1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX22-548-105

IND Number: 146185

Date of Protocol: 12 April 2023 (Version 4.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 3.0, 09 November 2022) was amended to create the current version (Version 4.0, 12 April 2023). The protocol history is below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 05 August 2022	Original version
Version 2.0, 12 October 2022	• Added exclusion criteria for history of QT prolongation or standard 12-lead ECG demonstrating median QTcF >450 msec at screening or baseline. • Added study drug interruption and stopping rules. • Clarified procedures for ECG safety monitoring after the first dose of study drug.
Version 3.0, 09 November 2022	• Permitted study drug to be taken with or without food after the first dose. • Updated the contraception requirement to the use of at least 1 acceptable method of contraception based on supporting nonclinical data. • Specified that numeric pain rating scale (NPRS) responder endpoints will be compared to placebo. • Expanded NPRS window at 48 hours to ± 15 min for operational feasibility. • Clarified details of the abdominoplasty procedure. • Added a requirement for medical monitor to authorize all cases of screening assessment repetition. • Restricted inhalational anesthetics use from admission through discharge. • Clarified that documentation of all medications administered in-clinic, including prior medications, will include the time of each administration.
Version 4.0, 12 April 2023	Current version

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

Change and Rationale	**Affected Sections**
Moved the last key secondary endpoint, "time to ≥1-point reduction in NPRS from baseline compared to placebo", to other secondary endpoints.	Sections 2, 7.2, and 12.3.3.3
Simplified the order of assessments for operational feasibility.	Section 3
Added an exception for Vertex personnel or vendor(s) who are not part of the study team to be unblinded for the analysis of pharmacokinetic (PK)/population PK data to support interactions with regulatory authorities, as applicable.	Section 10.8.1
Clarified viral load sample collection and reflex testing for human immunodeficiency viruses 1 and 2.	Table 3-1 and Section 11.5.2
Clarified that Exclusion Criterion 4 applies to standard 12-lead ECGs performed at the Screening Visit and on Day 1 (pre-procedure).	Section 8.2, Exclusion Criterion 4
Clarified the restrictions on analgesic medications, inhalational anesthetics, and steroids.	Table 9-2 and Section 9.4.1
Clarified that the timing of meals relative to dosing is only required to be recorded in the source for the first dose of study drug.	Section 11.2.1

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

2 PROTOCOL SYNOPSIS

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

Brief Title Evaluation of Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty

Clinical Phase and Clinical Study Type Phase 3, efficacy and safety

Objectives

Primary Objective

To evaluate the efficacy of VX-548 in treating acute pain after an abdominoplasty

Secondary Objective

To evaluate the safety and tolerability of VX-548

Other Objective

To evaluate the pharmacokinetics (PK) of VX-548 and its metabolite, [redacted]

Endpoints

Primary Endpoint

- Time-weighted sum of the pain intensity difference (SPID) as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48) compared to placebo

Key Secondary Endpoints

- SPID48 compared to hydrocodone bitartrate/acetaminophen (HB/APAP)
- Time to ≥2-point reduction in NPRS from baseline compared to placebo

Other Secondary Endpoints

- Time to ≥1-point reduction in NPRS from baseline compared to placebo
- Proportion of subjects reporting good or excellent on the Patient Global Assessment (PGA) at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- Time-weighted SPID as recorded on the NPRS from 0 to 24 hours (SPID24) compared to placebo
- Time to first use of rescue medication compared to placebo
- Proportion of subjects using rescue medication from 0 to 48 hours compared to placebo
- Total rescue medication usage from 0 to 48 hours compared to placebo
- Safety and tolerability based on the incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, vital signs, and ECGs

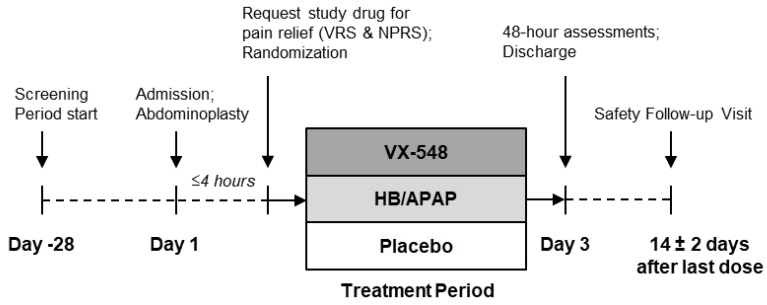
Other Endpoints

- Time-weighted SPID as recorded on the NPRS from 0 to 36 hours (SPID36) compared to placebo
- Time-weighted SPID as recorded on the NPRS from 0 to 12 hours (SPID12) compared to placebo
- Proportion of subjects with ≥30% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥50% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥70% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 24 hours compared to placebo

- Time to first use of rescue medication in the first 12 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 12 hours compared to placebo
- Proportion of subjects using rescue medication from 24 to 48 hours compared to placebo
- PK parameter estimates of VX-548 and its metabolite[redacted]

Number of Subjects	Approximately 1000 subjects
Study Population	Male and female subjects, 18 through 80 years of age (inclusive), with pain that is moderate or severe on the verbal categorical rating scale (VRS) and ≥4 on the NPRS after an abdominoplasty
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 and matching placebo for oral administration
Reference Drug	Active substance: HB/APAP Activity: opioid analgesic Strength and route of administration: 5-mg/325-mg capsules (over-encapsulated tablets) and matching placebo for oral administration
Study Duration	Excluding the Screening Visit, each subject will participate in the study for 3 days plus a Safety Follow-up Visit 14 ± 2 days after the last dose of study drug.
Study Design	This is a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel study design evaluating the efficacy and safety of VX-548 in treating acute pain after an abdominoplasty (Figure 2-1). On Day 1, subjects will undergo a standard ("full") abdominoplasty procedure (as defined in Section 8.1). After surgery completion, a subject will be randomized to 1 of 3 treatment groups 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 4 hours after surgery completion, the subject will not be eligible for this study. Approximately 1000 subjects will be randomized 2:2:1 to 3 treatment groups: VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]), HB/APAP (5 mg/325 mg every 6 hours [q6h]; opioid reference), or placebo (Table 2-1). Randomization will be stratified by site and baseline NPRS (<8 versus ≥8). To maintain the blind, all subjects will receive the same number of tablets and capsules q6h in a double-dummy design.

