1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2B Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy

Vertex Study Number: VX18-150-104

[redacted]

Date of Protocol: 26 September 2018 (Version 2.0).

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

2 PROTOCOL SYNOPSIS

Title A Phase 2B Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy

Brief Title A Dose-ranging Study to Evaluate Efficacy and Safety of VX-150 in Subjects With Acute Pain Following Bunionectomy

Clinical Phase and Clinical Study Type Phase 2B efficacy and safety

Objectives

Primary Objective

To evaluate the dose-response relationship of VX-150 in treating acute pain following bunionectomy

Secondary Objectives

- To evaluate the safety and tolerability of VX-150
- To evaluate the pharmacokinetics (PK) of VRT-1207355 and the metabolite VRT-1268114 (M5)

Endpoints

Primary Endpoint

Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a Numeric Pain Rating Scale (NPRS) 0 to 24 hours (SPID24) after the first dose

Secondary Endpoints

- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on an NPRS 0 to 48 hours (SPID48) after the first dose
- Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo
- Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo
- Plasma PK parameters of VRT-1207355 and the metabolite M5
- Safety and tolerability based on the incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, and vital signs at designated visits

[redacted]

Number of Subjects Approximately 242 subjects.

Study Population Male and female subjects who are between the ages of 18 and 65 years (inclusive) with pain that is ≥4 on the NPRS and is moderate or severe on the Verbal Categorical Rating Scale (VRS) after bunionectomy

Investigational Drug

Active substance: VX-150

Activity: Voltage-gated sodium channel (Na_v) 1.8 inhibitor

Strength and route of administration: 250-mg capsules administered orally

Study Duration

Excluding the Screening Period, each subject will participate in the study for 11 (± 2) days (from Day -1 to the Safety Follow-up Phone Interview).

Study Design

This is a Phase 2B randomized, double-blind, placebo-controlled, dose-ranging, 6-arm, parallel-design study. Subjects will receive a primary unilateral first metatarsal bunionectomy repair on Day -1. A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery and will be removed between 3AM and 5AM on Day 1. After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS. If a subject does not meet the NPRS and VRS criteria within 9 hours of removal of the popliteal sciatic block, the subject will not be eligible to enroll in the study.

A total of approximately 242 subjects will be randomized 2:2:2:2:1:2 to 6 treatment arms, evaluating a range of 5 VX-150 dose levels as shown in Table 2-1:

Table 2-1 VX-150 Doses by Treatment Arm

Treatment	Dose Level	Dose	Number of Subjects
VX-150	1 (highest)	First dose 1500 mg, then 750 mg q12h	44
	2	1000 mg qd	44
	3	500 mg q12h	44
	4	First dose 500 mg, then 250 mg q12h	44
	5 (lowest)	250 mg qd	22
Placebo			44

q12h: every 12 hours; qd: daily

Note: q12h dosing will be through 36 hours after the first dose of study drug throughout the protocol.

Randomization will be stratified by site and sex. To maintain the blind, all subjects will receive the same number of capsules in a double-dummy design.

Subjects will report their pain on the NPRS at scheduled time points 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. Subjects are encouraged to wait 90 minutes after the first dose of study drug to receive rescue medication, and subjects should generally not receive rescue medication unless their NPRS is ≥4. However, subjects may receive rescue medication at any time after the first dose of study drug per their request. The rescue medication will be ibuprofen (400 mg [oral] every 4 hours [q4h] as needed [prn]).

Assessments

Efficacy: 11-point NPRS, 4-point VRS, double-stopwatch assessment, [redacted]

Safety: AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and physical examinations.

PK: Plasma PK parameters of VRT-1207355 and the metabolite M5

[redacted]

[redacted]

Statistical Analyses

The primary efficacy endpoint is the time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 0 to 24 hours (SPID24) after the first dose.

The primary efficacy analysis will be using the MCP-Mod (multiple comparison procedures with modeling techniques) approach to detect the dose-response relationship from a candidate set of 4 dose-response models (Linear, E_{max}, Logistic, and Sigmoid E_{max}). Two-sided P value for each dose-response model will be provided.

Both MCP-Mod approach [redacted] in SPID24 between VX-150 and placebo will be based on an analysis of covariance (ANCOVA) model. The model will include the time-weighted sum of the pain intensity difference 0 to 24 hours (SPID24) after the first dose as the dependent variable, and treatment as a fixed effect, with adjustment for stratification factors, i.e., site and sex, and baseline pain as a covariate. [redacted]

3 SCHEDULE OF ASSESSMENTS

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

Table 3-1 Study VX18-150-104: Screening Period Prior to Surgery

Assessment	Screening Period Prior to Surgery Day -28 to Day -2
Outpatient visit	X
Informed consent form	X
Inclusion/exclusion criteria	X
Demographics	X
Medical history	X
History of drug and alcohol use	X
Weight, height, and BMI[a]	X
Vital signs[b]	X
Standard 12-lead ECG[c]	X
Physical examination	X
Serum FSH (postmenopausal female subjects only)	X
Serum β-hCG (all female subjects)[d]	X
Serology (HBsAg, HCV, and HIV 1/HIV 2)[e]	X
Serum chemistry[f]	X
Hematology[f]	X
Coagulation[f]	X
Urinalysis	X
Drug test (urine)	X
Prior use of opioid medications[g]	X
Medications review[h]	Continuous from signing of ICF through Safety Follow-up
Treatments and procedures review	Continuous from signing of ICF through Safety Follow-up
Adverse events	Continuous from signing of ICF through Safety Follow-up

β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV-1 and HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form

[a] Weight and height will be measured with shoes off.

[b] Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be assessed in the supine position after the subject has been instructed to rest for at least 5 minutes. Vital signs will be performed before blood draws or ECG assessments.

[c] ECGs will be done in the supine position and before any other procedures that may affect heart rate, such as blood draws. Subjects will rest for at least 5 minutes before having an ECG.

