assessment[a]	Day 1	Day 2	Discharge[b]	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (+ 3 days)	End of Dosing Visit[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Inpatient (e.g., hospital or ambulatory center), if required, or visit at medical facility	X	(X)							Non-surgical subjects are generally not anticipated to require admission.
Discharge (e.g., from hospital or ambulatory center), if required, or leaving medical facility		X							Discharge/leaving will be per clinical judgement. Although the inpatient period, if any, is generally expected to be <24 hours, subjects who turn out to require a stay of ≥24 hours do not need to discontinue study drug treatment or the study; Section 9.1.3.
Telephone contact				X					Assess the subject's status, any AEs, concomitant medications, treatments, and procedures
Clinic or home health visit					X			X	Subjects will have the option to complete these visits in the clinic or to have a home health visit. Home health visits are only an option if permitted by local regulations; Section 9.1.6.
Telemedicine video conference or telephone contact					(X)			(X)	A consultation between the subject and investigator or qualified delegate (LIP) must be **performed within 2 business days after the home health visit** (can be outside the visit window) and may also include a separate follow-up with the study coordinator. Required only for subjects who have a home health visit; not required for subjects who have a clinic visit; Section 9.1.6.
Clinic visit						X	X		

Table 3-4 Study VX22-548-107: Treatment Period and Safety Follow-up Visit (All Subjects)

Event/Assessment[a]	Day 1	Day 2	Discharge[b]	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (+ 3 days)	End of Dosing Visit[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
PGA		X			X	X	X		Recorded in the e-diary[d]; Section 11.4.1. Subjects should still complete the PGA even if the specified dose is not taken. **Day 2:** To be completed after the third study drug dose (approximately 24 hours after the first dose). **Day 7:** 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:** 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 (or presumed last) dose of study drug rather than waiting for their scheduled visit.
Vital signs			X (postdose)[b]		X	X	X	X	Vital signs will be collected after a ≥5-minute rest (seated or supine) and before any 12-lead ECG assessment or blood sampling; Section 11.5.3.
Standard 12-lead ECG	X (4 hours after first dose and at discharge or before leaving medical facility, as applicable)				X (4 hours after a dose)[e]	X (4 hours after a dose)[e,f]	X	(X)	Required at SFU only if any clinically significant abnormalities were noted on a prior ECG. Standard 12-lead ECGs will be performed in triplicate after a ≥5-minute rest (supine); these will be done after taking vital signs and before any procedures that may affect heart rate (e.g., blood sampling); Section 11.5.4.

Table 3-4 Study VX22-548-107: Treatment Period and Safety Follow-up Visit (All Subjects)

Event/Assessment[a]	Day 1	Day 2	Discharge[b]	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (+ 3 days)	End of Dosing Visit[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Symptom-directed PE	As applicable								Symptom-directed PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator; Section 11.5.3.
Focused PE **(surgical subjects only)**								X	Assessment of wound healing at the operative site; Section 11.5.3.
Complete PE								(X)	Required at SFU only if a clinical finding during the Treatment Period requires follow up, in which case the subject must have a clinic visit; Section 11.5.3.
C-SSRS			X (postdose)[b]		X	X	X		Section 11.5.5
Urine β-hCG						X	X	X	All female subjects of childbearing potential; Section 11.5.2.
Serum chemistry			X (postdose)[b]			X	X	(X)	Required at SFU only if a clinical finding during the Treatment Period requires follow up; Section 11.5.2.
Hematology			X (postdose)[b]			X	X	(X)	
Coagulation			X (postdose)[b]			X	X	(X)	
Urinalysis			X (postdose)[b]			X	X	(X)	
Fasting period	X (first dose only)								First dose: for at least 1 hour before (**surgical subjects:** starting from time of surgery completion) through 2 hours after, no food or drink (except ≤8 fluid ounces of water per hour); Section 9.4.2.
VX-548 dosing	Day 1 through Day 14[g] (q12h) or until pain resolves, whichever occurs first								Subjects will record the date and time of administration in an e-diary[d]; Section 9.6.
Rescue medication use	Day 1 through Day 14, completion of study drug treatment due to pain resolution, or study drug discontinuation, whichever occurs first								Subjects will record the date and time of administration in an e-diary[d]; Section 9.4.1.2.
Study drug count					X	X	X		
Adverse events	Continuous from signing of ICF through completion of study participation								Section 11.5.1

Table 3-4 Study VX22-548-107: Treatment Period and Safety Follow-up Visit (All Subjects)

Event/Assessment[a]	Day 1	Day 2	Discharge[b]	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (+ 3 days)	End of Dosing Visit[c]	Safety Follow-up Visit Day 28 (± 2 days)	Comments
Medications review	Continuous from signing of ICF through completion of study participation								All medications taken within 14 days before the Screening Visit through completion of study participation; Section 9.4.2.
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; β-hCG: beta-human chorionic gonadotropin; C-SSRS: Columbia-Suicide Severity Rating Scale; e-diary: electronic diary; EDV: End of Dosing Visit; ICF: informed consent form; LIP: licensed independent practitioner; PE: physical examination; PGA: patient global assessment; q12h: every 12 hours; SFU: Safety Follow-up

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

[a] When assessment time points coincide, assessments will be performed the following order: C-SSRS, vital signs, 12-lead ECG, PE, and blood sample collection.

[b] Discharge assessments should be completed for all surgical subjects and for any non-surgical subjects who required inpatient admission.

[c] If a subject discontinues or completes study drug treatment for any reason 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 pain resolution criteria are met (as applicable), and the Day 14 Visit will 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 or complete study drug treatment before Day 14 will be required to complete the Safety Follow-up Visit. In the unlikely event that the EDV is delayed and occurs 28 days or later following the first dose of study drug, then a separate Safety Follow up Visit will not be required.