Figure 2-1 VX22-548-105 Study Design



HB/APAP: hydrocodone bitartrate/acetaminophen; NPRS: numeric pain rating scale; VRS: verbal categorical rating scale

Notes: After surgery completion, a subject will be randomized to 1 of 3 treatment groups 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 4 hours after surgery completion, the subject will not be eligible for this study. Figure is not drawn to scale.

Table 2-1 Study VX22-548-105 Treatment Groups

Treatment	Active Dose	Number of Subjects
VX-548	100 mg first dose, then 50 mg q12h	400
HB/APAP	5 mg/325 mg q6h	400
Placebo	–	200

HB/APAP: hydrocodone bitartrate/acetaminophen; q6h: every 6 hours; q12h: every 12 hours

Notes: To maintain the blind, all subjects will receive the same number of tablets and capsules in a double-dummy design. VX-548 active or VX-548 placebo tablets will be administered to all subjects q12h as follows: 0 hours (first dose) and at 12, 24, and 36 hours after the first dose of study drug. HB/APAP active or HB/APAP placebo capsules will be administered to all subjects q6h as follows: 0 hours (first dose) and at 6, 12, 18, 24, 30, 36, and 42 hours after the first dose of study drug.

Subjects will report their pain intensity on the NPRS at each scheduled time point through 48 hours after the first dose of study drug. In addition, pain intensity will be recorded on the NPRS immediately before each administration of rescue medication.

Ibuprofen (400 mg orally q6h as needed) is permitted as a rescue medication for pain relief upon the subject's request starting any time after the first dose of study drug through 48 hours after the first dose of study drug. Subjects are encouraged to wait 90 minutes after the first dose of study drug to request rescue medication, and subjects should generally not receive rescue medication unless their NPRS score is ≥4.

Assessments

Efficacy: NPRS, use of rescue medications, and PGA of study drug

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

Other: DNA blood sample (optional) and PK parameters of VX-548 and [redacted]

Statistical Analyses

Assuming a standardized effect size of 0.40 for VX-548 compared to placebo and 0.25 for VX-548 compared to HB/APAP, 338 evaluable subjects per group for VX-548 and HB/APAP and 169 evaluable subjects for placebo will provide more than 90% power for the primary endpoint of VX-548 versus placebo on SPID48 and 90% power for the key secondary endpoint of VX-548 versus HB/APAP on SPID48, based on 2-sample *t*-tests with

significance level 0.05. To allow for about 15% dropout, a total of approximately 1000 subjects are planned to be enrolled.

The primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model. The model will include SPID48 as the dependent variable and treatment as a fixed effect, with site and baseline NPRS as covariates. If the model estimation does not converge, then site will be removed from the model. The least squares mean difference from placebo for VX-548 will be provided along with the 95% CI and *P* value.

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX22-548-105: Screening Visit Through Admission

Event/Assessment	Day -28 to Day -1 Screening Visit	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 occur before the day of surgery) and may 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 9.1.5.
Admission		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
Prior use of opioid medications	X	X	Any use within 12 months before the Screening Visit through admission will be recorded; Section 9.5
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 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 before any procedures that may affect heart rate (e.g., blood sampling). Section 11.5.4
PE	X	(X)	**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. Section 11.5.3
Weight, height, and BMI	X		Weight and height will be measured with shoes off. BMI = weight (kg) / [height (cm/100)]^2
Serology (HBsAg, HCV Ab, HCV RNA, HIV-1/HIV-2 Ab/Ag, and HIV-1/HIV-2 RNA)	X		RNA samples will only be analyzed as a reflex test following a positive antibody or antibody/antigen test; Section 11.5.2
Serum β-hCG	X		All biologically female subjects; Section 11.5.2
Serum FSH	X		Suspected postmenopausal female subjects only; Section 11.5.2
Serum chemistry	X		Section 11.5.2
Hematology	X		Section 11.5.2

Table 3-1 Study VX22-548-105: Screening Visit Through Admission

Event/Assessment	Day -28 to Day -1 Screening Visit	Day 1 Pre-procedure	Comments
Coagulation	X		Section 11.5.2
Urinalysis	X		Section 11.5.2
Urine β-hCG		X	All female subjects of childbearing potential. Assessed by staff onsite. Section 11.5.2
Drug test	X	X	Urine; Section 11.5.2 **Day 1:** Testing kit assessed by staff onsite.
Alcohol test		X	Urine, blood, or breath. Assessed by staff onsite. Section 11.5.2
Research subject responsibilities, placebo, and pain assessment trainings	X	X	Section 9.1.1
Blood sampling for PK		X	Sample collected after completion of pre-procedure eligibility assessments; Section 11.2.1
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 9.5
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation		All non-pharmacological 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; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; HIV-1/HIV-2 Ab/Ag: human immunodeficiency viruses 1 and 2 antibody/antigen; ICF: informed consent form; LIP: licensed independent practitioner; PE: physical examination; PK: pharmacokinetics

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

Table 3-2 Study VX22-548-105: Procedure Through Randomization

Event/Assessment	Day 1 Procedure Through Randomization / Predose[a]	Comments
Inpatient period	X	
Abdominoplasty	X	Section 9.1
Fasting period	X	No food or drink (except ≤8 fluid ounces per hour of water) from time of surgery completion through 4 hours after the first dose of study drug. Section 9.4.2
Record supplemental analgesic medication	X	Record pain medications given postoperatively through time subject is randomized. Refer to Section 9.4.1.1 for permitted pain medication.
Vital signs	X	Perform after surgery completion (at least 1 hour after surgery completion is recommended unless the subject requests study drug within 1 hour) and before the first dose of study drug. Vital signs will be collected after the subject has been at rest (seated or supine) for at least 5 minutes and before any blood sampling. Section 11.5.3
Standard 12-lead ECG	X	Perform after surgery completion (at least 1 hour after surgery completion is recommended unless the subject requests study drug within 1 hour) and before the first dose of study drug. Perform in triplicate after the subject has been at rest (supine) for at least 5 minutes; 12-lead ECGs will be done before any procedures that may affect heart rate (e.g., blood sampling). Section 11.5.4
VRS	X	Complete upon request for the first dose of study drug for pain relief after surgery completion. Pain intensity will be recorded after a ≥3-minute rest in bed; Section 9.1.1
NPRS	X	Complete immediately after VRS only if pain is rated moderate or severe on VRS. Pain intensity will be recorded after a ≥3-minute rest in bed; Section 11.4.1
Randomization	X	Subject must request study drug for pain relief and meet pain criteria (moderate or severe on VRS and ≥4 on NPRS) within 4 hours after surgery completion to be eligible for randomization (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 9.5
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation	All non-pharmacological 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.