[d] Serum β-hCG is required of all female subjects and must be conducted within 7 days before Day 1.

[e] Serology includes testing for HBsAg and antibodies to HCV and human immunodeficiency viruses 1 and 2 (HIV 1/HIV 2).

[f] Blood samples will be collected for clinical laboratory assessments following a fast of at least 4 hours.

[g] Any opioid medications taken within 12 months of Screening Visit will be recorded.

[h] All medications taken within 14 days before screening through the end of the study will be recorded.

Table 3-2 Study VX18-150-104: Day -1, Treatment Period and Safety Follow-up

Event/Assessment	Day -1	Day 1	Day 2	Day 3	Safety Follow-up 7 (± 2) Days After Last Dose of Study Drug
Admission to CRU	X				
Bunionectomy	X				
Randomization		X			
Study drug dosing[a]		X	X	X	
Discharge from CRU[b]				X	
Phone interview[c]					X
Vital signs[d]	X	X	X	X	
Standard 12-lead ECG		X[e]			
Physical examination	X				
β-hCG (urine)	X[f]				
Serum chemistry	X[g]				
Hematology	X				
Coagulation	X				
PK blood sample[h]		X	X	X	

[a] To maintain the blind, all subjects will receive the same number of capsules.

[b] Subjects will be discharged on Day 3 after completion of the Day 3 assessments.

[c] The Safety Follow-up will consist of a phone interview for the purpose of collecting information on adverse events, medications, and treatments and procedures. A visit will only be required if a clinical finding during the Treatment Period requires follow-up.

[d] On dosing days, vital signs will be collected before the first dose of the day. Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be assessed in the supine position after the subject has been instructed to rest for at least 5 minutes. Vital signs will be performed before blood draws or ECG assessments.

[e] Standard 12-lead ECGs will be measured before the first dose, and at 4 (± 1) hours after the first dose on Day 1. ECGs will be done in the supine position and before any other procedures that may affect heart rate, such as blood draws. Subjects will rest for at least 5 minutes before having an ECG.

[f] A β-hCG test on Day -1 is only required for women of childbearing potential.

[g] If less than 1 week has passed since a subject completed the screening assessments, clinical chemistry, hematology, and coagulation do not need to be performed at Day -1.

[h] PK blood samples will be collected at 0 hour (before dosing) and at 1, 2, 4, 6, 8, and 12 hours after the first and third dose of VX-150 or VX-150 placebo in the study. A PK blood sample will also be collected 12 hours after the last dose of VX-150 or VX-150 placebo in the study. Study drug dosing details for each treatment arm are described in Section 9.1. When NPRS assessments coincide with collection of PK blood samples, the NPRS assessment will be performed first.

Table 3-2 Study VX18-150-104: Day -1, Treatment Period and Safety Follow-up

Event/Assessment	Day -1	Day 1	Day 2	Day 3	Safety Follow-up 7 (± 2) Days After Last Dose of Study Drug
[redacted]					
Drug test (urine)	X				
Alcohol test (breath)	X				
NPRS[j]		X	X	X	
VRS[k]		X			
Double-stopwatch assessment		X			
[redacted]					
Medications review	Continuous from signing of ICF through Safety Follow-up				
Treatments and procedures review	Continuous from signing of ICF through Safety Follow-up				
Adverse events	Continuous from signing of ICF through Safety Follow-up				

β-hCG: beta-human chorionic gonadotropin; CRU: clinical research unit; NPRS: Numeric Pain Rating Scale; PK: pharmacokinetic; VRS: Verbal Categorical Rating Scale

[redacted]

Starting on Day 1, subjects will report their pain on the NPRS at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours (± 5 minutes) after the first dose of study drug. In addition, pain intensity on the NPRS will be recorded when the subject requests the first dose of study drug for pain relief and immediately before each administration of rescue medication.

[k] On Day 1, subjects will report their pain on the VRS when they request the first dose of study drug for pain relief.

4 TABLE OF CONTENTS

List of Tables

List of Figures

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
CD	compact disc
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
E_{max}	maximum effect attributable to the drug
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV-1 and HIV-2 Abs	antibodies against human immunodeficiency viruses 1 and 2
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
[redacted]	[redacted]
IRB	institutional review board
IXRS	interactive web or voice response system
max	maximum value
MCP-Mod	multiple comparison procedures with modeling techniques
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
n	number of subjects
Na_v	voltage-gated sodium channels
NPRS	Numeric Pain Rating Scale
PC	publication committee
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetic, pharmacokinetics
POC	proof-of-concept

Abbreviation	Definition
prn	as needed
PT	Preferred Term
q12h	every 12 hours
q2h	every 2 hours
q4h	every 4 hours
qd	daily
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SE	standard error
SET	Study Execution Team
SPID24	sum of the pain intensity difference 0 to 24 hours
SPID48	sum of the pain intensity difference 0 to 48 hours
SUSAR	suspected, unexpected, serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
VRS	Verbal Categorical Rating Scale
WHO-DD	World Health Organization-Drug Dictionary
WOMAC	Western Ontario and McMaster Universities

5 INTRODUCTION

5.1 Background

Pain is one of the most common symptoms for which patients seek medical attention. It is a protective mechanism designed to prevent tissue injury. When pain persists beyond its usefulness, it becomes pathological and can prove debilitating. Current pain therapies suffer from poor efficacy and a high risk of adverse events (AEs). For example, lidocaine (a nonselective sodium channel blocker) may effectively reduce pain, but its utility is limited because of prominent side effects when given at dose levels required for pain relief.[1] According to 2016 estimates, more than 42,000 deaths were attributable to opioids in the US, and in Europe, more than 80% of fatal drug overdoses involve opioids.[2, 3] The limited treatment options for pain, combined with a growing awareness of the risks of the current standards of care, underscore the need for new pain management therapies.