[d] For all e-diary assessments, a paper version will be available as a back-up option.

[e] Refer to Section 9.6 for instructions on dose and visit scheduling on days of postdose ECGs.

[f] Subjects who have their Day 14 Visit after Study Day 14 (per the visit window) and thus are no longer taking study drug will have an ECG any time that day rather than 4 hours postdose.

[g] For subjects who remain on study drug treatment at Day 14, only 1 dose of study drug should be taken on that day, and it will be the last dose of study drug for these subjects.

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIEP	deep inferior epigastric perforator
DRG	dorsal root ganglia
e-diary	electronic diary
ECG	electrocardiogram
EDC	electronic data capture
EDV	End of Dosing Visit
EENT	eyes, ears, nose, and throat
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
GPP3	Good Publication Practices
GPS	Global Patient Safety
H2	histamine type 2 receptor
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV-1/HIV-2 Abs	antibodies against human immunodeficiency viruses 1 and 2
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IV	intravenous
LIP	licensed independent practitioner
max	maximum value
min	minimum value
n	size of subsample
$Na_V1.8$	voltage-gated sodium channel 1.8

Abbreviation	Definition
N_2O	nitrous oxide
NPRS	numeric pain rating scale
NSAID	nonsteroidal anti-inflammatory drug
PE	physical examination
PGA	patient global assessment
prn	as needed
q6h	every 6 hours
q12h	every 12 hours
QTcF	QT interval corrected by Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCN10A	sodium voltage-gated channel alpha subunit 10
SD	standard deviation
SFU	Safety Follow-up (Visit)
SpO_2	oxygen saturation
SUSAR	suspected, unexpected, serious adverse reaction
TE	Treatment-emergent (Period)
TEAE	treatment-emergent adverse event
TRAM	traverse rectus abdominal muscle
US	United States
VRS	verbal categorical rating scale

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 more than 70,000 overdose deaths in the US in 2020 and in approximately 76% of fatal drug overdoses in the EU in 2019.[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 entity drugs 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.

Voltage-gated sodium channel 1.8 ($Na_V1.8$) plays a critical role in pain signaling.[9, 10] Support for this assertion arises from (1) evaluation of the role $Na_V1.8$ plays in normal physiology[11-15], (2) pathological states arising from mutations in the $Na_V1.8$ gene (SCN10A)[16, 17], (3) animal models[18-21], and (4) pharmacology of known $Na_V1.8$-modulating agents.[22-24] In addition, because $Na_V1.8$ expression is restricted to peripheral neurons, particularly those that sense pain (e.g., the dorsal root ganglia [DRG])[11, 13], $Na_V1.8$ inhibitors are less likely to be associated with the side effects commonly observed with other sodium channel modulators and the abuse liability associated with opioid therapies. Therefore, targeting the underlying biology of pain through selective $Na_V1.8$ inhibition represents a novel approach to analgesic drug development that has the potential to address an urgent unmet need for safe and effective acute and chronic pain therapies. These therapies include treatment where the primary mechanisms underlying pain are nociceptor hyperexcitability.

5.2 Study Rationale

This study will evaluate the safety and effectiveness of up to 14 days of treatment with VX-548 for acute pain.

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the safety and tolerability of VX-548

6.2 Secondary Objective

To evaluate the effectiveness of VX-548 in treating acute pain

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Safety and tolerability based on treatment-emergent adverse events (TEAEs), laboratory test results, vital signs, and ECGs

7.2 Secondary Endpoint

Subject perception of VX-548 effectiveness in treating pain at the end of treatment as measured by the proportion of subjects reporting good, very good, or excellent on a patient global assessment (PGA)

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

All Subjects (Before Surgery, If Applicable)

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) between the ages of 18 and 80 years, inclusive.
4. Body mass index (BMI) of ≥18.0 to <40.0 kg/m^2.
5. **Surgical subjects:** Scheduled to undergo an ambulatory orthopedic, plastic, breast, otorhinolaryngologic, colorectal, gynecologic, urologic, or general surgical procedure with pain that is expected to last for at least 72 hours and that is expected to require no more than short-term (i.e., <24-hour) admission (additional details on ineligible procedures are provided in Appendix A).

   Non-surgical subjects: Present to medical facility with pain of new origin (not related to a prior known condition) that is moderate or severe on the verbal categorical rating scale (VRS) and ≥4 on the numeric pain rating scale (NPRS), has been ongoing for ≤48 hours, is expected to last for at least 72 hours, and is expected to require no more than a short-term (i.e., <24-hour) admission, if any. Representative conditions include traumatic and atraumatic acute musculoskeletal pain, orofacial pain, burns, and cutaneous and soft tissue pain (additional details on ineligible conditions are provided in Appendix A).

After Surgery (Surgical Subjects Only)

6. Subject reported pain at the surgical site that is moderate or severe on the VRS and ≥4 on the NPRS within the following procedure-specific time periods:
   - Procedures performed with regional anesthesia: within 12 hours after surgery completion
   - All other procedures: within 4 hours after surgery completion

7. Subject is lucid, able to follow commands, and able to swallow oral medications.
8. All analgesic guidelines (Section 9.4.1) were followed during and after the procedure.

8.2 Exclusion Criteria

All Subjects (Before Surgery, If Applicable)

1. **Surgical subjects only:** History of previous surgery due to the same condition, except for procedures for which a previous surgery on the contra-lateral limb or organ is allowed.
2. **Surgical subjects only:** 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.
3. 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 in situ (i.e., no adjudication by the investigator is needed), so long as there has been no recurrence for the last 5 years.
4. 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 at screening.
5. Presence of an automated implantable cardioverter defibrillator, cardiac resynchronization therapy device, or pacemaker.
6. 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[25]).
7. Alanine transaminase or aspartate transaminase values >2.5 × upper limit of normal.
8. History of severe renal impairment defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73^2 calculated using the subject's measured serum creatinine; the suggested calculation method for eGFR is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
9. Any other abnormal laboratory results indicative of significant medical disease that, in the opinion of the investigator, would preclude the subject's participation in the study.
10. History of any sensory abnormality that, in the opinion of the investigator, may confound the ability of the subject to assess pain.
11. Subjects who have a painful physical condition that, in the opinion of the investigator, may confound the assessments of pain.