Table 3-3 Study VX22-548-105: Treatment Period and Safety Follow-up

Event/ Assessment[a]	Hours After First Dose of Study Drug																			Optional PK Visit[b]	SFU[c]	Comments
	0[d]	0.5	1	1.5	2	3	4	5	6	8	12	14	16	18	20	24	26 to 32	36	38 to 44	48			
Inpatient period	Continuous from admission through completion of 48-hour assessments																					
Discharge																				X			After completion of all study assessments.
Clinic visit																					X		Section 9.1.3
Clinic or home health visit																					(X)		Optional PK Visit is only required for subjects who opt into the additional PK sample collection (Section 11.2.1). 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 9.1.5
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** (can be outside the visit window) and may 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 9.1.5
PGA of study drug																				X			Complete before the start of any other assessments scheduled at the same time point. Section 11.4.3
Vital signs					X		X									X				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 blood sampling. Acceptable window is ± 1 hour from the scheduled time point. Section 11.5.3
Standard 12-lead ECG							X					X					26 h		38 h				Performed in triplicate after the subject has been at rest (supine) for at least 5 minutes; 12-lead ECGs will be done before any procedures that may affect heart rate (e.g., blood sampling). Acceptable window is ± 1 hour from the scheduled time point. Section 11.5.4
Complete PE																					X		Section 11.5.3
Focused PE																				X		X	Assess wound healing at the operative site; Section 11.5.3
NPRS		X	X	X	X	X	X	X	X	X	X		X		X	X	28 h 32 h	X	40 h 44 h	X			Pain intensity will be recorded after a ≥3-minute rest in bed. Complete before any blood sampling when time points coincide. Acceptable windows for scheduled time points are: • **<48 hours after first dose:** ± 5 minutes • **48 hours after first dose:** ± 15 minutes An unscheduled NPRS will be completed immediately before each administration of rescue medication. Section 11.4.1

[a] Assessments that coincide with study drug administration will be performed before dosing, unless noted otherwise.

[b] Approximately 375 subjects enrolled in the study will have an additional PK sample collected between 5 to 8 days after the last dose of study drug, either in the clinic or through a home health visit (Section 11.2.1). Vertex will manage the allocation of the subjects providing this additional PK sample across study sites.

[c] All subjects will have a SFU Visit 14 ± 2 days after the last dose of study drug (Section 9.1.3), including those who prematurely discontinue study drug dosing (Section 9.1.4).

[d] Time 0 hours is defined as the time of administration for the first dose of study drug, which must occur within 25 minutes after randomization (ideally within 15 minutes).

Table 3-3 Study VX22-548-105: Treatment Period and Safety Follow-up

Event/ Assessment[a]	Hours After First Dose of Study Drug																			Optional PK Visit[b]	SFU[c]	Comments
	0[d]	0.5	1	1.5	2	3	4	5	6	8	12	14	16	18	20	24	26 to 32	36	38 to 44	48			
Blood sampling for PK					X		X				X	X				X	26 h	X	38 h	X	(X)		**12, 24, and 36 hours after first dose:** Collect within 15 minutes before the next study drug dose. **All other time points ≤48 hours after first dose:** Collect within ± 30 minutes of scheduled time point. **Optional PK Visit:** Collect between 5 to 8 days after the last dose of study drug from subjects who opt into providing this additional PK sample. Section 11.2.1
DNA blood sample (optional)	X																						May be collected any time during confinement after randomization; Section 11.3.1
Serum chemistry																				X			Section 11.5.2
Hematology																				X			Section 11.5.2
Coagulation																				X			Section 11.5.2
Urinalysis																				X			Section 11.5.2
Fasting period	0 to 4 h																						No food or drink (except ≤8 fluid ounces per hour of water) from time of surgery completion through 4 hours after the first dose of study drug. Section 9.4.2
Study drug administration	X								X		X			X		X	30 h	X	42 h				To maintain the blind, all subjects receive the same number of tablets and capsules q6h; Section 9.6
Rescue medication use	Ibuprofen 400 mg orally q6h prn (upon request) after first dose of study drug																						Record NPRS immediately before each administration. Record date and time of administration. Section 9.4.1.2
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 9.5
Non-pharmacological treatment and procedures review	Continuous from signing of ICF through completion of study participation																						All non-pharmacological 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; LIP: licensed independent practitioner; NPRS: numeric pain rating scale; PE: physical examination; PGA: Patient Global Assessment; PK: pharmacokinetic; prn: as needed; q6h: every 6 hours; SFU: Safety Follow-up

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

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DRG	dorsal root ganglia
ECG	electrocardiogram
EDC	electronic data capture
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
h	hour
HB/APAP	hydrocodone bitartrate/acetaminophen
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV-1/HIV-2 Ab/Ag	human immunodeficiency viruses 1 and 2 antibody/antigen
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous
IXRS	interactive response system in which X represents voice or web, such as IWRS
LIP	licensed independent practitioner
max	maximum value
min	minimum value

Abbreviation	Definition
n	size of subsample
N	number of subjects
N_2O	nitrous oxide
$Na_V1.8$	voltage-gated sodium channel 1.8
NPRS	numeric pain rating scale
NSAID	nonsteroidal anti-inflammatory drug
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PGA	Patient Global Assessment
PK	pharmacokinetic, pharmacokinetics
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
SPID	sum of the pain intensity difference
SPID12	sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 12 hours
SPID24	sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 24 hours
SPID36	sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 36 hours
SPID48	sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 48 hours
SpO_2	oxygen saturation
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment-emergent
TEAE	treatment-emergent adverse event
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 77,000 overdose deaths in the US in 2021 and in approximately 74% of fatal drug overdoses in the EU in 2020.[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 $Na_V1.8$ is preferentially expressed in peripheral pain-sensing neurons (e.g., the dorsal root ganglia [DRG])[11, 13], $Na_V1.8$ inhibitors are not expected to be associated with the side effects commonly observed with other sodium channel modulators and are not expected to have the abuse liability associated with opioid therapies. Therefore, targeting the underlying biology of pain through selective $Na_V1.8$ inhibition represents a scientific 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.