Voltage-gated sodium channels (Na_v) play a critical role in pain signaling based on both nonclinical and clinical evidence. Evaluation of the role these channels play in normal physiology and the pathological states arising from mutations in sodium channel genes and animal models, as well as the pharmacology of known sodium channel modulating agents, all point to the critical role of Na_vs in pain sensation.[4-6] The $Na_v1.8$ channel is primarily restricted to peripheral neurons that sense pain (e.g., dorsal root ganglia) and is known to mediate pain sensation and chronic pain. For example, $Na_v1.8$ gain-of-function mutations are thought to directly cause chronic pain in patients with painful small fiber neuropathy.[7-9] This channel has been identified as a target for analgesia[10] and selective $Na_v1.8$ inhibitors, which have the potential to treat pain indications where the primary mechanism for pain is nociceptor hyperexcitability.

VX-150, an orally bioavailable prodrug that rapidly converts in vivo to the active moiety VRT-1207355, is being developed for the treatment of pain. VRT-1207355 is a $Na_v1.8$ blocker that is highly selective for $Na_v1.8$ relative to the other sodium channel subtypes. In vivo safety studies conducted with either VX-150 or VRT-1207355 have not identified target organs of toxicity.

5.2 Study Rationale

To date, 5 Phase 1 clinical studies and 2 Phase 2 proof-of-concept (POC) studies have been completed with VX-150. This Phase 2 dose-ranging study was designed to help inform dose selection for Phase 3 studies in acute pain.

Data from clinical and nonclinical studies of VX-150 and the current unmet medical need for new treatments for acute pain support clinical development of VX-150. Further details of the VX-150 development program are available in the VX-150 Investigator's Brochure.[11]

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the dose-response relationship of VX-150 in treating acute pain following bunionectomy

6.2 Secondary Objectives

- To evaluate the safety and tolerability of VX-150
- To evaluate the pharmacokinetics (PK) of VRT-1207355 and the metabolite VRT-1268114 (M5)

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a Numeric Pain Rating Scale (NPRS) 0 to 24 hours (SPID24) after the first dose

7.2 Secondary Endpoints

- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on an NPRS 0 to 48 hours (SPID48) after the first dose
- Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo
- Time to onset of "confirmed perceptible pain relief" and "meaningful pain relief" after the first dose of VX-150 versus placebo
- Plasma PK parameters of VRT-1207355 and the metabolite M5
- Safety and tolerability based on the incidence and type of adverse events (AEs), changes from baseline in clinically significant laboratory test results, and vital signs at designated visits

[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. Body mass index (BMI) of 18.0 to 38.0 kg/m^2, inclusive

4. Subjects (male and female) will be between the ages of 18 and 65 years, inclusive
5. Be scheduled to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures, under regional anesthesia (Mayo and popliteal sciatic block) not to include base wedge procedure

After surgery:

6. Subject reported pain of ≥4 on the NPRS and moderate or severe pain on the Verbal Categorical Rating Scale (VRS) within 9 hours after removal of the popliteal sciatic block on Day 1.
7. Subject is lucid and able to follow commands.
8. All analgesic guidelines (Section 9.4.1) were followed during and after the bunionectomy.

8.2 Exclusion Criteria

Before surgery:

1. History in the past 10 years of malignancy, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
2. History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s), or 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
3. History of abnormal laboratory results ≥2.5 × upper limit of normal (ULN) indicative of any significant medical disease that in the opinion of the investigator would preclude the subject's participation in the study
4. History of peripheral neuropathy
5. A known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses
6. Prior medical history of bunionectomy or other foot surgery on the index foot; or bunionectomy on the opposite foot as part of this study
7. Any prior surgery within 1 month before the first dose of study drug unless approved by the medical monitor
8. Other serious, acute, or chronic medical or psychiatric illness that, in the judgment of the investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study (e.g., peripheral arterial insufficiency, peripheral edema)
9. History of peptic ulcer disease, or intolerance or unwillingness to receive ibuprofen
10. For female subjects: Pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
11. For male subjects: Male subjects with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
12. Participated in another investigational study within 30 days of the first dose of study drug

13. History of drug or alcohol dependence in the past 3 years, or a positive test for drugs of abuse
    - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects; however, marijuana will not be allowed.
14. 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
15. Use of restricted medication or food within the specified duration before the first dose of study drug, as defined in Section 9.4
16. Participation in a previous study investigating VX-150

After surgery:

17. Subject had a type 3 deformity requiring a base wedge osteotomy or concomitant surgery such as hammertoe repair, or had medical complications during the bunionectomy that, in the opinion of the investigator, should preclude randomization

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2B randomized, double-blind, placebo-controlled, dose ranging, 6-arm, parallel-design study. Subjects will receive a primary unilateral first metatarsal bunionectomy repair on Day -1 (Figure 9-1). A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery and will be removed between 3AM and 5AM on Day 1. After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS. If a subject does not meet the NPRS and VRS criteria within 9 hours of removal of the popliteal sciatic block, the subject will not be eligible to enroll in the study.

A total of approximately 242 subjects will be randomized 2:2:2:2:1:2 to 6 treatment arms, evaluating a range of 5 VX-150 dose levels as shown in Table 9-1.