12. A known or clinically suspected active infection with human immunodeficiency virus or hepatitis B or C viruses. (**Note:** Testing in the absence of suspected active infection is required for surgical subjects only.)
13. Any surgery (except the protocol surgery for surgical subjects) within 1 month before the first study drug dose, unless approved by the medical monitor.
14. American Society of Anesthesiologists physical status classification[26] of ≥3.
15. Chronic use of opioids (pure agonists, agonist/antagonists, partial agonists, antagonists) or NSAIDs with dose escalation within 30 days before first dose of study drug.
16. Unwilling or unable to stop analgesics at least 5 half-lives or 2 days (whichever is longer) before first dose of study drug, with the following exception: for non-surgical subjects, use of a limited amount of pain medications before presentation at the medical facility and/or single use of any medication in the medical facility within the past 4 hours is not exclusionary.
17. Subjects who have started any non-analgesic new medications that have not been at a stable dose for at least 14 days before first dose of study drug.
18. Subjects unwilling to receive any protocol-related medicine (e.g., ibuprofen, acetaminophen, fentanyl).
19. Subjects with a history of allergy or significant adverse event (AE) to any opioid and/or NSAID that, in the opinion of the investigator, would significantly increase the chance of AEs from medicines used in the study.
20. Subjects with sleep apnea and/or on a home positive airway pressure device.
21. 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.
22. For female subjects: Pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last study drug dose.

    For male subjects: Male subjects with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last study drug dose.
23. Participation in a previous study investigating VX-548.
24. Participated in another investigational study within 30 days of the first dose of study drug.
25. Evidence of misuse, aberrant use, or addiction to alcohol or an illicitly used drug of abuse in the past 3 years, or a positive test for drugs of abuse as defined in Section 11.5.2.
    - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.
26. Use of the substances, activities, or devices, as indicated in Section 9.4, during the specified times.
27. 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.

After Surgery (Surgical Subjects Only)

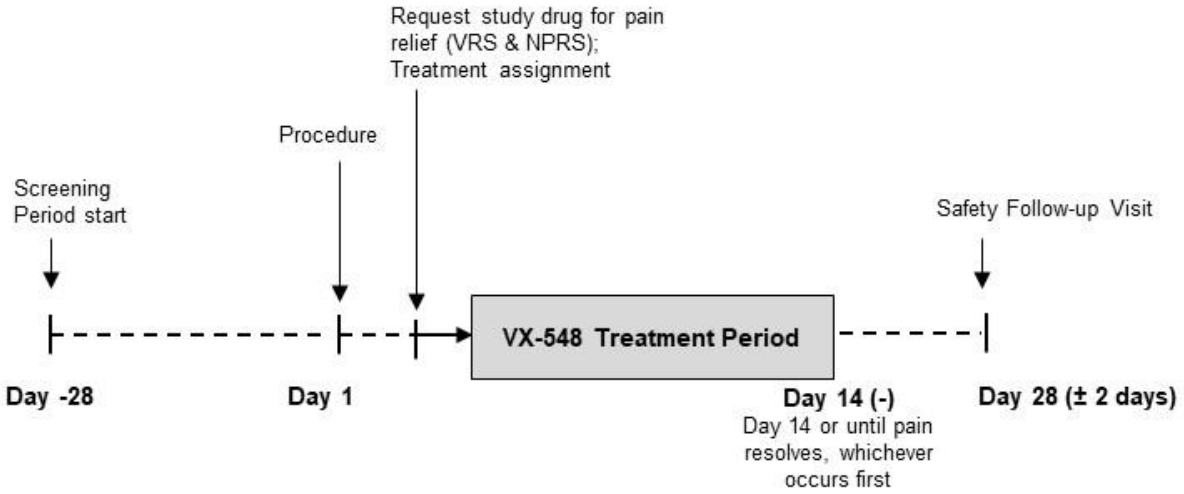
28. Subject had any surgical complications during the procedure.
29. Subject had a medical complication during the procedure that, in the opinion of the investigator, should preclude assignment to treatment.
30. Standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at baseline (Day 1 predose).

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 3, single-arm study evaluating the safety and effectiveness of VX-548 in treating acute pain (Figure 9-1 [surgical subjects] and Figure 9-2 [non-surgical subjects]).

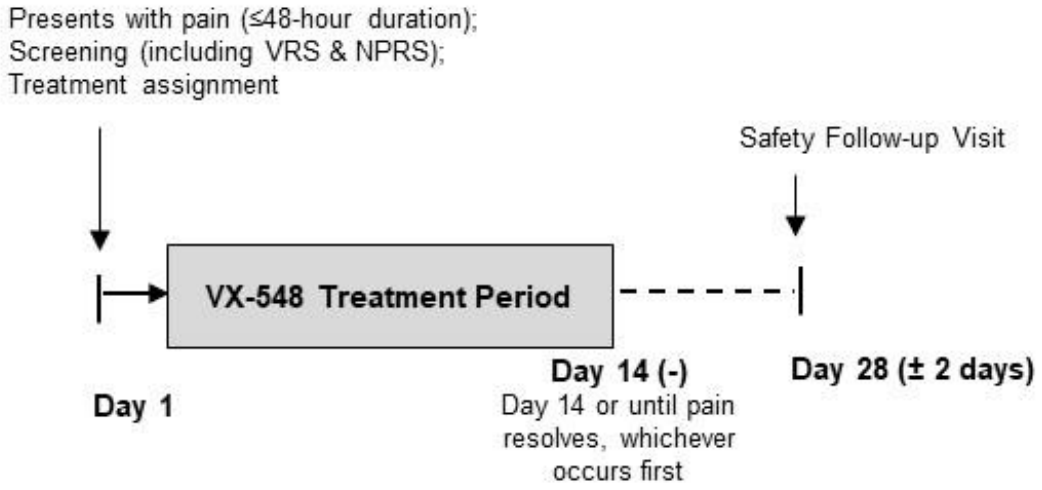
Figure 9-1 VX22-548-107 Study Design (Surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale

Notes: After surgery completion, a subject will be assigned to treatment if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS, and (3) the subject's pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within the protocol-specified, procedure-specific time period, the subject will not be eligible for this study. Figure is not drawn to scale.