VX-548 is being developed for the treatment of pain. VX-548 is a $Na_V1.8$ inhibitor that is highly selective for $Na_V1.8$ relative to other Na_V channels. Clinical data from Phase 1 studies in healthy subjects and Phase 2 proof-of-concept studies in subjects with moderate to severe acute pain demonstrate that VX-548 is generally safe and well tolerated. Refer to the VX-548 Investigator's Brochure for additional details.[25]

5.2 Study Rationale

This study will evaluate the efficacy and safety of VX-548 in treating acute pain after an abdominoplasty.

6 STUDY OBJECTIVES

6.1 Primary Objective

- To evaluate the efficacy of VX-548 in treating acute pain after an abdominoplasty

6.2 Secondary Objective

- To evaluate the safety and tolerability of VX-548

6.3 Other Objective

- To evaluate the pharmacokinetics (PK) of VX-548 and its metabolite, [redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

- Time-weighted sum of the pain intensity difference (SPID) as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours (SPID48) compared to placebo

7.2 Secondary Endpoints

7.2.1 Key Secondary Endpoints

- SPID48 compared to hydrocodone bitartrate/acetaminophen (HB/APAP)
- Time to ≥2-point reduction in NPRS from baseline compared to placebo

7.2.2 Other Secondary Endpoints

- Time to ≥1-point reduction in NPRS from baseline compared to placebo
- Proportion of subjects reporting good or excellent on the Patient Global Assessment (PGA) at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- Time-weighted SPID as recorded on the NPRS from 0 to 24 hours (SPID24) compared to placebo
- Time to first use of rescue medication compared to placebo
- Proportion of subjects using rescue medication from 0 to 48 hours compared to placebo
- Total rescue medication usage from 0 to 48 hours compared to placebo
- Safety and tolerability based on the incidence and type of AEs, changes from baseline in clinically significant laboratory test results, vital signs, and ECGs

7.3 Other Endpoints

- Time-weighted SPID as recorded on the NPRS from 0 to 36 hours (SPID36) compared to placebo
- Time-weighted SPID as recorded on the NPRS from 0 to 12 hours (SPID12) compared to placebo

- Proportion of subjects with ≥30% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥50% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects with ≥70% reduction in NPRS at 48 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 24 hours compared to placebo
- Time to first use of rescue medication in the first 12 hours compared to placebo
- Proportion of subjects using rescue medication from 0 to 12 hours compared to placebo
- Proportion of subjects using rescue medication from 24 to 48 hours compared to placebo
- PK parameter estimates of VX-548 and its metabolite, [redacted]

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

Before Surgery:

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, inclusive.
5. Subject scheduled to undergo a standard ("full") abdominoplasty procedure that:
    - o includes a horizontally oriented incision approximately extending to each anterior superior iliac spine;
    - o includes umbilical dissection and relocation, and plication of the fascia of the rectus muscle above and/or below the umbilical stalk;
    - o can include drain placement and skin closure at the discretion of the surgeon; and
    - o does NOT include a vertically oriented supra-umbilical incision or collateral procedures (e.g., liposuction).

After Surgery:

6. Subject reported pain that is moderate or severe on the verbal categorical rating scale (VRS) and ≥4 on the NPRS within 4 hours after surgery completion on Day 1.
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 abdominoplasty.
9. Abdominoplasty procedure duration ≤3 hours.

8.2 Exclusion Criteria

Before Surgery:

1. Prior history of abdominoplasty.
2. History of intra-abdominal and/or pelvic surgery (including hysterectomy and Cesarean section) that resulted in any complications (e.g., postoperative infections, incisional infections or dehiscence, wound infections, or re-exploration/redo surgery for the same condition) or, 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 the Screening Visit or on Day 1 (pre-procedure).
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, moderate or severe hepatic impairment (defined as Child-Pugh Class B or C).[26]
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) of <30 mL/min/1.73m^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 postoperative pain.
11. Subjects who have a painful physical condition that, in the opinion of the investigator, may confound the assessments of postoperative pain.
12. A known or clinically suspected active infection with human immunodeficiency virus or hepatitis B or C viruses.
13. Any prior surgery within 1 month before the first study drug dose, unless approved by the medical monitor.

14. American Society of Anesthesiologists physical status classification[27] of ≥3.
15. Chronic use of opioids (pure agonists, agonist/antagonists, partial agonists, antagonists) or NSAIDs with dose escalation within 30 days before admission; or unwilling or unable to stop analgesics at least 5 half-lives or 2 days (whichever is longer) before admission.
16. Subjects who have started new medications that have not been at a stable dose for at least 14 days prior to the scheduled abdominoplasty procedure and before dosing with investigational product.
17. Subjects unwilling to receive any protocol-related medicine (e.g., ibuprofen, acetaminophen, fentanyl, hydrocodone).
18. Subjects with a history of allergy or significant 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.
19. Subjects with sleep apnea and/or on a home positive airway pressure device.
20. 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.
21. For female subjects: Pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last dose of study drug.

    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 dose of study drug.
22. Participation in a previous study investigating VX-548.
23. Participated in another investigational study within 30 days of the first dose of study drug.
24. 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.
25. Use of the substances, activities, or devices, as defined in Section 9.4, during the specified times.
26. 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:

27. Subject had a non-standard abdominoplasty, collateral procedures during the abdominoplasty, or any surgical complications during the abdominoplasty.
28. Subject had a medical complication during the abdominoplasty that, in the opinion of the investigator, should preclude randomization.
29. Standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at baseline (Day 1 predose).

9 STUDY IMPLEMENTATION

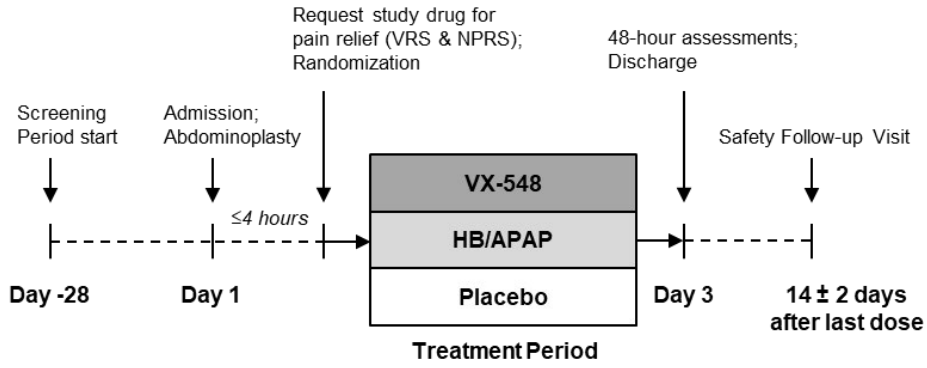
9.1 Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel study design evaluating the efficacy and safety of VX-548 in treating acute pain after an abdominoplasty (Figure 9-1).