Table 9-1 VX-150 Doses by Treatment Arm

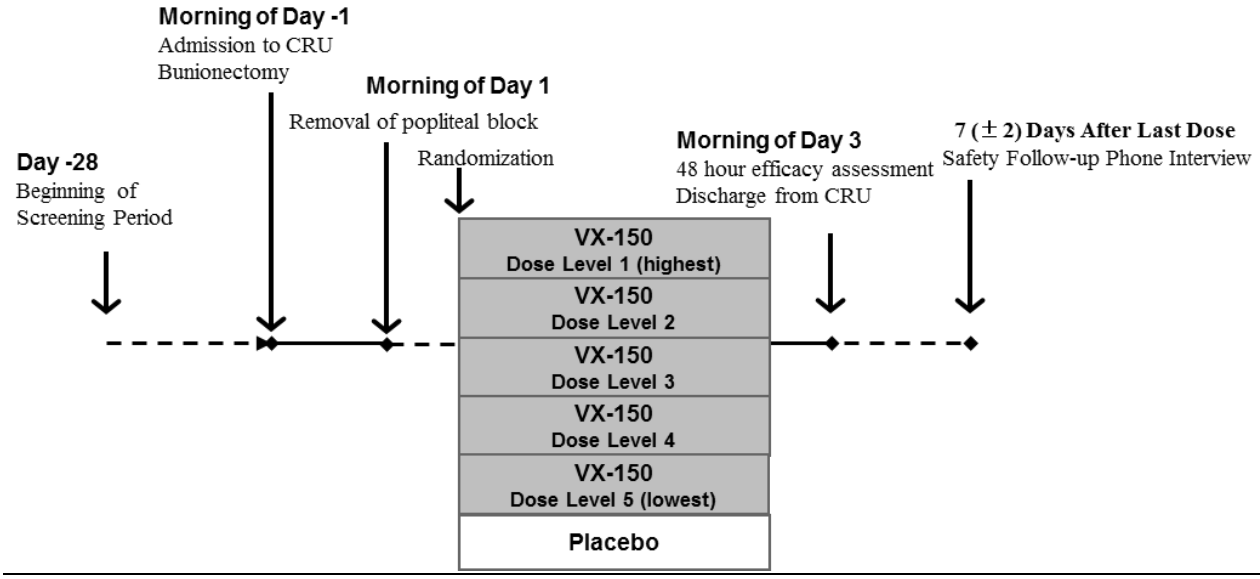
Treatment	Dose Level	Dose	Number of Subjects
VX-150	1 (highest)	First dose 1500 mg, then 750 mg q12h	44
	2	1000 mg qd	44
	3	500 mg q12h	44
	4	First dose 500 mg, then 250 mg q12h	44
	5 (lowest)	250 mg qd	22
Placebo			44

q12h: every 12 hours; qd: daily
Note: q12h dosing will be through 36 hours after the first dose of study drug throughout the protocol.

Randomization will be stratified by site and sex. To maintain the blind, all subjects will receive the same number of capsules in a double-dummy design.

Subjects will report their pain on the NPRS at scheduled time points (Table 3-2) 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. Subjects are encouraged to wait 90 minutes after the first dose of study drug to receive rescue medication, and subjects should generally not receive rescue medication unless their NPRS is ≥4. However, subjects may receive rescue medication at any time after the first dose of study drug per their request. The rescue medication will be ibuprofen (400 mg [oral] every 4 hours [q4h] as needed [prn]).

Figure 9-1 VX18-150-104 Study Design



CRU: clinical research unit; NPRS: Numeric Pain Rating Scale; VRS: Verbal Categorical Rating Scale

Notes: After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS. VX-150 dose levels (Dose Levels 1 [highest], 2, 3, 4, and 5 [lowest]) are shown in Table 9-1. To maintain the blind, all subjects will receive the same number of capsules.

9.1.1 Screening

Screening Visit assessments required before the day of surgery are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug; this includes the screening period before surgery and the day of surgery (Day -1). The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject.

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

9.1.1.1 Repetition of Screening Assessments

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).

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 study drug dose 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

Any subject who is rescreened for any of the exceptions listed above may have the screening window extended by 2 weeks before needing to undergo any rescreening assessments. If more than 35 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated.

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2. The study will be conducted as described in Section 9.1. Dosing details are given 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 in the clinical research unit (CRU) until such abnormalities resolve. If the subject is unable or unwilling to remain in the CRU, 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 Phone Interview 7 (± 2) days after the last study drug dose for the purpose of collecting information on AEs, medications, and treatments and procedures. A visit will only be required if a clinical finding during the Treatment Period requires follow-up.

9.1.4 Early Discontinuation

Subjects who prematurely discontinue study drug dosing will remain under observation for at least 12 hours after the last dose of study drug, after which point they can be discharged from the CRU. 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 in the CRU until such abnormalities resolve. If the subject is unable or unwilling to remain in the CRU, 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. See Section 9.8 for additional details on removal of subjects.

Subjects who prematurely discontinue study drug dosing will complete the Safety Follow-up Phone Interview 7 (± 2) days after the last study drug dose for the purpose of collecting information on AEs, medications, and treatments and procedures. A visit will only be required if a clinical finding during the Treatment Period requires follow-up.

9.2 Method of Assigning Subjects to Treatment Groups

An interactive 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 execution team.

9.3 Rationale for Study Elements

9.3.1 Study Design

This is a Phase 2B randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the effect of VX-150 on acute surgical pain. Bunionectomy 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 range of VX-150 doses will be evaluated to help inform dose selection for Phase 3 studies. A parallel design is considered most appropriate given the acute nature of bunionectomy surgery.

Following a standard study design, subjects will be randomized after removal of the popliteal sciatic block 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

Five dose levels of VX-150 (Dose Levels 1 [highest], 2, 3, 4, and 5 [lowest]) will be evaluated as shown in Table 9-1. The highest dose level (Dose Level 1 [first dose 1500 mg, then 750 mg every 12 hours (q12h)]) will not exceed a maximum dose of 2250 mg per day. The maximum dose has been selected on the basis of favorable safety and VRT-1207355 PK results after oral dosing with VX-150 in [redacted] VX16-150-103 (Study 103). Multiple oral doses up to 1750 mg qd VX-150 for 14 days have been evaluated and found to be safe and well tolerated. Additionally, the treatment duration is the same as in Study 103.