Figure 9-2 VX22-548-107 Study Design (Non-surgical Subjects)



NPRS: numeric pain rating scale; VRS: verbal categorical rating scale
Notes: After completion of screening assessments and confirmation of eligibility, a subject will be assigned to treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. Figure is not drawn to scale.

Surgical Subjects

On Day 1, subjects will undergo a scheduled ambulatory surgical procedure with pain that is expected to last for at least 72 hours and that is expected to require no more than a short-term (i.e., <24-hour) admission. After surgery completion, a subject will be assigned to treatment if (1) the subject requests the first dose of study drug for pain relief, (2) the subject's pain is moderate or severe on the VRS, and (3) the subject's pain is ≥4 on the NPRS. If a subject does not meet the VRS and NPRS criteria within the protocol-specified time period for the surgical procedure they underwent (e.g., 4 hours for most procedures; Section 8.1), the subject will not be eligible for this study.

Non-surgical Subjects

On Day 1, after completion of screening assessments and confirmation of eligibility, a subject will begin treatment if (1) the subject's pain is moderate or severe on the VRS, and (2) the subject's pain is ≥4 on the NPRS. For a subject to be eligible, their pain must have been ongoing for ≤48 hours at presentation.

All Subjects

Approximately 250 subjects will receive VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]). Subjects will continue to receive VX-548 for 14 days or until their pain resolves, whichever occurs first. An acetaminophen/ibuprofen combination may be used as a rescue medication for pain relief as needed (prn), starting any time after the first dose of study drug through Day 14, completion of study drug treatment due to pain resolution, or study drug discontinuation, whichever occurs first. Subjects will be permitted to take acetaminophen 650 mg/ibuprofen 400 mg every 6 hours (q6h) prn, up to a maximum of 2600 mg/1600 mg in any 24-hour period.

The following approach will be used to define pain resolution and completion of study drug treatment:

1. Pain is considered to be resolved and the study drug treatment will be considered completed if
   a. a subject takes no study drug during a 48-hour period (i.e., skipped at least 4 consecutive doses due to pain resolution); and
   b. a subject takes no more than 1 dose of acetaminophen/ibuprofen during each 24-hour period within the 48-hour period (i.e., no more than 2 doses in 48 hours).
2. If a subject stops taking study drug per Criterion 1a but does not meet Criterion 1b, they will be instructed to restart study drug (and prn rescue medication).
3. If a subject stops and restarts study drug (Criterion 2 above) and subsequently believes their pain is resolving and stops study drug a second time, they will be instructed to **not** restart study drug, regardless of whether the above criteria are met.
4. If a subject stops study drug a second time after the restart of dosing (Criterion 3 above) and then fulfills both Criterion 1a and 1b, the pain is considered resolved and study drug treatment will be considered completed. If the subject fulfills Criterion 1a but not Criterion 1b after the restart of dosing, the pain is considered not resolved and study drug will be considered discontinued.

Note If a subject stops study drug due to pain resolution less than 48 hours before the last scheduled dose of study drug (i.e., stops after the second dose on Day 12) and therefore cannot meet Criterion 1a by Day 14, the subject will be considered to have completed study drug dosing as long as they also meet Criterion 1b.

9.1.1 Screening

Surgical Subjects

Assessments from screening through admission (pre-procedure) are listed in Table 3-1.

The Screening Visit will occur within 28 days before the scheduled surgical procedure and may occur in the clinic or as a home health visit with a qualified visiting nurse if permitted by local regulations. 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 Visit assessments may be performed on different days within the screening period (e.g., informed consent may be obtained before the home health visit, if applicable).

Non-surgical Subjects

Assessments from screening through treatment assigned are listed in Table 3-3.

The Screening Visit will occur on Day 1 after the subject presents with pain at a medical facility. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject before performing any study-related procedure. However, previous test results from the facility's local laboratory may be used to establish eligibility if collected within 2 hours before ICF signing. All screening assessments must be completed, confirming

subject eligibility, before treatment assignment may occur, including VRS and (if the subject's pain is rated moderate or severe on the VRS) NPRS.

All Subjects

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 and the importance of accurately reporting their post-procedural pain. At the Screening Visit, subjects will receive trainings on accurate pain reporting, clinical study participation, and use of the electronic diary (e-diary) for recording study drug administration, rescue medication use, and the PGA. On Day 1 (pre-procedure), these trainings will be repeated for surgical subjects; for non-surgical subjects, only 1 training is required because the Screening Visit is on Day 1. 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). In all cases, the medical monitor must authorize retesting.

9.1.1.2 Rescreening (Surgical Subjects Only)

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 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 Surgical Procedure Through Treatment Assignment (Surgical Subjects)

Assessments to be completed after the surgical procedure through treatment assignment are listed in Table 3-2.

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

Use of drains for all relevant procedures will be at the discretion of the surgical team.

In the perioperative period, pain management agents will be used according to Section 9.4.1.1. All other standard-of-care agents (e.g., anti-emetics) are allowed except those which are specifically restricted (Table 9-1). Section 9.4 provides additional details on allowed and restricted agents.