On Day 1, subjects will undergo a standard ("full") abdominoplasty procedure (as defined in Section 8.1). After surgery completion, a subject will be randomized to 1 of 3 treatment groups 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 4 hours after surgery completion, the subject will not be eligible for this study.

Approximately 1000 subjects will be randomized 2:2:1 to 3 treatment groups: VX-548 (100 mg first dose, then 50 mg every 12 hours [q12h]), HB/APAP (5 mg/325 mg every 6 hours [q6h]; opioid reference), or placebo (Table 9-1). Randomization will be stratified by site and baseline NPRS (<8 versus ≥8). To maintain the blind, all subjects will receive the same number of tablets and capsules q6h in a double-dummy design.

Figure 9-1 VX22-548-105 Study Design



HB/APAP: hydrocodone bitartrate/acetaminophen; NPRS: numeric pain rating scale; VRS: verbal categorical rating scale

Notes: After surgery completion, a subject will be randomized to 1 of 3 treatment groups 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 4 hours after surgery completion, the subject will not be eligible for this study. Figure is not drawn to scale.

Table 9-1 Study VX22-548-105 Treatment Groups

Treatment	Active Dose	Number of Subjects
VX-548	100 mg first dose, then 50 mg q12h	400
HB/APAP	5 mg/325 mg q6h	400
Placebo	–	200

HB/APAP: hydrocodone bitartrate/acetaminophen; q6h: every 6 hours; q12h: every 12 hours
Notes: To maintain the blind, all subjects will receive the same number of tablets and capsules in a double-dummy design. VX-548 active or VX-548 placebo tablets will be administered to all subjects q12h as follows: 0 hours (first dose) and at 12, 24, and 36 hours after the first dose of study drug. HB/APAP active or HB/APAP placebo capsules will be administered to all subjects q6h as follows: 0 hours (first dose) and at 6, 12, 18, 24, 30, 36, and 42 hours after the first dose of study drug.

Subjects will report their pain intensity on the NPRS at each scheduled time point through 48 hours after the first dose of study drug. In addition, pain intensity will be recorded on the NPRS immediately before each administration of rescue medication.

Ibuprofen (400 mg orally q6h as needed [prn]) is permitted as a rescue medication for pain relief upon the subject's request starting any time after the first dose of study drug through 48 hours after the first dose of study drug. Subjects are encouraged to wait 90 minutes after the first dose of study drug to request rescue medication, and subjects should generally not receive rescue medication unless their NPRS score is ≥4.

9.1.1 Screening

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

Screening Visit through Admission

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

The Screening Visit will occur within 28 days before the scheduled abdominoplasty 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 visit window.

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

At the Screening Visit, subjects will receive trainings on appropriate expectations around their participation in a clinical study, placebo response reduction, and the importance of accurately reporting their post-procedural pain. On Day 1 (pre-procedure), these trainings will be repeated. Additional review of these educational materials may be repeated for some or all subjects, as needed.

Surgical Procedure Through Randomization

Assessments from the surgical procedure through randomization are listed in Table 3-2.

Subjects will receive 4 mg of intravenous (IV) ondansetron once at the beginning of surgery as prophylaxis of postoperative nausea and vomiting. No other agents should be used as standing

agents for postoperative nausea and vomiting prophylaxis. After surgery, subjects may receive 4 mg of IV ondansetron every 8 hours prn for the treatment of nausea and/or vomiting. Refer to Section 9.4.1.1 for details on perioperative pain management.

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

In the postoperative period before randomization, VRS will be completed upon request for the first dose of study drug for pain relief. Pain intensity will be recorded after a ≥3-minute rest in bed. 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 (Section 8.1) within 4 hours after surgery completion, the subject will not be eligible for this study.

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

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 the first dose of study drug, all screening assessments need to be repeated. The medical monitor must approve all rescreening and/or screening window extension requests before these occur.

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-3.

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 conclusion of the scheduled inpatient portion of the study, the medical monitor (or authorized designee) will be notified, and the subject will be asked to remain at the study site until such abnormalities resolve. If the subject is unable or unwilling to remain at the study site, 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.

9.1.3 Follow-up

Subjects will have a Safety Follow-up Visit 14 (± 2) days after the last dose of study drug. Safety Follow-up Visit assessments are listed in Table 3-3.

9.1.4 Early Discontinuation

Subjects who prematurely discontinue study drug dosing for any reason will remain under observation at the study site for at least 48 hours after the first dose of study drug and complete (1) all scheduled vital signs and 12-lead ECG assessments through 48 hours after the first dose of study drug and (2) all safety assessments listed for the 48-hour time point (Table 3-3), after which point they can be discharged. The reason, date, and time of discontinuation will be recorded for all subjects who prematurely discontinue study drug. All concomitant medications will continue to be recorded through completion of study participation as indicated in Section 9.5.

If a subject has any clinically significant, study-related abnormalities, the medical monitor (or authorized designee) will be notified, and the subject will be asked to remain at the study site until such abnormalities resolve. If the subject is unable or unwilling to remain at the study site, 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.

Subjects who prematurely discontinue study drug dosing will be required to complete the Safety Follow-up Visit 14 (± 2) days after the last dose of study drug. Safety Follow-up Visit assessments are listed in Table 3-3.

If a subject withdraws consent for the study, no further assessments will be performed; refer to Section 9.8 for information on the use of study data and samples already collected.

9.1.5 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.

9.1.6 Completion of Study Participation

Completion of study participation for each individual subject is defined as 1 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

Approximately 1000 subjects will be randomized 2:2:1 to 3 treatment groups: VX-548, HB/APAP (opioid reference), or placebo. The randomization ratio of 2:2:1 will be controlled for

the overall study, and the details of the randomization implementation will be specified in separate documents.

Each randomized subject will be assigned a unique subject number. Randomization will be stratified by site and baseline NPRS (<8 versus ≥8).

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the Study Team.

9.3 Rationale for Study Elements

9.3.1 Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel study design evaluating the efficacy and safety of VX-548 in treating acute pain after an abdominoplasty.