The highest dose level (Dose Level 1) to be tested (2250 mg per day; first dose 1500 mg followed by doses of 750 mg q12h) was evaluated in Study 103 in subjects with acute pain following bunionectomy. After administration of the first dose of VX-150 on Day 1 and Day 2, the mean VRT-1207355 maximum observed concentration (C_{max}) of 4.95 µg/mL (Day 1) and 4.92 µg/mL (Day 2) exceeded the concentration resulting in 50% of the maximum inhibition (IC_{50}) for inhibition of $Na_v1.8$. The maximum concentrations for VRT-1207355 were reached approximately 5.58 hours after the first dose on Day 1 and 4.03 hours after the first dose on Day 2. A statistically significant treatment effect was observed at 24 hours following the first and second doses, favoring VX-150 compared to placebo. VX-150 was generally well tolerated in these subjects without any significant safety concerns.

9.3.3 Rationale for Study Assessments

11-point (0 to 10) Numeric Pain Rating Scale: NPRSs are frequently used in bunionectomy studies and are recognized by the FDA as a valid pain intensity measure.[12]

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

Double-stopwatch assessment: The double-stopwatch assessment is a standardized assessment for determining the onset of pain relief.[13, 14] The stopwatches are started at the time of the first dose. Subjects are told to stop the first watch when they first feel "perceptible pain relief," and to stop the second watch when they first feel "meaningful pain relief."

[redacted]

9.4 Study Restrictions

Study restrictions are summarized in Table 9-2. [redacted] Study restrictions related to analgesic medications are described in Section 9.4.1.

A non-exhaustive list of study restrictions will be provided in the Study Reference Manual.

Table 9-2 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (Minimum)	To
Other investigational drugs or devices	30 days before first study drug dose, 5 half-lives before first study drug dose, or time determined by local requirements; whichever is longer	Completion of Safety Follow-up
[redacted]		
Analgesic medications	Starting 2 days before admission to the CRU, analgesic medication use will follow the guidelines outlined in Section 9.4.1	Until discharge from CRU
Dietary supplements [redacted] vitamin E supplements	24 hours before first study drug dose	Until discharge from CRU
Grapefruit or grapefruit juice, pomelos, star fruit; Seville oranges	7 days before first study drug dose	Until last PK sample is taken
Apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	24 hours before first study drug dose	Until last PK sample is taken

Table 9-2 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (Minimum)	To
[redacted]		
Alcohol	24 hours before admission to the CRU	Until discharge from CRU
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)	48 hours before first clinical laboratory testing	Completion of Safety Follow-up

CRU: clinical research unit; PK: pharmacokinetics

[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

- Apart from standard of care during admission, opioids are not allowed from 2 days before admission on Day -1 through discharge on Day 3.
- Perioperative pain management will follow the standard of care, becoming progressively more conservative before removal of the popliteal sciatic block:
    - Preoperatively, IV midazolam and/or fentanyl will be administered, followed by IV propofol, a popliteal sciatic block (0.5% ropivacaine), and a Mayo block (2% lidocaine without epinephrine).
    - A continuous popliteal sciatic block infusion (0.2% ropivacaine) will be started after surgery and will be removed between 3AM and 5AM on Day 1.
    - After surgery and before removal of the popliteal sciatic block:
        - The use of ice packs is required until removal of the popliteal sciatic block.
        - IV ketorolac can be administered q6h as needed until 6 hours before removal of the popliteal sciatic block for subjects with NPRS score of 4 through 6 after surgery.
        - Morphine sulfate 2- to 4-mg IV dose can be administered every 2 hours (q2h) as needed until 1.5 hours before removal of the popliteal sciatic block for subjects with NPRS score of 7 or above after surgery.
        - Bolus ropivacaine can be used prn until removal of the popliteal sciatic block.
- No pain treatments are allowed between removal of the popliteal sciatic block and the first dose of study drug
- Rescue medication:
    - Subjects are encouraged to wait 90 minutes after the first dose of study drug to receive rescue medication, and subjects should generally not receive rescue

medication unless their NPRS is ≥4. However, subjects may receive rescue medication at any time after the first dose of study drug per their request.

- The rescue medication will be ibuprofen (400 mg [oral] q4h prn).
- A record will be kept of all rescue medication use, and an unscheduled NPRS assessment will be completed immediately before each administration of rescue medication.

9.4.2 Additional Dietary Restrictions

- Subjects will abstain from all food and drink (except water) at least 4 hours before the screening serum chemistry assessment.
- On Day 1, subjects will be on a clear liquid diet until 11 hours after removal of the popliteal sciatic block (i.e., 2 hours after the end of the randomization window). Doses administered after the end of the clear liquid diet period can be administered without regard to meal timings.

[redacted]

9.5 Prior and Concomitant Medications

- Subjects will abstain from all concomitant medications as described in Exclusion Criterion 14 and Table 9-2.
- All opioid medications taken within 12 months of Screening Visit will be recorded with indication, route of administration, and start and stop dates of administration.
- All medications taken from 14 days before the Screening Visit through the end of the study will be recorded with indication, route of administration, and start and stop dates of administration.
- A female subject of childbearing potential using hormonal contraceptives does not need to stop taking hormonal contraceptives; however, they are not considered an approved form of contraception (Section 11.5.5.1).

9.6 Administration

Study drug will be administered as follows:

- Doses for the 5 VX-150 treatment arms are shown in Table 9-1. The total maximum daily dose will not exceed 2250 mg (1500 mg loading dose followed by doses of 750 mg q12h).
- VX-150 arms will receive a combination of VX-150 and VX-150 placebo capsules.
- Placebo arm will receive only VX-150 placebo.
- To maintain the blind, all subjects will receive the same number of capsules. All subjects will receive 6 capsules for the first dose and 4 capsules for the remainder of the dosing period. Additional details on dispensing will be included in the Pharmacy Manual.