Treatment assignment may not occur until at least 15 minutes after the last administration of supplemental analgesia (i.e., fentanyl; Section 9.4.1.1).

In the postoperative period before treatment assignment, VRS will be completed upon request for the first dose of study drug for pain relief. NPRS will be completed after VRS only if the subject's pain is rated moderate or severe on the VRS. If a subject does not meet the VRS and NPRS criteria within the protocol-specified time period for the surgical procedure they underwent (Section 8.1), the subject will not be eligible for this study.

9.1.3 Treatment Period

Treatment Period assessments are listed in Table 3-4 (surgical and non-surgical subjects).

All study periods will be conducted as described in Section 9.1. Dosing details are in Section 9.6.

If a subject has any clinically significant, study-related abnormalities at the time that they meet discharge/leaving criteria from where the surgical procedure was conducted or non-surgical condition was treated (e.g., hospital, clinic, or ambulatory center), the medical monitor (or authorized designee) will be notified, and the subject will be asked to remain (e.g., in the hospital, clinic, or ambulatory center) until such abnormalities resolve. If the subject is unable or unwilling to remain, the medical monitor (or authorized designee) will be notified, and the investigator will make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Although the inpatient period, if any, is generally expected to be <24 hours (Section 8.1), subjects who turn out to require a stay of ≥24 hours do not need to discontinue study drug treatment or the study.

Subjects who complete or 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 study visits, as described in Section 9.1.5.

9.1.4 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 3-4.

9.1.5 Study Drug Completion or Discontinuation

Subjects will receive VX-548 for 14 days or until their pain resolves, whichever occurs first, with pain resolution and study drug treatment completion as defined in Section 9.1. Subjects may also choose to discontinue study drug for other reasons.

If a subject discontinues or completes study drug treatment for any reason before Day 14, including AEs (considered treatment discontinuation) or reaching pain resolution (considered treatment completion), an End of Dosing Visit (EDV) should be scheduled to occur as soon as possible after treatment discontinuation or after pain resolution criteria are met (as applicable),

and the Day 14 Visit will 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 ideally occur within 72 hours after the last dose of study drug.

Subjects who discontinue or complete study drug treatment before Day 14 will also be required to complete the Safety Follow-up Visit (Section 9.1.4). In the unlikely event that the EDV is delayed and occurs 28 days or later following the first dose of study drug, then a separate Safety Follow-up Visit will not be required.

If a subject withdraws consent for the study, no further assessments will be performed; the study data and samples collected will remain part of the study (Section 9.8).

9.1.6 Home Health Visits

Home health visits are only an option if permitted by local regulations. Any visits that occur via home health must have a consultation (i.e., telemedicine video conference or telephone contact) between the subject and investigator or qualified delegate (licensed independent practitioner [LIP]) within 2 business days after the home health visit in order to check-in and collect AEs, and may also include a separate follow up with the study coordinator.

9.1.7 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: through 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 study.

9.3 Rationale for Study Elements

9.3.1 Study Design and Population

The study is designed to evaluate longer-term safety and sustained effect of VX-548 after multiple kinds of surgeries and non-surgical conditions resulting in acute pain; broad categories of surgeries and non-surgical acute pain conditions were included to obtain comprehensive safety data. Moreover, the use of VX-548 will be primarily in an outpatient setting as the selected surgeries/conditions generally require no more than a short-term (i.e., <24-hour) admission. For the surgical subjects, the procedures and postoperative care, including methods for acute pain management, follow standard of care with minimal restrictions on the surgical and anesthetic parameters for the specified procedures. Clinicians may generally use what they consider to be standard of care in the US, while remaining within protocol specifications. Given that the study is intended primarily to collect safety information, an open-label, single-arm study design is appropriate.

The guiding considerations for the eligible surgical models and non-surgical pain conditions are that (1) they result in at least a moderate level of pain that lasts between 7 and 14 days; and (2) the surgical procedures (where applicable) historically are performed on an ambulatory basis. Consistent with the FDA requirements for premarketing safety databases, the proposed population adequately represents the target population (i.e., patients with moderate to severe

acute pain).[27] To approximate use in a "real-world" setting, inclusion and exclusion criteria were designed to enroll a clinically diverse population that is more generalizable to clinical practice. The eligible surgical procedures and non-surgical conditions support an evaluation of VX-548 in subjects with sufficiently diverse sources of acute pain (e.g., both bony and soft tissue) for the expected duration of use. The surgical procedures represent the broad categories of general, orthopedic, otolaryngology, breast, colorectal, gynecologic, urologic, and plastic and reconstructive surgery. The non-surgical conditions include traumatic and atraumatic acute musculoskeletal pain, orofacial pain, burns, and cutaneous and soft tissue pain.

Following the scheduled surgical procedure or presentation at a medical facility with acute pain, subjects will be assigned to treatment after their pain meets threshold criteria using both a VRS and an NPRS. The pain threshold criteria are designed to ensure subjects have moderate to severe pain. A 4-point VRS (none, mild, moderate, or severe) is included as part of the pain threshold inclusion criterion to allow rapid assessment of subjects' baseline pain on a repeated basis in the immediate postoperative period. The NPRS, a frequently used, valid pain intensity measure recognized by the FDA[28], is included at baseline to further define and quantify subjects as having moderate to severe pain (i.e., ≥4 on an 11-point [0 to 10] scale).

Ibuprofen and acetaminophen were selected as the 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 VX-548 dosing regimen of 100 mg first dose (loading dose), then 50 mg q12h was selected based on favorable safety and pharmacokinetic data from healthy subjects and subjects with pain after bunionectomy or abdominoplasty. Exposures at the selected VX-548 dose are predicted to achieve $Na_V1.8$ inhibition levels of approximately 90% by 2 hours after administration of the 100 mg loading dose. Exposures corresponding to approximately IC_{90} are sustained with the administration of 50 mg q12h maintenance doses starting 12 hours after the loading dose.