Abdominoplasty is a well-established, multi-dose, surgical, acute pain model. A randomized, double-blind study design was selected to avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment. A parallel design is considered most appropriate given the acute nature of abdominoplasty surgery.

An opioid reference group assessing a standard-of-care treatment (HB/APAP 5 mg/325 mg q6h) was included to establish the ability of the study, as executed, to successfully observe a treatment effect.

Following a standard study design, subjects will be randomized after surgery and after the subject's pain meets the pain threshold criteria. The pain threshold criteria are designed to ensure subjects have sufficient pain to determine if the drug is effective. Ibuprofen was selected as the rescue medication because it is a commonly used, short-acting, standard-of-care treatment 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 PK 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 65% by 2 hours and approximately 90% by 24 hours after the start of dosing. After 24 hours, exposures corresponding approximately to IC_{90} are sustained for the duration of dosing.

The duration of dosing (48 hours) is a standard duration for postsurgical, acute pain models and is of sufficient length to assess efficacy and safety.

9.3.3 Rationale for Study Assessments

VRS: A 4-point VRS (none, mild, moderate, or severe) is included as part of the pain threshold inclusion criterion to ensure that all subjects have moderate or severe pain at baseline, which ensures subjects have sufficient pain to determine if the study drug is effective.

NPRS: NPRS is frequently used in abdominoplasty studies and is recognized by the FDA as a valid pain intensity measure.[28] Pain rated ≥4 on an 11-point (0 to 10) NPRS at baseline ensures subjects have sufficient pain to determine if the study drug is effective.

Use of rescue medications: The use of rescue medications is an important covariate in pain studies that can impact the analysis of other efficacy assessments.

PGA of study drug: The PGA of study drug is a single-item assessment of patient perceptions of pain control with the study drug and is evaluated on a 4-point Likert scale (poor, fair, good, or excellent).[29] The PGA of study drug provides subjects the ability to state their perceptions of the treatment that may not be captured by measuring pain intensity alone.

9.4 Study Restrictions

Study restrictions are summarized in Table 9-2. Additional details on study restrictions will be provided in the Study Reference Manual.

Table 9-2 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 longer)	Completion of SFU assessments
Analgesic medications (per guidelines in Section 9.4.1)	5 half-lives or 2 days (whichever is longer) before admission	Completion of 48-hour assessments (or after early discontinuation, if applicable)
Inhalational anesthetics (e.g., N_2O, sevoflurane, desflurane, isoflurane)	Admission	Completion of 48-hour assessments (or after early discontinuation, if applicable)
Oral steroids	5 half-lives or 2 days (whichever is longer) before admission	Completion of 48-hour assessments (or after early discontinuation, if applicable)
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, Seville oranges and 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 discharge
Alcohol	24 hours before first dose of study drug	Until discharge

Table 9-2 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction	
	Start	Stop
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)	48 hours before first clinical laboratory testing	Completion of SFU assessments

N_2O: nitrous oxide; 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 9.5 for guidance on concomitant medications.

9.4.1 Analgesic Medications

All medications with analgesic properties (e.g., opioids, NSAIDs, acetaminophen, ketamine, regional or neuraxial anesthesia, local anesthetic infiltration, IV steroids) are prohibited for 5 half-lives or 2 days (whichever is longer) before admission through completion of 48-hour assessments (or after early discontinuation, if applicable), except for those permitted for perioperative pain management (Section 9.4.1.1) and ibuprofen rescue (Section 9.4.1.2).

9.4.1.1 Perioperative Pain Management

Pre- and intra-operative:

- IV midazolam (≤2 mg) and/or fentanyl citrate (≤50 µg) may be used preoperatively.
- IV fentanyl citrate and propofol (doses at the discretion of the anesthesia provider) may be used for anesthesia induction.
- Only IV general anesthesia with propofol and fentanyl citrate will be used for anesthesia maintenance.
- After completing the rectus plication, the rectus fascia should be infiltrated above and below the umbilicus with 1% lidocaine without epinephrine for a total of approximately 4 mg/kg.
- Total fentanyl citrate from induction through emergence may not exceed 250 µg.
- A record (date and time of administration) will be kept of all medication use through surgery completion.

Postoperative:

- Postoperative supplemental analgesic medication is permitted in the postanesthesia care unit per the following guidelines:
    - Fentanyl citrate (12.5 to 25 µg IV prn) can be administered if the subject is: (1) not lucid enough for randomization but deemed to be in severe pain per clinical judgement and/or (2) unable to swallow oral medications.
    - Randomization may not occur until at least 15 minutes after the last administration of supplemental analgesic medication.
- The use of abdominal binders is permitted.
- The use of ice packs is NOT permitted.

- No pain treatments (except the permitted supplemental analgesic medication) are allowed from surgery completion through the first dose of study drug.

Refer to Section 9.1.1 for details on perioperative antiemetics.

9.4.1.2 Rescue Medication

- Ibuprofen (400 mg orally q6h prn) is permitted as a rescue medication for pain relief upon the subject's request starting any time after the first dose of study drug through 48 hours after the first dose of study drug.
- Subjects are encouraged to wait 90 minutes after the first dose of study drug to request rescue medication, and subjects should generally not receive rescue medication unless their NPRS score is ≥4.
- 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.
- An unscheduled NPRS will be completed immediately before each administration of rescue medication (Section 11.4.1).

9.4.2 Additional Dietary Restrictions

Subjects will abstain from all food and drink (except ≤8 fluid ounces per hour of water) from time of surgery completion through 4 hours after the first dose of study drug. 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 opioid medications taken within 12 months before the Screening Visit through admission will be recorded with indication, route of administration, and start and stop dates of administration.
- All medications taken within 14 days before the Screening Visit through completion of study participation (Section 9.1.6) will be recorded with indication, route of administration, and start and stop dates of administration. In addition, all medications administered in-clinic will also be recorded with the time of each administration, and analgesic concomitant medications will be recorded with the dose. All subjects will be questioned about medications at each visit.

9.6 Administration

Study drug will be administered according to the following guidelines:

- To maintain the blind, all subjects will receive the same number of tablets and capsules q6h in a double-dummy design:
    - VX-548 active or VX-548 placebo tablets will be administered to all subjects q12h: 0 hours (first dose) and at 12, 24, and 36 hours after the first dose of study drug.

  - HB/APAP active or HB/APAP placebo capsules will be administered to all subjects q6h: 0 hours (first dose) and at 6, 12, 18, 24, 30, 36, and 42 hours after the first dose of study drug.