- Study drug will be administered as described above, with the final dose of VX-150 or VX-150 placebo given 36 hours after the first dose.
- 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 the drug before swallowing.
- Study drug must be administered following the food restrictions outlined in Section 9.4.2.

9.7 Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.4).

9.8 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 or participate in a scheduled phone call, 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 participate in a Safety Follow-up Phone Interview, 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.

9.9 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG INFORMATION AND MANAGEMENT

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.

Capsules will be dispensed at the CRU 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 250-mg VX-150 capsules and matching placebos. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for VX-150 will be included 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 at United States Pharmacopeia controlled room temperature 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. Table 10-1 lists the storage conditions for the capsules.

Table 10-1 Study Drug

Drug Name	Dosing Form/Route	Dosage	How Supplied
VX-150	Capsule/Oral	≤2250 mg per day	Supplied as 250-mg capsules
VX-150 placebo	Capsule/Oral	None	Supplied as capsule

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received and (2) study drug dispensed to the subjects. 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. 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.

10.6 Compliance

For study drug doses administered during the inpatient periods, 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 in the CRU to ensure 100% study treatment compliance.

10.7 Blinding and Unblinding

This is a double-blind study.

10.7.1 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 the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the 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 contract research organization (CRO) laboratory/vendor personnel managed by Vertex Bioanalysis
- The Vertex bioanalytical personnel responsible for reviewing raw data from the bioanalytical CRO, who is not a member of the Study Execution Team (SET; the Vertex bioanalytical SET member will continue to be blinded)

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

A Vertex Modeling & Simulations and Biomarker scientist may be unblinded to individual subject PK data for conducting PK/pharmacodynamic (PD) analyses. In addition, a Vertex clinical pharmacologist will be partially unblinded to help in management of the PK workspace and ensure that only the blinded PK dataset is being provided for preliminary analysis. These individuals will not be a member of the study team and will not interact with the CRU or study personnel. No unblinded data or results of unblinded analyses will be shared with the CRU or with blinded Vertex personnel. Masked IDs will be used for PK and PK/PD analyses. All instances of unblinding by Vertex personnel will be documented.

10.7.2 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 a 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 and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for 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 without having successfully reached and discussed the situation with the medical

monitor. In case of emergency, the investigator will have the final decision and unilateral right for unblinding.

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

In addition, the Vertex Medical Information Call Center [redacted] will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

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 the sponsor (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 concerns, unblind individual subjects at any time.

11 ASSESSMENTS

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

11.1 Subject and Disease Characteristics

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

For the evaluation of plasma concentrations of VRT-1207355 and VRT-1268114, blood samples will be collected as shown in Table 3-2.

These samples may also be used for evaluations of rescue medication, VX-150, metabolites of VRT-1207355, analyses that provide information on the metabolic pathways used by or affected by VX-150 and VRT-1207355, and further evaluation of the bioanalytical method.

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. Samples collected outside of these acceptable windows will be considered protocol deviations. The following 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 the taking of each PK blood sample; and date and time of the last meal taken before each dose.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose on Day 1	Any time before first study drug dose on Day 1
Predose on Day 2	-15 minutes
From 1 up to 12 hours after study drug dosing	±30 minutes

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 provided in the PK Sample Handling Guidelines. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

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.

[redacted]

11.4 Efficacy

Pain scales: After removal of the popliteal sciatic block, a subject can be randomized once the subject requests the first dose of study drug for pain relief, and the subject's pain is ≥4 on the NPRS and is moderate or severe on the VRS. If a subject does not meet the NPRS and VRS criteria within 9 hours of removal of the popliteal sciatic block, the subject will not be eligible for the study.

Subjects will report their pain on the NPRS at scheduled time points (Table 3-2) through 48 hours after the first dose of study drug. In addition, pain intensity will be recorded on the NPRS scale immediately before each administration of rescue medication.

When NPRS assessments coincide with collection of PK blood samples, the NPRS assessment will be performed first.

Double-stopwatch assessment: At the time of first dose, 2 stopwatches will be started: 1 labeled "perceptible pain relief" and the other labeled "meaningful pain relief." Subjects will stop the "perceptible pain relief" stopwatch when/if they feel any pain relief at all and stop the "meaningful pain relief" stopwatch when/if they feel relief that is "meaningful" to them. If the subject does not stop both stopwatches by 6 hours after the first dose, or receives rescue medication, the stopwatches will be stopped.

[redacted]

11.5 Safety

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

11.5.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

At the Screening Visit, blood specimens will be collected for safety laboratory tests following at least a 4-hour fast. Fasting is not required at other time points.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-2. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-2.

Table 11-2 Safety Laboratory Test Panels

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

Note: Screening Visit blood draws will be done after a minimum 4-hour fast. All subsequent blood draws do not require fasting.

[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 from screening will 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 Tests at Screening: The following additional tests will be performed during screening to assess eligibility:

Serum follicle-stimulating hormone: Serum follicle-stimulating hormone will be tested at screening for female subjects who are suspected to be postmenopausal. For a subject to be considered of non-childbearing potential, the serum follicle-stimulating hormone levels will be within the laboratories' range for postmenopausal females.

Pregnancy testing: All female subjects must have a Screening serum pregnancy test within 7 days before Day 1. Female subjects of childbearing potential (as defined in Section 11.5.5.1), must also have a Day -1 urine pregnancy test. Both the pregnancy test at Screening and Day -1 must be negative to receive study drug.

Drug and alcohol screening (Screening Visit and Day -1): Opiates, methadone, cannabinoids, cocaine, amphetamines/methamphetamines, barbiturates, and benzodiazepines will be assessed by a urine test. Subjects may also undergo random urine drug screening and alcohol testing if deemed appropriate by the investigator. The drug test at Screening and Day -1 must be negative

for a subject to receive study drug. A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary (e.g., benzodiazepines) will not disqualify subjects; however, marijuana will not be allowed.