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 the study drug's effectiveness in treating pain using a validated, single-item questionnaire.[29] This study will use a 5-point Likert scale (poor, fair, good, very good, or excellent) for the PGA evaluation.[30]

9.4 Study Restrictions

Study restrictions that apply to all subjects 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	**Surgical subjects:** 5 half-lives or 2 days (whichever is longer) before admission for surgery and per guidelines in Section 9.4.1.1 and Section 9.4.1.2 **Non-surgical subjects:** at presentation with acute non-surgical pain (see also Section 8.2 and Section 9.4.1.2)	Until last dose of study drug is taken
Oral steroids	5 half-lives or 2 days (whichever is longer) before admission for surgery or at presentation with non-surgical pain	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
H2 blockers and proton pump inhibitors	72 hours before first dose of study drug	Until last dose of study drug is taken
Alcohol	24 hours before first dose of study drug	Until last dose of study drug is taken
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)	48 hours before first clinical laboratory testing	Completion of SFU assessments

H2: histamine type 2 receptor; SFU: Safety Follow-up

[a] Refer to the Study Reference Manual for a more complete list of medications prohibited/restricted in the study. See Section 9.4.2 for guidance on concomitant medications.

Surgical Subjects Only

Excluding agents for pain management (see Section 9.4.1.1), all perioperative 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). Commonly used medications may include those falling into the general categories of short-acting anxiolytics/sedatives (e.g., midazolam), antisialagogues (e.g., glycopyrrolate), anti-emetic or anti-nausea agents (e.g., ondansetron, metoclopramide), neuromuscular blockers (e.g., rocuronium), neuromuscular blockade reversal (e.g., neostigmine, sugammadex), hemodynamic control (i.e., positive/negative inotropes or chronotropes, vasopressors, antihypertensives), oxygen/air, IV fluids, antibiotics, anticoagulants (e.g., heparin), or antifibrinolytics (e.g., tranexamic acid).

9.4.1 Analgesic Medications

Non-surgical subjects do not have additional restrictions on analgesic medications besides those in the study restrictions table (Table 9-1). Additional restrictions for surgical subjects are described in Section 9.4.1.1.

9.4.1.1 Perioperative Pain Management (Surgical Subjects Only)

Pre- and Intraoperative Pain Management

Table 9-2 summarizes the allowed and prohibited anesthesia and analgesic agents during the pre- and intraoperative period.

Table 9-2 Guidance on Pre- and Intraoperative Anesthesia and Analgesic Agents

Agent Type	Allowed Agents	Prohibited Agents
General anesthesia	• Induction: propofol, etomidate, thiopental • Maintenance: propofol, desflurane, sevoflurane, N_2O • Analgesia: opioids (e.g., fentanyl), NSAIDs, acetaminophen	• Induction: ketamine • Maintenance: ketamine, isoflurane, dexmedetomidine • Analgesia: ketamine, gabapentinoids, dexamethasone
Local anesthetic infiltration or injection (non-catheter-based)	Any non-extended-release agent, with or without epinephrine[a]	• Liposomal bupivacaine • Bupivacaine/meloxicam • Clonidine
Neuraxial anesthesia (non-catheter-based)	Any non-extended-release local anesthetic, with or without epinephrine[a]	• Liposomal bupivacaine • Bupivacaine/meloxicam • Clonidine
Nerve block (non-catheter-based)	Any non-extended-release local anesthetic, with or without epinephrine[a]	• Liposomal bupivacaine • Clonidine

N_2O: nitrous oxide; NSAID: nonsteroidal anti-inflammatory drug

[a] The maximum dose should be calculated using ideal body weight and accepted standard-of-care recommendations for the specific agent and mode of administration. For example, for lidocaine the maximum doses would be 4 mg/kg ideal weight without epinephrine or 7 mg/kg ideal weight with epinephrine.

Postoperative Pain Management

Postoperative supplemental analgesic medication is permitted per the following guidelines until the first dose of study drug is administered:

- Intravenous (IV) fentanyl citrate (dosing at the discretion of the surgical and/or anesthesia teams) can be administered if the subject is (1) not lucid enough for treatment assignment but deemed to be in severe pain per clinical judgement; and/or (2) unable to swallow oral medications.
- Treatment assignment may not occur until at least 15 minutes after the last administration of supplemental fentanyl.

9.4.1.2 Rescue Medication

Rescue medication may be used per the following guidelines:

- Rescue medication for pain relief may be used prn any time after the first dose of study drug through Day 14, completion of study drug treatment due to pain resolution, or study drug discontinuation (e.g., due to AE), whichever occurs first. Subjects will continue to document rescue medication use through Study Day 14 or the EDV, whichever occurs first.
- Subjects will be permitted to take acetaminophen 650 mg/ibuprofen 400 mg q6h prn, up to a maximum of 2600 mg/1600 mg in any 24-hour period.
- No other analgesic medications (e.g., NSAIDs other than ibuprofen, opioids) are allowed from the start of the treatment period through the last dose of study drug.
- A record (date and time of administration) will be kept of all rescue medication use.

9.4.2 Additional Dietary Restrictions

Surgical subjects will abstain from all food and drink (except ≤8 fluid ounces per hour of water) from the time of surgery completion through 2 hours after the first dose of study drug (Table 3-2 and Table 3-4). After this period, study drug may be taken with or without food.

Non-surgical subjects will abstain from all food and drink (except ≤8 fluid ounces per hour of water) for 1 hour before through 2 hours after the first dose of study drug (Table 3-4). After this period, study drug may be taken with or without food.