- The first dose of study drug must be administered within 25 minutes after randomization (ideally within 15 minutes). The acceptable window for each subsequent dose of study drug is ± 45 minutes from the scheduled time point.
- 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. All doses will be administered by authorized study site personnel and following national and local laws and regulations.
- When assessment time points coincide with study drug administration, study drug will be administered after completing all assessments unless noted otherwise.
- Study drug must be administered following the dietary restrictions outlined in Table 9-2 and Section 9.4.2.

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 9.1.4).

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 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.

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 for a Safety Follow-up Visit, if applicable (see Section 9.1.4), 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, VX-548 placebo, HB/APAP, and HB/APAP placebo (Sections 10.1 through 10.6). Vertex will also supply the commercially available rescue medication (Section 10.7).

10.1 Preparation and Dispensing

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

Study drug will be dispensed at the study site to blinded 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, 5-mg/325-mg HB/APAP capsules, and matching placebos. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about study drug packaging, labeling, and dispensing 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. Specifically, study drug will be stored in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure. Access to study drug will be limited to prevent theft or diversion of the study drug. 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	How Supplied
VX-548	Tablet	Oral	Supplied as 50-mg tablets
VX-548 placebo	Tablet	Oral	Supplied as tablets
HB/APAP	Capsule	Oral	Supplied as over-encapsulated 5-mg/325-mg tablets
HB/APAP placebo	Capsule	Oral	Supplied as capsules

HB/APAP: hydrocodone bitartrate/acetaminophen

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 dispensed but not administered. 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 until the study monitor has performed drug accountability. If the study monitor authorizes destruction at the study site, 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

Study drug doses will be administered under the direct supervision of the investigator or designee. A hand-and-mouth check will be done after each dose administration at the study site to ensure 100% study treatment compliance.

10.7 Rescue Medication

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

10.8 Blinding and Unblinding

This is a double-blind study.

10.8.1 Blinding

All study personnel will be blinded to subject treatment assignments except for the following individuals:

- Any site personnel for whom this information is important to ensure the safety of a subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of a subject and a fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel responsible for the sample testing (Vertex or external)
- The Vertex bioanalytical personnel responsible for reviewing raw data from the bioanalytical contract research organization (CRO), who is not a member of the Study Team (the Vertex bioanalytical Study Team member will continue to be blinded)
- Vertex personnel or vendor(s), who are not part of the study team, and are responsible for analyzing PK/population PK data to support interactions with regulatory authorities, as applicable.

Vertex medical monitor may, for matters relating to safety, unblind individual subjects at any time.

10.8.2 Unblinding

At the initiation of the study, study site personnel will be instructed on the method for breaking the blind. The unblinding method will be either manual or electronic.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

Contact information for the medical monitor (or appropriate backup) will be in a separate document.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file.

Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with Vertex, the CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex may, for matters relating to safety, unblind individual subjects at any time.

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical and surgical history, baseline VRS and NPRS scores, height, weight, and BMI.

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

11.2.1 Blood Sampling

Blood samples will be collected from subjects for the evaluation of plasma concentrations of VX-548 and [redacted].

These samples may also be used for evaluations of other study medications (e.g., rescue medication, acetaminophen, hydrocodone), other metabolites of VX-548, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by VX-548.

Approximately 375 subjects enrolled in the study will have an additional PK sample collected between 5 to 8 days after the last dose of study drug, either in the clinic or through a home health visit. Vertex will manage the allocation of the subjects providing this additional PK sample across study sites.

Plasma concentration samples collected from subjects in the placebo treatment group will not be routinely analyzed.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. The following details will be recorded accurately in the source document on days of PK blood sample collection: date and time of administration of each dose; date and time of each of the PK blood samples; and date and time of the last meal taken before the first dose (Day 1 only).

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Any time after completion of eligibility assessments and before surgery on Day 1
At 12, 24, and 36 hours after the first dose of study drug	Within 15 minutes before the next study drug dose
At all other time points ≤48 hours after the first dose of study drug	Within ± 30 minutes of scheduled time point

Note: Refer to Table 3-1 and Table 3-3 for pharmacokinetic sampling time points.

11.2.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be in the Laboratory Manual.

11.2.3 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.3 Other Assessments

11.3.1 Exploratory Assessments: Pharmacogenomics

A blood sample (optional DNA sample) will be collected for potential exploratory evaluation of associations between DNA markers with other endpoints, PK, treatment response, AEs, and biomarkers related to health and disease, including pain, for subjects who choose to participate in this assessment.

These data will be used for internal exploratory purposes. Detailed procedures for the collection of blood samples and additional procedures for processing and handling samples for pharmacogenomics analysis will be provided in a separate document.

11.4 Efficacy

11.4.1 Numeric Pain Rating Scale

NPRS will be completed after a ≥3-minute rest in bed.

In the postoperative period before randomization, 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 (Section 8.1) within 4 hours after surgery completion, the subject will not be eligible for this study.

During the Treatment Period, subjects will report their pain intensity on the NPRS at each scheduled time point through 48 hours after the first dose of study drug. In addition, pain intensity will be recorded on the NPRS immediately before each administration of rescue medication (Section 9.4.1.2).

11.4.2 Use of Rescue Medications

Rescue medication is permitted for pain relief upon subject's request. Guidelines on administration of ibuprofen as rescue medication are included in Section 9.4.1.2. A record will

be kept of all rescue medication use. An unscheduled NPRS will be completed immediately before each administration of rescue medication.

11.4.3 Patient Global Assessment of Study Drug

The PGA of study drug must be completed before the start of any other assessments scheduled at the same time point. Detailed procedures for the administration of the PGA of study drug will be provided in a separate document.

11.5 Safety

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

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 for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-3.

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 11-2.

Table 11-2 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		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
Aspartate transaminase		
Alanine transaminase		
Lipase	**Coagulation**	
Gamma-glutamyl transferase	Activated partial thromboplastin time	
Protein	Prothrombin time	
Albumin	Prothrombin time International Normalized Ratio	
Creatine kinase		
Urate		

[a] If urinalysis results are positive for protein or blood, microscopic examination of urine will be performed and results 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.