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

With the exception of the Day -1 drug and alcohol tests and the pregnancy tests, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (Table 3-1 and Table 3-2). At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

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

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. Vital signs will be assessed in the supine position after the subject has been instructed to rest for at least 5 minutes. Vital signs will be performed before blood draws or ECG assessments.

11.5.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout (Table 3-1 and Table 3-2). 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 any other procedures that may affect heart rate, such as blood draws.
- 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. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Phone Interview 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 QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF

values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), 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. A subject with a QTcF value above the threshold value will discontinue dosing.

11.5.5 Contraception and Pregnancy

11.5.5.1 Contraception

At this stage in the development of VX-150, study participation requires a commitment from the subject that he/she and subject's respective partner use **1 acceptable method of birth control** listed in Table 11-3 from the Screening Visit through 90 days after the last dose of study drug. Male subjects must also not donate sperm from the time of first study drug dose through 90 days after the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements.

The contraception requirement for the couple is waived for the following:

- True abstinence for the subject, when this is consistent with the preferred and usual lifestyle of the subject. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal 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 2 years and a serum follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females
    - Documented bilateral oophorectomy and/or hysterectomy
- Same sex relationships.

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

Table 11-3 Acceptable Methods of Contraception

Contraceptive Method	Male Subjects and Their Female Partners	Female Subjects and Their Male Partners
Documented vasectomy (with a negative sperm postvasectomy semen analysis) at least 6 months before the study drug dose	Yes	Yes
Condom with spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products).	Yes[a]	Yes[a]
Documented bilateral tubal ligation performed at least 6 months before the first dose of study drug	Yes	Yes
Continuous use of an intrauterine device (nonhormone-releasing) for at least 90 days	Yes	Yes
Hormonal contraceptives, if successfully used for at least 60 days	Yes	No[b]

[a] Female condom cannot be used with male condom due to risk of tearing.
[b] A female subject of childbearing potential using hormonal contraceptives does not need to stop taking hormonal contraceptives; however, they are not considered an approved form of contraception.

11.5.5.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and up to 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, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

If confirmed to be on active drug, the subject or partner will be followed for safety (adverse events) until the end of the pregnancy and similarly, the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

12.1 Sample Size and Power

The sample size calculation is based on the primary analysis of the primary efficacy endpoint. The primary efficacy endpoint is the time-weighted sum of the pain intensity difference 0 to 24 hours after the first dose (SPID24). The primary analysis of this endpoint is to detect if there is a significant dose-response relationship across VX-150 dose groups and placebo using the MCP-Mod (multiple comparison procedures with modeling techniques). Under MCP-Mod, a

pre-specified candidate set of 4 dose-response models (Linear, E_{max}, Logistic, and Sigmoid E_{max}) is proposed.

Assuming the maximum effect size compared to placebo is 0.7, 40 evaluable subjects in the placebo, VX-150 Dose Level 1 (highest), 2, 3, and 4 groups, and 20 evaluable subjects in VX-150 Dose Level 5 (lowest) group would provide approximately at least 88% power to detect a dose-response relationship from the candidate set with a 5% level of significance. In addition, 40 evaluable subjects per treatment group can provide at least 85% power to detect an effect size of 0.7 compared to placebo. In order to allow for withdrawal of up to 10% of randomized subjects, the study will enroll and randomize approximately 242 subjects in total.

12.2 Analysis Sets

Assignment of subjects to analysis sets will be performed before the clinical data lock for the study.

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 table, 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 and not to the treatment they actually received.

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 and not according to their randomized treatment group.

The PK Set is defined as all subjects who have received at least 1 dose of study drug and for whom the primary PK data are considered to be sufficient and interpretable.

12.3 Statistical Analysis

The primary objective of this study is to evaluate the dose-response relationship of VX-150 in treating acute pain following bunionectomy.

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. Statistical Analysis System Version 9.4 or higher and R Version 3.5.0 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

Statistical analysis and presentation details will be provided in the Statistical Analysis Plan (SAP) for the study.

12.3.1 General Considerations

All individual subject data for all individual subjects randomized or exposed to study drug will be presented in data listings. Continuous data 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 data will be summarized using counts and percentages.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study drug.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The disposition summary will be based on the All Subjects Set.

The number and percentage of subjects in each of the following disposition categories will be summarized based on the FAS: completed treatment, prematurely discontinued the treatment and the reason for discontinuation, completed study, and prematurely discontinued study, with a breakdown of the reasons for discontinuation.

12.3.2.2 Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment group based on the FAS: sex, age, race, ethnicity, weight, height, BMI, and pain intensity.

No statistical tests will be carried out to evaluate any baseline imbalance between treatment groups.

12.3.2.3 Prior and Concomitant Medications

Medications taken 14 days before the Screening Visit and up to the Safety Follow-up Phone Interview will be summarized by Preferred Name using the World Health Organization-Drug Dictionary (WHO-DD) for the FAS as frequency tables in 2 parts:

Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended.

Concomitant medication: Medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug.

12.3.2.4 Study Drug Exposure and Compliance

Study drug will be administered to the subjects by site personnel at time points specified in Table 3-2 and as described in Section 9.6. All data collected during dispensation of study drug (i.e., time of intake and number of capsules taken) will be presented in data listings only.

12.3.3 Efficacy Analysis

Evaluation of the dose-response of the efficacy of VX-150 is the primary objective of this study. All efficacy endpoints will be analyzed based on the FAS.

12.3.3.1 Analysis of Primary Variable

The primary efficacy endpoint is the time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a Numeric Pain Rating Scale (NPRS) 0 to 24 hours (SPID24) after the first dose. The primary efficacy analysis will be using the MCP-Mod

approach to detect the dose-response relationship from a candidate set of 4 dose-response models (Linear, E_{max}, Logistic, and Sigmoid E_{max}). Two-sided *P* value for each dose-response model will be provided.