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).
- 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. All medications administered in-clinic will also be recorded with the time of each administration. Non-surgical subjects should provide the estimated time of administration for any medications taken on Day 1 before arriving at the medical facility. All subjects will be questioned about medications at each visit or telephone contact.

9.6 Administration

VX-548 will be administered to all subjects q12h.

Study drug will be administered according to the following guidelines:

- Study drug will be administered orally with approximately 240 mL (8 fluid ounces) of water.
- 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 must be administered following the dietary restrictions outlined in Table 9-1 and Section 9.4.2. Starting from the second dose of study drug, VX-548 may be taken with or without food.
- Study drug will be administered after baseline vital signs and ECGs are performed.

- Study drug should be administered q12h, with a window of ± 1 hour with respect to the most recent dose. For example, if the first dose of study drug is administered at 10:00 on Day 1, the next dose should be administered between 21:00 and 23:00 on Day 1; if the second dose is taken at 21:00 on Day 1, the next dose should be taken between 8:00 and 10:00 on Day 2. Depending on the timing of their visit and initial dose, the subject may take either 1 or 2 doses on Day 1.
    - If a subject forgets a dose and exceeds the suggested window but remembers within an additional 4 hours beyond the +1-hour window, they will take the dose at that time.
    - If a subject forgets a dose and more than 5 hours have elapsed, they are to skip that dose and resume at the next scheduled dose (i.e., a window of 24 hours ± 1 hour with respect to the prior dose before the one that was missed).
- On the date of the Day 7 Visit and on Study Day 14 (if applicable; Table 3-4), administration of a study drug dose should be timed so as to complete 4-hour postdose ECGs at the visit (clinic or home health, as applicable). The visit should ideally be scheduled to occur within approximately 4 hours after either the first or second planned daily dose of study drug, whichever is more convenient. If necessary for scheduling reasons, the subject may withhold a study drug dose for up to 3 hours after the planned dosing time point in order to align postdose ECGs with the scheduling visit timing.
- Subjects who choose to stop study drug before Day 14 may restart and stop 1 additional time per Section 9.1. For subjects who remain on treatment at Day 14, only 1 dose of study drug should be taken on that day, and it will be the last dose of study drug for these subjects.

Additional information is provided in the Pharmacy Manual.

9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.5).

9.8 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 VX-548 by the investigator or Vertex:

- ≥3 serious adverse events (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.

9.9 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 9.1.5.

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, if applicable (see Section 9.1.5), 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 will not be able to request the withdrawal of his/her information from the study data. 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.

9.10 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 VX-548 (Section 10.1 through Section 10.7). Vertex will also supply the commercially available rescue medication (Section 10.8).

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 VX-548 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for VX-548 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
VX-548	Tablet/ oral	100 mg first dose; all other doses 50 mg	Supplied as 50-mg tablets

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 designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel or approved home nurse 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 or checked by home nurse during home visits.

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.

10.8 Rescue Medication

Vertex will supply acetaminophen and ibuprofen for use as rescue medication during the Treatment Period. Drug accountability will be performed in a similar manner as for study drug.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical and surgical history, baseline VRS and NPRS scores, type of surgical procedure (for surgical subjects only), height, and weight.

Medical history will be elicited from each subject and extracted from medical records during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria (Section 8). The medical history will include a complete review of systems, past medical and surgical histories, concomitant medications, and any allergies.

11.2 Pharmacokinetics

Not applicable

11.3 Other Assessments

11.3.1 Use of Rescue Medications

Rescue medication is permitted for pain relief if needed. Guidelines on administration of ibuprofen and acetaminophen in combination as rescue medications are included in Section 9.4.1.2. Subjects will record rescue medication use in an e-diary; a paper back-up option will be available.

11.4 Effectiveness

11.4.1 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 e-diary; a paper back-up option will be available.

11.5 Safety

Safety evaluations will include AEs; clinical laboratory assessments; clinical evaluation of vital signs, standard 12-lead ECGs, and physical examinations (PEs); and Columbia-Suicide Severity Rating Scale (C-SSRS).

11.5.1 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.

11.5.2 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 11.5.1).

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

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Urobilinogen
Blood urea nitrogen[b]	Platelets	Urine protein
Creatinine	Leukocytes	pH
Sodium	Differential (percent):	Urine blood
Potassium	Eosinophils	Specific gravity
Calcium	Basophils	Urine ketones
Chloride	Neutrophils	Urine bilirubin
Magnesium	Lymphocytes	Urine glucose
Bicarbonate	Monocytes	
Phosphate	**Coagulation**	
Total bilirubin, direct bilirubin	Activated partial thromboplastin time	
Alkaline phosphatase	Prothrombin time	
Aspartate transaminase	Prothrombin time International Normalized Ratio	
Alanine transaminase		
Amylase		
Lipase		
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Urate		

[a] If urinalysis results are positive for protein or blood, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] 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. For non-surgical subjects, local laboratory results will be used during screening; previous test results from the facility's local laboratory may be used to establish eligibility if collected within 2 hours before ICF signing.

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

- Serology (surgical subjects only): Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), HCV RNA, and antibodies against human immunodeficiency viruses 1 and 2 (HIV-1/HIV-2 Abs). Subjects with detectable viral load will be excluded (Section 8.2).
- Serum Follicle-stimulating Hormone (FSH): Serum FSH will be tested at the Screening Visit for female subjects who are suspected to be postmenopausal (as defined in Section 11.5.6.1). For a subject to be considered of non-childbearing potential, the serum FSH levels will be

within the laboratory range for postmenopausal females. For non-surgical subjects, a test result is not required for eligibility; however, until the test result is received, a subject will be considered to be of childbearing potential and must follow contraception requirements (Section 11.5.6.1) until postmenopausal status is confirmed.