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

- Serology: Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), HCV RNA, human immunodeficiency viruses 1 and 2 antibody/antigen (HIV-1/HIV-2 Ab/Ag), and HIV-1/HIV-2 RNA. RNA samples will only be analyzed as a reflex test following a positive antibody or antibody/antigen test. Subjects with detectable viral load for HIV (≥200 copies/mL) or HCV 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 11.5.5.1). For a subject to be considered of non-childbearing potential, the serum FSH levels will be within the laboratory range for postmenopausal females.
- Pregnancy Testing: 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 11.5.5.1) will also have a urine β-hCG test before admission on Day 1. Both the serum and urine β-hCG tests (as applicable per Table 3-1) 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. Alcohol screening will be assessed before admission 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) drug and alcohol tests and urine β-hCG pregnancy tests will be assessed by staff onsite.
- Local laboratories may be used to repeat a screening assessment to determine eligibility on Day 1 (pre-procedure) if there is clear evidence of laboratory error (Section 9.1.1.1) in the central laboratory assessment.

Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessments will be performed during screening and at 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, an abbreviated PE will be performed at the Screening Visit and a complete PE will be performed on Day 1 (pre-procedure).

A complete 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 the complete PE during 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 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 for at least 5 minutes before having an ECG.
- The test should be performed in the supine position.

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 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.[25]

11.5.5.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below.

Contraception for the couple is waived for the following:

- True abstinence for the subject. The subject must confirm that they will practice true abstinence from the Screening Visit through 30 days after the last dose of study drug. True abstinence is important to differentiate from periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal, which are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen.

- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
    - Documented bilateral oophorectomy and/or hysterectomy
- Same biological sex relationships.

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception, as outlined in Table 11-3, is used as a couple from the Screening Visit through 30 days after the last dose of study drug.

Table 11-3 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 11-3.
- 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 the Screening Visit 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.

11.5.5.2 Pregnancy

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

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

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy only if on blinded treatment, or if they have been unblinded and have received active drug. 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

This section presents a summary of the principal features of the planned efficacy, safety, and PK analyses for the study. Safety and efficacy analysis details will be provided in the statistical analysis plan (SAP), and PK analysis details will be provided in the clinical pharmacology analysis plan (CPAP). Both the SAP and CPAP will be finalized before clinical data lock.

Final analyses will take place after all subjects have completed the study, all data have been entered in the clinical study database, and the clinical data have been locked.

12.1 Sample Size and Power

Assuming a standardized effect size of 0.40 for VX-548 compared to placebo and 0.25 for VX-548 compared to HB/APAP, 338 evaluable subjects per group for VX-548 and HB/APAP and 169 evaluable subjects for placebo will provide more than 90% power for the primary endpoint of VX-548 versus placebo on SPID48 and 90% power for the key secondary endpoint of VX-548 versus HB/APAP on SPID48, based on 2-sample *t*-tests with significance level 0.05. To allow for about 15% dropout, a total of approximately 1000 subjects are planned to be enrolled.

12.2 Analysis Sets

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study drug. This analysis set will be used in subject listings and disposition summary tables, unless otherwise specified.

The **Full Analysis Set (FAS)** is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

12.3 Statistical Analysis

12.3.1 General Considerations

All individual subject data for subjects who were randomized or 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 pretreatment measurements (triplicate) on Day 1.

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 9.1.6), whichever occurs first.

12.3.2 Background Characteristics

Unless otherwise specified, subject disposition, demographic and baseline characteristics, prior and concomitant medications, and important protocol deviations will be summarized.

12.3.3 Efficacy Analysis

Only the principal features of the efficacy analysis will be presented in this section. For more details, please refer to the SAP.

12.3.3.1 Analysis of Primary Endpoints

The primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model. The model will include SPID48 as the dependent variable and treatment as a fixed effect, with site and baseline NPRS as covariates. If the model estimation does not converge, then site will be removed from the model. The least squares mean difference from placebo for VX-548 will be provided along with the 95% CI and *P* value.

12.3.3.2 Analysis of Secondary Endpoints

SPID48 compared to HB/APAP and SPID24 compared to placebo will be analyzed in a similar manner as the primary endpoint.

The time to ≥2-point (or ≥1-point) reduction in NPRS from baseline is the time elapsed from the first dose of study drug to the first time the subject has at least a 2-point (or 1-point) reduction in the NPRS from baseline. These endpoints will be analyzed using the Kaplan-Meier method to estimate the median time to event and survival curve for each treatment group. The log-rank test will be used to compare the survival curves between VX-548 and placebo. The time to first use of rescue medication will be analyzed similarly.

The proportion of subjects reporting good or excellent on the PGA at 48 hours compared to placebo will be analyzed by the Cochran-Mantel-Haenszel test, stratified by baseline NPRS. The proportion of subjects using rescue medication from 0 to 48 hours compared to placebo will be analyzed similarly.

The incidence of vomiting or nausea compared to HB/APAP will be analyzed using Pearson's chi-squared test. If any expected counts are too small, Fisher's exact test will be used instead.

The total rescue medication usage from 0 to 48 hours will be analyzed by the Wilcoxon rank-sum test, stratified by baseline NPRS.

12.3.3.3 Multiplicity Adjustment

The following primary and key secondary efficacy endpoints will be tested using a hierarchical testing procedure. Each endpoint will be tested in the following order at the 2-sided significance level of 0.05:

- SPID48 compared to placebo
- SPID48 compared to HB/APAP
- Time to ≥2-point reduction in NPRS from baseline compared to placebo

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 treatment-emergent adverse events (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. For safety analyses, no statistical hypothesis testing will be conducted. Additional details will be provided in the SAP.

12.4 Interim Analysis

Not applicable

12.5 Independent Data Monitoring Committee Analysis

Not applicable

12.6 Clinical Pharmacology Analysis

12.6.1 Pharmacokinetic Analysis

The PK of VX-548 and [redacted], will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations.

Details of the analyses will be in the CPAP.

12.6.2 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VX-548 and [redacted] may be performed using the nonlinear mixed-effects modeling approach. A population approach may also be used to investigate the exposure-response relationship for the efficacy and safety variables. A more detailed description of the methodology to be followed will be presented in the modeling and simulation analysis plan. The results of the population PK and PK/pharmacodynamic (PD) analysis (if done) will be reported in a separate document.

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 9.1.6).

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 July 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 AE

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 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 case report forms (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).[30]

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 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX22-548-105	Version #: 4.0	Version Date: 12 April 2023
Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty		

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX22-548-105	Version #: 4.0	Version Date: 12 April 2023
Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of VX-548 for Acute Pain After an Abdominoplasty		

I have read Protocol VX22-548-105, Version 4.0, 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