Both MCP-Mod approach [redacted] in SPID24 between VX-150 and placebo will be based on an analysis of covariance (ANCOVA) model. The model will include the time-weighted sum of the pain intensity difference 0 to 24 hours (SPID24) after the first dose as the dependent variable, and treatment as a fixed effect, with adjustment for stratification factors, i.e., site and sex, and baseline pain as a covariate. [redacted]

Pain intensity scores that were collected within 4 hours after a dose of rescue medication will be taken as missing and will be imputed using the pre-rescue numerical pain rating scale. Missing values due to early withdrawal will be imputed using the last non-missing observation carried forward before the calculation of SPID24 values. [redacted]

12.3.3.2 Analysis of Secondary Efficacy Variables

- Time-weighted sum of the pain intensity difference between VX-150 versus placebo as recorded on a NPRS 0 to 48 hours (SPID48) after the first dose: analysis of this variable will be similar to the primary analysis.
- Proportions of subjects with at least 30%, 50%, or 70% reduction in NPRS at 24 hours after the first dose of VX-150 versus placebo: This variable will be analyzed using the Cochran-Mantel-Haenszel test, stratified by site and sex.
- Time to onset of "confirmed perceptible pain relief" after the first dose of VX-150 versus placebo: This variable will be analyzed using Cox regression model. The model will include a covariate for treatment and adjustment for site and sex. Additionally, the Kaplan-Meier method will be used to produce graphical presentation of the survival curves by treatment group and to estimate survival rates by treatment group.
- Time to onset of "meaningful pain relief" after the first dose of VX-150 versus placebo: The analysis of this variable will be similar to the analyses of time to onset of "perceptible pain relief."

[redacted]

12.3.4 Safety Analysis

The overall safety profile of VX-150 will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- ECG outcomes
- Vital signs

Safety endpoints will be analyzed based on the Safety Set.

All safety data will be presented in individual subject data listings.

12.3.4.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA System Organ Class and Preferred Term (PT), as well as by treatment group. AEs will be classified as pretreatment or treatment-emergent as follows:

Pretreatment AEs are defined as AEs that occurred or worsened after signing the ICF up to the start of study dosing.

Treatment-emergent AEs are defined as AEs that occurred or worsened on or after the start of drug dosing through the Safety Follow-up. Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by severity of the AE and the relationship to the study drug. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

SAEs and AEs leading to death, dose interruption, and permanent discontinuation will be listed separately. All AEs through Safety Follow-up will be listed in an individual subject data listing, including pretreatment AEs.

12.3.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using the International System of Units. Hematology and clinical chemistry results at baseline will be summarized by treatment group. Other assessments will be collected as needed (i.e., at unscheduled visits).

A listing containing individual subject hematology and clinical chemistry measurements outside the threshold value criteria at any visit will be provided. For each subject in the listing, measurements at all visits will be included. The threshold value criteria for clinical laboratory data will be provided in the SAP. Results of coagulation, urinalysis, and the urine/serum pregnancy test will be presented in individual subject data listings only. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.4.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the following ECG measurements: PR, QT, QRS, and QTcF

intervals and heart rate. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTcF intervals, categorized as ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

A listing containing individual ECG measurements that are outside the threshold value criteria at any time point will be provided. For each subject in the listing, measurements at all time points will be included. Clinically significant abnormal findings will be reported as AEs.

12.3.4.4 Vital Signs

The following vital signs will be summarized by treatment group at each scheduled visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

A listing containing individual vital signs measurements that are outside the threshold values criteria at any visit will be provided. For each subject in the listing, measurements at all visits will be included. Clinically significant abnormal findings in vital signs will be reported as AEs.

12.3.4.5 Physical Examination

PE results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.4.6 Other Safety Analysis

Not applicable.

12.3.5 Other Analysis

Not applicable.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

Not applicable.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK parameters of VRT-1207355 and VRT-1268114 will be determined by noncompartmental analysis and 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 clinical pharmacology analysis plan (CPAP).

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VRT-1207355 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 Population PK/PD Analysis Plan. The results of the population PK and PK/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 from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Phone Interview: through the Safety Follow-up Phone Interview
- For enrolled subjects who do not have a Safety Follow-up Phone Interview, 9 days after the last dose of study drug.

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 the CRF and source document. 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 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed November 2017). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." The severity of an AE 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	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death

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).

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	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.

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 followup)

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 and assent (where applicable) through the Safety Follow-up Phone Interview, 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 Phone Interview 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 and assent (where applicable) through the Safety Follow-up Phone Interview, 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: [redacted] (preferred choice)

Fax: [redacted]

For questions, contact telephone: [redacted]

SAEs that occur after the Safety Follow-up Phone Interview and are considered related to study drug(s) will be recorded on the Vertex Organized 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, IECs, and participating investigators in accordance with ICH 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.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH 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.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 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.

13.2.4 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.

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers will be limited to the site and the study physician and will not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the

review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

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

13.2.6 Record Retention

The investigator will maintain all study records according to ICH 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.

13.2.7 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.

13.2.8 End of Study

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

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. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP Guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

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

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

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

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

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.6 Publications and Clinical Study Report

[redacted]

13.6.2 Clinical Study Report

A CSR, written in accordance with the 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 #: VX18-150-104	Version #: 2.0	Version Date: 26 September 2018
Study Title: A Phase 2B Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy		

[redacted]

15.2 Investigator Signature Page

Protocol #: VX18-150-104	Version #: 2.0	Version Date: 26 September 2018
Study Title: A Phase 2B Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-150 for Acute Pain Following Bunionectomy		

I have read Protocol VX18-150-104, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-150 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date