- Pregnancy Testing: **Surgical subjects:** All biologically female subjects will have a serum beta-human chorionic gonadotropin (β-hCG) test during the Screening Visit. Female subjects of childbearing potential (Section 11.5.6.1) will also have a urine β-hCG test before admission on Day 1. Both the serum and urine β-hCG test must be negative to receive study drug. **Non-surgical subjects:** All biologically female subjects will have a urine β-hCG test during the Screening Visit, which occurs on Day 1; the test must be negative to receive study drug.
- Drug and Alcohol Screening: Drug screening for opioids, methadone, cannabinoids, cocaine, amphetamines/methamphetamines, barbiturates, and benzodiazepines will be assessed by a urine test at the Screening Visit and before admission on Day 1; for non-surgical subjects, only 1 test is required because the Screening Visit is on Day 1. Alcohol screening will be assessed before admission (surgical subjects) or treatment assignment (non-surgical subjects) on Day 1 by a urine, blood, or breath test. Subjects may undergo random urine drug screen and alcohol testing if deemed appropriate by the investigator. Drug and alcohol screen results must be negative for a subject to receive study drug; a positive marijuana screen will only be exclusionary on Day 1. A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects.

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:

- Day 1 (pre-procedure, if applicable) drug and alcohol tests and urine β-hCG pregnancy tests will be assessed by staff onsite.
- For **non-surgical subjects**, local laboratories will be used for safety laboratory tests at screening.
- For **surgical subjects**, 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.

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits. At other visits, symptom-directed PEs and symptom-directed vital signs assessments

can be performed at the discretion of the investigator or healthcare provider. If the Screening Visit occurs via home health (surgical subjects only), an abbreviated PE will be performed at screening and a complete PE will be performed on Day 1.

A PE includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat (EENT); 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 abbreviated PE will include an assessment of the following body systems: general; cardiovascular system; respiratory system; skin; and abdomen.

A focused PE of the operative site (surgical subjects only) will be performed in order to assess wound healing.

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.

If there is an abnormal clinical assessment during a home visit, depending on its severity and at investigator discretion, the subject may be instructed to have a PE or other evaluation in the clinic.

11.5.4 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:

- The ECG will be done before blood draws or any other procedures that may affect heart rate.
- 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.

The acceptable window for the 4-hour postdose ECG is ± 30 minutes relative to the scheduled nominal time.

A 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.

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 value 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.

11.5.5 Columbia-Suicide Severity Rating Scale

The C-SSRS, a series of questions about suicidal thoughts and behaviors, will be included (per Table 3-1, Table 3-3, and Table 3-4) for prospective assessment in accordance with regulatory guidance.[31]

11.5.6 Contraception and Pregnancy

The effects of VX-548 on conception, pregnancy, and lactation in humans are not known. Refer to the VX-548 Investigator's Brochure for additional details.

11.5.6.1 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, 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.

11.5.6.2 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 250 subjects are planned to be enrolled. With 250 subjects, there is a 92% probability of observing an AE in at least 1 subject if the true incidence is 1% and a 99% probability of observing an AE in at least 1 subject if the true incidence is 2%.

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 individual subject data for subjects who have received at least 1 dose of study drug 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.

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 non-missing pretreatment measurements (triplicate) on Day 1 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 9.1.7), 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 VX-548 effectiveness 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 VX-548 will be assessed in terms of the following safety and tolerability endpoints:

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

Safety endpoints will be summarized descriptively 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 9.1.7).

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 May 2022). 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 May 2022)
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 Section 9.7 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 the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the Safety Follow-up Visit 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 the Safety Follow-up Visit, 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:

Email: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

For technical issues related to submitting the form, contact telephone: +1-617-341-6677

SAEs that occur after the Safety Follow-up Visit 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 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 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.

13.7 Publications and Clinical Study Report

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[32]

Publication Planning: Vertex staff along with the lead principal investigators, the steering committee, and/or the publication committee will work together to develop a publication plan.

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

Contributors: Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors (ICMJE) criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., “study investigators”) or individually (e.g., “served as scientific advisor”).

Publication Review: As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

13.7.2 Clinical Study Report

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

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15 APPENDIX A: GUIDANCE ON SURGICAL PROCEDURES AND NON-SURGICAL ACUTE PAIN CONDITIONS

Representative eligible surgical procedures and non-surgical acute pain conditions are defined in Inclusion Criterion 5 (Section 8.1). Table 15-1 presents surgical procedures and non-surgical conditions representative of those which are NOT eligible.

Table 15-1 Representative Ineligible Surgical Procedures and Non-surgical Conditions Resulting in Acute Pain

Surgical Procedures	Non-surgical Conditions
Open joint arthroplasty (e.g., THA, TKA, TSA)	Pain resulting from presumed hollow organ obstructive pathology (e.g., pancreatitis, renal colic)
Thoracic surgery (open or laparoscopic)	Pain presumed to be primarily visceral in origin (e.g., appendicitis, ovarian cysts, diverticulitis)
Cardiac surgery	Pain in a subject with active cancer and/or undergoing treatment for same
Surgery in subject with active cancer – curative or palliative	
Major vascular surgery	
Spinal surgery	
Austin or Lapidus bunionectomy without concomitant surgery	
Full abdominoplasty	

THA: total hip arthroplasty; TKA: total knee arthroplasty; TSA: total shoulder arthroplasty

16 PROTOCOL SIGNATURE PAGES

16.1 Sponsor Signature Page

Protocol #: VX22-548-107	Version #: 2.0	Version Date: 09 November 2022
Study Title: A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of VX-548 for Acute Pain		

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

Printed Name	Title
Signature	Date

16.2 Investigator Signature Page

Protocol #: VX22-548-107	Version #: 2.0	Version Date: 09 November 2022
Study Title: A Phase 3, Single-arm Study Evaluating the Safety and Effectiveness of VX-548 for Acute Pain		

I have read Protocol VX22-548-107, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-548 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date